Effective Health Care Program

Hematopoietic Stem-Cell Transplantation in the Pediatric Population

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Hematopoietic Stem-Cell Transplantation in the Pediatric Population

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Hematopoietic Stem-Cell Transplantation in the Pediatric Population

Structured Abstract

Objectives. Assess comparative benefits and harms of hematopoietic stem-cell transplantation (HSCT) versus standard therapies or disease natural history in pediatric (age ≤21 years) patients with malignant solid tumors, inherited metabolic diseases, or autoimmune diseases.

Data Sources. MEDLINE®, Embase, and the Cochrane Database of Systematic Reviews weresearched from January 1995 through August 2011. Additional studies were identified from reference lists and technical experts.

Review Methods. Major data abstraction elements were patient and treatment characteristics, health outcomes (overall survival, remission, neurocognitive development, adverse events), and data analysis. The strength of the body of evidence for each indication was assessed according to the process developed by the Evidence-based Practice Center (EPC) Program of the Agency for Healthcare Research and Quality using four required domains specified in the EPC Methods Guide for Comparative Effectiveness Reviews: risk of bias, consistency, directness, and precision. In cases where there were no head-to-head comparative studies, directness was based on the outcome (e.g., overall survival) rather than on the comparison. For small series or a compilation of case reports in which the prognosis absent HSCT is uniformly fatal (e.g., Wolman's disease), the known natural history was considered an indirect comparator. An optional domain, strength of association (SOA, magnitude of effect) was applied to the body of evidence when there was an apparent benefit or harm, increasing the overall strength beyond what normally may be considered appropriate for such evidence. SOA was deemed not applicable for diseases where there was no clear evidence of benefit or harm with HSCT versus comparators, or if results of individual studies within a body of literature were inconsistent or conflicted. No quantitative scoring method was applied.

Results. Among 6,416 records screened, 251 primary studies were included. The strength of evidence for specific indications was graded as high for 2 indications, moderate or low for 19, and insufficient for 39.

- Evidence suggesting a benefit of HSCT for overall survival:
    - Wolman's disease compared to disease natural history (high strength)
    - Recurrent/progressive anaplastic astrocytoma compared to conventional therapy (low strength)
- Evidence suggesting a benefit of HSCT for neuromuscular symptoms:
    - Farber's disease Type 2/3 compared to symptom management and disease natural history (high strength)
- Evidence suggesting a benefit of HSCT for neurocognitive symptoms:
    - Infantile ceroid lipofuscinosis compared to symptom management or disease natural history (low strength)
    - Attenuated form of MPS (mucopolysaccharoidosis) II (Hunter's disease) compared to enzyme-replacement therapy (ERT) (low strength)

- Evidence suggesting a benefit of HSCT for neurodevelopmental symptoms:
  - Attenuated and severe forms of MPS II (Hunter's disease) compared to ERT (both low strength)
- Evidence suggesting no benefit of single HSCT for overall survival:
  - Metastatic rhabdomyosarcoma compared to conventional therapy (moderate strength)
  - Extraocular retinoblastoma with central nervous system involvement, high-risk Ewing's sarcoma family of tumors, high-risk relapsed Wilm's tumor compared to conventional therapy (all three low strength)
  - Niemann-Pick Type A compared to symptom management (low strength)
- Evidence suggesting no benefit of HSCT for neurodevelopmental symptoms:
  - Gaucher Type III compared to ERT (low strength)
  - Juvenile form of GM_1, juvenile Tay-Sachs compared to symptom management or disease natural history (both low strength)
  - MPS III (Sanfilippo) compared to symptom management, substrate reduction therapy, or disease natural history (low strength)
- Evidence suggesting no benefit of HSCT for neurocognitive symptoms:
  - Severe form of MPS II (Hunter's disease) compared to symptom management or disease natural history (low strength)
  - MPS III (Sanfilippo) compared to symptom management, substrate reduction therapy, or disease natural history (low strength)
  - Gaucher Type III compared to ERT (moderate strength)
- Evidence suggesting harm of HSCT for overall survival:
  - Nonanaplastic mixed or unspecified ependymoma compared to conventional therapy (both low strength)

Conclusions. Evidence demonstrating benefit or harm of HSCT versus standard therapies or disease natural history was insufficient for most pediatric indications.

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Executive Summary

Background

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic progenitor cells, including repopulating stem cells, are infused to restore bone marrow function in patients.[1,2,3] HSCT is categorized by the source of the stem cells, with its role in pediatric diseases dependent in part on the indication for which it is being used.[4] Autologous transplants involve harvesting the patient's own blood stem cells and then returning them, typically after the patient has received doses of chemotherapy that are myeloablative.[1,2] Allogeneic HSCT uses stem cells from a donor who is either matched or unmatched on human leukocyte antigen (HLA) and either related or unrelated; in malignant diseases, it exploits a graft-versus-tumor effect.[5,6]

In the pediatric population, HSCT is used to treat a wide variety of diseases, both malignant and nonmalignant.[7] For many of these diseases, HSCT is a well-established treatment. For example, the literature on the use of HSCT in hematologic malignancies is robust, including randomized controlled trials that date back 20 years, and its practice is supported by evidence-based guidelines. For many less common diseases—for example, the primary immunodeficiencies and hemoglobinopathies—although the evidence consists of case series and case reports, it is sufficient to demonstrate improved outcomes, supporting use of HSCT.

The success of treating many of the pediatric diseases with HSCT has resulted in an increased number of long-term survivors. As improvements in survival have been achieved, there is greater concern about long-term effects and how adverse effects (e.g., graft-vs.-host disease, opportunistic infections, future infertility, developmental delay, and secondary malignancies) might be mitigated.[7,8,9,10] The Key Questions for this review compared benefits and harms of HSCT and conventional therapy for pediatric diseases.

Objectives

Key Questions addressed in this report are split into three groups of two questions each. They pertain to malignant solid tumors, inherited metabolic diseases, and autoimmune diseases.

- Key Question 1. For pediatric patients with malignant solid tumors, what is the comparative effectiveness of HSCT and conventional chemotherapy regarding overall survival, long-term consequences of HSCT, and quality of life?
- Key Question 2. For pediatric patients with malignant solid tumors, what are the comparative harms of HSCT and conventional chemotherapy regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?
- Key Question 3. For pediatric patients with inherited metabolic diseases, what is the comparative effectiveness of HSCT, enzyme-replacement therapy (ERT), and substrate reduction with iminosugars regarding overall survival, cure, long-term consequences of HSCT, and quality of life?
- Key Question 4. For pediatric patients with inherited metabolic diseases, what are the comparative harms of HSCT, ERT, and substrate reduction with iminosugars regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?

- Key Question 5. For pediatric patients with autoimmune diseases, what is the comparative effectiveness of HSCT, immunosuppressants, targeted biologic therapies, and low-dose chemotherapy regarding overall survival, cure, and remission?
- Key Question 6. For pediatric patients with autoimmune diseases, what are the comparative harms of HSCT, immunosuppressants, targeted biologic therapies, and low-dose chemotherapy regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?

Analytic Framework

Analytic frameworks are detailed in Figures A, B, and C.

Figure A. Analytic framework for HSCT for pediatric malignant solid tumors
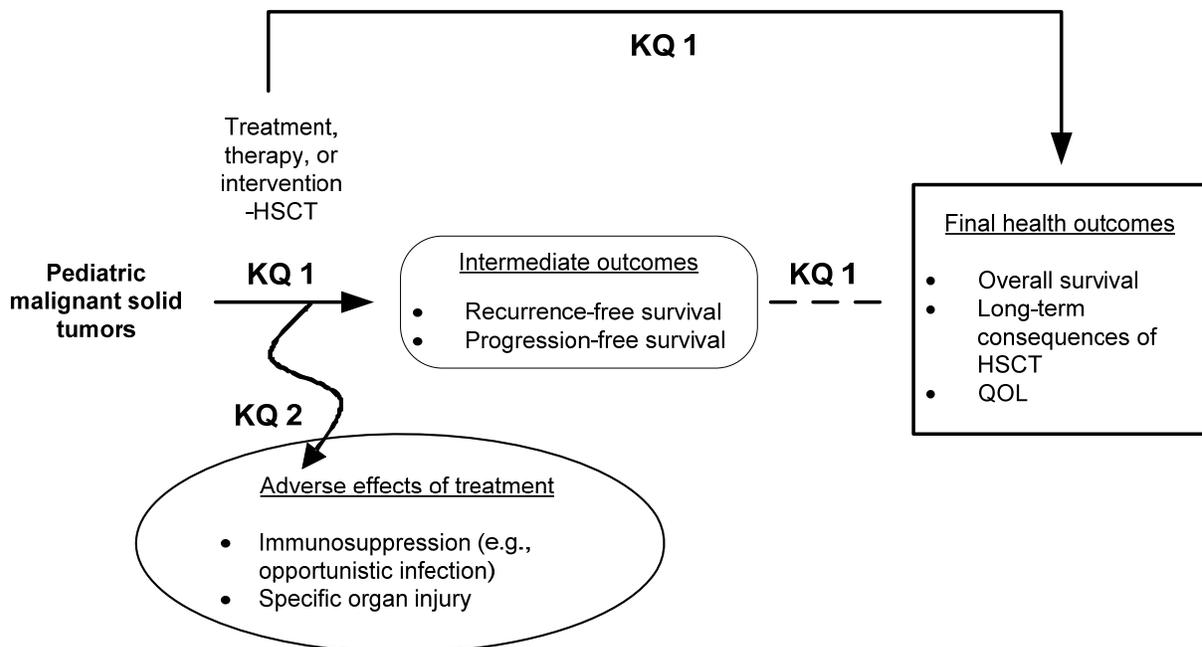
HSCT = hematopoietic stem-cell transplantation; KQ = Key Question; QOL = quality of life

Figure B. Analytic framework for HSCT for pediatric inherited metabolic diseases
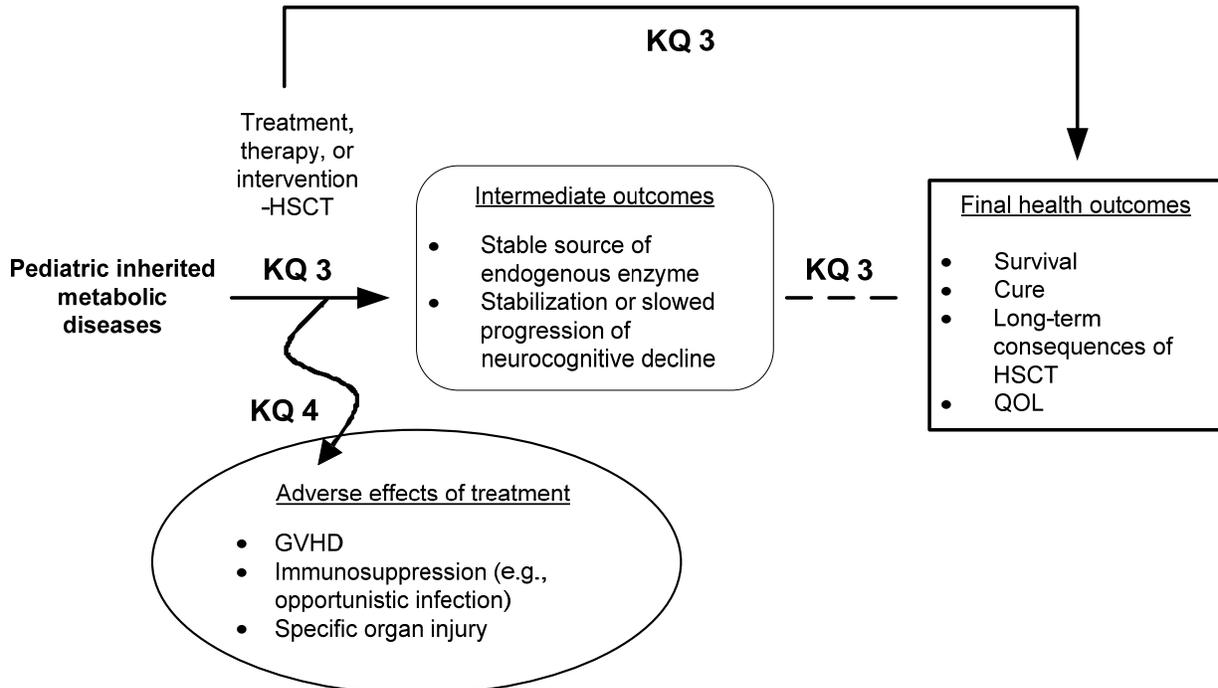
GVHD = graft-versus-host disease; HSCT = hematopoietic stem-cell transplantation; KQ = Key Question; QOL = quality of life

Figure C. Analytic framework for HSCT for pediatric autoimmune diseases
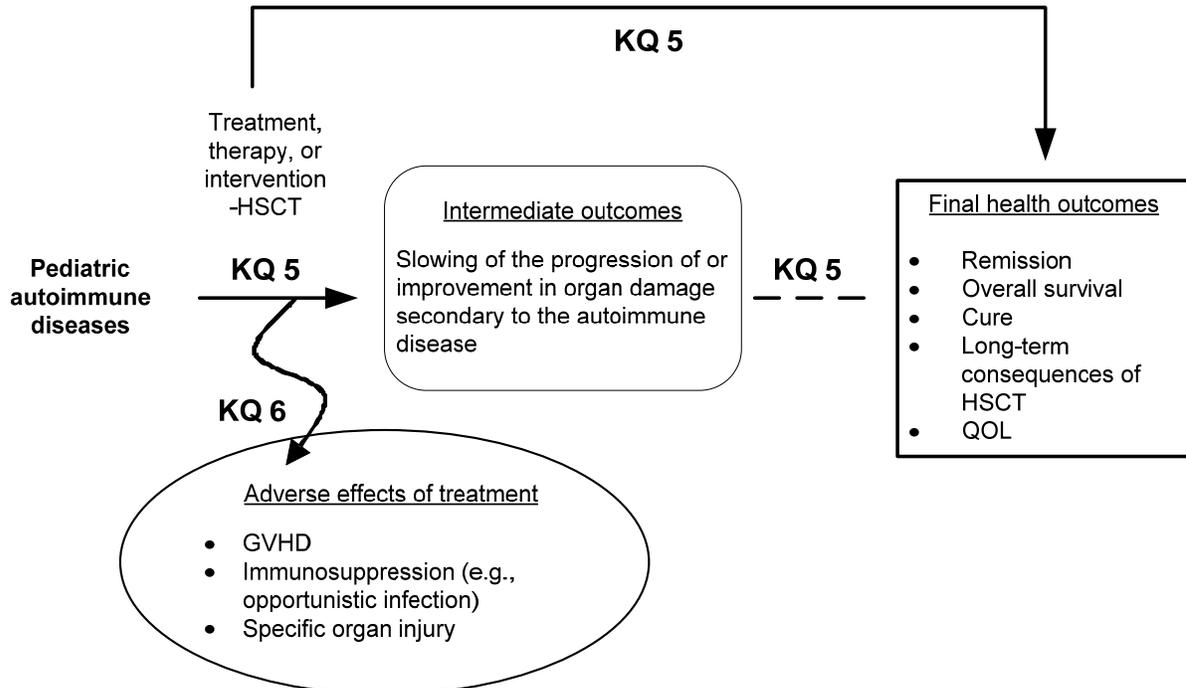
GVHD = graft-versus-host disease; HSCT = hematopoietic stem-cell transplantation; KQ = Key Question; QOL = quality of life

Methods

Topic Refinement

This report comprises a set of narrative reviews and systematic reviews that were defined during the topic refinement phase of the project. Topic refinement also outlined the frameworks and PICOTS (patients, interventions, comparator, outcome, timing, setting) that were posted for public comments and incorporated into the final version. Following completion of the topic refinement phase, a Technical Expert Panel (TEP) was formed. The TEP included original Key Informant (KI) panel members and clinical experts not previously involved. The TEP provided consultation on the development of the protocol and evidence tables for the review. In particular, the TEP provided advice on appropriate clinical outcome data to compile for both benefits and harms. Ad hoc clinical questions were also addressed to the TEP.

Narrative Reviews

The narrative review approach to the conditions presented in Table A was based on the recognition that there exists a substantial body of evidence from 20 years or more of transplantation research and experience that has been codified into published guidelines and reviews. Thus, systematic review of the evidence for these diseases would not be expected to offer new insights or information. In contrast, the Evidence-based Practice Center (EPC) recognized that there were a number of diseases for which evidence of benefits and harms was less clear or for which clinical practice was less established, so that systematic review of the literature would be more likely to provide new insight to inform the field (Table B).

The final categorization of indications for the narrative reviews was determined in an iterative process. Information sources for the narrative reviews were not identified by a systematic search of the literature. Rather, the EPC relied on recently published reviews of pediatric transplantation studies and publicly available sources, such as the National Guidelines Clearinghouse and the National Cancer Institute Physicians Data Query (PDQ) Web site, to develop an initial list of diseases for discussion with the KI panel. The EPC subsequently reexamined the lists and compared them with existing evidence in the context of the KI discussions. A final list of indications for narrative reviews compiled by the EPC was posted for public comment.

Neuroblastoma, germ cell tumors, and central nervous system embryonal tumors are covered in both narrative and systematic reviews. They are distinguished in each by the specific indication and the type of transplant procedure, as shown in Tables A and B.

Table A. Pediatric HSCT indications to be addressed with narrative review

Type	Disease	Indication(s)	Transplant Type
MH	Acute lymphoblastic leukemia (ALL)	In first (high-risk patients), second, or subsequent complete remission (CR)	Allo
MH	Acute myelogenous leukemia (AML)	In first, second, or subsequent CR; early relapse; induction failure	Allo
MH	Juvenile myelomonocytic leukemia (JMML)	As upfront therapy	Allo
MH	Myelodysplastic syndrome (MDS)	As upfront therapy for primary or secondary MDS	Allo
MH	Chronic myelogenous leukemia (CML)	Chronic phase or refractory to tyrosine kinase inhibitor (TKI)	Allo
MH	Non-Hodgkin's lymphoma (NHL)/ Hodgkin's lymphoma (HL)	Induction failure; first, second, third CR/partial remission	Auto/allo
MNH	Neuroblastoma (NB)	Consolidate high-risk (initial)	Auto
		Relapsed/refractory	Auto (allo in selected incidences)
MNH	Germ cell tumor (GCT)	Relapsed	Auto (allo if fail auto and in selected incidences)
MNH	Central nervous system embryonal tumors	Relapsed or residual	Auto
NM	Hemoglobinopathies	Variable	Allo
NM	Bone marrow failure syndromes (BMF)	Variable	Allo

Table A. Pediatric HSCT indications to be addressed with narrative review (continued)

Type	Disease	Indication(s)	Transplant Type
NM	Primary immunodeficiencies, including: *Lymphocyte immunodeficiencies* Adenosine deaminase deficiency Artemis deficiency Calcium channel deficiency CD 40 ligand deficiency Cernunnos-XLF immune deficiency CHARGE syndrome with immune deficiency Common gamma chain deficiency Deficiencies in CD45, CD3, CD8 DiGeorge syndrome DNA ligase IV Interleukin-7 receptor alpha deficiency Janus-associated kinase 3 (JAK3) deficiency Major histocompatibility class II deficiency Omenn syndrome Purine nucleoside phosphorylase deficiency Recombinase-activating gene (RAG) 1/2 deficiency Reticular dysgenesis Winged helix deficiency Wiskott-Aldrich syndrome X-linked lymphoproliferative disease Zeta-chain-associated protein-70 (ZAP-70) deficiency *Phagocytic deficiencies* Chediak-Higashi syndrome Chronic granulomatous disease Griscelli syndrome type 2 Interferon-gamma receptor deficiencies Leukocyte adhesion deficiency Severe congenital neutropenias Shwachman-Diamond syndrome *Other immunodeficiencies* Autoimmune lymphoproliferative syndrome Cartilage hair hypoplasia CD25 deficiency Familial hemophagocytic lymphohistiocytosis Hyper IgE syndromes ICF syndrome IPEX syndrome NEMO deficiency NF-κB inhibitor, alpha (IκB-alpha) deficiency Nijmegen breakage syndrome	Variable	Allo

Table A. Pediatric HSCT indications to be addressed with narrative review (continued)

Type	Disease	Indication(s)	Transplant Type
NM	Inherited metabolic diseases, including: *Mucopolysaccharidosis (MPS)* MPS I (Hurler), MPS VI (Maroteaux-Lamy), MPS VII (Sly syndrome) *Sphingolipidosis* Gaucher I, Niemann-Pick disease B, globoid leukodystrophy, metachromatic leukodystrophy *Glycoproteinosis* Fucosidosis, alpha-mannosidosis *Peroxisomal storage disorders* Adrenoleukodystrophy	Variable	Allo
NM	Osteopetrosis	Severe	Allo

allo = allogeneic; auto = autologous; CR = complete remission; HSCT = hematopoietic stem-cell transplantation; MDS = myelodysplastic syndrome; MH = malignant hematopoietic; MNH = malignant, nonhematopoietic; MPS = mucopolysaccharidosis; NM = nonmalignant

Systematic Reviews

Table B shows the indications that were systematically reviewed. Neuroblastoma, germ cell tumors, and central nervous system embryonal tumors are covered in both narrative and systematic reviews. They are distinguished in each by the specific indication and the type of transplant procedure, as shown in Tables A and B.

Table B. Pediatric HSCT indications to be addressed with systematic review

Type	Disease	Indication(s)	Transplant Type	Comparator
MNH	Ewing sarcoma family of tumors (ESFT)	Consolidate high risk (initial)	Auto	Conventional chemotherapy
		Relapsed/refractory	Auto	Conventional chemotherapy
			Tandem auto auto	Single auto
MNH	Wilms	Consolidate high risk	Auto	Conventional chemotherapy
		Relapsed/refractory	Auto	Conventional chemotherapy
			Tandem auto auto	Single auto
MNH	Rhabdomyosarcoma (RMS)	High-risk disease	Auto	Conventional chemotherapy
			Tandem auto auto	Single auto
MNH	Retinoblastoma	Extraocular spread	Auto	Conventional chemotherapy
			Tandem auto auto	Single auto
MNH	Neuroblastoma (NB)	Consolidate high risk (initial) Relapsed/refractory	Tandem auto auto	Single auto

Table B. Pediatric HSCT indications to be addressed with systematic review (continued)

Type	Disease	Indication(s)	Transplant Type	Comparator
MNH	Germ cell tumor (GCT)	Relapsed	Tandem auto auto	Single auto
MNH	Central nervous system embryonal tumors	Initial therapy	Auto	Conventional chemotherapy
			Tandem auto auto	Single auto
MNH	Central nervous system glial tumors	Consolidate high risk	Auto	Conventional chemotherapy
		Relapsed/refractory	Auto	Conventional chemotherapy
NM	Inherited metabolic diseases: *Mucopolysaccharidosis (MPS)* MPS II (Hunter's), MPS III (Sanfilippo), MPS IV (Morquio) *Sphingolipidosis* Fabry's, Farber's , Gaucher's II-III, GM_1 gangliosidosis, Niemann-Pick disease A, Tay-Sachs disease, Sandhoff's disease *Glycoproteinosis* Aspartylglucosaminuria, beta-mannosidosis, mucolipidosis III and IV *Other lipidoses* Niemann-Pick disease C, Wolman disease, ceroid lipofuscinosis *Glycogen storage* GSD type II *Multiple enzyme deficiency* Galactosialidosis, mucolipidosis type II *Lysosomal transport defects* Cystinosis, sialic acid storage disease, Salla disease *Peroxisomal storage disorders* Adrenomyeloneuropathy	Variable	Allo	Enzyme-replacement therapy, substrate reduction with iminosugars and chaperones
NM	Autoimmune, including juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE), scleroderma, immune cytopenias, Crohn's	Upfront therapy for severe/ refractory or salvage	Auto/allo	Immunosuppressants, targeted biologic therapies and/or low-dose chemotherapy
NM	Autoimmune type 1 diabetes mellitus (DM)	Variable	Auto	Immunosuppressants, targeted biologic therapies and/or low-dose chemotherapy, conventional management (i.e., insulin injections)

allo = allogeneic; auto = autologous; HSCT = hematopoietic stem-cell transplantation; MNH = malignant, nonhematopoietic; MPS = mucopolysaccharidosis; NM = nonmalignant

Systematic Review Data Sources and Study Selection

Electronic databases searched were MEDLINE®, Embase®, and the Cochrane Controlled Trials Register. Databases were initially searched without restriction on date, using the search strategy shown in Appendix A of the full report. However, during the topic refinement phase of this project, the KIs strongly recommended limiting study selection to the past 15 years to ensure that we identified evidence that is comparable in terms of therapeutic regimens and management protocols. Thus, we reviewed the literature from January 1995 up to August 17, 2011, the latter date just prior to delivery of the final report.

Abstract screening and study selection were performed by a single reviewer who was assigned to a specific section. Included studies reported on pediatric patients (age ≤ 21 years) who had a relevant disease and were treated with HSCT or a comparator of interest using a contemporary regimen; to be included, the study also had to report on an outcome of interest. For inherited metabolic diseases, studies reporting outcomes on the disease natural history were included as comparators if they reported on an outcome of interest.

Systematic Review Data Extraction and Quality Assessment

Major elements for data abstraction were patient characteristics (i.e., age, sex, disease stage), treatment characteristics (i.e., chemotherapy vs. chemoradiotherapy, immunosuppressive therapy, and supportive care), and outcomes and details of any data analysis.

Evidence consisted largely of case series and case reports; therefore, we did not attempt to assess the quality of individual studies. According to an Institute of Medicine report,[11] it is well recognized that a common challenge in the study of rare diseases is the preponderance of small uncontrolled studies. Therefore, because studies tended to be homogeneous in design, quality assessment would be unlikely to discriminate between higher and lesser quality studies.

Data were abstracted by a single reviewer and fact checked by another reviewer. If there were disagreements they were resolved through discussion among the review team.

Systematic Review Data Synthesis and Analysis

Data synthesis was qualitative. We attempted to identify subgroups based on prognostic factors such as tumor stage or location in solid tumors, or disease severity or rate of progression in the inborn metabolic disorders, to see if these subgroups showed patterns of treatment success or failure. Quantitative pooling was not attempted. Where possible we calculated confidence intervals for results and reported ranges of results for studies that addressed the same population and treatment.

The strength of the body of evidence for each indication was assessed according to the process specified in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews,[12] developed by the EPC Program of the Agency for Healthcare Research and Quality (AHRQ) This is an iterative, qualitative, consensus-driven process among EPC team members familiar with the summarized literature, using the four required domains specified in the Methods Guide: risk of bias, consistency, directness, and precision. There were no head-to-head comparative studies for most diseases; in those situations, directness was based on the outcome (e.g., overall survival or other clinically important health outcomes) rather than on the comparison. For small series or a compilation of case reports in which the prognosis without HSCT is uniformly fatal (e.g., Wolman's disease), the known natural history was considered an indirect comparator. An optional domain, strength of association (SOA, magnitude of effect) was thus ascribed to the body of evidence when there was an apparent benefit or harm, increasing the

overall strength beyond what normally might be considered appropriate for such evidence. SOA was deemed not applicable for diseases where there was no clear evidence of benefit or harm with HSCT versus comparators, or if results (e.g., overall survival rates) of individual studies within a body of literature were inconsistent or conflicted. No quantitative scoring method was applied.

Systematic Review Results

Figure D shows a PRISMA (Preferred Reporting Items of Systematic reviews and Meta-Analyses) diagram of the studies included in the systematic review. A list of excluded references with reasons for exclusion is available in Appendix B of the full report.

Figure D. PRISMA diagram of articles included in the systematic review

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                    ┌─────────────────────────────┐
                    │  5,181 records identified    │
                    │  through database searching  │
                    └─────────────────────────────┘
┌──────────────────────────┐              │
│ 1,235 records identified │              │
│ through updated          │─────────────→│
│ (08/2011) database       │              ↓
│ searching                │      ┌─────────────────────────┐     ┌──────────────────┐
└──────────────────────────┘      │ 6,416 records screened  │────→│ 5,203 records    │
                                  └─────────────────────────┘     │ excluded         │
                                            │                     └──────────────────┘
                                            ↓
┌──────────────────────────┐      ┌─────────────────────────┐     ┌──────────────────────┐
│ 21 additional            │      │ 1,234 unique, full-text │     │ 983 full-text        │
│ records identified       │      │ articles reviewed       │     │ articles excluded,   │
│ through other            │─────→│ (43 articles reviewed   │────→│ with reasons         │
│ sources (9 included,     │      │ for multiple sections)  │     │ (33 articles reviewed│
│ 12 excluded)             │      └─────────────────────────┘     │ for multiple sections)│
└──────────────────────────┘                │                     └──────────────────────┘
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                                  ┌─────────────────────────┐
                                  │ 251 unique articles     │
                                  │ included                │
                                  │ (10 articles included in│
                                  │ multiple sections)      │
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Disease	Total INCL	Total EXCL	(Hand Searched INCL)	(Hand Searched EXCL)	Totals (Total INCL & Total EXCL)
Autoimmune Disease	30	293	0	0	323
Embryonal Tumors	12	54	2	4	66
ESFT	36	88	0	0	124
GCT	4	7	2	7	11
Glial Tumors	38	90	2	1	128
IMD	56	114	0	0	170
Neuroblastoma	9	159	0	0	168
Retinoblastoma	20	21	0	0	41
Rhabdomyosarcoma	26	35	3	0	61
Wilm's Tumor	20	17	0	0	37
Other	0	105	0	0	105
Totals	251	983	9	12	1,234

ESFT = Ewing sarcoma family of tumors; GCT = germ cell tumor; IMD = inherited metabolic diseases; PRISMA = Preferred Reporting Items of Systematic reviews and Meta-Analyses

The strength of the body of evidence for each indication was assessed. For the diseases systematically reviewed here, the strength of evidence for specific indications (see below) was high in 2 instances, moderate or low in 19, and insufficient for the majority (n = 39) of indications and outcomes addressed. The SOA domain provided justification for increasing the overall GRADE (Grading of Recommendations Assessment, Development and Evaluation) evidence strength ratings for several diseases, despite the absence of a robust body of literature. SOA was not deemed applicable for settings where evidence was inconsistent.

Malignant Solid Tumors (Key Questions 1 and 2)

Evidence suggesting benefit of HSCT compared with conventional therapy:
- Low-strength evidence on overall survival suggests a benefit with single HSCT compared with conventional therapy for *high-risk recurrent or progressive anaplastic astrocytoma*.

Evidence suggesting harm of HSCT compared with conventional therapy:
- Low-strength evidence on overall survival suggests harm due to higher treatment-related mortality with single HSCT compared with conventional chemotherapy for *nonanaplastic mixed or unspecified ependymoma*.

Evidence suggesting no benefit of HSCT compared with conventional therapy:
- Moderate-strength evidence on overall survival suggests no benefit with single HSCT compared with conventional therapy for *metastatic rhabdomyosarcoma*.
- Low-strength evidence on overall survival suggests no benefit with single HSCT compared with conventional therapy for *extraocular retinoblastoma with CNS* (central nervous system) *involvement*, *high-risk Ewing's sarcoma family of tumors*, and *high-risk relapsed Wilm's tumor*.

Insufficient evidence:
- The body of evidence on overall survival with tandem HSCT compared with single HSCT is insufficient to draw conclusions for *high-risk Ewing's sarcoma family of tumors*, *neuroblastoma*, *CNS embryonal tumors*, and *pediatric germ cell tumors*.
- The body of evidence on overall survival with single HSCT compared with conventional therapy is insufficient to draw conclusions for *CNS embryonal tumors*, *high-risk rhabdomyosarcoma of mixed stages*, *congenital alveolar rhabdomyosarcoma*, *cranial parameningeal rhabdomyosarcoma with metastasis*, *allogeneic transplantation for metastatic rhabdomyosarcoma*, *extraocular retinoblastoma with no CNS involvement*, *trilateral retinoblastoma*, and six types of glial tumors (*newly diagnosed anaplastic astrocytoma*, *newly diagnosed glioblastoma multiforme*, *anaplastic ependymoma*, *choroid plexus carcinoma*, *recurrent/progressive glioblastoma multiforme*, and *nonanaplastic, mixed, or unspecified ependymoma*).

Nonmalignant Diseases: Inherited Metabolic Diseases (Key Questions 3 and 4)

The inherited metabolic diseases were split into three categories for this review. Rapidly progressive disease was defined as progression to death within 10 years; the outcome of interest is overall survival. Slowly progressive disease was defined as progression to death of 10 years or greater; the outcomes of interest are neurocognitive and neurodevelopmental outcomes. For diseases that have both rapidly and slowly progressive forms of disease, outcomes of interest are

overall survival for rapidly progressive forms and neurocognitive and neurodevelopmental outcomes for slowly progressive forms.

Rapidly Progressive Diseases

Evidence suggesting benefit of HSCT compared with conventional therapy:
- High-strength evidence on overall survival suggests a benefit with single HSCT compared with conventional management for *Wolman's disease*.

Evidence suggesting no benefit of HSCT compared with conventional therapy:
- Low-strength evidence on overall survival suggests no benefit with single HSCT compared with symptom management or disease natural history for *Niemann-Pick Type A*.

Insufficient evidence:
- The body of evidence on overall survival with single HSCT compared with symptom management is insufficient to draw conclusions for *mucolipidosis II* (I-cell disease), *Gaucher disease type II*, *cystinosis,* and *infantile free sialic acid disease*.

Slowly Progressive Diseases

Evidence suggesting benefit of HSCT compared with conventional therapy:
- Low-strength evidence on neurodevelopmental outcomes suggests a benefit with single HSCT compared with enzyme replacement therapy for *attenuated and severe forms of MPS* (mucopolysaccharidosis) *II* (Hunter's disease).
- Low-strength evidence on neurocognitive outcomes suggests a benefit with single HSCT compared with enzyme replacement therapy for *attenuated form of MPS II* (Hunter's disease).

Evidence suggesting no benefit of HSCT compared with conventional therapy:
- Low-strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared with enzyme replacement therapy for *Gaucher disease type III*.
- Low-strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared with enzyme replacement therapy for the *severe form of MPS II* (Hunter's disease).
- Low-strength evidence on neurocognitive or neurodevelopmental outcomes suggests no benefit with single HSCT compared with symptom management, substrate reduction therapy, or disease natural history for *MPS III* (Sanfilippo).

Insufficient evidence:
- The body of evidence on neurocognitive or neurodevelopmental outcomes with single HSCT compared with symptom management and/or disease natural history is insufficient to draw conclusions for *Niemann-Pick type C*, *MPS IV* (Morquio syndrome), *aspartylglucosaminuria*, *Fabry's disease*, *β-mannosidosis*, *mucolipidosis III*, *mucolipidosis IV*, *glycogen storage disease type II* (Pompe disease), *Salla disease*, and *adrenomyeloneuropathy*.

Diseases With Both Rapidly and Slowly Progressive Forms

Evidence suggesting benefit of HSCT compared with conventional therapy:

- High-strength evidence on number of subcutaneous nodules and number of joints with limited range of motion suggests a benefit with single HSCT compared with symptom management or disease natural history for *Farber's disease type 2/3*.

Evidence suggesting no benefit of HSCT compared with conventional therapy:

- Low-strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared with symptom management or disease natural history for *infantile ceroid lipofuscinosis*.

Insufficient evidence:

- The body of evidence on overall survival and/or neurocognitive and neurodevelopmental outcomes with single HSCT compared with symptom management and/or disease natural history is insufficient to draw conclusions for *galactosialidosis* (type unspecified), *Sandhoff disease* (type unspecified), *Farber's disease type I, infantile GM_1 gangliosidosis, juvenile GM_1 gangliosidosis, infantile Tay-Sachs, juvenile Tay-Sachs*, and *juvenile ceroid lipofuscinosis*.

Autoimmune Diseases (Key Questions 5 and 6)

The main consideration in this systematic review was the comparative balance of long-term benefits and harms of HSCT. With the exception of newly diagnosed type I juvenile diabetes, children in the studies reviewed had severe, typically disabling disease, refractory to a wide variety of standard therapies. Thus, the disease natural history in those cases assumed the role of comparator.

Insufficient evidence:

- The overall body of evidence is insufficient to draw conclusions about the comparative benefits (e.g., increased overall survival) or harms (e.g., treatment-related mortality, secondary malignancies) of single autologous or allogeneic HSCT versus conventional therapy or disease natural history in patients with *newly diagnosed type 1 juvenile diabetes mellitus* or those with severe, refractory, poor-prognosis autoimmune diseases, including *systemic lupus erythematosus, juvenile idiopathic arthritis, systemic sclerosis, malignant multiple sclerosis, Crohn's disease, myasthenia gravis, overlap syndrome, diffuse cutaneous cutis, Evans syndrome, autoimmune hemolytic anemia*, and *autoimmune cytopenia*.
- Although the overall body of evidence is insufficient to come to conclusions about the relative balance of benefits (e.g., increased overall survival) or harms (e.g., treatment-related mortality, secondary malignancies), moderate-strength evidence suggests that extended periods of drug-free clinical remission can be achieved in some cases with single autologous HSCT for patients with *newly diagnosed type I juvenile diabetes* and patients with severe refractory *juvenile idiopathic arthritis, systemic lupus erythematosus, systemic sclerosis*, and *Crohn's disease*.

Discussion

This systematic review of HSCT in the pediatric population addresses indications for which there is uncertainty or evolving evidence, often consisting of uncontrolled single-arm studies and case reports, although for some solid tumors there were substantial numbers of patients reported. Randomized controlled trials were rare for any of the indications included in this systematic review. HSCT is usually reserved for patients or subgroups of patients who have diseases that have very poor prognosis and often are refractory to the best available treatment.

The strength of the body of evidence for each indication was assessed according to the principles described in Grading the Strength of a Body of Evidence When Comparing Medical Interventions[13] in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews produced by AHRQ. The four required domains—risk of bias, consistency, directness, and precision—were considered for all indications. An optional domain, strength of association (magnitude of effect), was used in this process where a large magnitude of effect was particularly evident. This is exemplified by Wolman's disease, a very rare inherited metabolic disorder, where without treatment there is uniformly certain mortality in infancy, so that even very small case examples of survival or cure suggest a large effect of the intervention under consideration. Risk of bias is presumed to be high in a body of evidence comprising small numbers of case reports and series, thus reducing the strength of evidence. However, an obvious strength of association (magnitude of effect)—even if only based on case reports and case series—— increases our confidence that the intervention can be effective, thereby permitting assignment of strength greater than "insufficient." This does not imply that the intervention will succeed in all cases, but that the effects observed can be attributed to the intervention despite the absence of controlled data.

For inherited metabolic diseases, controlled trials with sufficient followup are needed to evaluate the long-term balance of benefit and harms associated with HSCT. Some of these diseases have a homogeneous and dismal natural history. For example, the implications of transplantation for a rapidly progressing lysosomal storage disorder such as Wolman's syndrome are clear; this is a choice between certain death and potential survival, albeit with a risk of adverse effects associated with transplant.

In contrast, type I autoimmune juvenile diabetes can be managed long term satisfactorily, at relatively low risk, in a large proportion of children with intensive insulin therapy (IIT) and lifestyle modifications. The risk-benefit ratio for HSCT compared with IIT must take into account contextual factors, including potential long-term benefit (cure) and harms, particularly those secondary to cytotoxic chemotherapy. The decision to apply a high-risk procedure such as HSCT to this population is not clear cut. For most conditions addressed in this systematic review, evidence is insufficient to draw conclusions as to the relative risk-benefit ratio of HSCT versus other management approaches.

For solid tumors, HSCT studies focused on a single disease and collected detailed information on prognostic factors that may allow for more refined stratification of high-risk categories of patients. A validated prognostic classification would reduce uncertainty in the interpretation of study results.

Overall, the results of this review are applicable primarily to the specific conditions that were evaluated among pediatric patients. We did not address the question of whether evidence from study of HSCT in adults is applicable to pediatric patients.

Explanation of Terms

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in patients. It is categorized by the source of the stem cells.

Autologous transplants involve returning the patient's own stem cells, typically after the patient has received doses of chemotherapy that are myeloablative or, for autoimmune disorders, lymphoablative.

Allogeneic HSCT uses stem cells from an HLA-matched donor, either related or unrelated. In malignant diseases, it exploits a graft-versus-tumor effect. Myeloablative or reduced-intensity (nonmyeloablative) conditioning regimens may be used.

Pediatric in this document refers to patients aged birth through 21 years. While the upper age limit varies, this definition is consistent with the definition found in several sources.[14,15,16]

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Introduction

Background

Hematopoietic stem-cell transplantation (HSCT) involves the infusion of pluripotent hematopoietic progenitor cells to an individual in the course of treatment of a variety of conditions, including certain malignancies, autoimmune diseases, anemias, immunodeficiencies and inborn metabolic disease.[1-3] While the term HSCT is used throughout this report, it is important to note that graft preparations actually contain a mixture of hematopoietic progenitor cells at different stages of maturity, including cells with self-renewal capability (stem cells).[4]

Hematopoietic progenitor cells arise in the bone marrow. These cells may be isolated from marrow that is aspirated from long bones or the pelvis; alternatively, they can be obtained from the blood by apheresis, and are termed peripheral blood stem cells (PBSC). The proportion of PBSCs circulating in the blood is normally very low, but can be significantly increased by the administration of cyclophosphamide, growth factors such as G-CSF, antibodies (e.g., anti-VLA-4), polyanions (e.g., fucoidan), chemokines (e.g., GROβ), and some signaling pathway inhibitors (e.g., AMD3100).[4] Target yields of PBSCs sufficient for transplantation (i.e., more than 2×10^6 CD34+ cells/kg) are usually obtained with one to three aphereses, although this may vary in patients with different malignancies or other conditions (e.g., Fanconi's anemia). PBSCs generally result in faster hematopoietic reconstitution than progenitor cell concentrates isolated from aspirated bone marrow, and are the preferred preparation for autologous transplantation in modern clinical practice.[4]

Two fundamentally different types of HSCT are in clinical use, depending on the indication and the patient.[1, 2] The first, autologous HSCT, involves infusion of hematopoietic progenitor cells obtained from the patient, with the sole intent to restore hematopoietic function following the administration of bone marrow ablative doses of cytotoxic agents. The effectiveness of autologous HSCT is derived entirely from the high-dose cytotoxic conditioning regimen, particularly for treatment of aggressive but chemosensitive malignancies, such as some Hodgkin's and non-Hodgkin's lymphomas. Tandem autologous HSCT refers to a planned treatment that involves administration of two cycles of myeloablative therapy, each followed by infusion of autologous HSCT.

The second type of HSCT, allogeneic HSCT, refers to the infusion of hematopoietic progenitor cells obtained from a donor, but has two purposes. It recreates a new immunohematopoietic system in patients who receive marrow ablative doses of cytotoxic agents. In addition, the nonself allogeneic immune effector cells contained in a donor stem cell preparation exert a therapeutic graft-versus-malignancy (GVM) effect, and in the case of autoimmune diseases, a possible graft-versus-autoimmune disease effect.

Allogeneic HSCT may involve the use of a fully marrow ablative, high-dose conditioning regimen, with accompanying tumor cytoreduction, or a nonmyeloablative regimen, that is referred to as reduced-intensity conditioning, with clinical benefit primarily secondary to the GVM effect.[5, 6] Reduced-intensity conditioning regimens have been designed to extend the potential benefits of allogeneic HSCT to patients who for reasons of age, disease, or underlying comorbidities, would not be considered candidates for a high-dose, myeloablative procedure. In essence, autologous HSCT is a lifesaving rescue procedure to restore bone marrow function, whereas allogeneic HSCT may be both a rescue and therapeutic procedure.

Umbilical cord blood (UCB) also is a source of hematopoietic stem cells for transplantation.[1] UCB is technically an allogeneic source of hematopoietic progenitor cells; it is hypothesized, however, that cord blood cells are more immunologically naïve than bone-marrow-derived progenitor cells. As a consequence, the incidence of acute and chronic graft-versus-host disease (GVHD) is lower with the use of UCB transplantation than with bone marrow-derived cell preparations. Human leukocyte antigen (HLA) matching requirements are thus less stringent than with marrow-derived progenitor cell preparations. However, the total number of progenitor cells that can be obtained from a single umbilical cord is relatively low, which has hampered the application of UCB transplantation in adults, even though outcomes are similar to those achieved with matched unrelated bone-marrow-derived cell preparations.[1]

HSCT of any type is associated with a number of adverse events, regardless of the conditioning regimen and type of transplant. Acute and chronic GVHD can be highly problematic in patients who undergo an allogeneic HSCT, and represent the major limitation to use of this procedure in older or otherwise debilitated patients.[5] Short term (i.e., days 0-100 post-transplant) complications of HSCT of either type include mucositis, hemorrhage, infections (e.g., bacterial, fungal, viral), veno-occlusive disease of the liver, and pulmonary complications. Long-term complications include infertility, impaired growth and cognitive development, and secondary malignancies. The long-term complications assume greater importance in pediatric patients than in older recipients, in particular as post-HSCT survival rates have increased and treatment-related mortality has decreased with improved life support and management.[7-10] Additional background information is presented in the discussion of each condition.

Scope and Key Questions

This comparative effectiveness review consists of two major sections, which were determined through the Agency for Healthcare Research and Quality (AHRQ) topic refinement process with input from Key Informants and AHRQ personnel (see Methods chapter). The first section comprises a set of narrative reviews on the use of HSCT in pediatric malignant and nonmalignant diseases for which HSCT is considered a well-established treatment option. The second section contains a set of systematic reviews of the use of HSCT in malignant and nonmalignant diseases, including solid tumors, inherited metabolic diseases, and autoimmune diseases. The indications systematically reviewed were those for which the therapeutic role of HSCT has not been established by clinical study. Specific settings are outlined in the Methods chapter. For pediatric malignancies, key outcomes of interest included overall survival, treatment-related mortality, and other severe adverse events.

For the inherited metabolic diseases, outcomes of interest were overall survival, neurocognitive and neurodevelopmental measures, treatment-related mortality, and other severe adverse events. For the autoimmune diseases, the key outcomes were drug-free clinical remission, as well as treatment-related mortality and other severe adverse events. No effort was made to systematically review outcomes in the context of different induction chemotherapy or consolidation conditioning regimens, supportive care, or stem-cell preparations. Rather, the document is intended to show the level of evidence in the literature on the use of HSCT for each indication, supposing that treatment will be delivered according to protocols in place at individual clinical institutions. The EPC Methods Guide process was used to provide an overall evaluation of the strength of evidence for each key outcome and for the overall body of evidence for each indication.

Table 1 displays the indications to be approached as a narrative review, while Table 2 displays the indications to be addressed in the systematic review. It is important to note that neuroblastoma, germ cell tumors, and central nervous system embryonal tumors are covered in both the narrative and systematic reviews; however, they are distinguished in each by the specific indication and the type of transplant procedure.

Table 1. Pediatric HSCT indications to be addressed with narrative review

Type	Disease	Indication(s)	Transplant Type
MH	Acute lymphoblastic leukemia (ALL)	In first (high-risk patients), second, or subsequent complete remission (CR)	Allo
MH	Acute myelogenous leukemia (AML)	In first, second, or subsequent CR; early relapse; induction failure	Allo
MH	Juvenile myelomonocytic leukemia (JMML)	As upfront therapy	Allo
MH	Myelodysplastic syndrome (MDS)	As upfront therapy for primary or secondary MDS	Allo
MH	Chronic myelogenous leukemia (CML)	Chronic phase or refractory to tyrosine kinase inhibitor (TKI)	Allo
MH	Non-Hodgkin's lymphoma (NHL)/ Hodgkin's lymphoma (HL)	Induction failure; first, second, third CR/partial remission	Auto/allo
MNH	Neuroblastoma (NB)	Consolidate high-risk (initial)	Auto
		Relapsed/refractory	Auto (allo in selected incidences)
MNH	Germ cell tumor (GCT)	Relapsed	Auto (allo if fail auto and in selected incidences)
MNH	Central nervous system embryonal tumors	Relapsed or residual	Auto
NM	Hemoglobinopathies	Variable	Allo
NM	Bone marrow failure syndromes (BMF)	Variable	Allo

Table 1. Pediatric HSCT indications to be addressed with narrative review (continued)

Type	Disease	Indication(s)	Transplant Type
NM	Primary immunodeficiencies, including: *Lymphocyte immunodeficiencies* Adenosine deaminase deficiency Artemis deficiency Calcium channel deficiency CD 40 ligand deficiency Cernunnos-XLF immune deficiency CHARGE syndrome with immune deficiency Common gamma chain deficiency Deficiencies in CD45, CD3, CD8 DiGeorge syndrome DNA ligase IV Interleukin-7 receptor alpha deficiency Janus-associated kinase 3 (JAK3) deficiency Major histocompatibility class II deficiency Omenn syndrome Purine nucleoside phosphorylase deficiency Recombinase-activating gene (RAG) 1/2 deficiency Reticular dysgenesis Winged helix deficiency Wiskott-Aldrich syndrome X-linked lymphoproliferative disease Zeta-chain-associated protein-70 (ZAP-70) deficiency *Phagocytic deficiencies* Chediak-Higashi syndrome Chronic granulomatous disease Griscelli syndrome type 2 Interferon-gamma receptor deficiencies Leukocyte adhesion deficiency Severe congenital neutropenias Shwachman-Diamond syndrome *Other immunodeficiencies* Autoimmune lymphoproliferative syndrome Cartilage hair hypoplasia CD25 deficiency Familial hemophagocytic lymphohistiocytosis Hyper IgE syndromes ICF syndrome IPEX syndrome NEMO deficiency NF-κB inhibitor, alpha (IκB-alpha) deficiency Nijmegen breakage syndrome	Variable	Allo

Table 1. Pediatric HSCT indications to be addressed with narrative review (continued)

Type	Disease	Indication(s)	Transplant Type
NM	Inherited metabolic diseases, including: *Mucopolysaccharidosis (MPS)* MPS I (Hurler), MPS VI (Maroteaux-Lamy), MPS VII (Sly syndrome) *Sphingolipidosis* Gaucher I, Niemann-Pick disease B, globoid leukodystrophy, metachromatic leukodystrophy *Glycoproteinosis* Fucosidosis, alpha-mannosidosis *Peroxisomal storage disorders* Adrenoleukodystrophy	Variable	Allo
NM	Osteopetrosis	Severe	Allo

ALL = acute lymphoblastic leukemia; allo = allogeneic; AML = acute myelogenous leukemia; auto = autologous; BMF = bone marrow failure; CML = chronic myelogenous leukemia; CR = complete remission; DM = diabetes mellitus; ESFT = Ewing sarcoma family of tumors; GCT = germ cell tumor; HL = Hodgkin's lymphoma; JRA = juvenile rheumatoid arthritis; MA = meta-analysis; MDS = myelodysplastic syndrome; MH = malignant, hematopoietic; MNH = malignant, nonhematopoietic; NB = neuroblastoma; NHL = non-Hodgkin's lymphoma (includes Burkitt/Burkitt-like, diffuse large B-cell lymphoma, lymphoblastic lymphoma and anaplastic large cell lymphoma); NM = nonmalignant; OS = osteosarcoma; PNET = primitive neuroectodermal tumor; SLE = systemic lupus erythematosus; TKI = tyrosine kinase inhibitor

Table 2. Pediatric HSCT indications to be addressed with systematic review

Type	Disease	Indication(s)	Transplant Type	Comparator
MNH	Ewing sarcoma family of tumors (ESFT)	Consolidate high risk (initial)	Auto	Conventional chemotherapy
		Relapsed/refractory	Auto	Conventional chemotherapy
			Tandem auto auto	Single auto
MNH	Wilms	Consolidate high risk	Auto	Conventional chemotherapy
		Relapsed/refractory	Auto	Conventional chemotherapy
			Tandem auto auto	Single auto
MNH	Rhabdomyosarcoma (RMS)	High-risk disease	Auto	Conventional chemotherapy
			Tandem auto auto	Single auto
MNH	Retinoblastoma	Extraocular spread	Auto	Conventional chemotherapy
			Tandem auto auto	Single auto
MNH	Neuroblastoma (NB)	Consolidate high risk (initial) Relapsed/refractory	Tandem auto auto	Single auto
MNH	Germ cell tumor (GCT)	Relapsed	Tandem auto auto	Single auto
MNH	Central nervous system embryonal tumors	Initial therapy	Auto	Conventional chemotherapy
			Tandem auto auto	Single auto

Table 2. Pediatric HSCT indications to be addressed with systematic review (continued)

Type	Disease	Indication(s)	Transplant Type	Comparator
MNH	Central nervous system glial tumors	Consolidate high risk	Auto	Conventional chemotherapy
		Relapsed/refractory	Auto	Conventional chemotherapy
<u>NM</u>	Inherited metabolic diseases: *Mucopolysaccharidosis (MPS)* MPS II (Hunter's), MPS III (Sanfilippo), MPS IV (Morquio) *Sphingolipidosis* Fabry's, Farber's, Gaucher's II-III, GM_1 gangliosidosis, Niemann-Pick disease A, Tay-Sachs disease, Sandhoff's disease *Glycoproteinosis* Aspartylglucosaminuria, beta-mannosidosis, mucolipidosis III and IV <u>*Other lipidoses*</u> Niemann-Pick disease C, Wolman disease, ceroid lipofuscinosis *Glycogen storage* GSD type II *Multiple enzyme deficiency* Galactosialidosis, mucolipidosis type II <u>*Lysosomal transport* defects</u> Cystinosis, sialic acid storage disease, Salla disease *Peroxisomal storage disorders* Adrenomyeloneuropathy	Variable	Allo	Enzyme-replacement therapy, substrate reduction with iminosugars and chaperones
NM	Autoimmune, including juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE), scleroderma, immune cytopenias, Crohn's	Upfront therapy for severe/ refractory or salvage	Auto/allo	Immunosuppressants, targeted biologic therapies and/or low-dose chemotherapy
NM	Autoimmune type 1 diabetes mellitus (DM)	Variable	Auto	Immunosuppressants, targeted biologic therapies and/or low-dose chemotherapy, conventional management (i.e., insulin injections)

allo = allogeneic; auto = autologous; DM = diabetes mellitus; ESFT = Ewing sarcoma family of tumors; GCT = germ cell tumor; HL = Hodgkin's lymphoma; JRA = juvenile rheumatoid arthritis; MDS = myelodysplastic syndrome; MNH = malignant, nonhematopoietic; NM = nonmalignant; OS = osteosarcoma; PNET = primitive neuroectodermal tumor; RMS = rhabdomyosarcoma; SLE = systemic lupus erythematosus; TKI = tyrosine kinase inhibitor

Systematic Review Key Questions

- Key Question 1. For pediatric patients with malignant solid tumors, what is the comparative effectiveness of HSCT and conventional chemotherapy regarding overall survival, long-term consequences of HSCT, and quality of life?
- Key Question 2. For pediatric patients with malignant solid tumors, what are the comparative harms of HSCT and conventional chemotherapy regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?
- Key Question 3. For pediatric patients with inherited metabolic diseases, what is the comparative effectiveness of HSCT, enzyme-replacement therapy (ERT), and substrate reduction with iminosugars regarding overall survival, cure, long-term consequences of HSCT, and quality of life?
- Key Question 4. For pediatric patients with inherited metabolic diseases, what are the comparative harms of HSCT, enzyme-replacement therapy (ERT), and substrate reduction with iminosugars regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?
- Key Question 5. For pediatric patients with autoimmune diseases, what is the comparative effectiveness of HSCT, immunosuppressants, target biologic therapies, and low-dose chemotherapy regarding overall survival, cure, and remission?
- Key Question 6. For pediatric patients with autoimmune diseases, what are the comparative harms of HSCT, immunosuppressants, target biologic therapies, and low dose chemotherapy regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?

The PICOTS (Patient, Intervention, Comparator, Outcome, Timing, and Setting) for the three indications addressed in the systematic review follow.

Indication 1. Malignant Solid Tumors (Key Questions 1 and 2)

P: Pediatric patients with malignant solid tumors including rhabdomyosarcoma and retinoblastoma

I: Hematopoietic stem-cell transplantation (HSCT)

C: Conventional chemotherapy

O: Overall survival (OS); long-term consequences of HSCT; quality of life (QOL)

T: All durations of followup will be included

S: Inpatient

Indication 2. Inherited Metabolic Disease (Key Questions 3 and 4)

P: Pediatric patients with inherited metabolic diseases

I: Hematopoietic stem-cell transplantation (HSCT)

C: Enzyme-replacement therapy (ERT) for IMDs with products approved by the U.S. Food and Drug Administration (FDA), substrate reduction with iminosugars disease natural history

O: OS; cure; long-term consequences of HSCT; QOL

T: All durations of followup will be included

S: Inpatient

Indication 3. Autoimmune Disease (Key Questions 5 and 6)

P: Pediatric patients with autoimmune diseases

I: Hematopoietic stem-cell transplantation (HSCT)

C: Immunosuppressants, targeted biologic therapies, low-dose chemotherapy

O: Remission, survival, cure

T: All durations of followup will be included

S: Inpatient

Analytic frameworks are detailed in Figure 1, Figure 2, and Figure 3.

Figure 1. Analytic framework for HSCT for pediatric malignant solid tumors
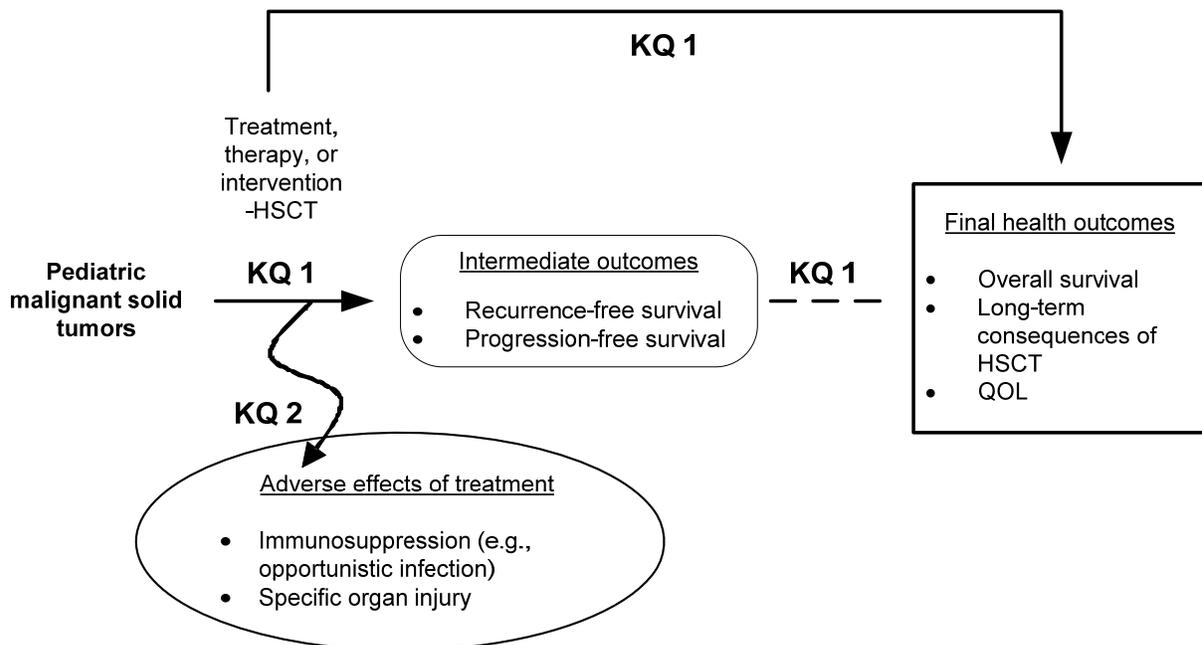
HSCT = hematopoietic stem-cell transplantation; KQ = Key Question; QOL = quality of life

Figure 2. Analytic framework for HSCT for pediatric inherited metabolic diseases
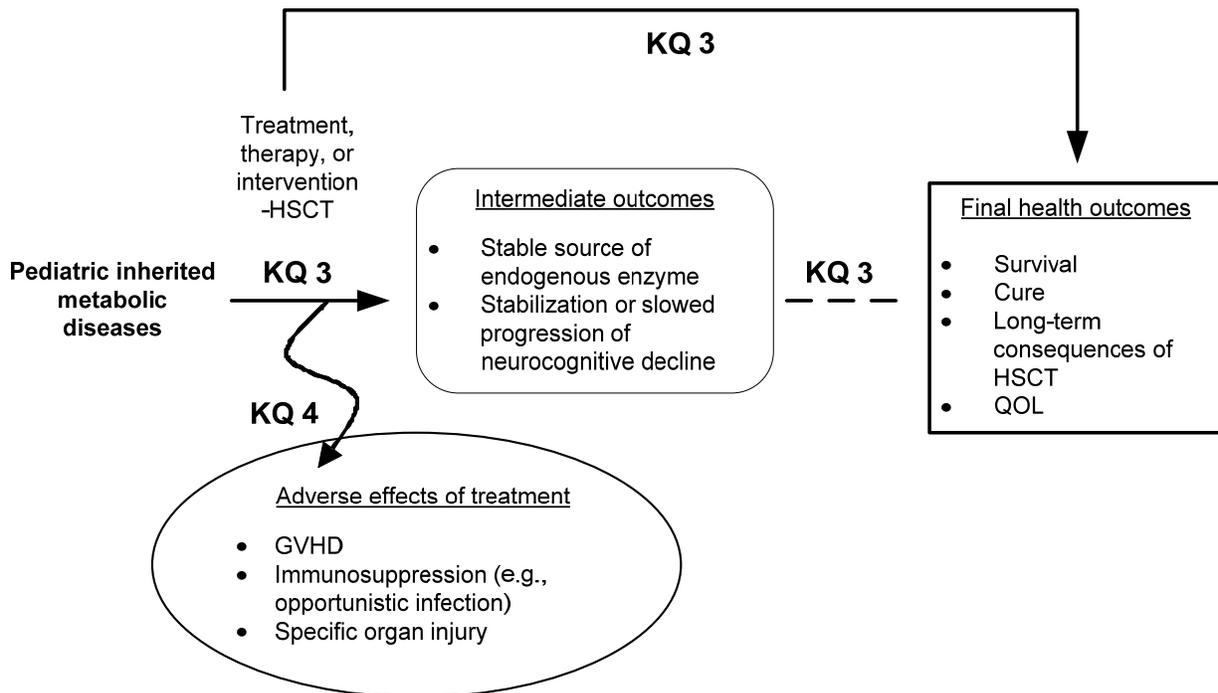
KQ 3

Treatment,
therapy, or
intervention
-HSCT

Pediatric inherited
metabolic
diseases

KQ 3

KQ 4

Intermediate outcomes

- Stable source of
  endogenous enzyme
- Stabilization or slowed
  progression of
  neurocognitive decline

KQ 3

Final health outcomes

- Survival
- Cure
- Long-term
  consequences of
  HSCT
- QOL

Adverse effects of treatment

- GVHD
- Immunosuppression (e.g.,
  opportunistic infection)
- Specific organ injury

GVHD = graft-versus-host disease; HSCT = hematopoietic stem-cell transplantation; KQ = Key Question; QOL = quality of life

Figure 3. Analytic framework for HSCT for pediatric autoimmune diseases
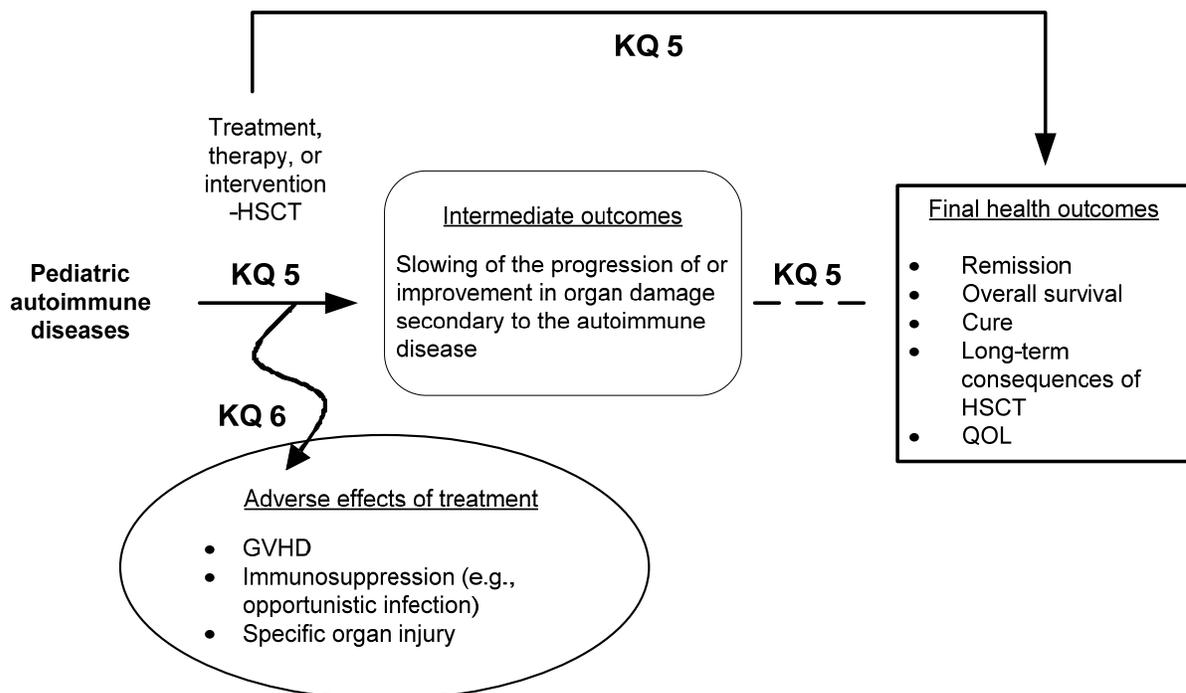
KQ 5

Treatment,
therapy, or
intervention
-HSCT

Pediatric
autoimmune
diseases

KQ 5

KQ 6

Intermediate outcomes

Slowing of the progression of or
improvement in organ damage
secondary to the autoimmune
disease

KQ 5

Final health outcomes

- Remission
- Overall survival
- Cure
- Long-term
  consequences of
  HSCT
- QOL

Adverse effects of treatment

- GVHD
- Immunosuppression (e.g.,
  opportunistic infection)
- Specific organ injury

GVHD = graft-versus-host disease; HSCT = hematopoietic stem-cell transplantation; KQ = Key Question; QOL = quality of life

Methods

Topic Development and Refinement

The topic of this report and preliminary Key Questions were developed through a public process involving the public, the Scientific Resource Center (available at: http://effectivehealthcare.ahrq.gov/index.cfm/who-is-involved-in-the-effective-health-care-program1/about-the-scientific-resource-center1/) for the Effective Health Care program of the Agency for Healthcare Research and Quality (AHRQ), and various stakeholder groups.

Recognizing that the scope was broad and that there were diseases for which 20 years of research had been codified into guidelines and reviews, as described in the Introduction, we took a "narrative review" approach to those diseases, reserving a systematic review approach for those indications for which the role of HSCT was not established by clinical study. This was done in consultation with a Key Informant panel and AHRQ personnel. The Key Informant panel comprised clinical experts in the various diseases covered in this report. The topic refinement process made us aware that the literature base for the systematic review was predominantly case series and case reports. This represents the circumstance that the diseases under consideration are rare diseases or in more common diseases, the subgroups of patients having poor prognosis or are refractory to therapy.

Topic refinement also outlined the frameworks and PICOTS which were also posted for public comment. In summary, the public comments addressed three main points. First, while successes have been seen with HSCT in many pediatric conditions, the measurement of comparative outcomes after HSCT is difficult due to the rarity of the conditions (e.g., retinoblastoma) and/or the number of transplants completed (e.g., autoimmune diseases). Second, comparative harms data are equally difficult to obtain, as separating out the harms associated with HSCT from the harms associated with other prior treatments or disease natural history is not possible in many cases. Third, it was suggested that we contact the Pediatric Blood and Marrow Transplant Consortium and Center for International Blood and Marrow Transplant Research (CIBMTR) to see if they could provide advice to guide the structure of the report. No major changes were made following the public comments. These points were taken into account in the CER.

Technical Expert Panel and Peer Review

With completion of the topic refinement phase, a Technical Expert Panel (TEP) was formed. The TEP included original Key Informant panel members and clinical experts not previously involved. The TEP provided consultation on the development of the protocol and evidence tables for the review. Ad hoc clinical questions were also addressed to the TEP. The draft report was reviewed by five external reviewers, including invited clinical experts and stakeholders. Revisions were made to the draft report based on reviewers' comments.

Narrative Reviews

The narrative review approach to a number of conditions presented in this report was based on recognition that there exists a substantial body of evidence from 20 years or more of transplantation research and experience that had been codified into published guidelines and reviews. Thus, systematic review of the evidence for these diseases would not be expected to

offer new insights or information. By contrast, the EPC recognized there were a number of diseases for which evidence of benefits and harms was less clear or for which clinical practice was less established, so that systematic review of the literature would be more likely to provide new insight to inform the field.

The final categorization of indications for the narrative reviews was determined in an iterative process. Information sources were not identified by a systematic review of the literature. Rather, the EPC relied on recently published reviews of pediatric transplantation studies, and publicly available sources such as the National Guidelines Clearinghouse and the National Cancer Institute's Physician Data Query (PDQ) Web site, to develop an initial list of diseases for discussion with the Key Informant panel. The EPC subsequently reexamined the lists, compared them to existing evidence, in the context of the Key Informant discussions. A final list of indications for narrative reviews compiled by the EPC was posted for public comment.

Systematic Reviews

The following methods apply only to the systematic reviews presented in this report.

Literature Search

Electronic databases searched were MEDLINE®, Embase®, and the Cochrane Controlled Trials Register. Databases were initially searched without restriction on date, using the search strategy shown in Appendix A. However, during the Topic Refinement phase of this project, the Key Informants strongly recommended limiting study selection to the past 15 years to ensure we identify evidence that is comparable in terms of therapeutic regimens and management protocols. Thus, we reviewed the literature from January 1995 up to November 9, 2009. Literature searches were updated to August 17, 2011, prior to delivery of the final report to ensure the identification of new literature that potentially had an impact on the review.

All search results were compiled into an EndNote® reference manager database with exclusion of duplicates. Additional details on these materials and results of our review are provided in the Results chapter. Search strategies and results are detailed in Appendix A.

Study Selection

Inclusion and exclusion criteria are for all Key Questions.
Inclusion criteria:

- Reports on pediatric patients (age ≤21 years) who have relevant diseases (malignant solid tumors, inherited metabolic diseases, or autoimmune disease).
- Reports on an outcome of interest.
- Reported on HSCT and/or a comparator of interest.
- Intervention and comparator used contemporary regimens with respect to chemotherapy, radiation therapy and supportive care.
- For Key Questions 3 and 4 (inherited metabolic diseases) studies reporting outcomes on the natural history of disease were included as comparators.

Exclusion criteria:
- Studies older than 15 years as they would not represent contemporary regimens except the natural history data for Key Questions 3 and 4.
- Studies where pediatric data could not be separated and abstracted from adult data.
- Duplicate studies or reports with duplicate patients were excluded except the study with the largest number of patients with the longest followup.

Abstract and study selection was performed by a single reviewer for each section of the report. If a reviewer was uncertain whether a study should be selected for inclusion, this was resolved through discussion at team meetings.

Figure 4 shows a PRISMA[11] diagram of the studies included in the systematic review. A listing of excluded references with reasons for exclusions is available in Appendix B.

Data Abstraction

Data were abstracted by a single reviewer, and fact checked by another reviewer. If there were disagreements, they were resolved through discussion among the review team. The following data elements of primary studies were abstracted from the articles meeting selection criteria:
- Critical features of the study design
  - Patient inclusion/exclusion criteria
  - Number of participants and flow of participants through steps of study
- Patient characteristics, including:
  - Age
  - Sex
  - Race/ethnicity
  - Disease and stage
  - Disease duration
  - Other prognostic characteristics
- Treatment characteristics, including
  - Stem-cell source
  - Chemotherapy versus chemo-radiotherapy
  - Immunosuppressive therapy as prophylaxis for graft versus host disease
  - Supportive care
- Outcome assessment details
  - Identified primary outcome
  - Secondary outcomes
  - Response criteria
  - Use of independent outcome assessor
  - Followup frequency and duration
- Data analysis details
  - Statistical analyses (statistical test/estimation results)
    - Test used
    - Summary measures
    - Sample variability measures
    - Precision of estimate
    - P values

Full data abstraction tables are available in Appendix C. Evidence tables were generated in Microsoft Excel® and Microsoft Word®.

Figure 4. PRISMA diagram of articles included in the systematic review

Disease	Total INCL	Total EXCL	(Hand Searched INCL)	(Hand Searched EXCL)	Totals (Total INCL & Total EXCL)
Autoimmune Disease	30	293	0	0	323
Embryonal Tumors	12	54	2	4	66
ESFT	36	88	0	0	124
GCT	4	7	2	7	11
Glial Tumors	38	90	2	1	128
IMD	56	114	0	0	170
Neuroblastoma	9	159	0	0	168
Retinoblastoma	20	21	0	0	41
Rhabdomyosarcoma	26	35	3	0	61
Wilm's Tumor	20	17	0	0	37
Other	0	105	0	0	105
Totals	251	983	9	12	1,234

Study Quality

Evidence consisted largely of case series and case reports; therefore we did not attempt to assess the quality of individual studies. It is well recognized in the study of rare diseases that a common challenge is the preponderance of small, uncontrolled studies.[12] Therefore, because studies tended to be homogenous in design, quality assessment would be unlikely to discriminate between higher and lesser quality studies.

Data Synthesis

Data synthesis was qualitative. We attempted to identify subgroups based on prognostic factors such as tumor stage or location in solid tumors, or disease severity or rate of progression in the inborn metabolic disorders, to see if these subgroups showed patterns of treatment success or failure. The evidence base was considered insufficient and too heterogeneous to use quantitative pooling methods. Where possible we calculated confidence intervals for results and reported ranges of results for studies that addressed the same population and treatment.

Grading the Evidence for Each Key Question

The strength of the body of evidence for each indication was assessed according to the process developed by the AHRQ EPC Program[13] for the EPC Methods Guide, based on a system developed by the GRADE Working Group.[14] This comprised an iterative, qualitative consensus-driven process among EPC team members familiar with the summarized literature, using the 4 required domains specified in the EPC Methods Guide: risk of bias, consistency, directness, and precision. There were no head-to-head comparative studies for most diseases; in those situations, directness was based on the outcome (e.g., overall survival or other clinically important health outcomes) rather than on the comparison. For small series or a compilation of case reports in which the prognosis absent HSCT is uniformly fatal (e.g., Wolman's disease), the known natural history was considered an indirect comparator. An optional domain, strength of association (SOA, magnitude of effect) was thus ascribed to the body of evidence when there was an apparent benefit or harm, increasing the overall strength beyond what may be normally considered appropriate for such evidence. SOA was deemed not applicable for diseases where there was no clear evidence of benefit or harm with HSCT versus comparators, or if results (e.g., overall survival rates) of individual studies within a body of literature were inconsistent or conflicted. No quantitative scoring method was applied.

Table 3 displays the EPC Methods Guide definitions and applications of GRADE and describes how we applied the domains in this review.

The overall grade of evidence strength was classified into the following four categories:

- High: Further research is very unlikely to change our confidence in the estimate of effect
- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate of effect
- Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Insufficient: Any estimate of effect is very uncertain

Table 3. Elements of evidence grading for Key Questions

Domain	Definitions and Elements From EPC Methods Guide	Score and Application by BCBSA in the HSCT Project
Risk of Bias	Risk of bias is the degree to which the included studies for a given outcome or comparison have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through two main elements: • Study design (e.g., RCTs or observational studies) • Aggregate quality of the studies under consideration. Information for this determination comes from the rating of quality (good/fair/poor) done for individual studies.	In the application of this domain one of three levels of aggregate risk of bias is typically used: • **Low** risk of bias was applied when evidence was available from randomized comparative trials. • **Medium** risk of bias was applied when evidence was available from large, nonrandomized comparative studies. • **High** risk of bias was applied to all other evidence. Because evidence for the majority of indications considered in the systematic reviews comprised case series or case reports, we did not individually assess study quality. As a consequence, the risk of bias was presumed to be high.
Consistency	The principal definition of consistency is the degree to which reported effect sizes from included studies appear to have the same direction of effect. This can be assessed through two main elements: • Effect sizes have the same sign (that is, are on the same side of "no effect"). • The range of effect sizes is narrow. **Application** Use one of three levels of consistency: • Consistent (i.e., no inconsistency) • Inconsistent • Unknown or not applicable (e.g., single study) As noted in the text, single-study evidence bases (even mega-trials) cannot be judged with respect to consistency. In that instance, use "consistency unknown (single study)."	In the application of this domain we used one of three levels of consistency: • **Consistent** (results appear to have one direction of effect i.e. HSCT appears to be an improvement over conventional therapy, HSCT appears not to be an improvement over comparator, or HSCT and conventional therapy appear to have the same survival benefit.) • **Inconsistent** (Results have more than one direction of effect leading to more than one conclusion.) • **Unknown or not applicable** (Results may be of unknown consistency is the evidence based consists of a single study or a few case reports.)

Table 3. Elements of evidence grading for Key Questions (continued)

Domain	Definitions and Elements From EPC Methods Guide	Score and Application by BCBSA in the HSCT Project
Directness	The rating of directness relates to whether the evidence links the interventions directly to health outcomes. For a comparison of two treatments, directness implies that head-to-head trials measure the most important health or ultimate outcomes. Two types of directness, which can coexist, may be of concern: Evidence is indirect if: • It uses intermediate or surrogate outcomes instead of health outcomes. In this case, one body of evidence links the intervention to intermediate outcomes and another body of evidence links the intermediate to most important (health or ultimate) outcomes. • It uses two or more bodies of evidence to compare interventions A and B— e.g., studies of A vs. placebo and B vs. placebo, or studies of A vs. C and B vs. C but not A vs. B. Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcomes. Directness may be contingent on the outcomes of interest. EPC authors are expected to make clear the outcomes involved when assessing this domain. **Application** Score dichotomously as one of two levels of directness: • Direct • Indirect If indirect, specify which of the two types of indirectness accounts for the rating (or both, if that is the case)—namely, use of intermediate/surrogate outcomes rather than health outcomes and use of indirect comparisons. Comment on the potential weaknesses caused by, or inherent in, the indirect analysis. The EPC should note if both direct and indirect evidence was available, particularly when indirect evidence supports a small body of direct evidence.	In the application of this domain we addressed the outcome and comparison separately. For the *outcome* it was scored dichotomously as one of two levels of directness: • Direct • Indirect It was considered direct if the measured outcome was a health outcome, and indirect if the outcome was measured by a surrogate or intermediate outcome. In general this literature commonly reported overall survival and toxicities which are direct health outcomes. For the *comparison* it was scored dichotomously as one of two levels of directness: • Direct • Indirect It was a direct comparison if outcomes were measured in a head-to head trial and indirect where two or more bodies of evidence were used to compare interventions. Direct comparisons were rare in this literature. For this dimension most were indirect.

Table 3. Elements of evidence grading for Key Questions (continued)

Domain	Definitions and Elements From EPC Methods Guide	Score and Application by BCBSA in the HSCT Project

Precision	Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome (i.e., for each outcome separately). If a meta-analysis was performed, this will be the confidence interval around the summary effect size.
	
	Application
	Score dichotomously as one of two levels of precision:
	• Precise
	• Imprecise
	
	A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions. For example, results may be statistically compatible with both clinically important superiority and inferiority (i.e., the direction of effect is unknown), a circumstance that will preclude a valid conclusion.
		In the application of this domain, we scored precision dichotomously as one of two levels of precision:
		
		• Precise
		An estimate was considered precise if one of three conditions were met:
		  1. A beneficial effect, highly unlikely to be affected by confounding, was observed.
		  2. A decrement was observed (e.g., no increase in survival, a decline in survival or high treatment related mortality) highly unlikely to be affected by confounding.
		  3. Qualitative comparison of the range of results of HSCT and comparator was plausible.
		
		• Imprecise
		An estimate was considered imprecise if none of the above applied.

Strength of association (magnitude of effect)	Strength of association refers to the likelihood that the observed effect is large enough that it cannot have occurred solely as a result of bias from potential confounding factors.	This optional domain was applied for indications with very large effect sizes evident. This additional domain should be considered if the effect size is particularly large. Use one of two levels: • Strong: large effect size that is unlikely to have occurred in the absence of a true effect of the intervention. • Weak: small enough effect size that it could have occurred solely as a result of bias from confounding factors.

BCBSA = Blue Cross Blue Shield Association; EPC = Evidence-based Practice Center; HSCT = hematopoietic stem cell transplant; RCT = randomized controlled trial

Narrative Reviews

Narrative Reviews: Malignant, Hematopoietic Disease

Acute Lymphoblastic Leukemia

Acute Lymphoblastic Leukemia Background

Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosed in children, accounting for 23 percent of cancer diagnoses among children younger than 15 years.[15] An estimated 2,400 children and adolescents younger than 20 years are diagnosed with ALL annually in the United States. Although acute lymphoblastic leukemia is more common in children than in adults, the incidence shows a slight bimodal distribution, with a very high peak early in life (age 1 to 4 years) and a much lower peak after age 70 years.[16] The incidence of ALL in children younger than 19 years of age in the United States in the year 2000 was 3.0 cases per 100,000. ALL is more common in white children than black children, with highest incidence among Hispanic children.[15]

Most cases of ALL do not have an identifiable genetic or environmental cause; it likely develops as a result of a combination of an environmental trigger (e.g., prenatal exposure to ionizing radiation, high postnatal dose of radiation) in individuals who have genetic susceptibilities such as upregulation of oncogenes or loss of inherent tumor suppressor proteins.[15, 16] A number of germline genetic defects or clinical syndromes (e.g., Down syndrome, neurofibromatosis, Schwachman syndrome, Bloom syndrome, ataxia telangiectasia) have been associated with higher risk for developing acute lymphoblastic leukemia, but these collectively account for a small proportion of cases.

ALL typically presents with nonspecific signs and symptoms that include fever, anemia, fatigue, shortness of breath, petechiae or purpura, and CNS findings such as headache, nausea and vomiting, lethargy, and cranial nerve dysfunction.[16] Total white blood count can be very low, or very high, ranging as high as greater than 100,000 per microliter. Patients may have low levels of neutrophils, erythrocytes, and platelets due to excessive acute lymphoblastic leukemia invasion of the bone marrow.

Morphologic, immunologic, and genetic methods are used to establish the diagnosis of any leukemia, its subtype, and specific type. For ALL, an individual prognostic risk profile is established.[17-23] Childhood acute cases are divided into three risk groups: low, intermediate, and high. These groups also are referred to as standard, high, and very high.[24] The Children's Oncology Group has used a four-category system that identifies patients with a very low probability of relapse.[18] Infants fall into a special ALL subgroup that requires different treatment.[25] Prognostic risk factors[18] used to direct ALL treatment are summarized in Table 4. Detailed discussion of risk factors is beyond the scope of this review.

Table 4. Prognostic factors in pediatric acute lymphoblastic leukemia

Factor	Favorable	Intermediate	Unfavorable
Age (yrs)	1 to 9	≥10	<1 and *MLL+*
WBC count (x 10⁹/L)	<50	≥50	
Immunophenotype	Precursor B cell	T cell	
Genetic factors	Hyperdiploidy >50 DNA index >1.16 Trisomy 4, 10, 17 t(12;21)/*ETV6-CBFA2*	Diploid t(1;19)/*TCF3-PBX1*	t(9;22)/*BCR-ABL1* t(4;11)/*MLL-AF4* Hypodiploid < 44
CNS status	CNS1	CNS2 Traumatic with blasts	CNS3
Minimal residual disease (end of induction)	<0.01%	0.01% to 0.99%	≥1%

CNS = central nervous system; WBC = white blood cell

Current management adjusts the intensity of ALL protocols according to specific presenting clinical and biologic features, as well as early treatment response, and is evolving with additional investigation. Therapy for most forms of ALL consists of four general phases: induction, intensification/consolidation, maintenance and early CNS prophylaxis. Induction therapy is started immediately, with the goal of achieving a CR, defined as fewer than 5 percent blast cells on morphological examination. Intensification or consolidation treatment is used after the patient achieves CR1, with the goal of long-term disease control and cure. Maintenance therapy typically continues in boys for 3 years and in girls for 2 years, with the goal to kill residual tumor cells.

ALL Evidence Base

The evidence base on the use of HSCT for treatment of pediatric ALL is summarized in Table 5. Evidence comprises systematic reviews, narrative reviews, genetically randomized clinical trials, as well as observational studies. A large number of HSCT procedures have been performed since the late 1960s. Two organizations, the European Group for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR) maintain data registries on HSCT procedures.

ALL Guidelines

In 2005, the American Society for Blood and Marrow Transplantation (ASBMT) published a systematic review and expert consensus panel recommendations for the role of cytotoxic therapy and HSCT in children with ALL.[26] These remain the most comprehensive recommendations for this indication and population, and are summarized in Table 6. It should be noted, however, that revised guidelines were in preparation at the time this CER was submitted to AHRQ in 2011, and were unavailable for use here.

ALL Summary

Contemporary treatment for newly diagnosed pediatric ALL aims to achieve complete first remission (CR1), with restoration of normal hematopoiesis, in about 1 to 1.5 months using chemotherapy.[23] In most study groups, this is achieved in approximately 98 percent of patients using three agents (a glucocorticoid, vincristine, and L-asparaginase) to which an anthracycline may be added.[15, 18, 20] Long-term event-free survival can now be expected in some 80 percent of

children overall who achieve CR1 with modern risk-adapted chemotherapy. However, outcomes vary, such that in children who meet good-risk criteria (e.g., age 1 to 9 years, white blood count less than 50,000 per µL), EFS rates exceed 85 percent, whereas in those with high-risk age and white blood count criteria EFS rates approximate 70 percent. Use of additional criteria to further stratify treatment can identify patient groups with expected EFS rates ranging from less than 40 percent to more than 95 percent.

Among children with standard or good-risk disease who are in CR1, physicians attempt to limit postremission use of alkylating agents or anthracyclines that are associated with increased risk of late toxic effects. HSCT is generally not indicated in these cases.[21, 23, 26] High-risk cases require more intensive consolidation that may entail the use of higher cumulative doses of multiple agents, including anthracyclines or alkylating agents and combinations thereof. Some 10 to 20 percent of patients with ALL are classified as very high risk, including infants, those with adverse cytogenetic abnormalities (e.g., t[4;11]; t[9;22] or low hypodiploid) and those with poor response to induction therapy with high end-induction minimal residual disease or high absolute blast count. These patients receive multiple cycles of intensive induction and consolidation chemotherapy, often including agents not used upfront for standard and less high-risk cases.

Despite such intense regimens and reported long-term event-free survival rates in high-risk patients (Table 7), they may be considered for allogeneic HSCT in CR1.[15, 21] Some patients with late bone marrow relapse and isolated extramedullary relapses may be successfully treated with chemotherapy.[27] However, HSCT is indicated for pediatric patients with ALL beyond CR1.[21, 23, 26]

As more pediatric ALL patients become long-term survivors, a host of treatment-related adverse events have assumed growing importance. These include cardiac late effects such as anthracycline-associated cardiomyopathy, neuropsychologic effects associated with methotrexate, endocrine deficits, and secondary malignancies such as AML associated with topoisomerase II inhibitor treatment or brain tumors associated with the use of radiotherapy.[23, 28-30] Thus, leukemia survivors require regular examinations by physicians who are familiar with leukemia treatment and its associated risks and who are able to recognize early signs of adverse therapeutic sequelae. The Children's Oncology Group has published risk-based, exposure-related clinical practice guidelines intended to promote earlier detection of and intervention for complications secondary to treatment for pediatric malignancies.[31] However, with the exception of GVHD, it is difficult to separate adverse effects associated with induction therapy and the subsequent consolidation treatment including HSCT.

Table 5. Evidence base for HSCT in pediatric leukemia

Disease	Year First HSCT Performed	No. of Transplants to Date	Existing Clinical Evidence	Registries
Acute lymphoblastic leukemia	late 1960s	5,064 HLA-matched sibling and unrelated donor transplants in patients younger than 20 years of age reported to CIBMTR for the period 1998–2007[32]	Systematic reviews, narrative reviews, observational studies	CIBMTR, EBMT
		More than 10,000 HSCT in patients younger than 18 years old reported to EBMT between 1994 and 2008, of whom 6,315 underwent allogeneic or autologous HSCT for ALL		
Acute and chronic myelogenous leukemia, myelodysplasia, juvenile myelomonocytic leukemia		9,577 HLA-matched sibling and unrelated donor transplants in patients younger than 20 years of age reported to CIBMTR for the period 1998–2007[32]	Systematic reviews, narrative reviews, genetically randomized clinical trials, observational studies	
		More than 30,000 HSCT in patients younger than 18 years of age reported to EBMT between 1970 and 2002, of whom about 10,000–11,000 underwent allogeneic HSCT for AML and myelodysplasia[33]		

AML = acute myelogenous leukemia; CIBMTR = Center for International Bone Marrow Transplant Research; EBMT = European Group for Blood and Marrow Transplantation; HSCT = hematopoietic stem cell transplant

Table 6. ASBMT treatment recommendations for therapy of pediatric acute lymphoblastic leukemia

Indication for SCT	Treatment Recommendation*	Highest Level of Evidence**	Comments
SCT vs. chemotherapy in CR1	B	2++	Demonstrated benefit only for matched related allogeneic SCT in very high-risk (Ph+ only) ALL. Not recommended for standard or other high-risk (i.e., induction failure, hypodiploidy, etc.) patients except in the context of clinical trial.
SCT vs. chemotherapy in CR2	B	2++	Recommended only for matched related allogeneic transplantation vs. chemotherapy; however, the recommendation is tempered because of one prospective trial that did not demonstrate a benefit for transplantation when analyzed by the presence vs. absence of a related donor in an intent-to-treat analysis. Evidence is insufficient to support a recommendation for an unrelated allogeneic transplantation vs. chemotherapy.

Table 6. ASBMT treatment recommendations for therapy of pediatric acute lymphoblastic leukemia (continued)

Indication for SCT	Treatment Recommendation*	Highest Level of Evidence**	Comments
Autologous purged SCT	C	2++	Although a majority of patients with late relapses achieve extended leukemia-free survival (LFS) with an autologous purged SCT, the evidence is insufficient to determine that this is better than chemotherapy alone. For those with an early relapse, the outcomes with autologous purged SCT are even less promising.
Autologous unpurged SCT	N/A	N/A	Data are unavailable on outcomes of unpurged autologous SCT.
Related allogeneic SCT	C	2++	A substantial proportion of patients achieve extended LFS.
Unrelated allogeneic SCT	C	2++	A substantial proportion of patients achieve extended LFS.
Related vs. unrelated allogeneic SCT	None	2++	Outcomes of related vs. unrelated donor allogeneic SCT have not been adequately studied, especially in patients who have had high resolution typing. No recommendation can be made at this time.
Comparison of conditioning regimens	B	1+	TBI-containing regimens have better outcomes than non-TBI containing regimens.
Autologous vs. allogeneic SCT	None	2+	The outcomes of autologous vs. allogeneic SCT have not been adequately studied. No recommendation can be made at this time.

ALL = acute lymphoblastic leukemia; ASBMT = American Society for Blood and Marrow Transplantation; CR = complete remission; LFS = leukemia-free survival; SCT = stem cell transplant; TBI = total body irradiation
*Grades of recommendation:
A At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

**Levels of evidence:
1++ High-quality meta analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+ Well-conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1 - Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++ High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relation is causal
2+ Well-conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relation is causal
2- Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relation is not causal
3 Nonanalytic studies, e.g., case reports, case series
4 Expert opinion

Table 7. Benefits and harms after treatment for pediatric leukemia

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Acute lymphoblastic leukemia	Narrative review[34]	allogeneic HSCT	CR1 Ph+	DFS: 65 ± 8% (n=276)[k] OS: 72 ± 8% [k]	NR	DFS p<0.001 MRD vs. chemotherapy at 5 years OS p=0.002 MRD vs. chemotherapy at 5 years
		chemotherapy		DFS: 25 ± 4%[k] OS: 42 ± 4% [a]		
	Narrative review[19]	allogeneic HSCT	CR1 infants	DFS: 64-76%[l-n]	Fully ablative conditioning plus TBI increases risk for late effects on growth and neurocognitive development	Related and unrelated donors
		chemotherapy		DFS: 33%[o]	Relapse risk is high	
		allogeneic HSCT	CR1 other high-risk	DFS: 56-76%[p-r]	NR	B- or T-cell ALL, marked leukocytosis, hypodipolid, inadequate response to induction therapy, persistent minimal residual disease
		chemotherapy		DFS: 40-45%[p-r]		
		allogeneic HSCT	Relapsed or salvage	DFS: 40-60%[s-v]	NR	It is likely that the response to salvage treatment is influenced by the intensity of primary therapy.[19]
		chemotherapy		DFS≤33-44%[u,v]		

Table 7. Benefits and harms after treatment for pediatric leukemia (continued)

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Acute myelogenous leukemia	Systematic review[35]	allogeneic HSCT	CR1	DFS RR: 0.71 (95% CI 0.58, 0.95, p=0.00007) versus patients with no MSD who received additional chemotherapy or no further therapy after induction OS RR: 0.68 (95% CI, 0.48, 0.95, p=0.02) vs. patients with no MSD who received additional chemotherapy or no further therapy after induction	TRM RR = 0.97 (95% CI, 0.40, 2.38, p = 0.28) versus patients with no MSD who received additional chemotherapy or no further therapy after induction	DFS analysis based on all 6 included studies in meta-analysis between 1986 and 1995 with 3-7 yrs followup[a-f] DFS RR reduction with allogeneic HSCT corresponds to absolute decrease in risk of relapse of -18% (95% CI, -0.24, -0.12) versus chemotherapy OS RR reduction with allogeneic HSCT corresponds to an absolute difference in risk of death of -15% (95% CI, -0.05, -0.25) versus chemotherapy OS analysis based on 4 studies[c-f]

Table 7. Benefits and harms after treatment for pediatric leukemia (continued)

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Acute myelogenous leukemia (continued)	Systematic review[35]	autologous HSCT		DFS RR: 0.70-1.10 versus patients with no MSD who received additional chemotherapy or no further therapy after induction (data not pooled due to heterogeneity) OS RR: 0.71-1.34 versus patients with no MSD who received additional chemotherapy or no further therapy after induction (data not pooled due to heterogeneity)	TRM$\leq$6% - 10% (data not pooled due to heterogeneity, total n = 404)	DFS risk difference= -17% versus patients with no MSD who received additional chemotherapy or no further therapy after induction[g] OS risk difference= -14% versus patients with no MSD who received additional chemotherapy or no further therapy after induction[f] TRM$\leq$6% in 2 studies[a,d] and 10% in a third study[f]

Table 7. Benefits and harms after treatment for pediatric leukemia (continued)

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Acute myelogenous leukemia (continued)	Systematic review[36]	allogeneic HSCT	CR1	DFS: 47 ± 5% OS: 54 ± 5%	TRM = 17 ± 4%	Analysis included 5 consecutive genetic randomization CCG studies[e,f,h-j] between 1979 and 1996 DFS p=0.075, 0.004 versus autologous HSCT and chemotherapy, respectively at 8 years followup OS p=0.031, 0.064 versus autologous HSCT and chemotherapy, respectively at 8 years followup TRM p=0.297, <0.001 versus autologous HSCT and chemotherapy, respectively at 8 years followup No statistically significant differences were reported for any outcome between chemotherapy and autologous HSCT
		autologous HSCT		DFS: 42 ± 7% OS: 49 ± 7%	TRM = 7 ± 4%	
		chemotherapy		DFS: 34 ± 4% OS: 42 ± 4%	TRM = 6 ± 3%	

Table 7. Benefits and harms after treatment for pediatric leukemia (continued)

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Acute myelogenous leukemia (continued)	Narrative review[37]	allogeneic HSCT	CR1	DFS: 51-52% OS: 47-70%	NR	3-5 yrs followup for DFS[a,g] 5-8 years' followup for OS[d-f,i] DFS p=0.01, 0.007 allogeneic HSCT versus autologous HSCT and chemotherapy, respectively OS p=0.002 allogeneic HSCT versus autologous HSCT OS p≤0.05–0.13 allogeneic HSCT versus chemotherapy
		autologous HSCT		DFS: 21-38% OS: 48%		
		chemotherapy		DFS: 27-36% OS: 34-60%		
Chronic myelogenous leukemia	Narrative review[38]	allogeneic HSCT	CP1 Ph+	OS: 66%[w] DFS: 55%[w]	TRM: 20% (MSD) TRM: 35% (URD) Grades 2-4 GVHD = 20% with MRD, 35% with URD[w]	Survival data for patients with matched related sibling donor

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Table 7. Benefits and harms after treatment for pediatric leukemia (continued)

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Myelodysplasia and JMML	Prospective studies	allogeneic HSCT	Upfront, primary or secondary	OS: 31% JMML[x] OS: 50% MDS[x] DFS: 49-55% JMML[y]	TRM: 13%[y]	Patients with JMML and refractory anemia (RA) or RA-excess blasts exhibited high induction failure rates[x] Actuarial OS at 6 years[x] DFS 55% at 5 years with MRD, 49% with matched URD[y] TRM at 5 years[y]

ALL= acute lymphoblastic leukemia; CCG= Children's Cancer Study Group; CR1= complete remission; DFS= disease free survival; GVHD= graft vs. host disease; HSCT= hematopoietic stem-cell transplantation; JMML= Juvenile myelomonocytic leukemia; MDS= myelodysplastic syndromes; MRD=matched related donor; NR= not reported; OS= overall survival; RA= refractory anemia ; RR= relative risk; CI= confidence interval; TRM= treatment related mortality; URD= unrelated donor

[a] Amadori et al., 1993[39]; RCT, n=161
[b] Michel et al., 1996[40]; prospective cohort study, n=171
[c] Shaw et al., 1994[41]; prospective cohort study, n=43
[d] Stevens et al., 1998[42]; RCT, n=359
[e] Wells et al., 1994[43]; RCT, n=591
[f] Woods et al., 1996[44]; RCT, n=589
[g] Ravindranath et al., 1996[45]; RCT, n=649
[h] Lange et al., 2004[46]; prospective study; n=65
[i] Smith et al., 2005[47]; RCT, n=485
[j] Woods et al., 1993[48]; prospective cohort study, n=142
[k] Arico et al., 2000[49]; retrospective study, n=326
[l] Jacobsohn et al., 2005[50]; prospective study, n=16
[m] Kosaka et al., 2004[51]; prospective study, n=44
[n] Sanders et al., 2005[52]; retrospective study, n=40
[o] Hilden et al., 2006[53]; prospective study, n=115
[p] Ribera et al., 2007[54]; RCT, n=106
[q] Satwani et al., 2007[55]; prospective study, n=28
[r] Schrauder et al., 2006[56]; prospective cohort study, n=387
[s] Boulad et al., 1999[57]; retrospective study, n=75
[t] Eapen et al., 2008[58]; prospective cohort study, n=209
[u] Einsiedel et al., 2005[59]; prospective study, n=207
[v] Gaynon et al., 2006[60]; RCT, n=214
[w] Cwynarski et al., 2003[61]; prospective study, n=314
[x] Woods et al., 2002[62]; prospective study, n=90
[y] Locatelli et al., 2005[63]; prospective study, n=100

Acute Myelogenous Leukemia

The myelogenous leukemias comprise a spectrum of hematological malignancies. The vast majority (90 percent) are defined as acute, with the rest including chronic or subacute myeloproliferative disorders such as chronic myelogenous leukemia (CML), juvenile myelomonocytic leukemia (JMML) and myelodysplastic syndromes (MDS).[64]

Acute Myelogenous Leukemia Background

Approximately 6,500 children younger than 20 years of age develop an acute leukemia annually in the U.S.; acute myelogenous leukemia (AML) represents about 15 percent, or about 1,000 cases per year. The incidence of AML is stable during childhood, except for a slight increase during adolescence and a peak in the neonatal period.[65] Some variation in the incidence of AML in children has been reported; for example, black children have an incidence of 5.8 cases per million compared to 4.8 cases per million among white children. The mortality rate from AML is estimated at 0.5 per 100,000 children younger than 10 years, and increases with age.

AML is a clonal malignancy that results from a series of somatic mutations in a hematopoietic multipotential cell, most commonly secondary to chromosomal translocations.[65] Rarely, it may stem from a more differentiated, lineage-restricted progenitor cell. It is characterized by accumulation of abnormal (leukemic) blast cells, principally in the bone marrow, and impaired production of normal blood cells. Classification of myeloid leukemia as acute requires greater than 20 percent leukemic blasts in the bone marrow. In general, the clinical presentation of AML varies as a function of the leukemic cell burden within the bone marrow, with anemia, thrombocytopenia, and a low or normal absolute neutrophil count depending on the total white blood cell count. Other signs and symptoms may stem from invasion of extramedullary sites such as soft tissues, skin, gingiva, orbit, and brain.

There is a high concordance rate of AML in identical twins, and an estimated 2- to 4-fold risk of fraternal twins both developing AML up to about 6 years of age, suggesting the disease has a genetic component. AML also has been associated with syndromes that predispose to its development secondary to chromosomal translocations or instabilities, DNA repair defects, altered cytokine receptor or signal transduction pathway activation, and altered protein synthesis.[64]

Treatment of AML consists of remission-induction, followed by a course of consolidation therapy and subsequent intensification, which may include autologous or allogeneic HSCT.[65, 66] Because the AML stem cell is inherently drug resistant, improvements in outcomes have been achieved through escalation of induction regimens to maximally tolerated dose levels that necessitate intensive supportive care measures. Further escalation and improvements in outcomes in AML are thus limited on the therapeutic side.

The therapeutic approach to a newly diagnosed pediatric patient with AML is dictated by a number of prognostic risk factors, including cytogenetics, mutations of signal transduction pathways, response to induction therapy, and others that may be termed novel.[66, 67] Detailed discussion of risk factors is beyond the scope of this review, but several are summarized in Table 8 and will be referred to in this discussion.

Table 8. Potential risk factors for pediatric acute myelogenous leukemia

Prognostic Factor Category	Poor Risk	Favorable Risk
Cytogenetics	Deletion of chromosome 5q	t(15;17)
	Monosomy of chromosome 5 or 7	inv(16)
	t(6;9)	t(8;21)
	Abnormal chromosome 3	t(9;11)
	Complex cytogenetics	
Mutations of signal transduction pathways	*FLT3/ITD*, high ITD-AR	*CEBP-α* mutation
	c-KIT	*NPM* mutation
	c-Fms	
	VEGF receptor	
	N- and K-RAS	
Response to therapy	Poor response	Rapid response
	Minimal residual disease	
Novel markers	High WT1 expression	Gene expression profile
	High VEGF expression	Proteomic signature
	High BAALC expression	
	Telomerase activity	
	Gene expression profile	
	Proteomic signature	

BAALC = brain and acute leukemia, cytoplasmic; CEBP-α = CCAAT/enhancer binding protein-alpha; FLT3/ITD = FLT3/internal tandem duplication; ITD-AR = internal tandem duplication allelic ratio; NPM = nucleophosmin; VEGF = vascular endothelial growth factor; WT1 = Wilms' tumor

AML Evidence Base

The evidence base available on the use of HSCT for treatment of AML is summarized in Table 5. Published evidence comprises systematic reviews, narrative reviews, genetically randomized clinical trials, as well as observational studies. Two systematic reviews and one narrative review provide the basis for this evaluation. Also shown in Table 5, a large number of allogeneic HSCT procedures have been performed since the late 1960s. Two organizations, the European Group for Blood and Marrow Transplantation (EBMT), and in the U.S., the Center for International Blood and Marrow Transplant Research (CIBMTR), maintain data registries on HSCT procedures.

AML Guidelines

In 2007, the American Society for Blood and Marrow Transplantation (ASBMT) published a systematic review and expert consensus panel recommendations for the role of cytotoxic therapy and HSCT in children with AML.[68] These remain the most comprehensive recommendations for this indication and population, and are summarized in Table 9. It should be noted, however, that revised guidelines were in preparation at the time this CER was submitted to AHRQ in 2011, and were unavailable for use here.

AML Summary

Survival rates in children with AML have increased with time as a result of numerous clinical trials conducted within pediatric cooperative cancer groups.[30, 35-38, 69] About 50 to 60 percent of newly diagnosed pediatric AML patients experience long-term survival with modern treatment and supportive care, as shown in Table 7. Chemotherapy and autologous and allogeneic HSCT are established methods in this setting, but there is uncertainty about when to use each. Current practice in European groups limits use of allogeneic HSCT in CR1 to patients with poor risk prognostic factors; in the U.S., patients with a matched sibling donor typically receive allogeneic HSCT in CR1.[38] In general, patients who relapse and can be brought into CR2 will receive an allogeneic HSCT if a matched sibling donor is available, or if at very high risk, with an unrelated matched donor.[38]

Although the data compiled in Table 7 were not stratified according to prognostic risk factors, the evidence generally supports use of allogeneic HSCT in children with poor- to intermediate-risk disease in CR1, and all who have refractory AML or who relapse. Substantial effort is being expended on identification of additional prognostic markers at the genetic level with the aim of personalizing AML therapy to improve survival rates. Risk stratification also has potential to reduce the burden of associated adverse effects of the procedure by targeting therapy intensification to appropriate groups, with less-intensive treatment for those who would not benefit.[66, 67]

Adverse effects with HSCT in any disease are referable to all major organ systems including cardiovascular, CNS, endocrine, digestive, urinary, and reproductive, and include secondary malignancies and graft-versus-host disease.[28, 29]

The Children's Oncology Group has published risk-based, exposure-related clinical practice guidelines intended to promote earlier detection of and intervention for complications secondary to treatment for pediatric malignancies.[31] However, with the exception of GVHD and treatment-related mortality, it is difficult to separate adverse effects associated with induction therapy and the subsequent consolidation treatment including HSCT.

Table 9. ASBMT treatment recommendations for therapy of pediatric acute myelogenous leukemia

Indication for HSCT	Treatment Recommendation Grade*	Highest Level of Evidence**	Comments
Auto-SCT vs. chemotherapy in CR1	A	1++	Auto-SCT and chemotherapy have equivalent survival outcomes. Lacking data on QOL, secondary malignancies and other late effects of treatment prevents a recommendation of one therapy over the other.
Allo-SCT vs. chemotherapy in CR1	B	2++	Allo-SCT has superior OS and LFS compared with chemotherapy and is recommended Additional prospective data regarding risk subgroups may alter this recommendation.
Allo-SCT vs. chemotherapy in CR2	D	2-	There is a lack of evidence comparing MRD allo-SCT compared to chemotherapy in CR2; however, the consensus recommendation of the expert panel is MRD allo-SCT if available.
Auto-SCT vs. allo-SCT in CR1	A	1++	MRD allo-SCT has superior survival outcomes compared to auto-SCT in CR1. Additional prospective data regarding risk subgroups may alter this recommendation. The consensus recommendation of the expert panel is to use bone marrow as the stem cell source in the MRD allo-SCT setting based on scientific, ethical, regulatory, and practical issues.
Auto-SCT vs. allo-SCT in CR2	C	2+	The consensus recommendation of the expert panel is to use any suitably matched related or unrelated allo- over auto-SCT; however, there is a lack of evidence that one has better outcomes than the other.

Table 9. ASBMT treatment recommendations for therapy of pediatric acute myelogenous leukemia (continued)

Indication for HSCT	Treatment Recommendation Grade*	Highest Level of Evidence**	Comments
Auto-SCT	No recommendation	2+	Current practice is to use PBSCT; however, there are very few patients in the 2 studies that fulfill review criteria. A randomized trial of auto-BMT vs. PBSCT is not feasible due to the infrequent use of auto-SCT for pediatric patients with AML. With current technology, there is a preference for using MUD or alternative donors over auto-SCT if a MRD is not available. There are no effective purging agents currently available, but if one were developed, it would increase interest for a trial of purged vs. unpurged auto-SCT.
Related vs. unrelated allo-SCT	D	2+	There are no data indicating that using one type of suitably matched allo-SCT is better than another. There are differences between institutions with regard to transplantation technique; however, there are no apparent differences in outcomes across institutions.
Related allo-SCT	B	2+	MRD allo-SCT is preferred in CR1 or CR2; in CR2, alternative donors could be considered if MRD is not available.
Unrelated allo-SCT	No recommendation	2+	No evidence for one preferred technique for unrelated allo-SCT (i.e., T cell depletion, cord blood vs. PBSCT vs. BMT, etc).
Comparison of allo-SCT myeloablative conditioning regimens	C	2+	There is no difference or preference of one conditioning regimen over another with respect to survival, LFS, or late effects.
Comparison of auto-SCT myeloablative conditioning regimens	No recommendation	NA	No evidence comparing conditioning regimens in the auto-SCT setting.

Table 9. ASBMT treatment recommendations for therapy of pediatric acute myelogenous leukemia (continued)

Indication for HSCT	Treatment Recommendation Grade*	Highest Level of Evidence**	Comments
APL in CR1	Not recommended	4	No evidence of a need for SCT.
APL in CR2	D	3	Standard practice is to use allo-SCT (preferred) or auto-SCT if there is no suitable MRD, MUD, or alternative donor, or a trial comparing haploidentical allo- vs. auto-SCT.

* See Table 6 above for key to recommendation grades.
** See Table 6 above for key to levels of evidence.

Chronic Myelogenous Leukemia

Chronic Myelogenous Leukemia Background

Chronic myelogenous leukemia (CML) is the most common of the chronic myeloproliferative disorders in children, but accounts for only 5 percent of childhood myeloid leukemia.[64] It occurs in very young children, but the majority is found in patients aged 6 years and older. CML is a clonal panmyelopathy that involves all hematopoietic cell lineages. The white blood count may be extremely elevated in CML without evidence of excess leukemic blasts in the bone marrow, and is often associated with thrombocytosis. The Philadelphia chromosome, which is a translocation between chromosomes 9 and 22 (t[9, 22]), is nearly always present in CML. Bone marrow is hypercellular, with relatively normal granulocytic maturation. Biologically, CML in children is very similar to that in adults, so adult data are often extrapolated to children.[38] It is the malignancy for which a graft-versus-leukemia (GVL) effect has most clearly been shown.[70]

CML occurs in three clinical phases: chronic, accelerated, and blast crisis. The chronic phase, which may last for 3 years, is associated with effects secondary to hyperleukocytosis, such as weakness, fever, night sweats, bone pain, and respiratory distress. The accelerated phase is characterized by progressive splenomegaly, thrombocytopenia, and increased proportion of peripheral and bone marrow blasts. In blast crisis, the bone marrow shows more than 30 percent blasts, with a clinical picture indistinguishable from acute leukemia. Patients who enter blast crisis will succumb to the disease within several months.[71] This narrative review focuses on patients with chronic phase CML.

CML Evidence Base

The evidence base available on the use of HSCT for treatment of CML is summarized in Table 5. Published evidence comprises narrative reviews as well as observational studies. Allogeneic HSCT remains the only known curative modality for CML.

CML Guidelines

We identified no clinical guidelines for the use of HSCT in children with CML.

CML Summary

The EBMT reported outcomes in 314 children who received allogeneic HSCT in the pre-imatinib era. As shown in Table 7, the best results were achieved among children in chronic phase who received a matched sibling donor transplant (75 percent 3-year OS, 63 percent leukemia-free survival).[61] Among patients who received an unrelated donor HSCT, procedural mortality reached 35 percent versus 20 percent with a MSD. Severe graft-versus-host disease (grades 2-3) occurred in 52 percent of unrelated donor HSCT recipients compared to 37 percent of recipients with a matched sibling donor. Similar results were reported by other groups who used allogeneic HSCT to treat children with chronic phase CML.[72, 73]

The introduction of imatinib mesylate (and newer tyrosine kinase inhibitors dasatinib and nilotinib) altered the paradigm of CML treatment, particularly in adults.[74] However, there is no consensus how to treat newly diagnosed children with CML if a matched sibling donor is available.[38, 75] Allogeneic HSCT may be delayed until imatinib fails to produce a major cytogenetic or molecular response, or if secondary resistance develops. However, relapse occurs

in previously responding patients who stop imatinib. Thus, children with CML who achieve molecular disease control are typically managed individually. The decision and timing to proceed to allogeneic HSCT given the necessity for life-long imatinib therapy and the prospect of resistance developing remain uncertain.[30]

Myelodysplastic Syndrome/Juvenile Myelomonocytic Leukemia

Myelodysplastic Syndrome/Juvenile Myelomonocytic Leukemia Background

In children, the myelodysplastic syndromes (MDS) comprise a heterogeneous group of disorders characterized by a constellation of ineffective hematopoiesis, impaired maturation of myeloid precursors with dysplastic morphologic features, and cytopenias.[64] Myelodysplastic disorders have been defined by their predilection to evolve into AML, yet not all cases terminate in leukemia. Mortality in myelodysplasia syndrome results from bleeding, recurrent infection, and leukemic transformation. In the absence of treatment, myelodysplasia syndrome can be rapidly fatal, with or without the transformation to AML.

The exact incidence of MDS in childhood has been difficult to estimate because of controversies regarding its classification, the heterogeneity of presentation, and the heterogeneity of risk factors in the population. MDS may occur either de novo or secondary to previous therapy for cancer. The annual incidence internationally is estimated at 0.5 to 4 per million population, and myelodysplasia syndrome accounts for about 2 to 5 percent of hematologic malignancies in children.[76] Fewer than 100 new cases of myelodysplasia are reported in the U.S. each year in children. The male-to-female ratio varies from 1.7 to 4.8:1 in different series.[77]

The significance of this male predominance is unclear but is attributed, in part, to the increased prevalence of juvenile myelomonocytic leukemia (JMML), which was previously termed "juvenile chronic myelogenous leukemia" (JCML), in boys and monosomy 7 syndrome in children.[78] JMML is very rare, accounting for less than 1 percent of all childhood leukemias.

MDS/JMML Evidence Base

Given the rarity of MDS in children, randomized trials have not been performed specifically for this disease. Children with MDS have been included in AML studies, with allogeneic HSCT representing the only curative therapy.[38] JMML historically has been fatal in more than 90 percent of patients despite the use of chemotherapy.[64] Allogeneic HSCT is the only intervention that can provide long-term disease control.[30] As shown in Table 5, available evidence includes narrative reviews that include information on MDS and JMML, and observational studies.

Outcomes data abstracted from recent narrative review articles on the use of HSCT to treat children with high-risk leukemias are summarized in Table 7.

MDS/JMML Guidelines

We identified no clinical guidelines for the use of HSCT in children with MDS, or JMML.

MDS Summary

Given the rarity of MDS in children, randomized trials have not been performed specifically for this disease. However, allogeneic HSCT is the only curative therapy.[38] Children with MDS have been included in AML studies.[62] This trial enrolled 77 patients with MDS or AML with antecedent MDS, randomly allocated to standard or intensively timed induction and subsequently

to allogeneic HSCT if there was a suitable matched related donor, or to autologous HSCT or chemotherapy in the absence of a donor.[62] Patients with refractory anemia (RA) or RA with excess blasts (RAEB) had a 45 percent remission rate and 6-year OS rate of 28 percent. Those with RAEB in transformation had a 69 percent remission rate and 30 percent 6 year OS rate. Patients with AML and history of MDS experienced an 81 percent remission rate and 50 percent OS rate with allogeneic HSCT, which was marginally significant compared to chemotherapy (p=0.08). The Children's Cancer Study Group investigators conclude that children with a history of MDS who present with AML (excluding those with monosomy 7) and a proportion with RAEB in transformation will do as well with AML chemotherapy remission induction and HSCT consolidation as those with AML. Among MDS patients who achieve remission following induction, but for whom a suitable stem cell donor is not available, optimum therapy is not established.[64]

JMML Summary

JMML historically has been fatal in more than 90 percent of patients despite the use of chemotherapy.[64] Allogeneic HSCT is the only intervention that can provide long-term disease control.[30] In a study of 100 JMML patients, OS of 64 percent has been reported at 5 years.[63] Among patients who had disease recurrence, 7 of 15 who underwent a second allogeneic HSCT survived free of disease. In a retrospective National Marrow Donor Program registry analysis, 46 JMML patients who underwent unrelated donor allogeneic HSCT achieved a 2-year DFS rate of 24 percent with relapse probability of 58 percent.[79]

Childhood Hodgkin's Lymphoma

Lymphomas, which are broadly divided into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) constitute 15 percent of all childhood cancers, and are the third most common childhood malignancy.[80]

Hodgkin's Lymphoma Background

Hodgkin's lymphoma, which comprises 6 percent of childhood cancers, shows a bimodal age incidence with most patients diagnosed between the ages of 15 and 30, and a second peak in adults 55 years of age and older. In the pediatric population, the incidence is highest among 15 to 19 year olds (29 per million per year), with children ages 10 to 14 years, 5 to 9 years, and 0 to 4 years having threefold, eightfold, and thirtyfold lower rates, respectively.[81]

Hodgkin's lymphoma, a B-cell lymphoma, is divided into two distinct subcategories, classical (which is characterized by multinucleated tumor cells known as Reed-Sternberg cells) and nodular lymphocyte predominant type (with large mononuclear tumor cells known as lymphocytic and histiocytic, or "L & H" cells), both with a background of inflammatory cells. Subtypes of classical HL include lymphocytic rich, nodular sclerosis, mixed cellularity and lymphocytic depleted. The most common subtypes seen in the pediatric population are the mixed cellularity, nodular lymphocyte predominant and nodular sclerosis.[80]

Most patients with Hodgkin's lymphoma present with painless adenopathy, commonly in the supraclavicular or cervical area. Whereas mediastinal involvement is present in approximately 75 percent of adolescents and adults, only about 35 percent of young children with Hodgkin's lymphoma have mediastinal presentation, in part because of the tendency of these patients to have disease with mixed cellularity or lymphocyte-predominant histology.[81] Approximately 80 to 85 percent of children and adolescents with Hodgkin's lymphoma have involvement of lymph

nodes and/or the spleen only (stages I-III), with the remaining 15 to 20 percent having noncontiguous extranodal involvement (stage IV).[81] The most common extranodal sites include the lung, liver, bone, and bone marrow.[81]

Contemporary treatment programs use a risk-adapted approach in which patients receive multi-agent chemotherapy with or without low-dose involved field radiation.[81] Prognostic factors considered include stage, presence or absence of B symptoms, and/or bulky disease.[81] With current therapy, the long-term disease-free survival (DFS) in children with newly diagnosed localized and advanced-stage Hodgkin's lymphoma ranges between 85 to 100 percent and 70 to 90 percent, respectively.[80]

However, high-risk patients with Hodgkin's lymphoma whose disease is refractory to initial therapy or relapse after primary initial chemotherapy (particularly with early relapse at 12 months or earlier) have a minimal chance for long-term survival with salvage chemotherapy alone (with 5-year OS rates of 20 to 25 percent).[80] Approximately 10 to 15 percent of patients with HL fail to achieve a complete remission (CR) or relapse, and it is in this population that more aggressive treatment strategies like HSCT are utilized.

Hodgkin's Lymphoma Evidence Base

The evidence compiled includes one review article, which summarizes the experience with autologous HSCT and childhood Hodgkin's lymphoma.[80] There have been no randomized trials in the pediatric population with Hodgkin's lymphoma using HSCT, and the data consist of several small, retrospective case series as summarized in Table 10. Outcomes with the use of autologous HSCT and pediatric Hodgkin's lymphoma show a wide range, with an overall survival (OS) from 43 to 95 percent and event-free survival (EFS) from 31 to 62 percent (Table 11).[82-86]

National Comprehensive Cancer Network (NCCN) clinical practice guidelines exist.[87] No health technology assessments were identified in the search.

A case-matched comparison of autologous HSCT in the pediatric population (n=81) versus adult patients (n=81) with Hodgkin's lymphoma suggested that pediatric and adult patients with HL have similar EFS and OS.[86]

There have been two randomized trials in adult patients with relapsed or refractory Hodgkin's lymphoma, comparing standard-dose salvage chemotherapy and high-dose chemotherapy with autologous HSCT.[88, 89] Both trials demonstrated significantly improved EFS and longer time to treatment failure in the HSCT group, but no significant difference in OS was observed between the two groups. Whether survival data from the adult population with Hodgkin's lymphoma can be extrapolated to the pediatric population is somewhat controversial.

In patients with Hodgkin's lymphoma who undergo HSCT, harms include secondary malignancies, including breast cancer and myelodysplastic syndrome/secondary acute myelogenous leukemia (MDS/sAML). In patients with recurrent lymphoma who undergo high-dose chemotherapy and autologous HSCT, the incidence of MDS/sAML is 4 to 20 percent at 5 years.[80]

Hodgkin's Lymphoma Guidelines

NCCN guidelines[87] for the treatment of Hodgkin's lymphoma with HSCT state the best option for patients with progressive disease or relapse is high-dose therapy with autologous stem-cell rescue and that allogeneic transplant may be an option in select patients with progressive or relapsed disease.

Hodgkin's Lymphoma Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of Hodgkin's disease with HSCT in patients with progressive disease or relapse, with OS and EFS rates ranging from 43 to 95 percent and 31 to 62 percent, respectively.[80] Patients who fail following autologous HSCT or for patients who cannot mobilize sufficient numbers of autologous stem cells, allogeneic HSCT is an option.

Current recommendations are based on small numbers from five case series. Future challenges in the treatment of Hodgkin's lymphoma include the development of risk-stratified treatment approaches for patients with high-risk disease and the possible use of allogeneic HSCT where graft versus lymphoma has been demonstrated.[80]

Table 10. Pediatric lymphomas and the evidence base

Disease	Year First Transplant Performed	No. of Transplants to Date	Existing Dlinical Data	Registries
Hodgkin's Lymphoma	Late 1970s	Not determined	Literature Review, case series, registry data	The Center for International Blood and Marrow Transplant Research (CIBMTR) registry describes the use and outcome of autologous and allogeneic hematopoietic cell transplantation in the more than 500 centers participating in the CIBMTR. It is estimated that data are collected on nearly all allogeneic transplants
Non-Hodgkin's Lymphoma	Late 1970s	Not determined	Literature Review, case series, registry data	performed in the U.S., approximately 25% of allogeneic transplants performed outside of the U.S. and approximately 60% of autologous transplants performed in North and South America. Prior studies suggest that these data are representative of transplants worldwide. For Hodgkin's and non-Hodgkin's lymphomas, the registry reports separate survival statistics for patients ≤20 years and >20 years of age. www.cibmtr.org/ReferenceCenter/SlidesReports/StatReport/index.html The European Group for Blood and Marrow Transplantation (EBMT) has an international registry which includes NHL and HL, with separate data for the pediatric population. www.ebmt.org/4Registry/registry1.html

Table 11. Benefits and harms after treatment for childhood Hodgkin's lymphoma

Disease	Source	Evidence Type	Treatment	Indication	Benefits	Harms
Hodgkin's lymphoma	Bradley and Cairo 2008[80]	Literature Review	Autologous HSCT	Relapsed or refractory[a,b,c,d,e] First, second and third CR, PR[c,e]	5-year OS 43-95% 5-year EFS 31-62% 5-year PFS 63% 5-year FFS 31% [a,b,c,d,e] 3-year PFS 39%[e]	Transplant-related deaths (including early and late) ranging from 0%-11.1% Risk of MDS/sAML is 4-20% at 5 years after autologous HSCT.

CR = complete response; EFS = event-free survival; FFS = failure-free survival; HSCT = hematopoietic stem-cell transplantation; MDS = myelodysplastic syndrome; OS = overall survival; PFS = progression-free survival; PR = partial remission; sAML = secondary acute myelogenous leukemia

a Stoneham et al. 2004[84]; n=51 case series, retrospective review of data from 8 centers transplanted between 1982-2000

b Lieskovsky et al. 2004[83]; n=41 case series, retrospective review of consecutive patients at one medical center transplanted between 1989-2001

c Verdeguer et al. 2000[85]; n=20 case series, retrospective review of clinical records from 8 hospitals transplanted between 1986-1997

d Baker et al. 1999[82]; n=53 case series transplanted between 1984 and 1996

e Williams et al. 1993[86]; n=81 case series of registry data, cases reported up to 1992. Eighty-one pediatric patients were case matched to adult patients from European Bone Marrow Transplant registry. Conclusions drawn included that pediatric patients with HL have the same outcome as their adult counterparts after autologous HSCT.

Childhood Non-Hodgkin's Lymphoma

Non-Hodgkin's Lymphoma Background

Non-Hodgkin's lymphoma (NHL) accounts for approximately 7 percent of cancers in children younger than 20 years of age.[90] Whereas NHL in adults is more commonly low or intermediate grade, in the pediatric population almost all non-Hodgkin's lymphomas are high grade, and differ from disease in adults with respect to disease types, staging system, biology, treatment, and outcome.[91] NHLs are broadly classified as being of B-cell, T-cell, or natural killer (NK) cell origin and by differentiation (precursor versus mature cell). NHLs in children and adolescence fall into three therapeutically relevant categories: (1) mature B-cell NHL: Burkitt and Burkitt-like lymphoma/leukemia (BL, 50 percent of pediatric NHL) and diffuse large B-cell lymphoma (DLBCL, 10-20 percent of pediatric NHL); (2) lymphoblastic lymphoma (LBL) primarily precursor T-cell and less frequently precursor B-cell (20 to 30 percent of pediatric NHL); and (3) anaplastic large cell lymphoma (ALCL), mature T-cell or null-cell lymphoma (10 percent). The other 10 percent of NHL observed in the pediatric population are comprised of diseases commonly seen in adults, such as follicular lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, cutaneous lymphoma, primary central nervous system lymphoma or mature T-cell or natural killer-cell lymphoma.[91] Approximately 100 of the 1,000 cases of childhood NHL that occur annually in the U.S. occur in children or adolescents with a primary or secondary immunodeficiency, and the majority are associated with Epstein-Barr virus.[91] The ultimate goal in treating these patients is improving immune function.

Burkitt and Burkitt-like lymphoma (BL) consistently exhibit very aggressive clinical behavior and show overlapping characteristics with acute lymphoblastic leukemia. BL exhibits rapid growth rate, and a tendency to involve extranodal sites and to disseminate to the bone marrow and meninges. Common primary sites include the abdomen and pelvis and the head and neck. The diagnosis of Burkitt-like lymphoma is somewhat controversial due to overlapping histologic features with DLBCL. Cytogenetic evidence of C-MYC rearrangement is the gold standard for the diagnosis of BL. BL can be sporadic or endemic, with endemic cases being Epstein-Barr virus-related and occurring commonly in equatorial Africa.

Diffuse large B-cell lymphoma (DLBCL) in the pediatric population occurs more commonly in the second decade of life than the first. DLBCL differs biologically in children and adolescents than in adults (except for those that present as primary mediastinal disease, which represents approximately 20 percent of pediatric DLBCL). The characteristic chromosomal translocation seen in adult DLBCL, t(14;18), is rarely observed in pediatric DLBCL. Outcomes for children with DCBCL are more favorable than those seen in adults.

Lymphoblastic lymphoma (LBL) occurs most commonly in young men as an anterior mediastinal mass. Chromosomal abnormalities in LBL are not well characterized. The disease course is aggressive with frequent involvement of the bone marrow and/or central nervous system. Patients with limited disease may fare well, but those with poor-risk disease (defined as bone marrow or central nervous system involvement or LDH greater than 300 IU/L) or recurrent disease have less favorable outcomes.[92]

Anaplastic large cell lymphoma (ALCL) has a broad range of clinical presentations, including involvement of lymph nodes and extranodal sites, particularly skin and bone. More than 90 percent of cases have a characteristic chromosomal translocation t(2;5) which leads to expression of a fusion protein NPM/ALK, although variant ALK translocations also occur.

ALCL is classified as a peripheral T-cell lymphoma (PTCL); however, ALK-positive ALCL has a superior prognosis to other forms of PTCL.

The St. Jude (Murphy) staging system is the most widely used for pediatric NHL, and differs from the Ann Arbor staging system (used in adult NHL) in the classification of abdominal, intrathoracic, and paraspinal/epidural disease.[91] The most important prognostic variable in pediatric NHL is tumor burden, evaluated by staging and serum lactate dehydrogenase (LDH) level. Patients with stage III/IV disease and serum LDH greater than 400 U/L have significantly worse outcomes than those with LDH less than 400 U/L.

Unlike adults with NHL, who usually present with lymph node disease, most pediatric patients present with extranodal disease. Approximately 70 percent of children with NHL present with advanced disease and/or have involvement of the bone marrow, central nervous system and/or bone.[80] The primary therapy for childhood NHL is multi-agent chemotherapy, with the length and intensity of therapy determined by the subtype and stage of disease.[80] Children with limited stage NHL have an excellent prognosis with conventional chemotherapy with or without radiation, with estimated event-free survival of 90 to 95 percent.[80] Patients with advanced stage disease have a variable prognosis depending upon disease subtype, with 5-year event-free survival rates ranging from 60 to 90 percent.[80]

If remission can be achieved in children and adolescents with recurrent or refractory B-cell NHL, HSCT is usually pursued.[91] Most pediatric transplant programs reserve the use of HSCT in children with NHL for after first relapse, with disease progression or induction failure.[80]

NHL Evidence Base

The evidence compiled includes one review article which summarizes the experience with autologous HSCT and childhood NHL.[80] There have been no randomized trials in the pediatric population with NHL using HSCT, and the data consist of five small, retrospective case series[93-97] and one nonrandomized, comparative study [98], as summarized in Table 12. Several of the studies report survival data combined for patients with different histologies, with median EFS of 50 percent (range: 27 to 59 percent).[93-96, 98] Studies that report survival data for one histologic type of NHL include ALCL: EFS 75 percent at 3 years[97] and OS 95 percent at 7 years;[99] LL: EFS 39 percent and 5-year OS of 44 percent for autologous HSCT, EFS 36 percent and 5-year OS 39 percent for allogeneic HSCT;[92] BL: EFS 57 percent.[100]

NCCN clinical practice guidelines (for all subtypes of pediatric NHL) and guidelines from the American Society for Blood and Marrow Transplantation (for DLBCL only) exist. No health technology assessments were identified in the search.

Harms associated with HSCT include secondary malignancies, which are a well-recognized complication in patients with lymphoma who undergo chemotherapy and/or radiation treatment. In patients with recurrent lymphoma who undergo high-dose chemotherapy and autologous HSCT, the incidence of myelodysplastic syndrome/secondary acute myelogenous leukemia is 4 to 20 percent at 5 years.[80]

Table 12. Benefits and harms after treatment for childhood Non-Hodgkin's lymphoma

Histology (n)	Source	Evidence Type	Treatment	Indications	Benefits	Harms	Comment
BL (6), LL (14), DLBCL (6), ALCL (7)	Won 2006[98f]	Nonrandomized comparative	Autologous HSCT	Relapsed/ refractory	2-year EFS 59.1% +/- 9.3% (BL 66.7% +/- 27.2% LL 50.5% +/- 14.8% DLBCL 55.6 +/- 24.9% ALCL 100	TRM 2/33 (6.1%)	Median followup 2.4 yrs (0.1-7.6)
			Conventional chemotherapy	Relapsed/ refractory	EFS 16.3% +/- 4.6%		
ALCL	Woessmann 2006[97g]	Case series, retrospective	Allogeneic	Relapsed/ refractory (included first relapse and multiple relapses)	EFS 75% +/- 10% at 3 years	TRM 3/20 (15%). Acute GVHD ≥2 in 8 patients; extensive chronic GVHD in 2 patients.	
LL	Levine et al. 2003[92h]	Case series from IBMTR and ABMTR	Autologous HSCT	CR1, CR2 or subsequent CR, relapse, primary induction failure	DFS/EFS 39% OS 6 months 75% 1 year 60% 5 year 44%	TRM 3% at 6 months	p values for OS differences between the autologous and allogeneic groups .01, .09 and .47 for 6 months, 1 year and 5 year, respectively. Study included adult patients with age range for autologous HSCT 2-67 (median 31) years and 5-53 (median 27) for allogeneic HSCT.
			Allogeneic HSCT	CR1, CR2 or subsequent CR, relapse, primary induction failure	DFS/EFS 36% OS 6 months 59% 1 year 49% 5 year 39%	TRM 18% at 6 months	
Mixed HL and NHL (including LL, LCL, BL and NOS)	Kobrinsky et al. 2001[94i]	Case series	Autologous or allogeneic	Recurrent	DFS/EFS 50%	TRM 5/50 (10%)	Median followup 44 months.

Table 12. Benefits and harms after treatment for childhood Non-Hodgkin's lymphoma (continued)

Histology (n)	Source	Evidence Type	Treatment	Indications	Benefits	Harms	Comment
ALCL	Fanin et al. 1999[99j]	Case series from EBMT	Autologous HSCT	CR1, CR2, CR≥3, PR1, PR≥2, sensitive relapse, primary refractory	OS for pediatric patients only (≤20 years) ~95% at 7 years.		Median followup 43.3 months. Study included adult patients. Age range was 3.2-53 (median 25). Eighteen of the 64 patients in the study were < 20 years old.
BL	Ladenstein 1997[100k]	Case series from EBMT	Autologous HSCT	Poor initial response to first-line chemotherapy (i.e., PR), sensitive relapse (SR), resistant relapse (RR)	5-year EFS 56.6% for patients in PR and 48.7% for patients in SR. All patients with RR died within one year.	TRM 11.1 %	Median followup 4.3 years (2-12)
LL (21), B-NHL (19), LCL (6)	Bureo et al. 1995[93l]	Case series	32 autologous and 14 allogeneic HSCT	CR1, CR2, CR3, refractory	EFS 58% [95%CI 42-73%]	TRM 13% [3/32 auto and 3/14 allo]	Median followup 33 months.
BL (16), LL (8)	Loiseau 1991[95m]	Case series	Autologous HSCT	Relapsed/ refractory	DFS 33%		

Table 12. Benefits and harms after treatment for childhood Non-Hodgkin's lymphoma (continued)

Histology (n)	Source	Evidence Type	Treatment	Indications	Benefits	Harms	Comment
BL (10), LL (2), DLBCL (5)	Philip 1988[96n]	Case series	Autologous HSCT	PR after first-line induction therapy	OS at 2 yrs 75% DFS/EFS 27%	TRM 2/17 (11.8%)	Median followup 2 yrs. Study included 11 children and 6 adults.

ABMTR = Autologous blood and marrow transplant registry; ALCL = anaplastic large cell lymphoma; BL = Burkitt lymphoma; CS = case series; DLBCL = diffuse large B-cell lymphoma; EBMT = European Group for Blood and Marrow Transplantation; GVHD = graft versus host disease; IBMTR = International Bone Marrow Transplant Registry; LL = lymphoblastic lymphoma; LCL = large cell lymphoma; NOS = not otherwise specified; SR = sensitive relapse; TRM = transplant-related mortality

f Won et al. 2006;[98] 33 patients underwent autologous HSCT and 73 received conventional chemotherapy; patients transplanted between 1997-2004.

g Woessmann et al. 2006;[97] n=20; patients transplanted between 1991-2003.

h Levine et al. 2003;[92] n=128 for autologous HSCT and n=76 for allogeneic HSCT; patients transplanted between 1989-1998.

i Kobrinsky et al. 2001;[94] n=50; study opened for accrual 1991 and closed 1994- bone marrow transplant was not a formal part of the study, but 42 patients were transplanted after induction therapy at the discretion of the treating physician and the remaining 8 patients underwent transplant between 5 and 84 weeks (median 14 weeks) from study entry.

j Fanin et al. 1999;[99] n=64; patients transplanted between 1983-1996.

k Ladenstein et al. 1997;[100] n=89; patients transplanted between 1979-1991.

l Bureo et al. 1995;[93] n=46;

m Loiseau et al. 1991;[95] n=24

n Philip et al. 1988;[96] n=17

NHL Guidelines

The American Society for Blood and Marrow Transplantation (ASBMT) issued a position statement on the use of HSCT in the treatment of diffuse large cell B-cell non-Hodgkin's lymphoma recommending its use in first chemotherapy-sensitive relapse, first complete remission in high/intermediate-high risk international prognostic index (IPI) patients, and as high-dose sequential therapy in intermediate-high/high risk IPI untreated patients.[101]

Guidelines from the ASBMT specifically addressing NHL and HSCT in the pediatric population were not identified.

NCCN clinical practice guidelines[102] for BL recommend that patients be considered for a clinical trial, which may include autologous or allogeneic stem-cell rescue. The recommendations for DLBCL are for autologous HSCT for relapsed or refractory disease in patients with either partial or complete response to second line therapy. Recommendations for LBL include consolidation of high-dose therapy with autologous or allogeneic stem-cell rescue in poor risk patients, allogeneic HSCT for patients with an initial CR who relapse and for patients with an initial partial response. Finally, recommendations for peripheral T-cell lymphomas, noncutaneous (including ALCL) include high-dose therapy and stem-cell rescue as first-line consolidation in all patients except those considered low risk (by age adjusted IPI), and autologous or allogeneic HSCT in patients with relapsed or refractory disease with a partial or complete response to additional therapy.

NHL Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of NHL with HSCT in patients with primary refractory or chemosensitive relapse. EFS for the various subtypes of NHL (except for ALCL) range from 27 to 59 percent,[92-94, 96, 98, 100] and for ALCL, EFS of 75 percent at 3 years[97] and OS 95 percent at 7 years[99] have been reported.

Current recommendations are based on small studies which have included heterogeneous patient populations with various tumor histologies and a mixture of adult and pediatric patients.

Future challenges in the treatment of NHL include the development of risk-stratified treatment approaches for patients with high-risk disease, defining the use of autologous HSCT as upfront consolidation for certain groups of high-risk NHL, and the possible use of allogeneic HSCT where graft versus lymphoma has been demonstrated.[80]

Narrative Reviews: Malignant, Nonhematopoietic Disease

Neuroblastoma

Background

Neuroblastoma is the most common extracranial solid tumor of childhood, and accounts for 8 to 10 percent of all childhood cancers and for approximately 15 percent of cancer deaths in children.[103] At least 40 percent of all children with neuroblastoma are designated as high-risk patients, based on adverse features including age 18 months or older at presentation, the presence of disseminated disease, unfavorable histologic features, and amplification of the MYCN oncogene.[103]

Low-risk patients are managed with surgery alone because excellent cure rates are achieved even when some tumor is left behind.[103] Intermediate-risk patients are still at low risk of succumbing to disease but require limited chemotherapy and/or surgery.[103, 104] The amount of

chemotherapy is determined in part by the biological features. High-risk patients receive treatment with an aggressive regimen of combination high-dose chemotherapy (HDC); long-term survival with current treatments is about 30 percent.[104] Children with aggressively treated, high-risk disease may develop late recurrences, some more than 5 years after completion of therapy.[103, 104] Many centers have used HDC with HSCT in the setting of high-risk or recurrent disease.[103, 105-108] Survivors have an increased rate of second malignant neoplasms, relative to the age- and sex-comparable U.S. population, and of chronic health conditions, relative to their siblings, which underscores the need for long-term medical surveillance.[109]

Evidence Base

The evidence compiled for this narrative review includes one systematic review,[110] of three randomized controlled trials (RCTs).[105, 107, 108] A followup analysis of one RCT[111] and reports from two European registries[112, 113] were also found (Table 13). No health technology assessments or clinical practice guidelines for the treatment of childhood neuroblastoma with HSCT were identified in the literature search.

The systematic review was a report published by the Cochrane Collaboration in May 2010, comparing the effectiveness of HDC with autologous HSCT versus conventional therapy in children with high-risk disease.[110] A meta-analysis of the three RCTs including 739 patients, independently identified in our search, showed a significant difference in both event-free and overall survival in favor of the transplant group (Table 14). Overall, no significant differences in the occurrence of adverse effects between treatment groups were identified in the Cochrane review (Table 14). These findings were further validated in a subsequent analysis of one RCT (not included in the Cochrane Review) with an 8-year median followup period (Table 14).[111]

Guidelines

No guidelines for the treatment of neuroblastoma were identified in the search.

Summary

Overall there appears to be a favorable risk-benefit profile for the role of HDC with autologous HSCT in children with high-risk disease, although possible higher levels of adverse effects should be kept in mind. Interpretation of these data is subject to the clinical context of the complete therapy which includes the effect of the induction regimen, the sources of stem cells, and presence and type of consolidation chemotherapy.

Table 13. Neuroblastoma evidence base

Year of First HSCT Performed	No. of Transplants to Date	Existing Clinical Evidence	Registries
Early 1980s	>4,100	Systematic review, randomized controlled trials	European Group for Blood and Marrow Transplantation (EBMT) registry (Ladenstein, 2008[113]): 4,098 procedures were registered between 1978 and 2006. In 3,974 patients, autologous stem cells were reinfused, while 124 patients were allocated for an allogeneic HSCT. Over 90% of patients were under the age of 10 years at diagnosis. The identified cases came from 27 European countries and at least seven international countries. Italian Neuroblastoma Registry (Garaventa, 2009[112]): 1,924 children were registered between 1979 and 2004.

HSCT = hematopoietic stem cell transplant

Table 14. Benefits and harms after treatment for neuroblastoma

Source (Evidence Type)	Treatment	Indications	Benefits	Harms	Comment
Yalçin, 2010[110] (Systematic Review)	Myeloablative therapy (high-dose chemotherapy and autologous bone marrow or stem-cell rescue (n=370)	Consolidate high-risk (initial)	Meta-analysis of three RCTs including 739 children. EFS (HR 0.78; 95% CI 0.67 to 0.90, p=0.0006) and OS (HR 0.74; 95% CI 0.57 to 0.98, p=0.04), both in favor of myeloablative therapy.[a]	No significant difference between groups in treatment-related death (RR 2.53; 95% CI 0.17 to 37.12, p=0.50),[b] secondary malignant disease (RR 0.99; 95% CI 0.14 to 7.00, p=0.99),[c] serious infections (RR 1.02; 95% CI 0.84 to 1.23, p=0.88), and sepsis (RR 0.93; 95% CI 0.67 to 1.30, p=0.67).[d]	All RCTs were multicenter studies, two of which were based in Europe (Berthold 2005[105]; Pritchard 2005[108]) and one in North America (Matthay 1999[107]); All trials used different myeloablative treatments. Patients were recruited between 1982 and 2002; none of the studies mentioned the exact patient age; only the number of cases above and below one year of age was stated; Data on adverse effects were very limited. None of the studies evaluated quality of life.
	Conventional therapy (conventional chemotherapy or no further treatment) (n=369)			Significant difference in favor of conventional therapy for renal effects (RR 2.28; 95% CI 1.28 to 4.04, p=0.005), interstitial pneumonitis (RR 9.55; 95% CI 2.26 to 40.43, p=0.002), and veno-occlusive disease (RR 35.18; 95% CI 2.13 to 580.88, p=0.01) based on data from one RCT.[d]	
Matthay, 2009[111] (RCT)	Myeloablative therapy (chemotherapy, total body irradiation, and ABMT)	Consolidate high-risk (initial)	5-year EFS was 30%; (compared to control group, p=0.04)	Treatment-related deaths occurred in 22 of 122 patients (compared to the control group, p=0.7408); AML in one patient at 2.7 years followup; Follicular carcinoma of the thyroid in one patient at 7 years followup.	This report was an 8-year median followup analysis of the RCT by Matthay 1999[107]; treatment-related toxicity data were unchanged from previous report.
	Conventional therapy (3 cycles of intensive chemotherapy)		5-year EFS was 19%	Treatment-related deaths occurred in 22 of 138 patients; T-cell ALL in one patient at 2 years followup; Clear-cell carcinoma in one patient at 2.5 years' followup	

ABMT = autologous bone marrow transplant; ALL = acute lymphoblastic leukemia; AML = acute myeloblastic leukemia; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; OS = overall survival; RCT = randomized controlled trial
a Results from two RCTs could be pooled for overall survival (Berthold 2005[105]; Pritchard 2005[108]). The RCT by Matthay 1999[107] only provided descriptive results: overall survival was similar for both regimens (n = 379 patients).
b Data on treatment-related death could be extracted from two trials with a total of 574 patients (Berthold 2005[105]; Matthay 1999[107]). There were 12 cases among 278 patients randomized to the transplant group and five among 296 patients randomized to the control group.
c Data on secondary malignant disease could be extracted from two trials with a total of 674 patients (Berthold 2005[105]; Matthay 1999[107]).
d Data on serious infections, sepsis, renal effects, interstitial pneumonitis and veno-occlusive disease could be extracted from Matthay 1999[107].

Germ-Cell Tumors

Background

Germ-cell tumors represent 3 percent of all childhood neoplasms.[114, 115] In the U.S., approximately 900 children and adolescents younger than 20 years of age are diagnosed with these tumors each year.[115, 116] Childhood germ-cell tumors are composed primarily of extragonadal neoplasms (e.g., mediastinal or retroperitoneal) whereas gonadal (ovarian and testicular) tumors are more common in adults.[115-118] Prognosis and appropriate treatment depend on factors such as histology (e.g., seminomatous vs. nonseminomatous), age (young children vs. adolescents), stage of disease, and primary site.[117, 118]

Germ-cell tumors are highly sensitive to chemotherapy.[114, 117, 118] Cisplatin-based combination chemotherapy, followed by appropriate surgical resection of residual disease, is curative in 80 percent of patients.[114, 118, 119] Reports of salvage treatment strategies used in adult recurrent germ-cell tumors include larger numbers of patients, but the differences between children and adults regarding the location of the primary tumor site, pattern of relapse, and the biology of childhood disease may limit the applicability of adult salvage approaches to children. Many centers have used HDC with HSCT in the setting of recurrent disease.[114, 119, 120]

Evidence Base

The evidence compiled for this review (Table 15) includes one cohort study,[120] two reports based on registry data,[114, 119] and two NCCN guidelines.[117, 118] A review of the NCI's PDQ® Cancer Clinical Trials Registry identified at least one ongoing trial involving HSCT in the setting of relapsed childhood germ-cell tumors.[121] No RCTs, systematic reviews or health technology assessments for childhood germ-cell tumors were identified in the literature search.

Agarwal and colleagues[120] reported their experience at Stanford University Medical Center in treating 37 consecutive patients who received HDC and autologous HSCT between 1995 and 2005 for relapsed disease (Table 16). Only four patients (11 percent) in this cohort were in the pediatric age group. Twenty-nine patients had received prior standard salvage chemotherapy. Three-year overall and event-free survival was 57 and 49 percent, respectively. Treatment-related mortality was reported at 3 percent. In terms of ongoing trials, there is a pilot study underway to assess the feasibility of HDC followed by autologous HSCT in patients with newly diagnosed or relapsed solid tumors (including GCTs). Twenty patients (6 months to 40 years of age) are expected to be enrolled in this single-center U.S. study with the expected final data collection date of December 2010.[121]

Table 15. Germ-cell tumor evidence base

Year of First HSCT Performed	No. of Transplants to Date	Existing Clinical Evidence	Registries
Late 1980s	>150 (pediatric age-group)	Cohort studies	European Group for Blood and Marrow Transplantation – EBMT (De Giorgi, 2005[114]): 160 patients with a diagnosis of extragonadal GCT registered between 1987 and 1999; analysis was undertaken of 23 children who received HDC with HSCT. Center for International Blood and Marrow Transplant Research – CIBMTR (Lazarus, 2007[119]): 300 patients with testicular cancer registered between 1989 and 2001; 198 patients received single HSCT, and 102 patients received tandem auto-transplants. Approximately 10% of patients were in the pediatric age-group. The identified cases came from 76 centers across eight countries.

HDC = high-dose chemotherapy; HSCT = hematopoietic stem cell transplant

Table 16. Benefits and harms after treatment for germ-cell tumors

Source (Evidence Type)	Treatment	Indications	Benefits	Harms	Comment
Agarwal, 2009[120] (cohort)	HDC with autologous HSCT	Relapsed	3-year overall survival of 57% (95% CI, 41-71%); 3-year event-free survival of 49% (95% CI, 33-64%).	The treatment-related mortality was 3%; four patients developed signs of mild VOD of liver.	37 consecutive patients between 1995 and 2005 at Stanford. Median patient age of 28 years at transplant (range: 9-59 years; 92% male); four patients (11%) between 0-19 years. Primary tumor sites included 24 testes/adnexal, 10 chest/neck/ retroperitoneal, and 3 central nervous system.

CI = confidence interval; HDC = high-dose chemotherapy; HSCT = hematopoietic stem-cell transplant; VOD = veno-occlusive disease

Guidelines

Our search identified two guidelines for the treatment of GCT. Both guidelines were from NCCN and were not specific to childhood disease.[117, 118] The NCCN testicular cancer guidelines[118] recommend HDC with HSCT as the preferred third-line option for metastatic disease if the patient experiences an incomplete response or relapses after second-line conventional dose chemotherapy. This recommendation is based on lower-level evidence and uniform NCCN consensus (Category 2A) In addition, HDC with HSCT is recommended as one therapeutic option for patients with poor prognostic features including an incomplete response to first-line therapy, high levels of serum markers, high-volume disease and presence of extratesticular primary tumor. This recommendation is based on lower-level evidence, including clinical experience and nonuniform NCCN consensus, but no major disagreement (Category 2B) Alternatively, the patients may be put on best supportive care or salvage surgery if feasible.[118] The NCCN ovarian cancer guidelines,[117] on the other hand, recommend HDC with HSCT as one therapeutic option for patients having persistently elevated alpha-fetoprotein and/or beta-human chorionic gonadotropin levels after first-line chemotherapy. This recommendation is based on lower-level evidence and uniform NCCN consensus (Category 2A)

Summary

Although there is not sufficient literature to firmly establish the role of HDC with autologous HSCT for relapsed pediatric germ-cell tumor, studies in adult patients with similar tumors show efficacy in poorly responsive or relapsed disease. Further study is needed in young children and adolescents to determine whether the efficacy noted in adult studies can be extrapolated to pediatric patients.

Central Nervous System Embryonal Tumors

Background

Classification of brain tumors is based on both histopathologic characteristics of the tumor and location in the brain.[122] Central nervous system (CNS) embryonal tumors are the most common malignant brain tumor in childhood. Embryonal tumors of the CNS include medulloblastoma, ependymoblastoma, supratentorial primitive neuroectodermal tumors (PNETs), medulloepithelioma, and atypical teratoid/rhabdoid tumor (AT/RT).[122]

Medulloblastomas account for 20 percent of all childhood CNS tumors.[123, 124] The other types of embryonal tumors are rare by comparison [122]. Surgical resection is the mainstay of therapy with the goal being gross total resection with adjuvant radiation therapy, as medulloblastomas are very radiosensitive tumors.[124, 125] Treatment protocols are based on risk stratification, as average or high risk. HSCT is used in high-risk disease, including metastatic, and recurrent or residual following surgery and chemotherapy. The average-risk group includes children older than 3 years, without metastatic disease, and with tumors that are totally or near totally resected (i.e., less than 1.5 cm² of residual disease).[124] In addition, patients with non-anaplastic medulloblastoma are considered to be at average (or standard) risk, and those with anaplastic disease at high risk. The high-risk group includes children aged 3 years or younger, or with metastatic disease, and/or subtotal resection (i.e., more than 1.5 cm² of residual disease).[124] The treatment of medulloblastoma continues to evolve, and, especially in children younger than 3 years because of the concern of the deleterious effects of craniospinal radiation on the immature nervous system, therapeutic approaches have attempted to delay and sometimes avoid the use of radiation, and have included trials investigating different chemotherapy regimens to improve outcome.[122]

PNETs are a heterogeneous group of highly malignant neoplasms comprising 3 to 5 percent of all childhood brain tumors, most commonly located in the cerebral cortex and pineal region.[123, 125] AT/RT, on the other hand, is a tumor of early childhood, with nearly two-thirds of cases diagnosed before the age of 3 years.[123, 125, 126] The prognosis for these tumors is worse than for medulloblastoma, despite identical therapies.[122, 123, 125] Recurrence of all forms of CNS embryonal tumors is not uncommon, usually occurring within 18 months of treatment; however, recurrent tumors may develop many years after initial treatment.[122] Many centers have used HDC with HSCT in the setting of high-risk disease.

Evidence Base

The evidence compiled for this review includes seven case series published since 2005.[127-133] No RCTs, registry reports, or clinical practice guidelines for the treatment of childhood CNS embryonal tumors with HSCT were identified in the literature search. In addition, no systematic reviews or health technology assessments were found on CNS embryonal tumors (Table 17).

Published information on outcome for children with CNS embryonal tumors is based on small series and is retrospective in nature (Table 18).

Table 17. CNS embryonal tumors evidence base

Year of First HSCT Performed	No. of Transplants to Date	Existing Clinical Evidence	Registries
Mid 1990s	>150	Retrospective case series	None

HSCT = hematopoietic stem cell transplant

Guidelines

No guidelines on the treatment of CNS embryonal tumors were identified in the search.

Summary

Overall, there is a favorable risk-benefit profile for the role of HDC with HSCT in young children with high-risk or recurrent medulloblastoma supported by case series published in the past 5 years. Data is limited regarding the use of this therapy for other childhood CNS embryonal tumors. Comparison of the effects of HSCT between treatment trials remains challenging given the heterogeneity of these tumors, use of different combinations of chemotherapy as well as radiation therapies, and varied patient selection.

Table 18. Benefits and harms after treatment for CNS embryonal tumors

Source (Evidence Type)	Treatment	Indications	Benefits	Harms	Comment
Butturini et al. 2009[127] (case series)	HDC with autologous HSCT	Relapsed or residual	3-year OS of 83% (SE, 15%); EFS of 83% (SE, 15%) [in patients without prior radiotherapy, n=6]; 3-year OS of 29% (SE, 13%); EFS of 20% (SE, 12%) [in patients with prior radiotherapy, n=13]	Treatment-related deaths in one patient without prior radiotherapy, and in four patients with prior radiotherapy; Post-transplant recurrence in six patients with prior radiotherapy.	19 patients recruited between 1992-2008; Median age at transplant, 4.5 years (range, 1.7-5.8) in patients with no prior radiotherapy; 9.9 years (4-18.2) in patients with prior radiotherapy; MB and PNET (supratentorial location at diagnosis, 17-30%)
Grodman et al. 2009[129] (case series)	HDC with autologous HSCT	Relapsed or residual	5-year OS of 50% (95% CI, 15-77%)	Neurotoxicity in two MB patients	8 patients recruited between 1995-2002; Mean age at transplant, 12.9 years (range, 5.6-27.8); MB (n=7, 87.5%) and germinoma (n=1)
Cheuk et al. 2008[128] (case series)	HDC with autologous HSCT	Relapsed or residual	5-year OS of 51.9%; EFS of 53.9%; Subgroup analysis for MB patients (n=9): 5-year OS of 51.9%; EFS of 55.6%	Transplant-related death in one patient; Hepatic VOD in two patients; Grade 4 renal toxicity in one patient	13 patients recruited between 1996-2006; Mean age at transplant, 8.5 years (range: 2.7-20); MB (n=9, 69%), PNET (n=1), ependymoma (n=1), germ-cell tumor (n=1), and cerebral rhabdoid (n=1)
Kadota et al. 2008[130] (case series)	HDC with autologous HSCT	Relapsed or residual	2-year OS of 59% (SE, 9%); PFS of 34% (9%).	No treatment-related deaths; Infections in 15 patients (52%); Stomatitis in 12 patients	29 patients recruited between 1994-2003; median age of 9.8 years (range, 4.3-17.1); MB (n=22, 76%) and germinoma (n=7)
Shih et al. 2008[132] (case series)	HDC with autologous HSCT	Relapsed or residual	5-year OS of 28% (SE, 9.8%); PFS of 18.5% (SE, 8.4%); 5-year PFS for patients aged <3 years at diagnosis significantly better than older patients (57% vs. 5%, p = 0.02)	Transplant-related death in two patients; 44% of patients experienced grade 3/4 transplant-related toxicity	27 children recruited between 1989-2004; Median age at transplant, 6.7 years (range, 1.1 – 18.5); Six patients aged ≤3 years at transplant) MB (n=13, 48%), PNET (n=5), AT/RT (n=2) and other CNS tumors (ependymoma, n=3; anaplastic astrocytoma, 2; glioblastoma, n=2)

Table 18. Benefits and harms after treatment for CNS embryonal tumors (continued)

Source (Evidence Type)	Treatment	Indications	Benefits	Harms	Comment
Ridola et al. 2007[131] (case series)	HDC with autologous HSCT	Relapsed or residual	5-year OS of 77.2% (95%CI, 58.3-89.1%); EFS of 66.7% (47.8-81.4%) [in patients with local recurrence, n=27] 5-year OS of 50% (95% CI, 25.4-74.6%); EFS of 50% (25.4-74.6%) [in patients with residual disease, n=12]	Two toxic deaths (5) from infections; Severe infections in 28%; Hepatic VOD in 33%	39 children with MB between 1988-2005; Median age at transplant, 3.25 years (range, 0.9-6.7); 64% (n=25) of patients received varied therapy prior to transplant
Sung et al. 2007[133] (case series)	HDC with autologous HSCT	Relapsed or residual	3-year OS of 25.6% (SE, 15%); EFS of 29.1 ± 15.7%	Transplant-related deaths in two patients	11 patients recruited between 1999-2005; median age, 8.2 years (3.75-17.2); MB (n=7, 64%) and PNET (n=4) 3 (of 11) MB patients received tandem therapy

AT/RT = atypical teratoid/rhabdoid tumor; CI = confidence interval; EFS = event-free survival; HDC = high-dose chemotherapy; HSCT = hematopoietic stem-cell transplant; MB = medulloblastoma; PFS = progression-free survival; PNET = supratentorial primitive neuro-ectodermal tumor; SE = standard error; OS = overall survival; VOD = veno-occlusive disease

Narrative Reviews: Nonmalignant Disease

Hemoglobinopathies

Characterized by inherited lifelong anemia hemoglobinopathies are a class of diseases defined by the abnormal function or synthesis of the hemoglobin molecule.[134] Within this disease class sickle-cell disease (SCD) and thalassemias are the most common (Table 19). The patients are faced with major morbidity and premature mortality. HSCT is the only treatment with a curative intent.

Sickle-Cell Disease

Background

Sickle-cell disease is a genetic hemoglobin disease causing severe pain crisis and dysfunction across organ systems, ultimately leading to premature death. The disease is caused by amino acid substitutions that alter the structure and function of the hemoglobin molecule. Sickle-cell disease occurs when the hemoglobin S gene is inherited from both parents. Worldwide, approximately 275,000 sickle-cell-affected conceptions and births occur each year.[135] Average life expectancy is estimated at between 42 and 53 years for men and between 48 and 58 years for women.[136] At age 5, 95 percent of patients will be asplenic, leaving them highly susceptible to infection and sepsis, the leading cause of death among young patients with sickle-cell disease.[134] Clinical management includes three major therapeutic options: chronic blood transfusion, hydroxyurea, or HSCT. While the long-term use of blood transfusion has been shown effective at preventing stroke and other sickle-cell complications, it may lead to iron overload, infection, and alloimmunization.[137] HSCT is the only treatment with a curative intent, aiming to remove sickled red blood cells and progenitor stem cells and replace them with stem cells able to express total or at least partial correction of the abnormal hemoglobin phenotype.[138]

Evidence Base

The evidence compiled for this review includes two literature reviews[139, 140] and one systematic review on the use of hydroxyurea containing data from one RCT and 22 observational studies.[141] One clinical practice guideline for the treatment of sickle-cell disease with HSCT[142] and no health technology assessments were identified in the literature search.

For patients in whom HSCT is indicated, the review of the literature (Table 20) shows for median followup ranging from 0.9 to 17.9 years overall survival of greater than 92 percent and event free survival of greater than 82 percent have been observed. Cord blood and marrow donations from family donations have been used with equal success; although current numbers are small.[143, 144]

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Table 19. Evidence base for HSCT in hemoglobinopathies

Disease	Year of First HSCT Performed	No. of Transplants to Date	Existing Clinical Data	Registries
Sickle cell disease	1984	Approximately 250	Review, case series, case reports	The Registry and Surveillance System in Hemoglobinopathies (RuSH) is a new collaborative registry with the NHLBI, CDC and six US states (California, Florida, Georgia, Michigan, North Carolina, and Pennsylvania) to study Hemoglobinopathies in the U.S.[145] EBMT has a hemoglobinopathies registry.
β-thalassemia	1981	>1600	Review, case series, case reports	Registries are maintained in the United Kingdom (National Register of Inherited Disorders), Iran and Oman The Registry and Surveillance System in Hemoglobinopathies (RuSH) is a new collaborative registry, with the NHBIL, CDC and six US states (California, Florida, Georgia, Michigan, North Carolina, and Pennsylvania) to study Hemoglobinopathies in the U.S.[145] (Under development, in pilot phase) EBMT has a hemoglobinopathies registry.

CDC = Centers for Disease Control and Prevention; EBMT = European Group for Blood and Marrow Transplantation; HSCT = hematopoietic stem cell transplant; NHLBI = National Heart, Lung and Blood Institute

Table 20. Benefits and harms after treatment for hemoglobinopathies

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Sickle cell disease	Inati, 2009[140] (literature review)	Blood transfusion with leukoreduced red cells	Acute or episodic symptoms or long term management of SCD Primary stroke prevention	Risk of stroke was 92% lower in the group receiving transfusions compared to the non-transfusion group at 26 months.	Chronic blood transfusion leads to iron overload and organ damage.	Trial was halted at 26 months followup because of ethical concerns of withholding transfusion.
Sickle cell disease	Strouse et al. 2008[141] (systematic evidence review)	Hydroxyurea (HU)	Primary treatment for patients experiencing recurrent pain crisis or acute chest syndrome Recurrent stroke prevention	Hemoglobin levels increased by a mean of 0.4 g/dl while on treatment. Both hospitalizations and hospitalized days were lower when on treatment 1.1 vs. 2.8 and 7.1 vs. 23.4 days respectively. Observed in 17 studies HbF% increased from 5-10% at baseline to 15-20% during treatment. Frequency of pain crisis decreased in three of four studies From an average of 3.4 to 1.3 per year,[k,l,m] with one study showing no difference [n].	Evidence was graded by the authors as Moderate to support an increased risk of reversible, usually mild, cytopenias and rash or nail changes in children treated with HU.	Systematic evidence review contained data from one RCT and 22 observational studies. Data from the observational studies were largely consistent with the RCT. We summarize the most relevant outcomes from the RCT and observational data. Evidence was graded [146] by the authors as insufficient to assess the risk of leukemia or other secondary malignancies, splenic sequestration, and leg ulcer development.

Table 20. Benefits and harms after treatment for hemoglobinopathies (continued)

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Sickle cell disease	Bhatia and Walters 2008[139] (literature review)	Allogeneic HSCT	Severe SCD	-Overall survival 92-94% [a,b,c] -Patients with asymptomatic disease do better OS 100 vs. 88% and EFS 93 vs. 76% [b] -Event free survival 82-86.1% [a,b,c]	-15-20% aGVHD ≥ grade 2 -cGVHD 12-20% -Treatment related mortality 6-7% - Graft rejection 7-10% (all data from a,b,c) - ovarian failure is common among SCD patients after HSCT, however the sample sizes are too limited to make inferences. 5/6 females who received Bu16/CY200 had primary amenorrhea,[b] and in the Multicenter collaborative study six of the seven evaluable females had primary amenorrhea [a]. In the three major series of HSCT among SCD, males receiving Bu16/CY200 had normal sexual development.	Age range at transplant (0.9-22 years)[a,b,c] Median years of followup ranged from 0.9 to 17.9 years.[a,b,c,] Infections are the major cause of treatment related mortality. All patients in these series were conditioned with Bu 14-16 mg/kg or 485 mg/m^2 with CY200; ATG was also used in the French and multicenter studies. Note, the intervention (allogeneic HSCT) refers to HLA-identical donors only.

Table 20. Benefits and harms after treatment for hemoglobinopathies (continued)

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
β-thalassemia major	Bhatia and Walters 2008[139]	Transfusion with leukoreduced red cells	Long term management		Chronic blood transfusion leads to Iron overload and organ damage.	
		Allogeneic HSCT		-Thalassemia free survival (TFS) 73% [d] -TFS by class; 94, 77 and 53% for class 1,2 and 3 respectively[d]. -Overall survival 65-100% [e,f,g,h] - 2 year event free survival 79% [f]	32-47.3% aGVHD ≥ grade 2 [e,g,h] 14-37.5% cGVHD [e,g,h] 10-34% Treatment related mortality[e, g,h] Rates are unclear due to small numbers but a study of endocrine function after HSCT in 15 patients (10 male 5 female) followed for 12 years, 20% of boys (2/10) had gonadal failure, 100% of girls experienced ovarian failure, an additional five girls who had entered puberty prior to HSCT also experienced 100% ovarian failure after HSCT.[i]	Overall survival estimate of 100 came from a mixed cohort of thalassemia and SCD[f]. - 2 year EFS came from 33 thalassemia patients in the cohort.[f] Rates for aGVHD and cGVHD include transplants with related and unrelated donors. One study reported aGVHD in 11% and cGVHD of 6% of patients but 25% of that cohort are patients with SCD.[f] The largest study (886 patients) does not report on aGVHD.[d]

aGVHD = acute graft vs. host disease; ATG = antithymocyte globulin; cGVHD = chronic graft versus host disease;
HSCT = hematopoietic stem cell transplant; RCT = randomized controlled trial; SCD = sickle-cell disease
a Walters et al. 2000[138] multicenter study of 59 children with SCD treated with HSCT;
b Vermylen et al. 1998[147] case series of first 50 patients with SCD transplanted in Belgium;
c Bernaudin et al. 2007[148] results from 87 patients with SCD treated with HSCT;
d Lucarelli et al. 2002[149] 886 patients with thalassemia;
e La Nasa et al. 2005[150] 68 patients;
f Locatelli et al. 2003[144] 33 thalassemia and 11 patients with SCD;
g Hongeng et al. 2006[151] 49 thalassemia;
h Gaziev et al. 2000[152] 29 thalassemia;
i Li et al. 2004[153] study of endocrine function after HSCT for thalassemia;
j Ferster et al. 1996[154] randomized cross-over trial of 25 patients receiving hydroxyurea for SCD at 2 sites;
k Olivieri and Vichinsky, 1998[155];

l Santos et al. 2002[156];
m Svarch et al. 2006[157];
n Hankins et al. 2005[158];
o Adams et al. 1998[159] RCT on transfusion for SCD of 130 children

Guidelines

Guidelines for the treatment of sickle-cell disease with HSCT come from the criteria developed by Walters et al.[142]

Patients younger than 16 years old with sickle-cell disease who have an HLA-identical sibling bone marrow donor with one or more of the following are eligible for HSCT:

- Stroke, central nervous system (CNS) hemorrhage or a neurologic event lasting longer than 24 hours or abnormal cerebral magnetic resonance imaging (MRI) scan or cerebral arteriogram or MRI angiographic study and impaired neuropsychological testing
- Acute chest syndrome with a history of recurrent hospitalizations or exchange transfusions
- Recurrent vaso-occlusive pain three or more episodes per year for 3 or more years or recurrent priapism
- Impaired neuropsychological function and abnormal cerebral MRI scan
- Stage I or II sickle lung disease
- Sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate [GFR] 30–50 percent of the predicted normal value)
- Bilateral proliferative retinopathy and major visual impairment in at least one eye
- Osteonecrosis of multiple joints with documented destructive changes
- Requirement for chronic transfusions but with RBC alloimmunization of more than two antibodies during long-term transfusion therapy

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of severe sickle cell disease with HSCT for patients aged younger than 16 years who have an HLA-identical sibling donor and are candidates for transplant as indicated by the presence of one of the complications listed above. Approximately 14 to 18 percent of patients with sickle-cell disease have an HLA-identical matched sibling, and therefore the majority of patients rely on transfusion and/or hydroxyurea for their clinical management. The use of well-matched unrelated donors for HSCT for patients with severe sickle cell disease is currently under study (ClinicalTrials.gov record NCT00745420 BMT-CTN trial 0601).

β-Thalassemia Major

Background

Thalassemia is considered to be the most common genetic disorder in the world.[160] Thalassemia is caused by mutations in the globin genes that either reduce or eliminate the production of one of the globin chains.[161] Reduction or absence of the β-globin chain results in β-thalassemia. The most severe form is β-thalassemia major, where individuals have severe anemia and are dependent on transfusions for survival. Approximately 150 million people carry β-thalassemia genes. β-thalassemia major defines the most severe group of patients who have transfusion-dependent anemia with transfusions often beginning as early as 6 months of age. Signs of the disease usually appear within the first year of life and life expectancy is severely reduced among these patients. Prior to 1980, median survival was 17.1 years with 50 percent of patients dying before age 15 years.[162-165] Among patients who are adherent with iron chelation therapy, there is a 30 to 60 percent chance of being alive at age 30 versus 10 percent for a those

who are not.[164, 166, 167] Clinical management for β-thalassemia major relies on life-long transfusion support, which when adequately provided can prevent much of the morbidity and mortality of the disease. However, the only potentially curative treatment for thalassemia is to correct the genetic defect through HSCT.

Evidence Base

The evidence compiled for this review was contained in a 2008 literature review by Bhatia and Walters.[139] No clinical practice guidelines or health technology assessments on the use of HSCT for β-thalassemia major were identified in the search.

Patients with β-thalassemia major selected for transplant are placed into one of three risk categories based on clinical features of the disease:
- Adherence to a program of regular iron chelation therapy
- Presence or absence of hepatomegaly
- Presence or absence of portal fibrosis observed by liver biopsy

Patients placed in class 1 have none of the risk factors, class two patients have one or two, and patients in class three have all three risk factors. Outcomes after HSCT vary by class (Table 20).[149]

Review of the literature shows thalassemia-free survival after HSCT of 73 percent overall, and 94, 77, and 53 percent for classes 1, 2, and 3, respectively. Overall survival estimates range from 65 to 100 percent.

Guidelines

No guidelines for the treatment of β-thalassemia major with HSCT were identified in the search.

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of β-thalassemia major with HSCT for patients who have an HLA-identical family donor. Approximately 30 to 36 percent[149] of patients has an HLA-identical family donor, the remainder rely on lifelong transfusion for the clinical management of the disease. For those patients with a suitable donor, avoidance of the complications of long-term transfusion may outweigh the risks of HSCT. However, prior to HSCT, adherence to iron chelation is essential, as rates of thalassemia-free survival are worse for those with complications due to iron overload.

Bone Marrow Failure Syndromes

Bone marrow failure syndromes (BMF) comprise a broad number of diseases with varying etiologies (Table 21). The unifying factor is that hematopoiesis is abnormal or fully arrested in at least one cell line.[168] BMF can either be acquired, as in acquired aplastic anemia, or congenital as is the case in patients with Fanconi anemia, Diamond Blackfan anemia, and Schwachman Diamond syndrome.

Acquired Bone Marrow Failure Syndrome

Acquired Aplastic Anemia

Background

Acquired aplastic anemia is a failure of the bone marrow to produce red and white blood cells, as well as platelets. Approximately 80 percent of all cases of aplastic anemia are acquired versus congenital. While disease onset can occur at any age, it preferentially occurs in young adults and individuals over 60 years of age.[169] Patients with acquired aplastic anemia are classified according to the severity of marrow aplasia.[170] The urgency of treatment is dictated by the patient's absolute neutrophil count and the duration of severe neutropenia, which is correlated to survival.

Table 21. Listing of bone marrow failure syndromes and their evidence base

Disease	Year of First HSCT Performed	No. of Transplants to Date	Existing Clinical Data	Registries
Acquired Aplastic Anemia	Early 1970s	Unclear	RCTs, review, case reports, case series	None
Fanconi Anemia	Early 1970s	Unclear	Review, case series, case reports	The International Fanconi Anemia Registry (est. 1982) to study the features of Fanconi anemia. The registry is housed at Rockefeller University, and contains data on more than 1000 patients with FA in the U.S. (www.rockefeller.edu)
Schwachman Diamond Syndrome	1991	Approximately 30 reported	Review, case series, case reports	The North American SDS Registry, Fred Hutchinson Cancer Research Center, seeks to register all SDS cases in the U.S. and Canada. (www.shwachman-diamond.org/)
Dyskeratosis Congenita	Unclear	30 patients reported	Reviews, case series, case reports	The Dyskeratosis Congenita Registry established in 1995, Hammersmith Hospital, London, and includes data on the epidemiology pathophysiology, genetics and treatment of DC. Information from 200 families, in 40 countries and more than 350 affected individuals.[171]
Congenital Amegakaryocytic Thrombocyto-penia	1990	52 patients	Reviews, case series, case reports	None found
Diamond Blackfan Anemia		Unclear	Reviews, case series, case reports	The Diamond Blackfan Anemia registry of North America, established in 1993 and housed at Schneider Children's Hospital, New York includes demographics, lab, and clinical data on over 500 patients with DBA in the U.S. and Canada. (Bagby et al. 2004[172] and www.dbar.org)

Table 21. Listing of bone marrow failure syndromes and their evidence base (continued)

Disease	Year of First HSCT Performed	No. of Transplants to Date	Existing Clinical Data	Registries
Severe Congenital Neutropenia/ Kostmann Syndrome	1980	40 patients	Reviews, case series, case reports	The Severe Chronic Neutropenia International Registry, est.1994, University of Washington has the largest collection of SCN long-term data (depts.washington.edu/registry). As of 2003, the French Severe Chronic Neutropenia Registry, created in 1994 included 101 patients with SCN (Ferry et al. 2005[173])

DC = Dyskeratosis congenita; DBA = Diamond Blackfan anemia; FA = Fanconi anemia; RCT = randomized controlled trial; SCN = severe congenital neutropenia; SDS = Schwachman Diamond syndrome

The standard of care for treatment of aplastic anemia is immunosuppression and/or HSCT. The patient's age, medical history (such as number of prior blood transfusions and infections) and the availability of a matched sibling donor guide treatment decisions.[172]

Evidence Base

The evidence compiled for this review includes one literature review.[168] One clinical practice guideline[172] but no health technology assessments for the treatment of childhood acquired aplastic anemia with HSCT were identified in the literature search. The evidence base on the use of HSCT for treatment of acquired aplastic anemia is summarized in Table 22.

The literature review[168] reports for patients without a matched sibling donor immunosuppression can offer 89 percent 10-year survival among responders. Seventeen to 34 percent will eventually require HSCT as salvage therapy and the long term use of immunosuppressants leave the patient at higher risk for infection and an increased rate of MDS/AML of 8 to 25 percent. For patients with a matched sibling donor survival rates after transplant are far better reaching 98 percent in some series. A matched sibling bone marrow transplant may offer better survival 85 percent versus 73 percent with peripheral blood stem cells and a lower risk of graft versus host disease. Various conditioning regimens are available and are associated with varied rates of adverse events.

Guidelines

Guidelines for the treatment of acquired aplastic anemia with HSCT were published by Bagby et al.[172]

The treatment algorithm recommends:
- patients younger than 35 years with a matched sibling donor, HSCT as first-line therapy,
- patients older than 35 years or no matched sibling donor, immunosuppressive therapy as first-line therapy,
- HSCT as treatment for those refractory to immunosuppression.

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of acquired aplastic anemia with HSCT. Clinical management entails immunosuppression and HSCT. In general younger patients with a matched sibling donor are encouraged to pursue HSCT, while older patients who are less tolerant of transplant or those without a matched sibling donor are

first put on immunosuppressive therapy. For those receiving transplant, control of graft-versus-host disease is essential in achieving high rates of survival. Selection of a conditioning regimen influences the harms associated with transplantation.

Table 22. Benefits and harms after treatment for bone marrow failure syndromes

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Acquired Aplastic Anemia	Myers and Davies, 2008[168] (Literature review)	Immuno-suppres-sive therapy	- Front line therapy in those without a matched sibling donor	- 68%[a]-80%[b] overall survival at 10 years. - 89%[b] overall survival if confined to responders to therapy. - disease free survival 40% at 10 years [c]	- Patients left at higher risk for infection due to use of IST for 2-3 years. -Higher rates of clonal evolution with repeat IS [d]. - increased rates for MDS and AML ranging from 8%-25%[d, e, f]	-17-34% of SAA patients treated with IST will eventually require HSCT as salvage therapy [g]. Not pediatric patients median age 32 (2-80) [e].
		Allogeneic HSCT	- Front line therapy for those with a matched sibling donor	- matched sibling donors overall survival ranges from 85-98% [c,g,h,i]. -Survival for those with GVHD grade 0-1 98% versus 70% in recipients with grade II-IV [i]. - Five year overall survival after transplant with matched sibling peripheral blood stem cells 73% versus 85% after matched sibling bone marrow transplant.	-relative risk for mortality of 2.04 (1.09-3.78) for those receiving PBSC versus bone marrow. - relative risk of GVHD 2.82 (1.46-5.44) for PBSC vs. BMT[j]. - Kaplan-Meier estimate of risk of secondary malignancy after myeloablative transplantation for SAA 14%[k] -Development of GVHD -restrictive or obstructive pulmonary disease 24%[l]	Age range at transplant 4-46 (median ~19) [i]. The type of conditioning regimen seems to have a greater association with adverse outcomes such as stunted growth, altered endocrine and pulmonary function, bone marrow density, and for those receiving radiation-containing regimens affects on fertility.
			- Treatment for those refractory to immuno-suppressive therapy. (Unrelated donor)	-84% 5 year failure free survival for unrelated matched donor HSCT vs. 11% for repeat course of immunotherapy after one failed course. -73% 2 year survival, and 84% for children 14 years or younger -unrelated [m]. mismatched donor 34-40% survival [n,o]	-Development of GVHD -restrictive or obstructive pulmonary disease 24%[l]	Age range at transplant = 1.8-67, median 14 years [k]. Age range at transplant 1-42, median 18 years [l]. Five donors (13%) were HLA mismatched family members [m]. Median age of these patients is approximately 18 years with a range of (1-65), and all patients may not be refractory to suppressive therapy [o].

Table 22. Benefits and harms after treatment for bone marrow failure syndromes (continued)

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Fanconi Anemia	Dufour and Svahn, 2008[174] (Literature Review)	Androgen Therapy	- Front line therapy for those with no matched sibling donor	75% of patients will respond to androgen therapy [p] within 2-12 months	- virilization - hyperactivity - renal toxicity - hypertension -Possible adverse effect on subsequent HSCT [q, r]	Response is incomplete and generally drug dependent, additionally the age of responders is not mentioned in this article. [p] Age range at transplant = 4-37.4, median 10.8 years [q.] Age range at transplant = 7-31, median 8 years [r.] Combining androgens with corticosteroids can help to minimize liver toxicity [s.] however, age of patients is not discussed in this article.

Table 22. Benefits and harms after treatment for bone marrow failure syndromes (continued)

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Fanconi Anemia	Myers and Davies, 2008[168] (Literature Review)	Allogeneic HSCT	- Front line therapy for those with a matched sibling donor	-10 year survival of 89% after transplant with peritransplantation ATG[qq] - 88% sustained engraftment and 93% overall survival when Cyclophosphamide (Cy) is used alone as immunosuppressive agent[ff]	-acute GVHD 23% -chronic GVHD 12%[q] with peritransplantation ATG -acute GVHD 57% for those receiving 80 mg/kg, 14% aGVHD for patients receiving 60 mg/kg of CY. -chronic GVHD 33% for those receiving 80 mg/kg and 11% for those receiving a dose of 60 mg/kg[v]	Age range at transplant = 5-29, median 9[u] Age at transplant 2.7-22.9 years, median 7.6 years[q]
			- Front line therapy in those using an unrelated donor	-survival rates 38%-96% when using Flu-based conditioning regimen[w,x,y,z,aa] -decrease in treatment related mortality from 81% to 47%[w] - 3 year overall survival 52% for fludarabine containing regimens vs. 13% for fludarabine-free regimens - 42% overall survival (50% for those on fludarabine vs. 25% for those on fludarabine free regimens) when using umbilical cord blood transplant[bb]	-acute GVHD 21% with Flu-free[ww] -acute GVHD 16% with Flu[vv] -chronic GVHD 31%[dd] -acute GVHD 32.5% -chronic GVHD 16% when using umbilical cord blood transplant[cc]	Of total n=98, 39% (n = 38) ≤ 10 years, 44% (n = 43) 11-20 years, and 17% (n = 17) > 20 years at transplant. No age-group analysis of the flu group provided[w]. Age range at transplant 7-31, median age 8 years, and survival of 38% reported in a group with mixed conditioning regimens[z]. Age range at transplant = 5-24, median 11. Fourteen of 18 patients (78%) < 20 years[aa]. For the Flu vs. Flu free sub-group analysis age range 1-45, median age 8.6 years[bb]. This is using t-cell depleted stem cells. FA patients have heightened sensitivity to GVHD tissue damage and GVHD likely increases an already high rate of later malignancy

Table 22. Benefits and harms after treatment for bone marrow failure syndromes (continued)

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Schwachman-Diamond Syndrome	Myers and Davies, 2009 [168] (Literature Review)	Allogeneic HSCT	SDS patients with marrow aplasia, MDS/AML	-60% 5-year survival using a fully myeloablative regimen, with a matched or unmatched donor [ee, f.] -100% engraftment and 100% survival among 7 patients with marrow aplasia or MDS/AML who received a reduced intensity Flu-based conditioning regimen [99]. Overall survival 64.5% at 1.1 years [hh.]	- virilization - hyperactivity - renal toxicity - hypertension	Transplants with matched related or unrelated donor. Case report of 3 patients, only one followed >5 years.[ee.] Survival >60% if one adult patient who died 32 days after transplant is excluded.[f.] Six of seven patients <13, one patient was age 29.[99]
	Burroughs, Woolfrey and Shimamura, 2009[175] (Literature Review)		SDS patients with marrow aplasia, MDS/AML		-Grade III and Grade IV GVHD 24% and 29% [ii.] Transplant related Mortality 35.5%, with higher rates 67% vs. 20% for those receiving a TBI containing regimen[ii.] 19% graft failure (5 patients)	Burroughs, Woolfrey and Shimamura, 2009[175] (Literature Review)

Table 22. Benefits and harms after treatment for bone marrow failure syndromes (continued)

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Dyskeratosis Congenita	Myers and Davies, 2009[168] (Literature Review)	Androgen therapy with oxymetholone	First line therapy for those in bone marrow failure without a matched donor.	Androgen therapy may produce some improvement in hemopoietic function in some patients for a variable amount of time.	- increased incidences of chronic pulmonary and vascular complications, particularly pulmonary fibrosis. For patients with matched donor Mortality rates of - 50% using CY and ATG conditioning - 85% using CY alone.[jj] (ages 2-33, 1/3 of patients were over 18)	No quantitative data were found. The mechanism of action is also not well understood, but it appears to promote direct growth of hemopoietic progenitors.[kk] Long term toxicity and harm data is not available as followup has only reached two years on a few patients alive after transplant.
	De la Fuente and Dokal, 2007[176] (Literature Review)	Allogeneic HSCT	First line therapy for those with bone marrow failure who have a matched related donor.	- 86% survival among 7 patients transplanted using nonmyeloablative procedures [u -qq.]		These are a mixture of matched related and matched unrelated donors. Long term outcomes do not exist due to the fact that survival from HSCT has historically been low.
Dyskeratosis Congenita	MacMillan et al. 1998[177] (two case reports)	Allogeneic HSCT	First line therapy Matched Unrelated		-Patient 1 developed grade 1 GVHD, hemorrhagic cystitis, three episodes of E. coli sepsis and hypertension -Patient 2 developed grade 2 GVHD, hemorrhagic cystitis and hypertension.	

Table 22. Benefits and harms after treatment for bone marrow failure syndromes (continued)

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Congenital Amegakaryocytic Thrombocytopenia	Kudo et al. 2002[178] (Case Reports)	Allogeneic HSCT	First line therapy matched unrelated donor	-Patient 1 engrafted after 16 days and survived for one year post-transplant - Patient 2 engrafted on day 14 and was alive at the time of publication		
	MacMillan, et al. 1998[177] (Case Reports)			- Patient 1 was alive 16 months after a second transplant (failed engraftment on the first transplant) - Patient 2 failed two transplants (UCB, BM), then engrafted after the third transplant (UCB) and was alive 7 months after transplant		
	Steele et al. 2005[179] (Case Report)			Patient was alive 21 months after transplant - engraftment on day 10	-Developed grade 1 GVHD, and alopecia - had a severe allergic and febrile reaction to equine ATG so was switched to rabbit ATG.	
	Al-Ahmari et al. 2004[180] (Five Case Reports)		First line therapy matched related	80% of the patients were alive at a median followup of 30 months. - one patient failed to engraft and subsequently died after another failed transplant.	aGVHD ≥ grade 2 was observed in three patients - one patient has cGVHD but symptoms were under control. -80% developed transient hypertension - one patient developed veno-occlusive disease, which resolved with conservative measures	Three donors were siblings and two were parents.

Table 22. Benefits and harms after treatment for bone marrow failure syndromes (continued)

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Congenital Amegakary-ocytic Thrombocy-topenia	Yesilipek et al. 2000 [181] (Case Report)	Allogeneic HSCT	First line therapy matched related	- patient alive 20 months post transplant with PSC		
	Lackner et al. 2000 [182] (Case Series of eight)		First line therapy both matched related and unrelated	- 75% of patients were alive at a median of 17 months followup - 88% (7) of patients engrafted	- three patients developed aGVHD grade 2	Five bone marrow One cord blood Two peripheral stem cells
Diamond-Blackfan Anemia (DBA)	Lipton and Ellis, 2009 [183] (Literature Review)	Corticosteroids and/or red cell transfusion	First-line therapy corticosteroids	-~80% of patients respond. Of the 80%; 20% achieve Remission 40% require continued steroid therapy 40% remain transfusion and chelation dependent [v.]	-22% develop pathologic fractures and 12% cataracts with the use of corticosteroids. 5/36 deaths reported to the DBAR were due to complications of iron overload from red cell transfusion.	-17% are nonresponsive to corticosteroids.[v] Steroid use has been modified since these estimates.

Table 22. Benefits and harms after treatment for bone marrow failure syndromes (continued)

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Diamond-Blackfan Anemia (DBA)	Lipton and Ellis, 2009[183] (Literature Review)	Allogeneic HSCT	For patients who have become transfusion dependent or steroid intolerant	-overall actuarial survival at greater than 40 years is 75.1% (65.9-84.9) 100% for those in sustained remission 86.7%(73.0-100) for corticosteroid-maintained patients and 57.2 (39.7-74.7) for transfusion dependent patients. 72.7% 5-year survival for matched sibling donor and 19.1% for alternative donor's [ss.] 76% 3-year survival after sibling versus 39% with alternative donor transplantation.[tt.] 90% survival for children under 10 transplanted with matched sibling donor. Unpublished data from the DBAR shows actuarial survival, since 2000, for all DBA patients transplanted using alternative donors to be 80%. Patients were carefully selected when they lacked a suitable matched-related donor.	14 of 36 deaths reported to the DBAR were complications of HSCT	

Table 22. Benefits and harms after treatment for bone marrow failure syndromes (continued)

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Severe Congenital Neutropenia/Kostmann Syndrome	Elhasid and Rowe, 2010[184] (Literature Review)	Human Granulocyte colony-stimulating factor (G-CSF)	First-line therapy	>90% of patients respond to G-CSF with an increase in total neutrophil count and ANC as well as a decrease in the incidence of infection [uu,vv.]	Incidence of MDS/Acute leukemia increases from 2.9% to 8% per year by 12 years of G-CSF therapy [ww.] Osteoporosis may develop in as many of 50% of patients on G-CSF therapy [xx.] Vasculitis has been reported in 3.3% (9/270) SNC patients [xx.] Incidence of splenomegaly increased from baseline 20.6% prior to treatment to 38.9% during the first year and remained (33.8-47.6%) over the course of 10 years of treatment [xx.]	It is unclear if the increased incidence is indeed a medication side effect or the natural history of disease as until G-CSF therapy life expectancy was too short to observe these effects.
		Allogeneic HSCT	Refractory to G-CSF	88% engraftment (7/8) among those receiving HLA-identical sibling donor. Three with alternate donors 1/3 survived with excessive cGVHD [zz.]	Grade 0-1 acute GVHD, one patient who received UCB had fatal acute grade IV GVHD. Additionally one case of extensive chronic GVHD was observed. Severe infection occurred in 4 pts, 3 were fatal [yy.]	Eight of nine patients engrafted after HSCT with 61% Five year survival among nine patients (four refractory, one BMF, four MDS/acute leukemia). The three deaths occurred at a median time of 0.7 years after transplant [aaa.]
			Occurrence of MDS and acute leukemia	Three of 18 patients survived after HSCT.		

a Pongtanakul, et al. 2008[185] retrospective study of immunosuppressive therapy in AA, n=42;
b Scheinberg et al. 2008[186] retrospective study of immunosuppressive therapy in severe AA, n=77 ;
c Kojima et al. 2000[187] retrospective study comparing HSCT and immunosuppressive therapy in AA, n=100;
d Kojima et al., 2002[187] cohort study of immunosuppressive therapy and the subsequent development of MDS and AML, n=113 ;
e Frickhofen et al., 2003[188];
f Kosaka et al., 2008[189] cohort study of immunosuppressive therapy in severe and very severe AA, n=201;
g Locasciulli et al. 2007[190] retrospective study comparing immunosuppressive therapy and HSCT in two sequential cohorts, n=2479;
h Bacigalupo et al. 2000[191] outcomes for 1,759 patients treated with matched sibling transplant in Europe ;
i Locatelli et al. 2000[192] randomized trial on the effect of GVHD on survival after matched sibling HSCT, n=71;

j Farzin et al. 2007[193] cohort study of matched sibling donor HSCT in FA, n=18;

j Schrezenmeier et al., 2007[194] retrospective analysis comparing survival after PBSC and BM in 692 (134 PBSC, 558 BM) patients with SAA.;

k Deeg et al. 1996[195] analysis of secondary malignancies after myeloablative transplantation for SAA, n=700;

l Deeg et al. 1998[196] cohort study of long-term survivors of HSCT for AA, n=212;

m Bacigalupo et al. 2005[197] prospective cohort of 38 patients with SAA, reporting outcomes after HSCT;

n Deeg et al. 2006[198] nonrandomized trial of conditioning regimens for unrelated donor HSCT; n=87;

o Viollier et al. 2008[199] retrospective study of unrelated HSCT, n=498;

p Dufour and Svahn, 2008[174] review;

q Guardiola et al. 2000[200] retrospective analysis of 69 allogeneic stem-cell transplants for FA from EGBMT;

r de Medeiros et al. 2006[201] retrospective analysis of FA patients from a single institution who underwent alternative HSCT, n=47;

s Dufour and Svahn 2008[174] review;

u Zanis-Neto et al. 2005[202] nonrandomized trial of low-dose cyclophosphamide conditioning for matched related HSCT, n=30;

v Zanis-Neto et al. 2005[202] nonrandomized trial of low-dose cyclophosphamide conditioning for matched related HSCT, n=30;

w Wagner et al. 2007[203] retrospective study of alternative donor transplants in FA, n=98;

x Locatelli et al. 2007[204], cohort study of outcomes after HSCT, n=26 for those with an unrelated donor ;

y Yabe et al. 2006[205] cohort study of alternative donor HSCT, n=27;

z de Medeiros et al. 2006[201] retrospective analysis of FA patients from a single institution who underwent alternative HSCT, n=47;

aa Chaudhury et al. 2008[206] retrospective study of fludarabine-based conditioning regimen for HSCT in high-risk FA, n=18;

bb Gluckman et al. 2007[207] retrospective registry review of cord blood transplant in FA, n=93;

cc Gluckman et al. 2007[207], retrospective registry review of cord blood transplant in FA, n=93;

dd Wagner et al. 2007[203] retrospective study of alternative donor transplants for FA, n=98;

ee Vibhakar et al. 2005[208] case report of umbilical cord blood HSCT for SDS, n=3;

ff Donadieu et al. 2005[209] retrospective registry analysis of unrelated and identical sibling donor HSCT for SDS, n=10;

gg Bhatla et al. 2008[209, 210] series of 7 SDS patients with marrow aplasia or MDS/AML;

hh Cesaro et al. 2005[211] report on 26 patients with SDS;

ii Cesaro et al. 2005[211] report on 26 patients with SDS;

jj de la Fuente and Dokal 2007[176], review of 28 cases of HSCT for DC;

kk Beran et al. 1982[212] in vitro study of the effects of testosterones on human erythroid progenitor cells;

ll Ayas et al. 2005[213] case report;

mm Dror et al. 2003[214] case report;

nn Brazzola et al. 2005[215] case report;

oo Gungor et al. 2003[216] case report;

pp Cossu et al. 2002[217] case report;

qq Nobili et al. 2002[218] case report;

rr Vlachos et al. 2008[219] consensus document from the 2005 Diamond Blackfan Anemia International Consensus Conference;

ss Lipton et al. 2006[220] series of 36 patients from the DBA registry;

tt Roy et al. 2005[221] series of 61 patients with DBA who underwent HSCT;

uu Zeidler et al. 2000[222] management of Kostman syndrome with G-CSF;

vv Rosenberg et al. 2006[223] review of harms associated with long-term G-CSF treatment in 29 SCN patients;

ww Rosenberg et al. 2006[223] harms associated with long term G-CSF treatment in 29 SCN patients;

xx Yakisan et al. 1997[224] cohort of 30 patients with SCN;

yy Ferry et al. 2005[173] HSCT among 9 patients in the French SCN registry;

zz Zeidler et al. 2000[225] HSCT among 11 patients without malignant transformation;

aaa Ferry et al. 2005[173] HSCT among 9 patients in the French SCN registry

Inherited/Congenital Bone Marrow Failure Syndromes

Fanconi Anemia

Background
First described in 1927,[226, 227] Fanconi anemia is an inherited chromosomal instability that affects all of the bone marrow elements. It is associated with various physical malformations, including pigmentary changes of the skin, and predisposes to malignancy. Fanconi anemia is the most common inherited bone marrow failure syndrome, with thirteen identified subtypes.[172] With the exception of subtype B, all follow an autosomal recessive pattern of inheritance.[228, 229] Among patients with Fanconi anemia, bone marrow failure, typically occurs between 5 and 10 years of age with a cumulative risk of 50 to 90 percent by age 40. Patients are highly susceptible to cancer, with a cumulative incidence of hematologic malignancy of 22 to 33 percent by age 40.[223, 230] While malformations are common, approximately 25 to 40 percent of affected individuals have no visible anomalies.[172]

Evidence Base
The evidence compiled for this review includes two literature reviews.[168, 174] One clinical practice guideline[231] but no health technology assessments for the treatment of childhood Fanconi anemia with HSCT were identified in the literature search. The evidence base on the use of HSCT for treatment of Fanconi anemia is summarized in Table 22.

The literature review by Dufour and Svahn[174] reports on androgen therapy, the frontline treatment choice for children without a matched sibling donor. According to the review, approximately 75 percent of such patients respond to androgen therapy within 2-12 months. Reported harms associated with androgen therapy include, but are not limited to, virilization, hyperactivity, renal toxicity, and possible adverse effects on subsequent HSCT. Myers and Davies[168] report survival after HSCT using matched sibling donor of about 90 percent, but with a transplant comes the risk of peritransplant mortality of 10 to 15 percent and a risk of chronic graft-versus-host disease from 12 up to 28.5 percent, based on the conditioning regimen.

Guidelines
Guidelines for the treatment of Fanconi anemia with HSCT were developed at a conference held April 10-11, 2008 in Chicago, Illinois and are published by the Fanconi Anemia Research Fund.[231] HSCT is currently the best therapy available to cure the patient of marrow aplasia, to prevent progression to myelodysplastic syndrome or AML, or to cure existing MDS or AML.

Among patients with a matched sibling donor, treatment with HSCT may proceed if there is:
- Platelet count of less than 50,000
- Hemoglobin less than 8 gm/dL
- Transfusion dependence
- Absolute neutrophil count less than 1,000
- Absolute neutrophil count greater than 1,000 with frequent infection

Among patients with no matched related donor and adequate organ function and controlled infection treatment with HSCT may be considered if:
- Persistent and severe cytopenia develops
  - Hemoglobin less than 8 g/dL

o Absolute neutrophil count less than 500/mm^3
o And/or platelets less than 20,000/mm^3
- There is evidence of myelodysplastic syndrome or leukemia

Other indications for transplant:

Absolute indication
- For patients with high-risk myelodysplastic syndrome or AML, HSCT is recommended

Relative indication
- For patients with moderate isolated cytopenias or moderate aplastic anemia with evidence toward progression towards transfusion dependence
- For low-risk myelodysplastic syndrome

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of Fanconi anemia with HSCT. The vast majority of patients with Fanconi anemia will progress to aplastic anemia or myelodysplastic syndrome/AML without transplant. HSCT using matched sibling donor have survival rates of about 90 percent. In general, patients are transplanted prior to the development of myelodysplastic syndrome/AML, as the outcomes are better for patients with aplastic anemia. Age also is considered, as younger age is associated with better outcomes. Androgen therapy has a long history of use in patients with Fanconi anemia; however, due to adverse effects to liver function, other significant adverse effects, and its effect on later adverse effects after transplant, it is generally recommended this therapy be reserved for patients with no matched sibling donor, but not as a definitive long-term treatment.

Schwachman Diamond Syndrome

Background

Schwachman Diamond syndrome is a rare disorder characterized by pancreatic insufficiency, skeletal abnormalities, and bone marrow failure. The disease has an autosomal recessive pattern of inheritance, with almost all affected persons having a mutation in the SBDS gene on chromosome 7q11.23[2] Approximately 200 cases have been reported, with very few patients being treated with allogeneic HSCT.[170, 233] These patients are at higher risk than the general population for myelodysplastic syndrome and leukemia, specifically AML.[172] Approximately 20 percent will develop aplastic anemia, 20 to 33 percent develop myelodysplastic syndrome or cytogenetic abnormalities, and 12 to 25 percent will eventually develop acute leukemia.[209, 234-236] Nonhematologic malignancies have not been associated with Schwachman Diamond syndrome.[171] Median survival in Schwachman Diamond syndrome is more than 35 years, but less for those developing aplastic anemia or leukemia. Clinical management consists of symptom-specific treatments, close monitoring of peripheral blood counts, and annual marrow evaluation allowing for treatment prior to clinical complications. Infections and hemorrhage associated with hematologic abnormalities are the primary causes of Schwachman Diamond syndrome-associated death after infancy.[175] HSCT may provide a cure[233] but significant cardiac and other organ toxicities have been described.[175] Most patients do not require transplantation. Those who develop marrow aplasia or MDS/AML are candidates for HSCT.

Evidence Base

The evidence compiled for this review includes two literature reviews.[168, 174] No health technology assessments or clinical practice guidelines for the treatment of Schwachman

Diamond syndrome with HSCT were identified in the literature search. The evidence base on the use of HSCT for treatment of Schwachman Diamond is summarized in Table 22.

In the review by Burroughs and colleagues,[175] performance of HSCT is reported to be associated with improved outcomes when performed before the development of overt leukemia. Significant organ toxicities, specifically cardiac, have been reported and are thought to occur by the aggravation of underlying organ dysfunction caused by conditioning regimens. Fludarabine-based regimens appear to reduce the toxicity for these patients, although reported numbers are small.[168] Survival among 7 patients transplanted with myelodysplastic syndrome and/or AML who received fludarabine-based conditioning was 100 percent, compared to 60 percent 5-year survival (n=10) using a fully myeloablative regimen, with matched or unmatched donor.[168]

Guidelines

No guidelines for the treatment of Schwachman-Diamond syndrome were identified in the search.

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of Schwachman-Diamond with HSCT. While supportive measures such as transfusions, pancreatic enzymes, antibiotics are used, the only curative therapy for marrow failure, myelodysplastic syndrome, or leukemia is HSCT. Performance of HSCT is associated with better outcomes when performed prior to the development of overt leukemia. Aggravation of underlying organ dysfunction can occur with various conditioning regimens. Children with Schwachman-Diamond undergoing HSCT may receive a preparative regimen not including high-dose total body irradiation or cyclophosphamide.

Dyskeratosis Congenita

Background

Dyskeratosis congenita is a rare disorder related to a defect in telomere maintenance[237] that is characterized by abnormal skin pigmentation, nail dystrophy, and mucosal leucoplakia.[238] Ninety percent of reported cases are male with observed linkage to Xq28. Autosomal recessive and dominant inheritance have been noted.[239] While precise estimates of incidence are unknown, dyskeratosis congenita has been recognized across racial groups, with an estimated prevalence of 1 in 1,000,000 persons. This disease presents with both clinical and genetic heterogeneity, even within families, making diagnosis and treatment challenging. The dyskeratosis congenita registry includes approximately 350 cases to date,[171] and through 2008, approximately 552 cases have been reported in the literature.[240] Patients exhibit a predisposition to bone marrow failure, malignancy and pulmonary dysfunction. Eighty to 90 percent of patients develop bone marrow failure by age 30.[171] Bone marrow failure accounts for the majority of deaths (approximately 60 to 70 percent), while pulmonary complications (approximately 10 to 15 percent) and malignancies (approximately 10 percent) account for the rest.[241] Commonly, bone marrow failure and/or other complications present prior to diagnosis.[242]

Dyskeratosis congenita has highlighted the critical role of telomerase in human growth and development, the major complication of which is bone marrow failure. The only curative treatment for severe bone marrow failure is allogeneic HSCT; however, in patients with dyskeratosis congenita, this is not a cure for the underlying disease, as HSCT does not address the telomerase defect.[176] The median survival for patients with dyskeratosis congenita is 44 years

of age. For patients with severe subsets of disease, such as Hoyeraal-Hreidarsson syndrome (n=30 cases ever described) and Revesz syndrome (n=20 reported cases), median survival is dramatically reduced to 5 years and approximately 11 years, respectively. There are no cases of either of these severe disease subtypes in patients older than 20 years.[243]

Evidence Base

The evidence compiled for this review includes two literature reviews.[168, 176] No health technology assessments or clinical practice guidelines for the treatment of dyskeratosis congenita with HSCT were identified in the literature search. One clinical practice guideline[243] follows the model of Fanconi anemia to determine treatment for bone marrow failure from dyskeratosis congenita. The evidence base on the use of HSCT for treatment of dyskeratosis congenita is summarized in Table 22.

Survival estimates when using nonmyeloablative regimens are improved over the 50 to 85 percent mortality seen with prior regimens.[168] However, as stated previously, HSCT is not a cure for this disorder as it does not remedy the underlying telomerase defect. Patients who survive transplant are at increased risk of pulmonary and vascular complications, although, due to the small number of patients, complication rates are not available.

Guidelines

No guidelines specific for the treatment of dyskeratosis congenita were identified in the search. However, in a recent publication by Savage and Alter,[243] following the model of Fanconi anemia consensus guidelines, treatment for bone marrow failure is recommended if:

- Hemoglobin is consistently less than 8 g/dL, platelets less than 30,000/mm^3, and neutrophils less than 1000/mm^3.
- The first consideration for treatment for hematologic problems such as bone marrow failure may be HSCT, if there is a matched related donor.
- HSCT from an unrelated donor can be considered, although a trial of androgen therapy may be chosen.

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of dyskeratosis congenita with HSCT. For patients who have developed severe bone marrow failure with hemoglobin consistently less than 8 g/dL, platelets less than 30,000/mm^3, and neutrophils less than 1000/mm^3 and they have a matched related donor, HSCT is first-line treatment. HSCT is not a cure for dyskeratosis congenita as it does not address the underlying telomerase defect. Patients who survive transplant are at increased risk of pulmonary and vascular complications although due to the small numbers of patients, complication rates are not available.

Congenital Amegakaryocytic Thrombocytopenia

Background

Congenital amegakaryocytic thrombocytopenia is an extremely rare disorder characterized by isolated thrombocytopenia, reduction/absence of megakaryocytes in the bone marrow with in most cases no somatic abnormalities.[171] It follows an autosomal recessive inheritance pattern and is caused by mutations in the thrombopoietin receptor MPL.[244] While disease incidence is unknown, severe thrombocytopenia is observed in 0.12 to 0.24 percent of all newborns, and congenital amegakaryocytic thrombocytopenia represents a very small percentage of those. The

diagnosis is made after excluding other acquired and inherited forms of thrombocytopenia.[245] Affected individuals are identified shortly after birth.[170] In the absence of HSCT, patients will develop severe aplastic anemia, leading to death. Median age of progression to severe aplastic anemia is 3.7 years.[246]

Evidence Base

The evidence compiled for this review includes one case report[181] and five case series.[177-180, 182] No health technology assessments or clinical practice guidelines for the treatment of congenital amegakaryocytic thrombocytopenia with HSCT were identified in the literature search.

Data from the case series are consistent in reporting high levels of engraftment and short-term survival data. The largest case series of eight patients reported 75 percent survival at a median followup of 17 months.[182] In that same series, three patients developed grade 2 acute graft-versus-host disease.

Guidelines

No guidelines for the treatment of congenital amegakaryocytic thrombocytopenia were identified in the search.

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of congenital amegakaryocytic thrombocytopenia with HSCT. Clinical management utilizes platelet transfusions to prevent a patient from bleeding. HSCT from matched related donors have been encouraging but due to the lack of healthy matched related donors for these patients, often matched unrelated donors are needed, which carry a higher risk of graft failure and transplant-related toxicity. Without HSCT, these children will die at a median age of 3 years.

Diamond Blackfan Anemia

Background

Diamond Blackfan anemia, or congenital pure red cell aplasia, was reported in four children in 1938 by Diamond. It usually presents in infancy, although a subset of cases may present in adulthood, with symptoms of anemia such as pallor or failure to thrive. Most familial cases display an autosomal dominant pattern of inheritance.[171] Based on an analysis by the Diamond Blackfan anemia registry of North America, the annual incidence is approximately 5 per million live births with 93 percent of patients presenting in the first year.[220] Rates of cancer among patients with Diamond Blackfan are lower than rates among other hereditary bone marrow failure syndromes; however, with 4 percent of children with Diamond Blackfan diagnosed with cancer by age 15, the rate is much higher than the general population.[219]

Evidence Base

The evidence compiled for this review includes one literature review.[183] One clinical practice guideline[219], but no health technology assessments for the treatment of Diamond Blackfan anemia with HSCT were identified in the literature search. The evidence base on the use of HSCT for treatment of Diamond Blackfan is summarized in Table 22.

Data included in the literature review report that 80 percent of patients respond to first-line corticosteroids and that of those, 20 percent achieve remission. Twenty-two percent of patients

develop pathologic fractures and 12 percent develop cataracts as a result of corticosteroid treatment.[183] Survival after HSCT has been reported at longer than 40 years, 100 percent for those in remission prior to transplant, 87 percent for corticosteroid-maintained patients, and 57 percent for transfusion-dependent patients.[183]

Guidelines

Guidelines for the treatment of DBA with HSCT were published by Vlachos et al.[219] Treatment with HSCT is recommended in patients with Diamond Blackfan whether corticosteroid responsive or transfusion dependent; patients typically are younger than 10 years of age, preferably between 2 and 5 years of age, if an HLA-matched donor is available.

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of DBA when an HLA-matched donor is available. HSCT is curative in DBA and deaths after HSCT appear to be attributed to toxicities rather than graft failure. Data on the effects of various conditioning regimens is too limited to draw conclusions.

Severe Congenital Neutropenia/Kostmann Syndrome

Background

First described in 1956 by Kostmann, severe congenital neutropenia is a rare genetic condition. Children with the disorder typically present with severe neutropenia, fever, and recurrent infections of the upper respiratory tract, lungs, and skin. Among the nine inbred families in which severe congenital neutropenia was first noted, the inheritance pattern is autosomal recessive;[247] however, most other documented cases follow an autosomal dominant or sporadic pattern of inheritance.[248] The incidence is approximately 3 to 4 per million births, with the majority of patients identified in the first three months of life. A subset of patients also has a mutation in the cytoplasmic component of the granulocyte colony-stimulating factor (G-CSF) receptor gene. These patients are at increased risk of developing acute myeloid leukemia.[249]

Evidence Base

The evidence compiled for this review includes one literature review.[184] No health technology assessments for the treatment of severe congenital neutropenia with HSCT were identified in the literature search. The evidence base on the use of HSCT for treatment of severe congenital neutropenia is summarized in Table 22.

Ninety percent of patients are reported to respond after first-line treatment with G-CSF.[184] However, long term treatment with G-CSF may lead to the development of myelodysplastic syndrome/acute leukemia, or osteoporosis. For patients refractory to G-CSF, Elhasid and Rowe[184] reported 61 percent survival at 5 years, and for those who had developed myelodysplastic syndrome/acute leukemia, three of 18 survived.

Guidelines

Guidelines for treatment of severe congenital neutropenia with HSCT were published by Elhasid and Rowe.[184] These recommendations are broken down into two groups, absolute and probable indications.

Absolute indications:
- Refractory to G-CSF therapy

- Occurrence of MDS and acute leukemia

Probable indications:

- Gly185Arg missense mutation
- Wild-type ELA2 not responding to standard doses of G-CSF

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of severe congenital neutropenia with HSCT. Development of MDS and acute leukemia are absolute indications for HSCT as this would be the only curative option. Patients with a matched donor are followed closely as outcomes are better if the transplant is completed prior to the development of MDS/acute leukemia. It is important to note that current recommendations are based on very small numbers of patients due to the rarity of this condition.

Primary Immunodeficiencies

Background

The primary immunodeficiencies are a genetically heterogeneous group of diseases that affect distinct components of the immune system (Table 23). More than 120 gene defects have been described, causing more than 150 disease phenotypes.[250] The most severe defects (collectively known as "severe combined immunodeficiency" or SCID) cause an absence or dysfunction of T lymphocytes, and sometimes B lymphocytes and natural killer cells.[250]

Without treatment, patients with severe combined immunodeficiency usually die by 12 to 18 months of age. With supportive care, including prophylactic medication, the lifespan of these patients can be prolonged, but long-term outlook is still poor, with many dying from infectious or inflammatory complications or malignancy by early adulthood.[250]

Evidence Base

The evidence compiled for this review (Table 24) includes three literature reviews (Table 25).[250-252] No health technology assessments or clinical practice guidelines for the treatment of primary immunodeficiencies with HSCT were identified in the literature search.

HSCT using HLA-identical sibling donors can provide correction of underlying primary immunodeficiencies such as SCID, Wiskott-Aldrich syndrome, and other prematurely lethal X-linked immunodeficiencies in approximately 90 percent of cases where a donor is available.[251] According to a European series of 475 patients collected between 1968 and 1999, 3-year survival rates for SCID were 81 percent with a matched sibling donor, 50 percent with a haploidentical donor, and 70 percent with a transplant from an unrelated donor.[253] Since 2000, overall survival for patients with SCID who have undergone HSCT is 71 percent.[250] For non-SCID patients, 3 year survival rates were 71 percent, 42 percent, and 59 percent for genotypically HLA-matched, phenotypically HLA-matched and HLA-mismatched related, and HLA-mismatched unrelated, respectively.[253]

For Wiskott-Aldrich syndrome, which has a median survival of 15 years, an analysis of 170 patients transplanted between 1968 and 1996 demonstrated the impact of donor type on outcomes.[254] Fifty-five transplants were from HLA-identical sibling donors, with a 5-year probability of survival of 87 percent (95 percent CI: 74–93 percent); 48 were from other relatives, with a 5-year probability of survival of 52 percent (37 to 65 percent); and 67 were from unrelated donors with a 5-year probability of survival of 71 percent (58 to 80 percent; p=0.0006).

In patients with genetic immune/inflammatory disorders such as hemophagocytic lymphohistiocytosis the current results with allogeneic HSCT are 60 to 70 percent 5-year disease-free survival. Survival rates for patients with other immunodeficiencies are similar at 74 percent, with even better results (90 percent) when well-matched donors are used for defined conditions such as chronic granulomatous disease. Survival after HSCT for primary immunodeficiencies is good, and data show that patients surviving 12-24 months post-transplant generally have good long-term outcomes since relapse does not occur, as it may with hematologic malignancy.[250]

Table 23. Primary immunodeficiencies successfully treated with HSCT

Disease
Lymphocyte immunodeficiencies
Adenosine deaminase deficiency
Artemis deficiency
Calcium channel deficiency
CD 40 ligand deficiency
Cernunnos-XLF immunodeficiency
CHARGE syndrome with immune deficiency
Common gamma chain deficiency
Deficiencies in CD 45, CD3, CD8
DiGeorge syndrome
DNA ligase IV
Interleukin-7 receptor alpha deficiency
Janus-associated kinase 3 (JAK3) deficiency
Major histocompatibility class II deficiency
Omenn syndrome
Purine nucleoside phosphorylase deficiency
Recombinase-activating gene (RAG) 1/2 deficiency
Reticular dysgenesis
Winged helix deficiency
Wiskott-Aldrich syndrome
X-linked lymphoproliferative disease
Zeta-chain-associated protein-70 (ZAP-70) deficiency
Phagocytic deficiencies
Chediak-Higashi syndrome
Chronic granulomatous disease
Griscelli syndrome, type 2
Interferon-gamma receptor deficiencies
Leukocyte adhesion deficiency
Severe congenital neutropenias*
Shwachman-Diamond syndrome*
Other immunodeficiencies
Autoimmune lymphoproliferative syndrome
Cartilage hair hypoplasia
CD25 deficiency
Familial hemophagocytic lymphohistiocytosis
Hyper IgD and IgE syndromes
ICF syndrome
IPEX syndrome
NEMO deficiency
NF-κB inhibitor, alpha (IκB-alpha) deficiency
Nijmegen breakage syndrome

* While considered primary immunodeficiencies these conditions are described in the section dealing with bone marrow failure syndromes.

Table 24. Evidence base for HSCT in primary immunodeficiencies

Disease	Year of First HSCT Performed	No. of Transplants to Date	Existing Clinical Data	Registries
Primary Immunodeficiencies	1968	>2000	Reviews, Case series, Case reports	The Stem Cell Transplantation for Immunodeficiencies registry in France contains outcome data from many European centers. European Blood and Marrow Transplant network and the Center for International Blood and Marrow Transplantation both have registries covering people with Primary Immunodeficiencies. Specific registries exist for diseases such as; X-linked lymphoproliferative disease, chronic granulomatous disease, CD40 ligand deficiency, Wiskott-Aldrich syndrome.

Guidelines

No guidelines for the treatment of primary immunodeficiencies were identified in the search.

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of SCID and other primary immunodeficiencies, including Wiskott-Aldrich syndrome and congenital defects of neutrophil function.[257]

While primary immunodeficiency diseases are heterogeneous, it is universally accepted that HSCT offers the only chance of cure. The best outcomes have been reported to occur when children are transplanted in infancy, prior to the development of organ damage.[258, 259] Conventional therapies including treatment with IVIG may decrease morbidity and mortality but do not address the underlying problem or alter the long-term outcome.[250] Gene therapy has been performed for over a decade now for ADA deficiency, X-linked SCID and WAS. It is, however, considered experimental.[26]

Table 25. Benefits and harms after treatment for primary immunodeficiency

Disease	Source	Treatment	Indications	Benefits	Harms	Comment
Primary Immunodeficiency	Orange et al. 2006[252] (Literature review)	IVIG (Intravenous immunoglobulin) SCIG (Subcutaneous immunoglobulin)	Primary treatment for those producing no antibodies, limited antibodies, and those with impaired specific antibody production	Reduction in both acute and chronic infections.	Up to 44% of patients may experience adverse reactions not related to rate of infusion[¥]	Additional harms are associated with the risks of placing a indwelling venous catheter for IVIG or the additional needed sticks for SCIG [¥] from a 2002 Immune Deficiency patient survey.
	Ginnery and Cant, 2008[250] (Literature review)	HSCT	Primary treatment for patients with Severe combined immune-deficiency and second line treatment for other PID	5 year survival 90%*, after transplant from matched sibling donor and 69%* using matched unrelated donor. Other series report overall survival estimates ranging from 92-100% for related matched donors and 78-80% for matched unrelated donors [alb] and 52% for mismatched unrelated donors. [a]	Acute GVHD developed in about 31-36% of children transplanted with related identical marrow, 50-73% in those receiving matched unrelated marrow [alb], and 45% in those transplanted with mismatched related donor marrow. [a]	* Survival rates were communicated as personal communication from P Landaus to the review papers authors.
	Filipovich, 2008[251] (Literature review)		Primary treatment for patients with Severe combined immune-deficiency and second line therapy for other PID	3 year survival of approximately 80%, 50% and 70% from matched sibling, haploidentical and unrelated donors.[c]		

[a]Grunebaum et al. 2006[255] retrospective cohort study of 94 SCID patients treated with HSCT
[b]Buckley et al. 1999[256] report on 89 infants treated with HSCT for SCID
[c]Antoine et al. 2003[253] registry report of 475 SCID and 512 non-SCID transplants

Inherited Metabolic Diseases: Mucopolysaccharidoses

Mucopolysaccharidoses (MPS) are a group of disorders caused by single-gene defects leading to a deficiency in one of the 11 lysosomal enzymes needed to metabolize glycosaminoglycans (Table 26). As glycosaminoglycans accumulate in the cells, blood, and connective tissues, progressive damage to the skeletal structure and multiple organ systems occurs.[261] Mucopolysaccharidoses are autosomal recessive disorders, with the exception of Hunter disease (MPS II), which is X-linked recessive. The severity of symptoms varies by subtype as well as within each subtype. The overall frequency of these disorders is estimated to be 3.5-4.5 per 100,000.[262-264] MPS I, MPS VI, and MPS VII will be discussed in this section (Table 27) and MPS II, MPS III, and MPS IV will be discussed in the context of the Systematic Review.

Hurler Syndrome (MPS I)

Background

Hurler Syndrome is caused by a deficiency of the lysosomal enzyme α-L-iduronidase, which is needed to break down heparan sulfate and dermatan sulfate. The disease is panethnic and has an estimated incidence of 1 per 100,000 live births. The disease is categorized into three types. The most severe form is Hurler (MPS IH), with two attenuated forms, Hurler-Scheie (MPS IH/S) and Scheie (MPS IS). Approximately 50-80 percent of cases are the severe form. In MPS IH, developmental delays are evident by 12 months of age.

Table 26. Evidence base for HSCT in MPS I, MPS VI and MPS VII

Disease	Treatment	Year of First Treatment	No. Patients Receiving Treatment to Date	Type of Research Available	Registries
MPS I	HSCT	1980	>500	Case reports, case series, retrospective studies	Established in 2003: Genzyme Corporation and BioMarin Pharmaceutical initiated international observational database with treatment and outcome information; aggregate data available for research queries. Over 700 patients in registry.
MPS VI	HSCT	1982	>12	Case reports, case series	BioMarin Pharmaceutical and the Women's and Children's Hospital in Adelaide, Australia have coordinated a registry; aggregate data available for research.
MPS VII	HSCT	1994	2	Case reports	None

Table 27. Treatment benefits and harms for Hurler Syndrome (MPS I), Maroteaux-Lamy Syndrome (MPS VI), and Sly Syndrome (MPS VII)

Disease	Treatment	Source and Evidence Type	Indications	Clinical Benefits	Clinical Harms
MPS I	ERT	Brady and Schiffman 2004,[265] literature review Wraith 2005,[266] literature review Tolar and Orchard 2008,[267] literature review	- all attenuated cases - severe cases, dx ≤2 years, DQ* <70	- enzyme activity detected within 6-8 wks, with 50-80% reduction in excess glucosaminoglycans (GAG) secretion in urine; 63% mean reduction maintained following 1 year of ERT[a] - liver volume decreased by 19% in ERT grp, increased by 1% in placebo grp[b] - 1 year ERT: mean range of shoulder flexion increased 26-28 degrees, knee extension restriction decreased by 3-3.2 degrees, but skeletal abnormalities persist[a,c] - 61% decrease in number of episodes of apnea and hypopnea after 1 year ERT[a] - left ventricular hypertrophy resolves, but mitral and aortic valves remain thickened[c] - 1 year on ERT: 25% mean reduction in liver size, 20% mean reduction in spleen size[a]; 6 years on ERT: liver volume in normal range for 100% pts, spleen volume near normal range in 50% pts[c] - further coarsening of facial features did not progress as expected after 6 years of ERT in 100% of pts[c] - worsening of pre-existing neurological symptoms can be expected[c] - quality of life improvements include: increased energy and endurance, independence in normal daily activities, socializing, setting new goals for future such as college and marriage[c]	- infusion-related reactions such as flushing, fever, headache, or rash experienced by 32% in ERT grp and 48% in placebo grp[b] - IgG antibodies to enzyme develop in 100% of pts, but does not affect clinical efficacy of treatment[b]

Table 27. Treatment benefits and harms for Hurler Syndrome (MPS I), Maroteaux-Lamy Syndrome (MPS VI), and Sly Syndrome (MPS VII) (continued)

Disease	Treatment	Source and Evidence Type	Indications	Clinical Benefits	Clinical Harms
MPS I	Allogeneic HSCT	Prasad and Kurtzberg 2010,[268] literature review Boelens 2006,[269] literature review Peters 2004,[270] literature review Aldenhoven et al. 2008,[271] literature review	- severe cases with stable cardiopulmonary function, dx $\leq$2 yrs, DQ $\geq$70 - consider-ed in rare attenuated cases, dx >2 yrs, DQ $\geq$70	- 67% reach normal enzyme activity level[d] - improves hearing in 30-40%, but does not reverse profound conductive and sensorineural abnormalities[e] - improves joint mobility, but skeletal abnormalities persist in over 90% due to poor enzyme penetration of chondrocytes and failure to replace osteocytes[f,g] - improves respiratory function relating to sleep apnea and persistent rhinorrhea within 3-6 months of transplant[h] - improves myocardial muscle function and coronary artery patency within 1 year of transplant, but cardiac valvular deformities persist[i] - resolves hepatosplenomegaly within 3 months of transplant[h] - if transplant at $\leq$2 years, normal or near normal intellectual development reported in 64% of 12 cases; if transplant at >2 years, normal or near normal intellectual development in 25% of 12 cases[j] - life expectancy prolonged[e,j]	- acute graft vs. host disease 32% with HLA genotypically identical sibling donors and 55% for HLA haploidentical related donors[j] - chronic graft vs. host disease 0% for HLA genotypically identical sibling donors and 24% for HLA haploidentical related donors[j] - 8.3% pulmonary complications (hemorrhages and infections)[d] - 10% viral, bacterial, and fungal infections[d] - 15%[d]-42%[q] treatment-related mortality reported (42% from transplants performed from 1980-1995; 15% from transplants performed 1994-2004 – improvements in donor matching and improved supportive care following transplant may be responsible for decrease in treatment-related mortality rate)

Table 27. Treatment benefits and harms for Hurler Syndrome (MPS I), Maroteaux-Lamy Syndrome (MPS VI), and Sly Syndrome (MPS VII) (continued)

Disease	Treatment	Source and Evidence Type	Indications	Clinical Benefits	Clinical Harms
MPS VI	ERT	Brady and Schiffman 2004,[265] literature review Harmatz et al. 2008[272] (Phase III trial, N=56 age range 5-29)	- all cases as first-line therapy	- statistically significant difference in GAG secretion by week 24 between ERT group and placebo group in phase 3 trial (p<0.001) providing evidence of enzyme activity among ERT group[k] - 5 of 9 experience improved joint mobility[l] - hepatosplenomegaly improved in 5 of 9, worsened in 2 of 9, and remained stable in 2 of 9[l] - sustained statistically significant improvement through phase 2 and phase 3 trials in 3-minute stair climb and 6- or 12-minute walk tests[m]	- >50% experienced one or more infusion-related reactions such as flushing, fever, headache, or rash[m] - one report of respiratory difficulty and anaphylaxis resulting in emergency tracheostomy (possibly exacerbated by underlying disease)[r] - if central venous access port required for infusions, risk of infection and possibly endocarditis[r]
	Allogeneic HSCT	Peters 2004,[270] literature review	- if ERT fails	- enzyme activity within normal range in 100% of pts[n,o] - hepatosplenomegaly decreased[n] - facial features became less coarse in 4 of 4 pts[o] - dysphonia and hoarseness resolves in 2 of 2 pts[o] - cardiac evaluation normal, but valve disease persists[n,o] - sleep apnea resolved[n] - significant improvement in posture, but dystosis multiplex persists[o] - life expectancy prolonged[n,o]	- acute graft vs. host disease in 3 of 4 pts[o]

*DQ=developmental quotient
[a]Kakkis et al. 2001,[273] 10 MPS I pts on ERT weekly for one year
[b]Wraith et al. 2004,[274] RCT of MPS I pts, 22 receiving ERT, 23 receiving placebo
[c]Sifuentes et al. 2007,[275] 6-yr followup study of 5 pts in phase I/II trial for MPS I ERT
[d]Boelens et al. 2007,[276] retrospective study of 146 MPS I pts in the European Blood and Marrow Transplantation registry
[e]Krivit et al. 1995,[277] audiological evaluation on 12 MPS I pts following HSCT
[f]Field et al. 1994,[278] followup of skeletal development in 11 MPS I pts up to 13 yrs post-HSCT
[g]Weisstein et al. 2004,[279] musculoskeletal followup on 7 MPS I up to 7.6 yrs pts post-HSCT
[h]Souillet et al. 2003,[280] report on 27 MPS I pts following HSCT
[i]Braunlin et al. 2003,[281] report on cardiac ultrasound findings in 10 MPS I pts following HSCT

[j]Peters et al. 1998,[282] 46 MPS I pts undergoing HSCT: 28 HLA-genotypically identical sibling donors, 26 HLA-haploidentical related donors

[k]Harmatz et al. 2006,[283] Phase III trial of 39 MPS VI pts, 19 ERT and 20 placebo, treated for 48 wks

[l]Scarpa et al. 2009,[284] followup from 6 months to 4.5 yrs of 9 MPS VI pts receiving ERT

[m]Harmatz et al. 2008,[272] followup report of 56 MPS VI pts receiving ERT, from 3 clinical studies

[n]Krivit et al. 1984,[285] case report, MPS VI following HSCT

[o]Herskhovitz et al. 1999,[286] 1-9 yr followup of MPS VI pts after HSCT

[p]Yamada et al. 1998,[287] case report MPS VII pt after HSCT

[q]Vellodi et al. 1997,[288] 38 MPS I pts undergoing HSCT

[r]Giugliani et al. 2007,[289] ERT guidelines for MPS VI

Symptoms include respiratory insufficiency, hearing loss, joint movement restriction, distinct facial features such as a flat face and bulging forehead, and enlargement of the heart, spleen, and liver. Life expectancy is less than 10 years, with cause of death most commonly due to obstructive airway disease, upper respiratory infections, or cardiac complications. In MPS IH/S, symptoms begin between the ages of 3 and 8, and include moderate mental retardation, growth deficiencies, deafness, coarse facial features, clouded corneas, umbilical hernia, and heart disease. Life expectancy is the late teen years to early twenties. Children with MPS IS, the mildest form, have normal intelligence or mild learning disabilities and psychiatric problems. Other symptoms include nerve compression, aortic valve disease, sleep apnea, and impaired vision due to glaucoma, retinal degeneration, or clouded corneas. Affected individuals can live into adulthood, although with significant morbidity.[263, 264]

Clinical management requires coordination of a multidisciplinary team, to assess neurologic, ophthalmologic, auditory, cardiac, respiratory, gastrointestinal, and musculoskeletal symptoms at baseline prior to treatment designation, and subsequently at specified intervals following treatment.[270, 290] Severity of neurologic symptoms and age at diagnosis are key elements in determining the treatment course for MPS I. Enzyme replacement therapy is available for MPS I, but the manufactured enzyme cannot cross the blood-brain barrier, so it cannot improve cognitive function or central nervous system function.

Evidence Base

The evidence compiled for this review includes seven literature reviews.[265-271] Two clinical practice guidelines[290, 291] but no health technology assessments for the treatment of MPS I with HSCT were identified in the literature search.

Treatment with enzyme replacement has been shown to be effective in increasing the enzyme activity level, reducing hepatosplenomegaly, and improving joint mobility and respiratory symptoms.[273-275] Increased energy and endurance and improvement in the ability to perform normal activities of daily living have been reported following enzyme replacement.[275] Because enzyme therapy does not cross the blood-brain barrier, neurologic symptoms persist.[275] Like enzyme replacement, HSCT has also been shown to increase enzyme activity, reduce hepatosplenomegaly, improve joint mobility and improve respiratory symptoms.[279, 280] The most beneficial outcome of HSCT is the potential to preserve intellectual development. Normal or near normal intellectual development has been reported if HSCT is performed prior to the onset of neurological symptoms.[282] Disease management for MPS I also consists of a combination of palliative and symptom-specific treatments. Adaptive or supportive devices, physical and occupational therapy, symptom-based medications, and surgery may be necessary.

Guidelines

Guidelines for the treatment of MPS I with HSCT were published by The National Marrow Donor Program, International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group in a collaborative 2003 publication of practice guidelines regarding HSCT for inherited metabolic diseases.[291] A set of guidelines specific to MPS I was published in 2009 by a 12-member International Consensus Panel on the Management and Treatment of Mucopolysaccharidosis I.[290]

Enzyme-replacement therapy is recommended for all MPS I attenuated cases as first-line therapy. Enzyme replacement is also recommended for severe MPS I cases if the diagnosis was made at 2 years of age or younger and the developmental quotient (DQ) is less than 70.

HSCT is recommended for severe cases with stable cardiopulmonary function, if the disease is diagnosed at 2 years of age or younger and the DQ is 70 or greater. HSCT can also be considered in rare attenuated cases in which the diagnosis is made at older than 2 years of age and the DQ is 70 or greater.[290]

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of MPS I with HSCT for severe cases with stable cardiopulmonary function, if the disease is diagnosed at 2 years of age or younger and the DQ is 70 or greater. It is also recommended that overall there appears to be a favorable risk-benefit profile for the treatment of MPS I with HSCT for rare attenuated cases in which the diagnosis is made at older than 2 years of age and the DQ is 70 or greater.[290]

Maroteaux-Lamy Syndrome (MPS VI)

Background

There are three types of Maroteaux-Lamy Syndrome: severe, intermediate, and mild. A deficiency in the arylsufatase B enzyme results in the accumulation of dermatan sulfate. The clinical characteristics are similar to MPS I, except with a later onset and a slower progression of symptoms. Symptoms such as an enlarged head and deformed chest may be present at birth. Growth and development can be normal the first few years of life, but seem to decline around age 6. Other symptoms include coarseness of facial features, bone abnormalities in the hands and spine, corneal clouding, hepatomegaly, umbilical or inguinal hernias, pain from compressed nerves, and thickening and stenosis of the aortic and mitral valves. Mental development is usually normal, but psychomotor skills are affected by the physical and visual impairments of the disease. Life expectancy is less than 20 years.[263, 264]

Clinical management typically comprises a coordinated effort to address the diverse spectrum of respiratory, cardiac, skeletal, ophthalmologic, and central and peripheral nervous system symptoms.

Evidence Base

The evidence compiled for this review includes two literature reviews[265, 270] and a Phase III clinical trial.[272] Two clinical practice guidelines[289, 291] but no health technology assessments were identified in the search.

Enzyme replacement therapy has proven to be a successful treatment for MPS VI, increasing enzyme activity level and improving joint mobility. A Phase III enzyme replacement trial showed sustained significant improvements in physical endurance tests such as stair climbing and walking.[283] Because mental development in MPS VI patients is usually normal, there is no need for the manufactured enzyme to cross the blood-brain barrier. HSCT has been shown to increase enzyme activity levels, decrease hepatosplenomegaly, and improve visual acuity, and joint mobility.[270]

Guidelines

Guidelines for the treatment of MPS VI with HSCT were published by The National Marrow Donor Program, International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group in a collaborative 2003 publication of practice guidelines regarding HSCT for inherited metabolic diseases.[291]

Guidelines specific to MPS VI were developed in 2004 at the International MPS Symposium and approved by an international consensus panel of specialists in medicine, genetics, and biochemistry.[289]

Enzyme-replacement therapy is recommended as first-line therapy for all cases of MPS VI. If enzyme replacement fails, then HSCT is recommended.

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of MPS VI with HSCT when enzyme replacement is not available or after failure of enzyme replacement. Supplemental treatment may include physical therapy, occupational therapy, and treatment-related surgery and medications.[289]

Sly Syndrome (MPS VII)

Background

Sly syndrome is a rare disease caused by a deficiency in the enzyme ß-glucuronidase. There have been fewer than 100 cases reported world-wide. As in the other mucopolysaccharidoses, a wide range in severity of symptoms exists. In most severe cases, neonatal jaundice and hydrops fetalis are present at birth, and survival is a few months. In less severe cases, growth retardation is evident in the first two years of life. Symptoms include coarse facial features, macrocephaly, hepatosplenomegaly, nerve entrapment, short stature, joint stiffness, inguinal and umbilical hernias, and corneal opacities. Respiratory insufficiency and frequent upper respiratory infections may occur. Mental retardation is moderate and nonprogressive. Life expectancy for the milder form is late teenage years through adulthood.[263, 264]

Clinical management for Sly syndrome is symptom specific. Surgery can relieve some of the respiratory problems and chronic ear infections and physical therapy can improve joint flexibility and range of motion.

Evidence Base

The evidence compiled for this review includes one literature review[270] and one case report.[287] One clinical practice guideline,[291] but no health technology assessments were identified in the search.

HSCT has been performed in two patients with Sly syndrome. Enzyme activity levels have increased, upper respiratory infections have decreased, and motor function has improved.[287]

Guidelines

Guidelines for the treatment of MPS VII with HSCT were published by The National Marrow Donor Program, International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group in a collaborative 2003 publication of practice guidelines regarding HSCT for inherited metabolic diseases.[291]

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of MPS VII with HSCT only in cases with severe physical disabilities, if the neuro-psychological and clinical status of the patient is good.[291]

Inherited Metabolic Diseases: Sphingolipidoses

Sphingolipidoses are a group of autosomal recessive diseases characterized by a deficiency in one of several enzymes needed to metabolize lipids. The accumulation of lipids primarily affects the development and functioning of the central nervous system.[292] The evidence base for these disorders is in Table 28 and the review of benefits and harms is in Table 29.

Gaucher Disease Type I

Background

Gaucher disease, the most common lysosomal storage disorder, is caused by a deficiency in the enzyme ß-glucocerebrosidase, which leads to an accumulation of glucosylceramide in the spleen, liver, lungs, bone marrow, and sometimes the brain. There are three types of Gaucher disease, based on the absence or presence, and progression of neurologic involvement. Gaucher disease Type II and Type III, the neuronopathic forms, are discussed in the Systematic Review section. Type I is non-neuronopathic, and is the most common form of the disease (about 90 percent), with a prevalence of 1 in 100,000 in the general population.[293] Those of Eastern and Central European (Ashkenazi) Jewish descent are at highest risk for this type (estimated at 1 in 450-1000).[261, 293] Symptoms can develop from early childhood to late adulthood. Patients presenting in early childhood have a more severe course of the Type I disease; those presenting later in life are more likely of Jewish descent.[261] Symptoms include anemia, hepatosplenomegaly, skeletal disorders, and lung and kidney impairment. The clinical course, disease progression, severity among the different organ systems, and life expectancy vary markedly among cases.[294] There can be both central and peripheral nervous system involvement in this form of the disease, but the nervous system symptoms are distinct from Type II and Type III because there is no neuronal loss in Type I.[295] Some developmental delays may occur as a consequence of the persistent clinical symptoms.[261]

Evidence Base

The evidence compiled for this review includes two literature reviews.[270, 296] Three clinical practice guidelines,[291, 297, 298] but no health technology assessments were identified in the literature search.

Enzyme-replacement therapy has been shown to be effective in increasing ß-glucocerebrosidase enzyme activity levels, resulting in improvements in visceral symptoms.[296] Evidence from a retrospective analysis of 1,028 patients in the International Collaborative Gaucher Group has shown that enzyme-replacement therapy can provide rapid and sustained improvements in anemia, decrease bone pain, and decrease organomegaly.[299] Adverse effects from enzyme replacement are primarily infusion related.[300] Treatment of Gaucher Type I is life-long, in which enzyme-replacement therapy dosages may need to be adjusted,[301] and ERT may need to be supplemented with medications or surgery to address issues of pain, pre-existing irreversible skeletal complications, and hypertension.

HSCT may be considered for Gaucher Type I if there is a persistence or progression of severe bone pain or if access to ERT is limited.[270] HSCT is effective in alleviating most symptoms of Gaucher Type I, in particular, the skeletal symptoms in the early onset severe form of Type I. Cure of Gaucher Type I can be achieved with HSCT if engraftment is successful and complications from the procedure are minimal.[302-304] Complications range in severity, including graft-versus-host disease and treatment-related mortality.[303, 305]

Table 28. Evidence base for HSCT in sphingolipidoses

Disease	Year of First HSCT	No. Transplants to Date	Type of Research Available	Registries
Gaucher Disease Type I	1982	unclear	Case reports, case series	Est. 1991: Genzyme Corporation sponsors the International Collaborative Gaucher Group (ICGG) to create an observational longitudinal database of clinical outcomes. Over 3,000 patients in registry.
Niemann-Pick Disease Type B	1987	3	Case reports	None
Globoid Cell Leukodys-trophy (Krabbe Disease)	1998	>34	Case reports, case series	None
Meta-chromatic Leuko-dystrophy	1982	<100	Case reports, case series	None

Guidelines

Guidelines for the treatment of Gaucher Type I with HSCT have been made by the National Marrow Donor Program, International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group in a 2003 publication of practice guidelines regarding HSCT for inherited metabolic diseases,[291] the Global Experts Meeting on Therapeutic Goals for the Treatment of Gaucher Disease,[298] and the U.S. regional coordinators of the International Collaborative Gaucher Group (ICGG) Registry.[298]

Following a multisystem evaluation to assess the severity of symptoms, HSCT is recommended for Gaucher Type I patients if there is a persistence or progression of severe bone pain that is not resolved by enzyme-replacement therapy or if enzyme replacement is unavailable.

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of Gaucher Type I with HSCT if there is a persistence or progression of severe bone pain or if ERT is unavailable,[270], HSCT is effective in alleviating most symptoms of Gaucher Type I, in particular, the skeletal symptoms in the early onset severe form of Type I.[291]

Table 29. Treatment benefits and harms for Gaucher Type I, Niemann-Pick Type B, Krabbe disease, and metachromatic leukodystrophy

Disease	Treatment	Source, Evidence Type	Indications	Clinical Benefits	Clinical Harms
Gaucher Disease Type I	ERT	Jmoudiak and Futerman 2005,[296] literature review	- all cases, as first line therapy	- rapid and sustained improvements in anemia for about 90% of pts over 2 year period[a] - among pts with bone pain, 52% pain free and 94% report no additional crises after 2 years[a] - hepatomegaly decreased by 30-40% and splenectomy decreased by 50-60%, but liver and spleen remain larger than normal size[a]	- intravenous catheterization in children can be difficult, causing pain and apprehension in pts[b] - infusion-related adverse events can be expected, including nausea, headache, rash, malaise, chest pain, vomiting; most can be managed through slower infusion rates or pre-treatment with antihistamines[c]
	Allogeneic HSCT	Peters 2004,[270] literature review	- recommended for more severe cases	- increase in enzyme activity level, though still below normal[d,e] - decrease in liver size, though liver still enlarged, 3-6 months post HSCT[d,e,f,g] - growth pattern returned to normal by 3 years post HSCT[e,f,g] - psychological development normal[f]	- 1 treatment-related mortality due to aspergillosis reported, out of 6 in case series[g] - 5 of 6 had mild acute GVHD[g] (- 2 of 2 had grade I acute GVHD[f] - 1 of 2 developed septicemia[f]
Niemann-Pick Disease Type B	Allogeneic HSCT	Peters 2004,[270] literature review Schuchman 2007,[306] literature review	- recommended for pts with early severe liver disease or pulmonary symptoms - considered experimental therapy for pts with neurological symptoms	- reduction in liver size, though liver still enlarged[h,i,j] - enzyme level increased[i,j] - interstitial lung disease resolved, though mild restrictive lung disease persists[i,j] - 5.5 years post transplant, either stable or improved in cognitive function, verbal skills, performance skills, receptive vocabulary, and expressive vocabulary[i] - 10 yrs post transplant, pt can perform majority of activities of daily living without assistance, though mild gross motor delay persists[j]	- acute and chronic GVHD[h,i,j] - septicemia and pneumonitis[h] - veno-occlusive disease[i] - mild to moderate respiratory distress[i] - deficits in memory, but not known if underlying disease or transplant are responsible[i,j] - engraftment decreasing with time, so disease progression continued several yrs post transplant; pt now severely mentally and physically disabled[k]

Table 29. Treatment benefits and harms for Gaucher Type I, Niemann-Pick Type B, Krabbe disease, and metachromatic leukodystrophy (continued)

Disease	Treatment	Source, Evidence Type	Indications	Clinical Benefits	Clinical Harms
Globoid Cell Leukodystrophy (Krabbe Disease)	Allogeneic HSCT	Peters 2004,[270] literature review Pastores 2009,[307] literature review	- recommended for severe early onset form if disease is diagnosed antenatally, so that HSCT can be performed during neonatal period, prior to onset of symptoms - recommended for late onset form of disease if symptoms are not severe	- enzyme activity levels in pts reached donor levels after 1 year post-transplant[l] - 2 pts with late onset form and neurologic disability: tremors and ataxia resolved by 6 months, motor incoordination resolved by 1 year, and gait dysfunction resolved slowly over 7 years post-transplant[l] - 3 late onset pts developed normally in: cognition, language, and memory[l] - asymptomatic newborns survival better compared to untreated controls (p=0.001) and better than treated symptomatic patients (p=0.01)[m] -early onset pts with no symptoms prior to transplantation maintained normal vision, hearing, and cognitive development; variable motor function was maintained[m] - central nervous system deterioration reversed in 4 out of 4 pts[n]	- 3 of 5 pts had graft-vs.-host disease, grade I-II[l] - complications among 25 transplant pts: 17 graft-vs.-host disease grades I-IV, 3 brief episodes of autoimmune hemolytic anemia, 1 catheter-related silent brain infarct, 2 asymptomatic hypertrophic cardiomyopathies, 1 symptomatic hypertrophic cardiomyopathy[m] - treatment-related mortality among 25 transplant pts: 1 GVHD, 1 aspiration pneumonia, 1 adenoviral infection, 1 complication from liver biopsy for GVHD[m]

Table 29. Treatment benefits and harms for Gaucher Type I, Niemann-Pick Type B, Krabbe disease, and metachromatic leukodystrophy (continued)

Disease	Treatment	Source, Evidence Type	Indications	Clinical Benefits	Clinical Harms
Metachro-matic Leukody-strophy	Allogeneic HSCT	Peters 2004[270], literature review Biffi et al. 2008,[308] literature review	- not recommended if neuro-psychologic and/or neurologic symptoms are advanced - recommended in pre-symptomatic pts (usually diagnosed early post-natally or prenatally) or pts with good neuropsychologic function	- enzyme activity reaches donor levels[o,p] - no further deterioration of white matter in the brain following transplant[o] - some mental capabilities preserved (well-developed language, for example), but physical limitations persisted (difficulty with gross and fine motor skills)[o] - nerve sensory velocities improved from abnormal to normal, 2 years post transplant[q] - serial MR findings support neuropsychological and neurophysiological tests that show disease stabilization 2-6 years post-transplant[r] - disease progression halted for over 11 years post-transplant, based on clinical, electrophysiological, and neuroradiological data: wheelchair bound, IQ stable at mild mental retardation, auditory evoked responses stable, nerve conduction velocities stable[s]	- 3 of 4 pts experienced acute GVHD[p]; 1 of 2 pts experienced chronic GVHD[r] - 4 pts with mild to moderate symptoms at time of transplant deteriorated mentally and physically post-HSCT[p]

[a]Weinreb et al. 2002,[299] 1028 Gaucher I pts, 2-5 yrs followup of ERT
[b]Charrow et al. 2003,[297] ERT consensus recommendations for Gaucher type I
[c]Starzyk et al. 2007,[300] review of adverse event reports from 1994-2004 for ERT
[d]Chan et al. 1994,[302] Gaucher type I case report, 2.8 yrs post HSCT
[e]Yen et al. 1997,[304] Gaucher I case report, 3 yrs post HSCT
[f]Ringden et al. 1995,[303] case series of 2 Gaucher type I pts, 3-8 yrs post HSCT
[g]Hobbs et al. 1987,[305] case series of 6 Gaucher type I pts, 1-3.3 yrs post HSCT
[h]Vellodi et al. 1987,[309] Niemann-Pick Type B case report, 9 months post HSCT
[i]Shah et al. 2005,[310] Niemann-Pick Type B case report, 5.5 yrs post HSCT
[j]Schneiderman et al. 2007,[311] Niemann-Pick Type B case report, 10 yrs post HSCT
[k]Victor et al. 2003,[312] Niemann-Pick Type B case report 16 yrs post HSCT
[l]Krivit et al. 1998,[313] case series of 5 GLD pts, 1-9 yrs post HSCT
[m]Escolar et al. 2005,[314] case series of 25 GLD pts, 11 asymptomatic and 14 symptomatic, 4 months - 6 yrs post HSCT
[n]Kurtzberg et al. 2002,[315] case series of 5 GLD pts, 1-9 yrs post HSCT
[o]Krivit et al. 1990,[316] MLD case report, 5 yrs post HSCT
[p]Malm et al. 1996,[317] case series of 4 MLD pts, 2-3 yrs post HSCT
[q]Pierson et al. 2008,[318] case series of 3 MLD siblings, 2 yrs post HSCT
[r]Stillman et al. 1994,[319] case series of 2 MLD pts, 2-6 yrs post HSCT
[s]Gorg et al. 2007,[320] case report of 1 MLD pt, 13-yrs post HSCT

Niemann-Pick Disease Type B

Background

Niemann-Pick disease is characterized by a deficiency in acid sphingomyelinase activity, resulting in the accumulation of lipids in the spleen, liver, lungs, bone marrow, and the brain, causing lack of muscle coordination, brain degeneration, feeding and swallowing difficulties, and hepatosplenomegaly. There are three types of this disease, Type A, B, and C. Type B is discussed in this section and Types A and C are discussed in more detail in the Systematic Review. Type B is panethnic and is the least severe form of the disease. It is usually diagnosed during childhood or preteen years, because of the development of hepatosplenomegaly.[261] Severity of symptoms varies in Type B, and as the disease progresses, the pulmonary system becomes compromised, and bronchopneumonias may occur. Liver complications develop in more severe cases, leading to cirrhosis or portal hypertension.[261, 321] This form usually does not involve neurological symptoms, and cases can survive into adulthood.

Evidence Base

The evidence compiled for this review includes two literature reviews.[270, 306] One clinical practice guideline,[291] but no health technology assessments were identified in the literature search.

Three transplantations for Niemann-Pick Type B have been reported in the literature. Two have reported successful outcomes,[310, 311] and one showed initial improvements followed by neurological and physical deterioration after several years post-transplant.[312] HSCT can be expected to increase enzyme activity level, reduce liver size, stabilize or improve cognitive function, and improve lung function, resulting in the ability to perform activities of daily living without assistance. Adverse events reported from the three transplantations include acute and chronic graft versus host disease, veno-occlusive disease, and infections.

Enzyme-replacement therapy is currently not available for pediatric cases. A Phase I trial in adults is complete, and enrollment in a Phase II trial was begun in 2010.

Guidelines

Recommendations for HSCT for Niemann-Pick Type B can be found in a publication of practice guidelines regarding HSCT for inherited metabolic diseases by the National Marrow Donor Program, International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group.[291]

HSCT is recommended for Niemann-Pick Type B patients with early severe liver disease or pulmonary symptoms. HSCT is considered experimental therapy for patients with neurologic symptoms.

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of patients with HSCT who have severe symptoms from Niemann-Pick Type B particularly those with severe liver disease or pulmonary disease. The procedure will ideally be performed as early in the disease process as possible for maximum benefit.[291, 306]

Globoid Cell Leukosystrophy (Krabbe Disease)

Background

Globoid cell leukodystrophy, is a disease caused by a deficiency of the enzyme galactocerebrosidase, resulting in progressive destruction of central and peripheral myelin. The estimated incidence is 1 to 2 per 100,000 live births. Symptoms in the most common and more severe form of the disease (90 percent), sometimes called Krabbe disease, begin early in life, between 2 and 10 months of age. In the initial stages of the disease, there is irritability, feeding problems, and a general failure to thrive. Subsequent symptoms include stiffness, seizures, and slow development. Progression of the disease is quick, leading to a chronic vegetative state and death usually by 2 years of age.[261] In the late-onset form of this disease, the juvenile or adult form, symptoms may begin later in childhood or adulthood, beginning with optic atrophy and cortical blindness. Gait disturbances, such as spasticity and ataxia, develop and progress slowly for about a decade, prior to death.[322]

Evidence Base

The evidence compiled for this review includes two literature reviews.[270, 306] One clinical practice guideline,[291] but no health technology assessments were identified in the literature search.

Transplantation in the early onset form of the disease has only been successful if performed during the neonatal period, prior to the development of any symptoms. These cases have been diagnosed antenatally, screened for the disease because an older sibling had died from the disease.[314]

Patients with the late form of the disease have had more success with stem-cell transplantation because the symptoms are less severe and the disease progression is slower. Both improvements in neuromuscular symptoms and continued neurocognitive development have been reported among late-onset patients undergoing transplantation.[313-315] Adverse events reported include acute and chronic graft-versus-host disease, hemolytic anemia, asymptomatic and symptomatic cardiomyopathies, and transplant-related mortality.[313, 314]

Guidelines

Guidelines for the treatment of globoid cell leukodystrophy with HSCT can be found in a publication of practice guidelines regarding HSCT for inherited metabolic diseases by the National Marrow Donor Program, International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group.[291]

HSCT is recommended for the severe early onset form of the disease if the disease is diagnosed antenatally, so that HSCT can be performed during the neonatal period, prior to the onset of symptoms. Screening for the disease is recommended in particular for families who have had a child previously diagnosed with the disease, allowing for an antenatal diagnosis and an early transplantation.[291]

HSCT is recommended for patients with the late onset form of disease if symptoms have not become severe.[291]

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of severe early onset globoid cell leukodystrophy with HSCT, when the disease has been diagnosed antenatally,

and the transplant is performed in the neonatal period prior to the development of symptoms. It is also recommended that there appears to be a favorable risk-benefit profile for the treatment of the late form of globoid cell leukodystrophy with HSCT.

Metachromatic Leukodystrophy

Background

Metachromatic leukodystrophy (MLD) is an autosomal recessive disease caused by either a deficiency in the enzyme arylsulfatase A or a deficiency in a sphingolipid activator protein needed to form the substrate-enzyme complex. Absence of either substance leads to a buildup of cerebroside sulfate in the central nervous system and in peripheral nerves, causing demyelination and a neurodegenerative course.[261] The incidence is approximately 1 in 40,000 births. There are three forms of the disease: late infantile, juvenile, and adult. The late infantile form is the most common, with the following symptoms occurring in the second year of life: muscle weakness and wasting, muscle rigidity, developmental delays, convulsions, loss of vision, and paralysis. Life expectancy is 5 to 6 years, with death usually due to aspiration or bronchopneumonia.[292] The juvenile form presents between the ages of 3 and 12 years, beginning with mental deterioration, dementia, and urinary incontinence, followed by the same symptoms as the late infantile form, but progressing at a slower pace. Life expectancy is through mid-adolescence.[261] Dementia and behavioral disturbances are the most notable symptoms in the adult form, which may begin in the mid-teenage years through adulthood. Neurological symptoms progress slowly, leading to a bedridden state. Life expectancy can extend beyond a decade following the onset of symptoms.[261]

Evidence Base

The evidence compiled for this review includes two literature reviews.[270, 308] In addition, one clinical practice guideline,[291] but no health technology assessments were identified in the literature search.

A wide range of effectiveness of HSCT in the treatment of MLD has been reported. Severity of the disease, in particular, the extent of neurological symptoms at the time of transplant, may determine whether there is a stabilization of symptoms or continued degeneration.[308] The most beneficial results occur when HSCT is performed prior to the onset of clinical symptoms and if the donor has homozygous normal arylsulfatase A enzyme activity.[270] The benefits of HSCT are primarily to the central nervous system, so symptoms related to the peripheral nervous system remain unresolved.[270]

Guidelines

Guidelines for the treatment of metachromatic leukodystrophy with HSCT can be found in a publication of practice guidelines regarding HSCT for inherited metabolic diseases by the National Marrow Donor Program, International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group.[291]

HSCT is recommended for early onset severe patients if they are presymptomatic, usually diagnosed in an early postnatal or prenatal screening, because of an older affected sibling.

HSCT is not recommended for patients with the early onset severe form of the disease if neurophysiologic and neurologic symptoms have already occurred, since stabilization of symptoms is expected to take 6 to 12 months following transplant.

For patients with the juvenile or adult onset form of the disease, HSCT is recommended if comprehensive neurologic, neuropsychologic, neuroradiologic, and neurophysiologic assessments demonstrate the existence of functional abilities.[291]

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of the late infantile form of MLD, HSCT is recommended for presymptomatic patients only, usually those diagnosed early in the postnatal or prenatal stages, because of an older affected sibling. It is also recommended that overall there appears to be a favorable risk-benefit profile for the treatment of the juvenile and adult forms of MLD with HSCT if comprehensive neurologic, neuropsychologic, neuroradiologic, and neurophysiologic assessments demonstrate the existence of functional abilities.

Inherited Metabolic Diseases: Glycoproteinoses

Glycoproteinoses are a group of lysosomal storage diseases characterized by a deficiency in enzymes needed to break down glycoproteins (Table 30). The accumulation of glycoproteins in the organs and central nervous system causes progressive damage and a neurodegenerative course.[261]

Table 30. Evidence base for HSCT in glycoproteinoses

Disease	Year of First Treatment	No. Transplants to Date	Existing Clinical Evidence	Registries
Fucosidosis	1995	3	Case reports	None
α-Mannosidosis	1987	<20	Case series	None

Fucosidosis

Background

Fucosidosis is a rare autosomal recessive disorder caused by a deficiency in the enzyme α-fucosidase, resulting in the accumulation of glycolipids and glycoproteins in the liver, spleen, skin, heart, pancreas, kidneys, and brain.[323] While cases have been reported throughout the world, most cases have come from Italy, Cuba, and the southwestern portion of the U.S. There are no estimates of incidence of the disease, with less than 100 cases having been reported in the literature. The signs and symptoms of the disease range in severity, presenting in a wide continuous clinical spectrum.[324] The most severe form of the disease presents in the first year of life, beginning with developmental delays and coarse facial features. Growth retardation and mental retardation occur in over 90 percent of cases.[324] Other symptoms include hepatosplenomegaly, seizures, optical abnormalities, frequent upper respiratory infections, angiokeratomas, and visceromegaly. Both physical and mental deterioration progresses with age. In the most severe form, life expectancy is late childhood. The milder form becomes evident at 1 to 2 years of age and life expectancy extends to mid-adulthood.[261] There is no cure for fucosidosis.

Evidence Base

The evidence compiled for this review (Table 31) includes two literature reviews,[270, 325] which describe three patients with fucosidosis undergoing HSCT, two reports in the literature and one conference abstract.[326, 327] No health technology assessments or clinical practice guidelines for the treatment of fucosidosis with HSCT were identified in the literature search.

Both cases reported in the literature were diagnosed early because of disease in an older sibling. Transplantations were performed prior to the onset of symptoms, and the success of the transplants is attributed to the timing of the procedures. Leukocyte enzyme levels rose quickly following engraftment, and remained in the normal range 1 to 3 years post-procedure. Most promising is the detection of enzyme activity in cerebrospinal fluid, indicating that the enzyme had reached the central nervous system.[327] MRIs from 1 to 3 years post-procedure showed a consistent progression of myelination following the transplants. Both cases reported in the literature showed better mental and physical development and improved quality of life compared to their affected siblings. Complications included GVHD and infections.[326, 327]

Guidelines

No guidelines for the treatment of fucosidosis with HSCT were identified in the search.

Conclusions

Overall there appears to be a favorable risk-benefit profile for the treatment of fucosidosis with HSCT when performed on presymptomatic patients who have had an early diagnosis. HSCT is only recommended for patients who have not shown any signs of central nervous system deterioration.[270, 325]

α-Mannosidosis

Background

Alpha-mannosidosis is an autosomal recessive disease caused by a deficiency in the enzyme α-mannosidase, resulting in the accumulation of oligosaccharides in the liver, bone marrow, and central nervous system. The estimated incidence of the disease is 1 in 500,000 world-wide. This disease exhibits a wide spectrum of clinical symptoms. Symptoms include mental retardation, impaired hearing, degeneration of previously acquired developmental skills, coarse features, hepatosplenomegaly, immunodeficiency, ataxia, and metabolic myopathy. There is a severe infantile form (Type I), with an onset of symptoms occurring before 12 months of age. Progressive deterioration in this type leads to death between 3 to 12 years of age. Type II is the less severe form, with symptoms beginning in late childhood to adulthood. The symptoms are milder and progress more slowly in this form. Life expectancy can extend through the fifth decade of life.[331]

Table 31. Treatment benefits and harms for fucosidosis and α-mannosidosis

Disease	Treatment	Source, Evidence Type	Indications	Clinical Benefits	Clinical Harms
Fucosidosis	Allogeneic HSCT	Peters 2004,[270] literature review Heese 2008,[325] literature review	- recommended only for pre-symptomatic pts with an early diagnosis, before central nervous system starts to deteriorate	- enzyme activity detected in cerebrospinal fluid 1 yr post HSCT, indicating enzyme has reached central nervous system[a] - myelination proceeding, though delayed compared to expected for age of pt[a] - able to function in slightly low average range, sociable, happy, engaged at 1 yr post[a] - progressive rise in enzyme levels, peaking at 30 months post HSCT[b] - slight improvement in white matter myelination at 13 months post, more evident improvement by 24 months post, good myelination by 32 months post, near normal by 38-46 months post[b]	- complications: graft vs. host disease, transient episode of idiopathic thrombocytopenic purpura, and repeated sepsis from central venous catheter[b] - moderately severe graft vs. host disease[b]
α-Mannosidosis	Allogeneic HSCT	Peters 2004,[270] literature review Heese 2008,[325] literature review	- recommended for all pts with severe Type I form prior to onset of significant symptoms - recommended for Type II pts if early neurocognitive deficits present	- hepatosplenomegaly resolved within 1 mo post[c,d] - bony abnormalities improved significantly in skull, thoracolumbar spine, and hands[c] - trabeculation of long and short bones normalized[c] - 2 of 3 pts with hearing deficits improved to near normal frequency range, except high frequency difficulties persisted, by 2 yrs post[d] - neuropsychologic testing shows stabilization[c] or improvement[d] of neuropsychologic symptoms - improvement in expressive speech at 3 yrs post in symptomatic pt[e] - overall normal development at 6 yrs post in asymptomatic pt; attends mainstream school[e]	- acute GVHD[c,d] - graft vs. host disease led to obliterative bronchiolitis[e]

[a]Vellodi et al. 1995,[327] case report, fucosidosis pt, 1 yr post HSCT

[b]Miano et al. 2001,[326] case report, fucosidosis pt, 4 yrs post HSCT

[c]Wall et al. 1998,[328] case report, α-mannosidosis pt, 15 months post HSCT

[d]Grewal et al. 2004[329], case series, 3 pediatric 1 adult α-mannosidosis pts, 1-6 yrs post HSCT

[e]Broomfield et al. 2010,[330] comparison of 2 α-mannosidosis siblings, 1 late transplant to relieve symptoms, 1 presymptomatic transplant, 3-6 yrs post HSC

Evidence Summary

The evidence compiled for this review includes two literature reviews (Table 31).[270, 325] One clinical practice guideline[291] but no health technology assessments for the treatment of α-mannosidosis with HSCT were identified in the literature search. Included literature reviews contain all identified reports of HSCT for α-mannosidosis.

Results have shown favorable outcomes, with resolutions in organomegaly, bony disease, and either stabilization or improvement of neuropsychologic symptoms.[328, 329] A comparison of two α-mannosidosis siblings, one undergoing a late transplant to relieve symptoms, and one receiving a presymptomatic transplant, shows clearly that transplants earlier in the course of the disease are more beneficial.[330] For untreated patients with the severe form of the disease, there is rapid physical and mental degeneration and life expectancy is 3 to 12 years; following HSCT, patients have survived beyond the expected lifespan and several attend mainstream school and participate in sports.[329, 330]

Guidelines

Guidelines for HSCT in α-mannosidosis can be found in a publication of practice guidelines regarding HSCT for inherited metabolic diseases by the National Marrow Donor Program, International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group.[291]

HSCT is recommended for all patients with severe Type I form prior to the onset of significant symptoms, and recommended for Type II patients if early neurocognitive deficits are present.

Conclusions

Overall there appears to be a favorable risk-benefit profile for the treatment of severe Type I α-mannosidosis with HSCT, if performed prior to the onset of significant symptoms. It is also recommended that overall there appears to be a favorable risk-benefit profile for the treatment of Type II α-mannosidosis is early neurocognitive deficits are present.

Inherited Metabolic Diseases: Peroxisomal Storage Disorders

Peroxisomal storage disorders are a heterogeneous group of congenital diseases in which there is either a dysfunction of the peroxisomes or a deficiency in the enzymes which are necessary for the metabolism of very-long-chain-fatty-acids (VLCFA). The accumulation of VLCFA in the central nervous system leads to demyelination of the nerve fibers in the brain and nerves, resulting in slower conduction of nerve impulses. Developmental delays and mental retardation are common in all peroxisomal storage disorders.[332] The combined incidence of peroxisomal disorders is estimated at over 1 in 20,000 in the U.S.

Adrenoleukodystrophy

Background

Adrenoleukodystrophy is a demyelinating disorder of the central nervous system caused by the accumulation of very long chain fatty acids in the brain and adrenal cortex, due to a deficiency in the enzyme that breaks down fatty acids. The estimated incidence is 1 in 100,000.[333] Symptoms range in severity, from the X-linked form which is the most severe form,

to the milder adult-onset form. Onset of symptoms in the severe form occurs between 4 to 8 years of age, and is characterized by adrenal insufficiency in 90 percent and neurological deterioration in 100 percent of the cases.[334] Symptoms include behavioral changes such as withdrawal or aggression, poor memory, and learning disabilities. Physical manifestations of the disease progress quickly and include visual loss, seizures, difficulty swallowing, deafness, fatigue, an increase in skin pigmentation, weakness of the lower limbs, intermittent vomiting, and progressive dementia. This severe form is often referred to as "childhood onset of cerebral adrenoleukodystrophy" (COCALD). In the milder adult-onset form, symptoms begin between the ages of 21 to 35 and progress more slowly. Stiffness, limb weakness, and ataxia may occur, along with deterioration of brain function. Expected survival is 1 to 10 years following the onset of symptoms.[335]

The severity and extent of symptoms determines the course of treatment. Patients with adrenocortical insufficiency need steroid hormone replacement therapy. In patients without neurologic symptoms, dietary therapy consisting of fat restriction and an oral supplement called "Lorenzo's oil," a mixture of oleic acid and erucic acid, is recommended. Dietary therapy alone is not effective once neurological symptoms have progressed because erucic acid cannot enter the CNS in significant amounts.[336]

The severity of symptoms in adrenoleukodystrophy varies widely from the early onset form through the milder adult onset form. The severity of symptoms determines which therapeutic options to consider. Studies have shown that an MRI severity score of 2-3 in boys younger than 10 years of age, will most likely develop progressive cerebral disease and are therefore candidates for HSCT.[291]

Evidence Base

The evidence compiled for this review (Table 32) includes two literature reviews.[270, 337] One clinical practice guideline[291] but no health technology assessments for the treatment of adrenoleukodystrophy with HSCT were identified in the literature search.

Outcomes following HSCT have varied from complete resolution of symptoms to having no effect (Table 33). Disease status prior to the procedure is the best predictor of outcomes.[338, 339] The most successful outcomes are when the HSCT has been performed prior to the onset of neurologic symptoms. In a report on 94 boys with X-linked adrenoleukodystrophy receiving HSCT, 5-year survival rates were 70 percent with no neurological deficits, 67 percent with one neurological deficit, and 35 percent with two or more neurological deficits. The 5-year survival rates of boys with X-linked adrenoleukodystrophy not receiving HSCT have been reported as less than 40 percent.[339]

Table 32. Evidence base for HSCT in adrenoleukodystrophy

Disease	Year of First Treatment	No. Transplants to Date	Existing Clinical Evidence	Registries
Adrenoleukodystrophy	1984	>125	Case series, case reports	None

Guidelines

Guidelines for the treatment of adrenoleukodystrophy with HSCT can be found in a publication of practice guidelines regarding HSCT for inherited metabolic diseases by the

National Marrow Donor Program, International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group.[291]

HSCT is recommended only for the early onset severe form, once there is definitive evidence of cerebral disease, usually determined by MRI.[291]

Summary

Overall there appears to be a favorable risk-benefit profile for the treatment of severe adrenoleukodystrophy with HSCT. HSCT is indicated at the first signs of demyelination due to the rapid progression of mental deterioration once cerebral disease is detected.[291]

Table 33. Treatment benefits and harms for adrenoleukodystrophy

Disease	Treatment	Source, Evidence Type	Indications	Benefits	Harms
Adreno-leukodys-trophy	Allogeneic HSCT	Peters 2004,[270] literature review Krivit et al. 1999,[337] literature review	- recommended as soon as diagnosis for child onset of cerebral adrenoleukody-strophy is confirmed	- 18 months post HSCT, behavioral and cognitive functions improved[a] - MRI showed complete disappearance of lesions in brain if demyelination moderate[a,b,c] - MRI showed deterioration stabilized if demyelination more extensive[b,c] - cognitive function stabilized or improved in 7 of 12 pts[b] - 8 of 12 functioning normally in school with no additional support[b] - 5 yr survival: 70% with 0 neurologic deficits, 67% with 1 neurological deficit, 35% with 2 or more neurological deficits[d] - 31 of 58 had no further neurological progression of disease[d]	- treatment-related mortality at 3 yrs: 10% with related donor, 18% with unrelated donor[d] - severe acute GVHD: 17% with related donor, 8% with unrelated donor[d]

[a]Aubourg et al. 1990,[340] case report, 18 months post HSCT
[b]Shapiro et al. 2000,[341] case series of 12 pts, 5-10 yrs post HSCT
[c]Loes et al. 1994,[342] case series of 7 pts, 1-2 yrs post HSCT
[d]Peters et al. 2004,[270] case series of 94 pts, 0.4-11.2 yrs post HSCT

Osteopetrosis

Background

Osteopetrosis is a group of rare inherited disorders of the skeleton characterized by a defect in the form or function of osteoclasts. Osteoclasts degrade bone in the bone remodeling process, so a decrease in osteoclast activity causes an increase in bone density, an impairment of longitudinal growth of the bone, and bone marrow failure.[343] There is a wide spectrum of presentation and severity of symptoms, which have been classified into three primary clinical types: autosomal recessive infantile ("malignant") osteopetrosis, autosomal recessive "intermediate" osteopetrosis, and autosomal dominant osteopetrosis. The estimated incidence of the autosomal recessive type is 1 in 250,000–300,000 births, though in Costa Rica the incidence is three times as high, and for the autosomal dominant type, the estimated incidence is 1 in 20,000 births.[344] The autosomal recessive infantile form is the most severe and is characterized by hepatosplenomegaly, cranial-nerve dysfunction, hearing loss in about one-third of cases, and visual deficits in a majority of the cases, all of which are detected within the first several months of life.

Because of neutrophil defects, anemia, and complications of the ear, nose, and throat, patients with osteopetrosis are susceptible to frequent infections, usually affecting the respiratory tract.[345] Life expectancy is less than 10 years, with cause of death most commonly thrombocytopenia, anemia, or infectious complications.[343] There are rare variants of the autosomal recessive type, a neuronopathic form characterized by seizures and a milder form exhibiting renal tubular acidosis are two examples. There is also a rare X-linked form characterized by severe immunodeficiency. Symptoms of the more common, but less severe autosomal dominant form are primarily skeletal, such as fractures, scoliosis, and osteomyelitis, with onset in late childhood or adolescence and a normal life expectancy.[344]

Clinical management of osteopetrosis is supportive, with fractures and arthritis treated by experienced orthopedic surgeons due to the brittleness of the bone, hypocalcemic seizures treated with calcium and vitamin D supplements, and bone marrow failure treated with red blood cell and platelet transfusions.[345]

Evidence Base

The evidence compiled for this review (Table 34) includes four literature reviews[345-348] of osteopetrosis and HSCT (Table 35). In a retrospective study of over 100 osteopetrosis patients undergoing HSCT, 5-year disease free survival rates ranged from 24 percent with a mismatched unrelated donor to 73 percent with a matched sibling donor.[349] Some patients experienced improvements in visual symptoms and either stable or improved growth.[349] Risks related to HSCT include hypercalcemia, graft versus host disease, and infections.[349, 350]

Age at transplantation and availability of a suitable HLA matched donor determine the quality and durability of engraftment, which in turn affects the extent of benefit of HSCT.[345, 350] Engraftment can significantly alter the course of the disease, and prolong life expectancy from less than 10 years of age, to adulthood. Despite successful engraftment, some patients may still experience growth retardation, visual impairment, and damage to permanent teeth.[346] Additionally, susceptibility to fractures is expected for some time after successful transplantation. Monitoring of symptoms continues, by a multidisciplinary team including a pediatrician, an ophthalmologist, an audiologist, and a dentist.[345]

Table 34. Evidence base for HSCT in osteopetrosis

Disease	Year of First Transplant	No. Transplants to Date	Existing Clinical Evidence	Registries
Osteopetrosis	1977	> 125	Case reports, case series, retrospective analyses	None

Guidelines

No guidelines for the management of osteopetrosis were identified in the search.

Summary

Overall there appears to be a favorable risk-benefit profile for the use of HSCT in the severe autosomal recessive infantile malignant form of osteopetrosis. For this indication HSCT is the only curative treatment. HSCT is performed as early as possible, once symptoms clearly indicate the severe form, usually before 3 months of age.[346, 348] Symptom-specific treatment is recommended for the milder autosomal recessive form and the autosomal dominant form.

Table 35. Treatment benefits and harms for osteopetrosis

Disease	Treatment	Source, Evidence Type	Indications	Clinical Benefits	Clinical Harms
Osteopetrosis	Allogeneic HSCT	Steward 2010,[348] literature review Askmyr et al. 2008,[346] literature review Or et al. 2004,[347] literature review Wilson and Vellodi 2000,[345] literature review	- recommended only for the severe form of autosomal recessive osteopetrosis	- 5-yr disease free survival rates: 73% with HLA identical genotype sibling donor, 43% with HLA identical phenotype or one mismatch related donor, 40% with HLA matched unrelated donor, 24% with HLA mismatch related donor[a] - 56 of 122 have normal osteoclast function following HSCT and 6 of 122 survived with persistent osteopetrosis[a] - in 42 evaluable pts, 29 had no further visual deterioration, 3 improved vision, 10 had further deterioration; better conservation of vision if HSCT performed before 3 months of age[a] - in 18 evaluable pts: 11 had same or better percentile growth, 7 had lower percentile growth at last followup[a] - following HSCT, most children can attend regular school, those with visual disability need special education[a] - if engraftment successful, no clinical evidence of progressive disease[b]	- 58 of 122 deaths related to HSCT or osteopetrosis, most common causes: 14 septicemia, 13 pneumonia, 8 veno-occlusive disease, 7 aplasia/hemorrhage[a] - hypercalcemia in 8 of 50 evaluable pts; significantly higher risk if HSCT after 2 yrs of age[a] - 4 of 10 pts had acute GVHD grades I-III[b] - 5 of 10 pts died of transplant complications: 4 of interstitial pneumonitis, 1 of which had chronic GVHD involving respiratory and gastrointestinal tract, and 1 from *Aspergillus* infection[b]

[a]Driessen et al. 2003 [349], retrospective analysis of 122 pts, up to 10 yrs post-HSCT, extended followup on patients reported in Gerritsen et al. 1994[351]
[b]Eapen et al. 1998 [350], case series of 10 pts, 2-18 yrs post-HSCT

Systematic Reviews

Table 36 lists the indications to be addressed as part of the systematic reviews of this report.

Table 36. Pediatric HSCT indications to be addressed with systematic review

Condition	Indication(s)	Type of Transplant	Comparator
Malignant Nonhematopoietic			
Ewing sarcoma family of tumors (ESFT)	Consolidate high-risk (initial) Relapsed/refractory	Auto Auto Tandem Auto Auto	Conventional Chemotherapy Conventional Chemotherapy Single Autologous
Wilms	Consolidate high risk Relapsed/refractory	Auto Auto Tandem Auto Auto	Conventional Chemotherapy Conventional Chemotherapy Single Autologous
Rhabdomyosarcoma (RMS)	Metastatic Disease	Auto Tandem Auto Auto	Conventional Chemotherapy Single Autologous
Retinoblastoma	Extraocular Spread	Auto Tandem Auto Auto	Conventional Chemotherapy Single Autologous
Neuroblastoma (NB)	Consolidate high-risk (initial) Relapsed/refractory	Tandem Auto Auto	Single Autologous
Germ cell tumor (GCT)	Relapsed	Tandem Auto Auto	Single Autologous
Central Nervous System Embryonal Tumors	Initial therapy	Auto Tandem Auto Auto	Conventional Chemotherapy Single Autologous
CNS Glial Tumors	Consolidate high risk Relapsed/refractory	Auto Auto	Conventional Chemotherapy
Nonmalignant			
Inherited metabolic diseases **Mucopolysaccharidosis** MPS II (Hunter's), MPS III (Sanfilippo), MPS IV (Morquio) **Sphingolipidosis** Fabry's, Farber's , Gaucher II-III, GM_1 gangliosidosis, Niemann-Pick disease A, Tay-Sachs, Sandhoff's disease **Glycoproteinosis** Aspartylglucosaminuria, beta-Mannosidosis, Mucolipidosis III and IV **Other lipidoses** Niemann-Pick disease C, Wolman disease, Ceroid lipofuscinosis **Glycogen storage** GSD type II **Multiple enzyme deficiency** Galactosialidosis, Mucolipidosis type II **Lysosomal transport defects** Cystinosis, Sialic acid storage disease, Salla disease **Peroxisomal storage disorders** Adrenomyeloneuropathy	Variable	Allo	Enzyme-replacement therapy, substrate reduction with iminosugars and chaperones

Table 36. Pediatric HSCT indications to be addressed with systematic review (continued)

	Indication(s)	Type of Transplant	Comparator
Autoimmune including juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE), scleroderma, immune cytopenias, Crohn's	Upfront for severe/ refractory or salvage	Auto/allo	Immunosuppressants, targeted biologic therapies and low-dose chemotherapy
Autoimmune type 1 diabetes mellitus (DM)	Variable	Auto	Immunosuppressants, targeted biologic therapies and low-dose chemotherapy, conventional management (i.e., insulin injections)

allo = allogeneic; auto = autologous; DM = diabetes mellitus; ESFT = Ewing sarcoma family of tumors; GCT = germ cell tumor; HL = Hodgkin's lymphoma; JRA = juvenile rheumatoid arthritis; MDS = myelodysplastic syndrome; OS = osteosarcoma; PNET = primitive neuroectodermal tumor; RMS = rhabdomyosarcoma; SLE = systemic lupus erythematosus; TKI = tyrosine kinase inhibitor

Systematic Reviews: Malignant, Nonhematopoietic Disease

Ewing's Sarcoma Family of Tumors Systematic Review

Background and Indication

The Ewing's sarcoma family of tumors (ESFT) is the second most common primary malignant bone tumor in children, adolescents and young adults. ESFTs include Ewing tumor of bone (classic Ewing sarcoma and primitive neuroectodermal tumor or PNET) and extraosseous Ewing (i.e., Ewing sarcoma in a site other than bone). The incidence of ESFT is approximately 3 cases per 1,000,000 persons per year. The incidence in the U.S. population is one per 1,000,000 in the population.[352] The median age of patients is 15 years, and more than 50 percent of patients are adolescents. Primary sites of bone disease include lower extremity (41 percent), pelvis (26 percent), chest wall (16 percent), upper extremity (9 percent), spine (6 percent) and skull (2 percent).[352] Primary sites of extraosseous Ewing's are trunk (32 percent), extremity (26 percent), head and neck (18 percent), retroperitoneum (16 percent) and other sites (9 percent).[352] Approximately 25 percent of patients will have metastatic disease at diagnosis.[352]

Certain adverse prognostic factors place some patients with ESFT into a high-risk category: relapsed or resistant disease, primary tumor site in the axial skeleton, including pelvis, large tumor volume, and the presence of metastatic disease (patients with isolated lung metastases are considered to have better prognosis than patients with metastases to bone and/or bone marrow). Treatment of ESFT includes systemic chemotherapy in conjunction with either surgery or radiation or both for local tumor control.

Overall survival rates for localized ESFT have dramatically improved over the last 30 years, however, the prognosis for patients with high-risk tumors treated with conventional chemotherapy, radiation and surgery remain poor, with long-term survival rates for patients with metastatic disease less than 35 percent.[352] Patients with lung-only metastases have been reported to have 4-year EFS of approximately 40 percent, whereas patients with bone/bone marrow metastases have 4-year EFS of approximately 28 percent and with combined lung and bone/bone marrow metastases 4-year EFS of approximately 14 percent. Relapsed ESFT treated with conventional-dose chemotherapy, radiation and surgery has been reported to have a 2-year event free survival of less than 10 percent.

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Chemotherapy for patients with ESFT initially was based on four drugs: doxorubicin, cyclophosphamide, vincristine, and dactinomycin. More recently, treatment has included ifosfamide, with or without etoposide. Dose-intensive chemotherapy regimens as well as HSCT have been investigated in patients with high-risk ESFT in an effort to improve survival.

Evidence Summary

The overall grade of strength of evidence for overall survival and the use of single and tandem HSCT for the treatment of high-risk Ewing's Sarcoma Family of Tumors (ESFT) is shown in Table 37.

Single HSCT

The literature using dose-intensive chemotherapeutic regimens or HSCT consists of case series with small numbers of patients and case reports without direct comparisons between conventional or dose-intensive chemotherapy and HSCT. The evidence compiled for this review includes, for HSCT, 24 case series[353-376] (including two Phase II studies) and six case reports.[377-382] The comparator is conventional chemotherapy and includes seven case series (including one Phase II study).[116, 376, 383-387] No information on quality of life (QOL) was provided and data on adverse events were sparse and based on small numbers of patients.

The evidence suggests that treatment-related mortality is higher in the patients that underwent HSCT compared to the chemotherapy comparators. The rate of secondary malignancies appeared lower in some reports of dose-intensive chemotherapy compared to HSCT and similar in one report of dose-intensive chemotherapy compared to HSCT.

Tandem Autologous-Autologous HSCT

The literature using tandem HSCT consists of case series with small numbers of patients and a case report.[355, 380] A direct comparison between tandem HSCT and single HSCT is reported in one case series.[354] The evidence compiled for this review includes, for tandem HSCT, two case series and one case report. The comparator is single HSCT and includes 24 case series and six case reports. Data on transplant-related mortality and infectious complications were sparse; data on other adverse effects were not reported.

Table 37. Overall grade of strength of evidence for overall survival and the use of single and tandem HSCT for the treatment of high-risk Ewing's Sarcoma Family of Tumors (ESFT)

HSCT Type	Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
Single HSCT	For pediatric patients with high-risk ESFT, what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Comparator is conventional chemotherapy. Outcome of interest is overall survival.	The evidence for HSCT consists of 24 case series and 6 case reports. Comparator data consists of 7 case series. Data consist of 446 HSCT patients and 283 conventional chemotherapy patients.	The risk of bias in this evidence is high. Studies consisted of case reports or small case series, and incorporated heterogeneous patient populations.	Results for overall survival are consistent. Among the larger studies, for both HSCT and chemotherapy, the 5-year OS outcomes fall within the same range.	The outcome reported, overall survival, is direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is precise. While the evidence is qualitative, it is unlikely that a clinically important superiority exists for HSCT for the treatment of high-risk ESFT compared to conventional chemotherapy.	Not applicable due to lack of obvious effect size.	Low strength evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for the treatment of high-risk ESFT.
Tandem autologous-autologous HSCT	For pediatric patients with high-risk ESFT, what is the comparative effectiveness and harms of tandem autologous-autologous HSCT and single HSCT regarding overall survival? Comparator is single HSCT. Outcome of interest is overall survival.	Evidence for tandem HSCT consists of 2 case series and 1 case report. Comparator data used consists of 24 case series and 6 case reports. Data consist of 22 tandem HSCT patients and 446 single HSCT patients.	The risk of bias in this evidence is high. Studies consisted of 1 case report and 2 small case series.	Results for overall survival are unknown. Among the 3 studies using tandem HSCT, overall survival was not reported, and overall survival data could be calculated from one study only.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is imprecise; effects are uncertain. There is uncertainty on whether tandem HSCT is inferior, equivalent or superior to single HSCT.	Not applicable due to lack of obvious effect size.	The body of evidence on overall survival with tandem HSCT compared to single HSCT for the treatment of high-risk ESFT is insufficient to draw conclusions.

Results

Table 38 arrays the study selection criteria for ESFT.

Table 38. Study selection criteria for ESFT

Study Design	Population	Intervention	Comparators	Outcomes	Followup	Setting
Any study design	Pediatric patients (0-21-yr) with high-risk ESFT	Single Auto of Allo HSCT Tandem	Chemotherapy +/- RT Single auto HSCT	OS; EFS (DFS; PFS); adverse events;	All durations of followup	Inpatient for HSCT and/or conventional chemotherapy and outpatient for conventional chemotherapy.

Auto = autologous; DFS = disease-free survival; EFS = event-free survival; HSCT = hematopoietic stem-cell transplant; OS = overall survival; PFS = progression-free survival

Table 39 shows the study design and population. Seventeen studies were based in Europe,[353, 354, 356, 360, 362, 363, 366, 368, 369, 372, 374-376, 378, 380, 385, 386] seven in Asia,[357, 358, 370, 371, 379, 382 373] and 12 in the U.S. and Canada.[355, 359, 361, 364, 365, 367, 377, 381, 383, 384, 387, 388] The total number of patients for which data was abstracted from the 36 studies was 751 (468 HSCT and 283 chemotherapy). Twenty-eight studies included patients who underwent a single autologous or allogeneic HSCT.[353, 354, 356-371, 377-379, 381, 382 372-376] Three studies reported outcomes for tandem autologous-autologous HSCT.[354, 355, 380]

Seven studies included in this analysis involved patients who underwent conventional chemotherapy.[383-388 376] The patients who underwent conventional therapy were used as the comparators to the single HSCT population and the single HSCT population was used as the comparator to tandem HSCT population.

Table 40 shows the outcomes that were reported across studies.

Overall Survival

Data on overall survival were reported or generated in 20 HSCT studies[353, 355-358, 360, 362-366, 368-371, 373-376, 389] and four comparator studies (Table 41).[385-388] No direct comparisons can be made from the published data as there are no comparative studies.

Event-free Survival

Information on event-free survival can be found in Appendix D.

Table 39. ESFT study characteristics and population

Study	Design	Median Age (Range)	Gender (M,F%)	Histology, Site, Stage (%)	HSCT (N)	Comparator (N)	Treatment Period	Comment
Oberlin, France, 2008[366] a	case series	12.3 yrs (2 onths-25 years)*	59,41*	ES/PNET Cannot separate out sites of primary tumor and metastases by age <15 yrs old.	Autologous Total study n=97 (patients <15 n=61)	Not applicable	1991-1999	Only abstracted data for patients <15 years old as survival was reported as < 15 and >/= 15 in a univariate analysis
Meyers, USA, 2001[364] b	case series	13 yrs (1-22 yrs)	63,37	primary site: pelvis n=12 chest wall n=5 femur n=3 multiple sites n=6 other n=6	Autologous n=32	Not applicable	1996-1998	32 pts were eligible for HSCT, 9 did not proceed to consolidation: 4 secondary to progression, 3 secondary to toxicity or death during 1st two courses of induction CT, 1 patient refused therapy during induction, and insufficient data in 1 pt.
Burdach, Germany and Austria, 2003[354]	case series				Single auto HSCT n=18 Tandem auto HSCT n=14	Not applicable		Only abstracted for patients ≤17 yrs

Table 39. ESFT study characteristics and population (continued)

Study	Design	Median Age (Range)	Gender (M,F%)	Histology, Site, Stage (%)	HSCT (N)	Comparator (N)	Treatment Period	Comment
Burdach, Germany and Austria, 2000[353] c	case series	At HSCT 15 yrs (8-21 yrs)	50, 50*	Ewing's: Primary tumor site for relapsed patients: long bone n=9, pelvis n=1,scapula n=1, chest wall/ribs n=1 Primary tumor site for multifocal disease: various including long bones, pelvis, rib, vertebrae, skull, sternum, clavicle, liver, bone marrow, thigh, lungs, lymph node	Auto n=21 Allo n=7	Not applicable	1986-1994	Study included a total of 32 patients; data only abstracted for pts <21 yrs at HSCT
Drabko, Poland, 2005[356] d	case series	At tx 15 yrs (6-21 yrs)	52,48	primary tumor site (reported for 19 patients): long bone n=9 pelvis n=3 clavicle or sternum n=3 scapula n=1 vertebra n=1 skull n=1 rib n=1 metastatic sites: lung n=6 bones n=3 lung/BM n=1 lungs/skull n=1 bone marrow n=3 no data for 4 pts	21 Auto	Not applicable	1996-2002	
Prete, Italy, 1998[369] e	case series	At tx 8 yrs (5-14 yrs)	65,35	bone marrow involvement n=3	17 Auto	Not applicable	1993-1997	
Hawkins, USA, 2000[359] f	case series	At tx 14.6 yrs (6-21)	NR	long bone n=7 Axial n=8 Kidney n=1	16 Auto	Not applicable	1993-1997	

Table 39. ESFT study characteristics and population (continued)

Study	Design	Median Age (Range)	Gender (M,F%)	Histology, Site, Stage (%)	HSCT (N)	Comparator (N)	Treatment Period	Comment
Ozkaynak, USA, 1998[367] g	case series	15 yrs (5-21)	53,47	Ewing's/PNET	15 Auto	Not applicable	1992-1995	Study included a total of 27 patients with solid tumors who underwent HSCT; only abstracted those with PNET/Ewing's
Yaniv, Israel, 2004[371] h	case series	13 yrs (0.3-19)	64,36	primary tumor site long bone n=3; pelvis n=5; cranium n=1; scapula n=1; abdomen n=1	11 Auto	Not applicable	NR	
Kushner, USA, 2001[361] i	case series	16.5 yrs (8-21 yrs)	70,30	primary tumor site pelvis n=4; long bone n=3; perineum n=1; paraspinal n=1; chest wall n=1	10 Auto 5 of the 10 pts did not proceed to HSCT b/c of progressive disease	Not applicable	1990-1998	Study included 21 pts, only abstracted data for pts <21 yrs old.
Navid, USA and Canada, 2006[365] j	prospective Phase II trial	15 yrs (12-17 yrs)	67,33	primary tumor site long bone n=2; pelvis n=2; rib n=2; kidney n=1; chest wall n=1; thorax n=1 sites of metastases bone n=2; bone, BM n=1; bone, BM, lung n=1; lung n=1; regional LN n=1	9 Auto (4 pts did not undergo HSCT b/c did not achieve a PR or CR to induction CT)	Not applicable	1996-2000	Study included a total of 24 patients with various histologies; only abstracted pts with Ewing's

Table 39. ESFT study characteristics and population (continued)

Study	Design	Median Age (Range)	Gender (M,F%)	Histology, Site, Stage (%)	HSCT (N)	Comparator (N)	Treatment Period	Comment
Burke, USA, 2007[355] k	case series	14 yrs (.5-17)	71,29	primary tumor site pelvis n=5 scapula n=1 chest wall n=1 metastatic disease n=4	Tandem auto-auto N=6 Single auto n=1 (pt did not receive the second HSCT b/c of progressive disease)	Not applicable	1992-2003	8 pts in study; only included <21 yrs
Tanaka, Japan, 2002[370] l	case series	17.5 yrs (8-19)	67,33	primary tumor site pelvis n=2 sternum n=1 chest wall/lung n=1 long bone n=1 spinal cord n=1	6 Auto	Not applicable	"since 1986"	Study Included 7 pts; only abstracted <21
Kasper, Germany, 2006[360] m	case series	At tx 19 yrs (17-21)	NR	metastatic sites lung n=2 bone n=1	5 Auto	Not applicable	1998-2004	Study included a total of 30 pts with various histologies; only abstracted Ewing's pts <21 yrs (total of 9 Ewing's pts)
Hara, Japan, 1998[357] n	case series	5 yrs (2-12 yrs)	NR	stage 3 n=1 stage 4 n=1 relapsed n=1	3 Auto	Not applicable	1993-1997	
Pession, Italy, 1999[368] o	case series	6 yrs (3-12 yrs)	33,66	Ewing's Site and stage NR	3 Auto	Not applicable	1992-1994	Study included 19 pts with various histologies; only abstracted pts with Ewing's

Table 39. ESFT study characteristics and population (continued)

Study	Design	Median Age (Range)	Gender (M,F%)	Histology, Site, Stage (%)	HSCT (N)	Comparator (N)	Treatment Period	Comment
Lucidarme, France, 1998[363] p	Phase II study	8.5 yrs (2-17 yrs)*	68,32*	Metastatic disease n=3	Single auto n=1 auto x 2 n=2	Not applicable	1987-1995	Study included a total of 22 patients with mixed histologies; only abstracted pts with ESFT. It is not clear whether the 2nd auto HSCTs were planned tandem.
Laws, Germany, 2003[362] q	case series	9 and 17 yrs	0,100	primary tumor femur n=2 metastatic site scapula n=1 skull, pleura, humerus n=1	2 Auto	Not applicable	1988-1998	Study included a total of 18 pts, but age was only reported for 2.
Harimaya, Japan, 2003[358] r	case series	13 yrs (12-14 yrs)	50,50	Spinal column	2 Auto	Not applicable	NR	Study included 4 pts; did not abstract for 2 pts treated without HSCT
Costa, USA, 2008[377]	case report	At first HSCT 15 yrs	NR	NR	1 Auto	Not applicable	2000-2007	Pt developed AML at 53 months post HSCT and underwent a second HSCT.
Lucas, USA, 2008[381] s	case report	4 yrs	0,100	primary iliac crest, stage IV	1 Allo	Not applicable	NR	
Kogawa, Japan, 2004[379] t	case report	7 yrs	0,100	Cervical spine, epidural	1 Auto	Not applicable	NR	
Numata, Japan, 2002 u	case report	20 yrs at HSCT	0,100	Tumor site inguinal	1 Auto	Not applicable	1993	
Fazekas, Austria, 2008[378] v	case report	13 yrs	100,0	Stage IV	1 Auto	Not applicable	NR	

Table 39. ESFT study characteristics and population (continued)

Study	Design	Median Age (Range)	Gender (M,F%)	Histology, Site, Stage (%)	HSCT (N)	Comparator (N)	Treatment Period	Comment
Koscielniak, Germany, 2005[380] w	case report	15 yr	0,100	primary tumor site thorax	1 Tandem auto auto then an allo after relapse	Not applicable	1998	
Diaz, Spain, 2010[372] x	case series	13 yrs (3-21)	68,32	localized/regional at diagnosis in 57% metastases at diagnosis in 43% primary site of tumor distal extremity 23%, proximal extremity 13%, pelvis 30%, chest 19%, spine/paravertebral 15%	47	Not applicable	1995-2009	
Kwon, Korea, 2010[373]	case series	8 yrs*	100,0	stage IV	1	Not applicable	2005-2007	Study included a total of 11 patients with mixed histologies; only abstracted pt with ESFT.
Ilari, Italy, 2010[374] y	case series	103 mo (12-192)	42,58	localized n=16 metastatic n=8 primary tumor extremity n=7 axial n=17 Sites of mets lung n=5, BM n=3, bone n=3, other n=2	24	Not applicable	1998-2007	2 patients rapidly progressed during induction and did not proceed to HSCT

Table 39. ESFT study characteristics and population (continued)

Study	Design	Median Age (Range)	Gender (M,F%)	Histology, Site, Stage (%)	HSCT (N)	Comparator (N)	Treatment Period	Comment
Ladenstein, Austria/France/UK/ Switzerland/ Netherlands/ Germany/ Sweden, 2010[375] z	case series	NR	NR	disseminated multifocal Ewing's sarcoma Primary not reported separately for ≤ 14 years but for entire study population of 281 patients, extremity 31%, chest/spine/head and neck 24%, abd/pelvis 45% and sites of mets BM plus lung 10%, bone plus lung 45%, bone plus BM plus lungs 36%, other plus lungs 10%	99	Not applicable	1999-2005	Age and gender not reported separately for ≤14 years (entire study included 281 patients median age 16.2 years (range 0.4-49 years) . Survival data divided ≤14 years of age and >14
Burdach, Germany and Austria, 2010 [376] aa	case series	HSCT:15 (6-17) Comparator: NR	HSCT: 37,63 Comparator: NR	multiple primary bone metastases in 100% sternum n=1, VC n=7, pelvis n=7, lung n=4, LN n=1, MB nonspecified n=1, rib n=1, humerus n=4, cranium n=3, scapula n=1, femur n=3, fibula n=1, tibia=1, talus n=1, clavicle n=1	8	13	HSCT 1999-2000 Comparator1992-1996	Age and gender not reported separately for ≤17 years (comparator n=26 patients median age 17 yrs (6-37). Survival data for comparator does not separate ≤17 yrs and >17.

Table 39. ESFT study characteristics and population (continued)

Study	Design	Median Age (Range)	Gender (M,F%)	Histology, Site, Stage (%)	HSCT (N)	Comparator (N)	Treatment Period	Comment
Bernstein, USA/Canada 2006[388] bb	Phase II study	14.6 yrs (3.0-27.3)	39,61	Primary extremity 36%, pelvis 29%, spine 5%, chest wall 16%, other 14%) Metastatic sites: Isolated lung 35%, Lung plus other 15%, isolated bone 13%, isolated BM 7%, other 30%	Not applicable	110	NR	Study included 12% of patients between 20 and 30 yrs of age; survival data not separated by age.
Bhatia, USA, 2007[383] cc	case series	12 yrs (0-30)*	56,44		Not applicable	60	1992-1994	Study included 578 patients with Ewing's treated with one of three regimens, one of which was high-intensity and it is for this group only that data abstracted.
Sari, Turkey, 2010[386] dd	case series, retrospective	12 yrs (3-18)*	39;61	Primary tumor site: Extremity 53%, pelvis 28%,vertebrae 8%,chest wall 11%	Not applicable	36	1992-2005	Study included a total of 87 pts- only abstracted data for the 36 patients with metastatic disease (high-risk) and b/c survival was reported by metastatic vs. nonmetastatic disease

Table 39. ESFT study characteristics and population (continued)

Study	Design	Median Age (Range)	Gender (M,F%)	Histology, Site, Stage (%)	HSCT (N)	Comparator (N)	Treatment Period	Comment
Kushner, USA, 1995[384] ee	prospective case series	nonmetastatic disease 15 yrs (1.5-21) metastatic disease 17 yrs (9-21)	Nonmet disease 76,24 Met disease 86,14	Nonmet disease primary tumor site chest wall 24%long bone 41%paraspinal 6%pelvis18%thigh 6% retroperitoneum 6% Metastatic disease primary tumor site illium n=1 Fibula n=1 Femur n=1 Pubis bone n=1 Bone marrow, dura, cranium, sacrum n=1 Pubis, bone marrow n=2	Not applicable	24	NR	Study included 36 patients; only abstracted data for those <21 yrs (17 patients with nonmetastatic disease and 7 with metastatic)
Van Winkle, USA, 2005[387] ff	case series	14.1 yrs (2.8-22,5)*	57,43	Ewing's of bone n=21 Extraosseous Ewing's n=1 Sites of recurrence: lung 28%, extremity 28%, pelvis 10%, head/neck10%,other 24%	Not applicable	22	1992-1996	Study included a total of 97 patients with various histologies-only abstracted those with Ewing's.
Milano, Italy, 2006[385] gg	case series	115 mos (20-214)	NR	PNET/ES Metastatic disease in 33%	Not applicable	18	1990-2005	Only abstracted data for patients who received ICE/CAV CT (study included a total of 36 pts)

BM = bone marrow; CR = complete remission; CT = chemotherapy; LN = lymph node; NR = not reported; RT = radiation
*age or gender reported for all pts in study
Therapeutic setting
a Newly diagnosed with metastases;
b Newly diagnosed with metastases to bone and/or BM;
c Relapsed (early, late or multiple) n=12 primary multifocal disease n=16;

d high risk- poor local control or metastases at presentation (n=14; no data on metastatic status for 4 patients);
e Metastatic disease at diagnosis n=14 localized disease n=3;
f Metastatic disease n=2; Recurrent disease n=14;
g Relapsed or metastatic disease with bone and/or BM involvement;
h Metastatic at diagnosis, poor response defined as <90% necrosis at definitive surgery or primary tumor not resectable with clear margins, relapsed;
i Newly diagnosed with metastases to bone or BM
j Metastatic (n=6) or tumor >8 cm in greatest dimension;
k Pelvic primary and/or metastatic disease;
l Large tumor, pelvic primary, intracranial extension, lung mets or pleural cavity involvement;
m Newly diagnosed with metastatic disease n=3; Newly diagnosed without metastatic disease n=2;
n Relapsed n=1, or advanced stage;
o Relapsed or disseminated disease
p Refractory;
q Relapsed;
r primary tumor, high risk site;
s Relapsed with metastases
t Primary diagnosis, no metastatic disease
u primary diagnosis;
v primary diagnosis;
w Disseminated at diagnosis;
x high-risk localized tumor (tumor volume >200mL, inoperable tumor, or poor histological response to neoadjuvant CT) and those with mets at diagnosis;
y Poor prognosis ESFT (metastasis or axis location, or tumor >200 mL or necrosis <95%);
z primary treatment;
aa high-risk with multiple primary bone mets
bb Metastatic disease at diagnosis;
cc Metastatic disease;
ddMetastatic disease at diagnosis;
ee Newly diagnosed deemed poor-risk because of tumor volume >100 cm^3 or metastases to bone or BM.;
ff Recurrent/refractory;
gg high risk including tumor volume >200 mL, site with poor prognosis or lung and/or bone marrow metastases

Table 40. ESFT outcomes reported

Study	OS	EFS (DFS, PFS)	Quality of Life	Treatment-Related Mortality	Second Malignancies	Other Adverse Effects
Oberlin, France, 2008[366]	√	√	NR	√	√	√
Meyers, USA, 2001[364]	√	√	NR	√	NR	√
Burdach, Germany and Austria, 2000[353]	NR	√	NR	√	√	√
Drabko, Poland, 2005[356]	√	√	NR	√	NR	√
Prete, Italy, 1998[369]	√	√	NR	√	NR	NR
Hawkins, USA, 2000[359]	NR	√	NR	√	√	√
Ozkaynak, USA, 1998[367]	NR	√	NR	√	NR	√
Yaniv, Israel, 2004[371]	NR	NR	NR	√	NR	NR
Kushner, USA, 2001[361]	NR	√	NR	√	NR	√
Navid, USA and Canada, 2006[365]	√	√	NR	√	√	√
Burke, USA, 2007[355]	NR	NR	NR	√	NR	√
Tanaka, Japan, 2002[370]	√	√	NR	√	√	√
Kasper, Germany, 2006[360]	√	√	NR	NR	NR	√
Hara, Japan, 1998[357]	NR	NR	NR	√	NR	√
Pession, Italy, 1999[368]	NR	NR	NR	√	NR	√
Lucidarme, France, 1998[363]	NR	NR	NR	√	NR	√
Harimaya, Japan, 2003[358]	NR	NR	NR	NR	NR	NR
Laws, Germany, 2003[362]	√	√	NR	NR	NR	NR
Numata, Japan, 2002[382]	NR	NR	NR	NR	√	NR
Costa, USA, 2008[377]	NR	NR	NR	NR	√	NR
Lucas, USA, 2008[381]	NR	NR	NR	NR	NR	√
Kogawa, Japan, 2004[379]	NR	NR	NR	NR	NR	√
Fazekas, Austria, 2008[378]	NR	NR	NR	NR	NR	√
Koscielniak, Germany, 2005[380]	NR	NR	NR	NR	NR	√
Diaz, Spain, 2010[372]	NR	√	NR	NR	NR	√
Kwon, Korea, 2010[373]	√	NR	NR	NR	NR	NR
Ilari, Italy, 2010[374]	√	√	NR	√	√	√

Table 40. ESFT outcomes reported (continued)

Study	OS	EFS (DFS, PFS)	Quality of Life	Treatment-Related Mortality	Second Malignancies	Other Adverse Effects
Ladenstein, Austria/France/UK/ Switzerland/ Netherlands/ Germany/ Sweden, 2010[375]	√	√	NR	√	√	√
Burdach, Germany and Austria, 2010 [376]	√	NR	NR	√	√	√
Bernstein, USA/Canada 2006[388]	√	√	NR	√	√	√
Bhatia, USA, 2007[383]	NR	NR	NR	NR	√	NR
Sari, Turkey, 2010[386]	√	√	NR	√	√	√
Kushner, USA, 1995[384]	NR	√	NR	√	√	√
Van Winkle, USA, 2005[387]	√	NR	NR	√	NR	√
Milano, Italy, 2006[385]	√	√	NR	NR	NR	√

DFS = disease-free survival; EFS = event-free survival; NR = not reported; OS = overall survival; PFS = progression-free survival

Table 41. Overall survival for treatment (single HSCT and tandem auto HSCT) and comparison (conventional chemotherapy +/- radiation) groups

Followup	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
1 year	~75%	Not applicable		Meyers, USA, 2001[364] (n=32)
	54% (35-72)*	Not applicable		Burdach, Germany and Austria, 2000[353] (n=28)
	82% (59-100)*	Not applicable		Yaniv, Israel, 2004[371] (n=11)
	89% (68-100%)*	Not applicable		Navid, USA and Canada, 2006[365] (n=9)
	71% (38-100)*	Not applicable		Burke, USA, 2007[355] (n=7)
	100%*	Not applicable		Tanaka, Japan, 2002[370] (n=6)
	100*	Not applicable		Kasper, Germany, 2006[360] (n=5)
	100%*	Not applicable		Kasper, Germany, 2004[389] (n=4)
	67% (13-100%)*	Not applicable		Hara, Japan, 1998[357] (n=3)
	67% (13-100%)*	Not applicable		Pession, Italy, 1999[368] (n=3)
	33% (0-87%)*	Not applicable		Lucidarme, France, 1998[363] (n=3)
	100% (0-100%)*	Not applicable		Harimaya, Japan, 2003[358] (n=2)
	50% (0-100%)*	Not applicable		Laws, Germany, 2003[362] (n=2)
	DOD at 11 mo	Not applicable		Kwon, Korea, 2010[373]
	Not applicable	77% (+/-4%) [isolated lung mets vs. other or more than isolated lung mets 82% +/-6% and 74% +/-5% p=0.47]		Bernstein, USA/Canada 2006 [388] (n=110)
	Not applicable	~68%		Sari, Turkey, 2010[386] (n=36)
	Not applicable	43%		Van Winkle, USA, 2005[387] (n=22)
1 year OS ranges	54-75%[353, 364]	43-77%[386-388]		

Table 41. Overall survival for treatment (single HSCT and tandem auto HSCT) and comparison (conventional chemotherapy +/- radiation) groups (continued)

Time Period	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
2 year	~35	Not applicable		Meyers, USA, 2001[364] (n=32)
	68%	Not applicable		Drabko, Poland, 2005[356] (n=21)
	70%	Not applicable		Prete, Italy, 1998[369] (n=17)
	33% (0-87%)*	Not applicable		Lucidarme, France, 1998[363] (n=3)
	50% (0-100%)*	Not applicable		Laws, Germany, 2003[362] (n=2)
	Not applicable	46% (+/-5%) [isolated lung mets vs. other or more than isolated lung mets 49% +/-8% and 44% +/-6% p=0.47]		Bernstein, USA/Canada 2006[388] (n=110)
	Not applicable	~36%		Sari, Turkey, 2010[386] (n=36)
	Not applicable	33%		Van Winkle, USA, 2005[387] (n=22)
3 year	39% (21-57)*	Not applicable		Burdach, Germany and Austria, 2000[353] (n=28)
	54% (16-75)*	Not applicable		Yaniv, Israel, 2004[371] (n=11)
	56% (23-88%)*	Not applicable		Navid, USA and Canada, 2006[365] (n=9)
	71% (38-100)*	Not applicable		Burke, USA, 2007[355] (n=7)
	83% (54-100)*	Not applicable		Tanaka, Japan, 2002[370] (n=6)
	80% (52-100)*	Not applicable		Kasper, Germany, 2006[360] (n=5)
	75% (33-100)*	Not applicable		Kasper, Germany, 2004[389] (n=4)
	67% (13-100%)*	Not applicable		Hara, Japan, 1998[357] (n=3)
	67% (53-100%)*	Not applicable		Pession, Italy, 1999[368] (n=3)
	50% (0-100%)*	Not applicable		Harimaya, Japan, 2003[358] (n=2)
	46%	Not applicable	<.001	Ladenstein, Austria/France/UK/ Switzerland/ Netherlands/ Germany/ Sweden, 2010[375]
	Not applicable	isolated lung mets ~34% other or more than isolated lung mets ~24%		Bernstein, USA/Canada 2006[388] (n=110)
	Not applicable	~32%		Sari, Turkey, 2010[386] (n=36)
	Not applicable	67% +/-12%		Milano, Italy, 2006[385] (n=18)
3 year OS ranges	32-39%[353]	24-67%[385, 388]		

Table 41. Overall survival for treatment (single HSCT and tandem auto HSCT) and comparison (conventional chemotherapy +/- radiation) groups (continued)

Time Period	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
5 year	49%	Not applicable		Oberlin, France, 2008[366] (n=61)
	24% (8-40)*	Not applicable		Burdach, Germany and Austria, 2000[353] (n=28)
	18% (0-41%)*	Not applicable		Yaniv, Israel, 2004[371] (n=11)
	56% (23-88%)*	Not applicable		Navid, USA and Canada, 2006[365] (n=9)
	54% (14-93%)*	Not applicable		Burke, USA, 2007[355] (n=7)
	83% (54-100)*	Not applicable		Tanaka, Japan, 2002[370] (n=6)
	80% (52-100)*	Not applicable		Kasper, Germany, 2006[360] (n=5)
	67% (13-100%)*	Not applicable		Hara, Japan, 1998[357] (n=3)
	67% (53-100%)*	Not applicable		Pession, Italy, 1999[368] (n=3)
	50% (0-100%)*	Not applicable		Harimaya, Japan, 2003[358] (n=2)
	A NED at 73+ months	Not applicable		Costa, USA, 2008[377] (n=1)
	A NED 60 months after surgery	Not applicable		Kogawa, Japan, 2004[379] (n=1)
	64% (38-81)	Not applicable		Ilari, Italy, 2010[374]
	50%*	Not applicable		Burdach, Germany and Austria, 2010[376]
	Not applicable	isolated lung mets ~24% other or more than isolated lung mets ~20%		Bernstein, USA/Canada 2006[388] (n=110)
	Not applicable	27%		Sari, Turkey, 2010[386] (n=36)
	Not applicable	~67%		Milano, Italy, 2006[385] (n=18)
5 year OS ranges	24-49% [353, 366]	20-67%[385, 386, 388]		

A = alive; NED = no evidence of disease; DOD = dead of disease
~= estimated from K-M curve in study
*=generated for this SR
Costa- pt underwent 2nd HSCT at 53 months for AML- at 73 months NED (ESFT or AML)

Adverse Effects

None of the studies evaluated quality of life. Data on treatment-related mortality was reported in 14 HSCT studies[353, 355, 356, 363-365, 367-371, 374, 375 376] and three comparative studies.[385, 387, 388] (Table 42). Eleven HSCT[353, 355, 356, 359, 360, 364, 370, 372, 374, 375 376] and two comparator studies[385, 388] reported serious infectious complications. Six HSCT studies[353, 365, 374, 375, 377 376] and four comparator studies[383, 384, 386, 388] reported a secondary malignancy. Seven HSCT studies[356, 359, 361, 381 372, 374, 375] and one comparator study[385] reported other long-term complications involving severe organ dysfunction.

Ongoing Studies

Two ongoing Phase III trials will include an HSCT arm in the treatment of patients with high-risk ESFT:

- A study in localized and disseminated Ewing Sarcoma (EWING 2008; NCT00987636) will include a randomized trial arm for high-risk Ewing's (localized and unfavorable histological response or tumor volume greater than 200 mL) examining whether HSCT compared with standard chemotherapy improves EFS. Patients with pulmonary metastases will be randomized to HSCT versus standard chemotherapy and whole lung irradiation. Very high-risk patients (with primary disseminated disease) will be randomized to HSCT versus standard chemotherapy. Estimated enrollment is 1,383 with an estimated study completion date of March 2018.
- A randomized trial is comparing chemotherapy with or without peripheral stem-cell transplantation, radiation, and/or surgery (EURO-EWING 99; NCT00020566). Primary outcome measures include EFS and OS. Estimated enrollment is 1,200 with an estimated primary completion date of December 2011.

Conclusion

Low strength evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for the treatment of high-risk ESFT.

The body of evidence on overall survival with tandem HSCT compared to single HSCT for the treatment of high-risk ESFT and overall survival is insufficient to draw conclusions.

Table 42. Adverse effects for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups

Outcome	Intervention (HSCT [%])	Comparator (Chemo [%])	Study
Treatment-related mortality	12%	Not applicable	Meyers, USA, 2001[364]
	18%	Not applicable	Burdach, Germany and Austria, 2000[353]
	5%	Not applicable	Drabko, Poland, 2005[356]
	13%	Not applicable	Ozkaynak, USA, 1998[367]
	18%	Not applicable	Yaniv, Israel, 2004[371]
	2%*	Not applicable	Ladenstein,Austria/France/UK/Switzerland/Netherlands/Germany/Sweden, 2010[375]
	0%	Not applicable	Navid, 2006[365]; Prete, 1998[369]; Burke, 2007[355]; Tanaka, 2002[370]; Pession, 1999[368]; Lucidarme, 1998[363] Ilari, 2010[374]
	38%	Not applicable	Burdach, Germany and Austria, 2010 [376]
	Not applicable	5%	Bernstein, USA/Canada 2006[388]
	Not applicable	0.6%*	Van Winkle, USA, 2005[387]
	Not applicable	0%	Milano, Italy, 2006[385]
Infectious complications	5% septic death	Not applicable	Meyers, USA, 2001[364]
	18% septic death	Not applicable	Burdach, Germany and Austria, 2000[353]
	5% septic death	Not applicable	Drabko, Poland, 2005[356]
	6% death due to CMV infection	Not applicable	Hawkins, USA, 2000[359]
	Sepsis 28% (not leading to death)	Not applicable	Burke, USA, 2007[355]
	4/24 (17%) cases of sepsis	Not applicable	Ilari, Italy, 2010[374]
	1/47 (2%) septic shock 1/47 (2%) fungal infection	Not applicable	Diaz, Spain, 2010[372]
	13%	Not applicable	Burdach, Germany and Austria, 2010 [376]
	0%	Not applicable	Tanaka, 2002[370]; Kasper, 2006[360]
	Not applicable	6/110 (5%) septic deaths	Bernstein, USA/Canada 2006[388]
	Not applicable	2/18 (11%) cases of sepsis	Milano, Italy, 2006[385]

Table 42. Adverse effects for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups (continued)

Outcome	Intervention (HSCT [%])	Comparator (Chemo [%])	Study
Secondary malignancies	11% (MDS n=2 liposarcoma n=1)	Not applicable	Burdach, Germany and Austria, 2000[353]
	0%	Not applicable	Navid, 2006[365], Ilari, 2010[374], Ladenstein, 2010[375]
	n=1 (AML)	Not applicable	Costa, USA, 2008[377]
	25%	Not applicable	Burdach, Germany and Austria, 2010 [376]
	Not applicable	1/110 (1%) MDS	Bernstein, USA/Canada 2006[388]
	Not applicable	10% (MDS/AML)	Bhatia, USA, 2007[383]
	Not applicable	1/1 CML	Numata, Japan, 2002[382]
	Not applicable	0%	Sari, Turkey, 2010[386]
	Not applicable	1/24 (4%) AML	Kushner, USA, 1995[384]
Long-term complications	10% n=1 died (pulmonary failure)	Not applicable	Kushner, USA, 2001[361]
	n=1 dilated CMP, pulmonary HTN, renal failure, interstitial pneumonia	Not applicable	Lucas, USA, 2008[381]
	n=1 short stature/growth retardation n=5 ovarian impairment	Not applicable	Ilari, Italy, 2010[374]
	Not applicable	0/18 (0%)	Milano, Italy, 2006[385]
Veno-occlusive disease	10% (n=2 moderate/severe VOD)	Not applicable	Drabko, Poland, 2005[356]
	6% (n=1 severe VOD)	Not applicable	Hawkins, USA, 2000[359]
	n=5* (grade 3 VOD)	Not applicable	Ladenstein,Austria/France/UK/Switzerland/Netherlands/Germany/Sweden, 2010[375]

AML = acute myelogenous leukemia; MDS = myelodysplastic syndrome; vod = veno-occlusive disease

* For total population

Wilms Tumor Systematic Review

Background and Setting

Wilms tumor is the fifth most common pediatric malignancy and the most common type of renal tumor in children. The incidence of Wilms tumor is approximately 0.8 cases per 100,000 persons, with approximately 500 new cases diagnosed each year in the U.S., 6 percent involving both kidneys.[390] Most cases occur sporadically, whereas some are hereditary or associated with certain syndromes. Wilms tumor is diagnosed at a mean age of 3.5 years, and is unusual after the age of 6.[391] Overall survival rates for Wilms tumor are approximately 90 percent with first-line therapy consisting of surgery, chemotherapy and in some cases radiation therapy (to the abdomen and/or lungs).[390] However, approximately 15 percent of patients with favorable (nonanaplastic) histology and 50 percent of patients with anaplastic histology experience tumor recurrence.[381] Recurrent Wilms tumor is a heterogeneous disease and treatment is generally based upon patient risk stratification. For patients with favorable prognostic features, standard-dose chemotherapy may be curative.

Patients with relapsed disease and adverse prognostic factors are considered as a high-risk relapse category. Adverse prognostic factors include initial advanced tumor stage, anaplastic histology, early recurrence (less than 6 months after diagnosis), recurrence in multiple organs or in a previously irradiated field, and initial chemotherapy consisting of vincristine, actinomycin D, and doxorubicin (versus vincristine and actinomycin D alone). Since the identification of this high-risk group of patients with relapsed disease and the poor outcome after initial treatment with chemotherapy consisting of vincristine, actinomycin D, and doxorubicin (VAD) and radiation therapy, investigation now focuses on the activity of ifosfamide, etoposide, and platinum analogs as single agents or in combination, and in more intensive doses. Other intensive dose strategies include the use of myeloablative chemotherapeutic regimens and HSCT.

Evidence Summary

The overall grade of strength of comparative study evidence for overall survival and the use of HSCT for the treatment of high-risk relapsed Wilms tumor is shown in Table 43.

The literature using dose-intensive chemotherapeutic regimens consists of case series with small numbers of patients, without direct comparisons between conventional intensive chemotherapy and HSCT.

The evidence compiled for this review includes 13 case series[364, 392-403] and seven case reports.[378, 404-409] The comparator is conventional chemotherapy. Although direct comparisons are difficult to make between dose-intensive chemotherapy and HSCT in high-risk relapsed Wilms, based on the current systematic review, there does not appear to be a difference in progression-free or overall survival between the two groups. No information on quality of life was provided and data on adverse events was sparse and therefore insufficient to make conclusions regarding adverse effects and quality of life.

Results

Thirty-eight articles were retrieved for full-text screening. Twenty reports were included in this review, and the remaining 18 articles were excluded. Table 44 arrays the criteria that were used to select studies for this section.

Table 45 shows the study designs and population. Of the included publications, 13 were case series[364, 392-403] and seven were case reports.[378, 404-407] Nine studies were based in Europe,[378, 392-394, 397, 398, 400, 404, 405] one in Asia,[401] two in South America,[399, 410] and eight in the U.S.[395, 396, 402, 403, 406-409]

The total number of patients for which data was abstracted from the twenty studies was 202: 114 patients received HSCT, whereas 88 patients received chemotherapy.

Fifteen studies included patients who underwent HSCT,[378, 392-400, 404, 406, 407] two studies contained data for patients treated either with HSCT or conventional therapy,[401, 410] one study contained a report of double sequential high-dose chemotherapy with HSCT,[405] and two studies included in this analysis contained only patients that underwent conventional chemotherapy.[402, 403] The patients who underwent conventional therapy were used as the comparators to the HSCT population. No studies were identified using tandem autologous HSCT. Patients from these 20 studies received HSCT or conventional chemotherapy for relapsed (first or subsequent), progressive disease, or metastatic disease and one study included patients in first complete remission with bilateral disease (stage V).

Table 43. Overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of high-risk relapsed Wilms tumor

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with high-risk relapsed Wilms tumor, what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Outcome of interest is overall survival. The comparator is conventional chemotherapy.	The data for HSCT consists of 11 case series and 7 case reports. The comparator data used consists of 2 case series. Total number of patients HSCT n=114 Comparator n=88	The risk of bias in this evidence is high. Studies consisted of case reports or small case series and incorporated heterogeneous patient populations.	Results for overall survival are consistent. Ranges of outcomes across the different studies are similar.	Where outcomes were reported, the evidence is direct. The comparators are indirect in that the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is precise. While the evidence is qualitative, it is unlikely that a clinically important superiority exists for HSCT for the treatment of high-risk relapsed Wilms compared to conventional chemotherapy.	Not applicable due to lack of obvious effect size.	Low strength evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for the treatment of high-risk relapsed Wilms tumor.

Table 44. Wilms tumor study selection criteria

Study Design	Population	Intervention	Comparators	Outcomes	Followup	Setting
Any study design	Pediatric patients (0-21-yr) with high-risk relapsed or resistant Wilms tumor	Single Auto HSCT Tandem Auto HSCT	Chemotherapy +/- RT Single auto HSCT	OS; EFS (DFS; PFS); adverse events;	All durations of followup	Inpatient (HSCT and /or comparator chemotherapy) and outpatient (comparator chemotherapy)

Auto = autologous; DFS = disease-free survival; EFS = event-free survival; HSCT = hematopoietic stem-cell transplant; OS = overall survival; PFS = progression-free survival

Table 45. Wilms tumor study characteristics and population

Study	Design	Median Age (Range)	Sex (M, F%)	Histology, Site, Stage (%)	HSCT (N)	Comparator (N)	Treatment Period	Comment
Pein, France, 1998[398]	Case Series	6 years (2-16 years)	41, 59	Initial stage: I n=4 II n=12 (5 were LN +) III n=5 IV n=6 V n=2 FH n=23 UH n=6	Autologous HSCT (n=28)	Not applicable	1988-1994	Includes 3 patients with clear cell sarcoma of the kidney 1 pt. lost to follow up
Kremens, Germany, 2002[392]	Case Series	at diagnosis 74 months (11-210 months)	52, 48	Initial stage: I n=4 II n=4 III n=3 IV n=13 (does not total 23) Intermediate risk n=14 High-risk n=5 Completely necrotic tumor n=1	Autologous HSCT (n=23)	Not applicable	1992-1998	Includes one patient with clear cell sarcoma
Spreafico, Italy, 2008[394]	Case Series	at diagnosis 4.1 years (1.1-11.2 years)	30, 70	High risk n=3 relapsed in prior RT field Initial stage: I n=1 II n=2 III n=8 IV n=8 Wilms n=19 CCSK n=1	Autologous HSCT (n=20)	Not applicable	2001-2006	20 patients were enrolled; 5 did not receive HSCT (3 due to progressive disease and 2 at the discretion of the treating physician) Includes one patient with clear cell sarcoma
Campbell, USA, 2004[395]	Case Series	at diagnosis 4.8 years (1-15 years)	31, 69	Initial stage: I n=2 II n=1 III n=5 IV n=5 FH n=12 UH n=1	Autologous HSCT (n=13)	Not applicable	1991-2001	

Table 45. Wilms tumor study characteristics and population (continued)

Study	Design	Median Age (Range)	Sex (M, F%)	Histology, Site, Stage (%)	HSCT (N)	Comparator (N)	Treatment Period	Comment
Hempel, Germany, 1996[400]	Case Series	at HSCT 6.25 years (3.9-14.8 years)*	86, 14	UH n=1, FH n=6	Autologous HSCT (n=7)	Not applicable	1992-1995	Study included 8 patients; one patient was misdiagnosed as Wilms (had a rhabdomyosarcoma) and is not included in this analysis.
Kullendorff, Sweden, 1997[397]	Case Series	at diagnosis median 55 months (43-119 months)	33,66	Initial stage: I n=2 III n=2 FH n=3 UH n=1 Site of relapse lung n=2 and bone n=2	Autologous HSCT (n=4)	Not applicable	1987-1992	Includes one patient with clear cell sarcoma of the kidney
Valera, Brazil, 2004[399]	Case Series	at diagnosis 7 years (3-9 years)	66,33	Initial stage: II n=1 III n=1 IV n=1	Autologous HSCT (n=3)	Not applicable		
Saarinen-Pihkala, Finland, 1998[393]	Case Series	at diagnosis 46 months (6-60 months)	66,33	Stage: V n=3 Metastases to lung n=1 FH n=2, rhabdomyomatous n=1	Autologous HSCT (n=3)	Not applicable		
Termuhlen, USA, 2006[396]	Case Series phase 1 study	40.5 months (21-60 months)	0,100	Stage V n=2	Autologous HSCT (n=2)	Not applicable		Study included 4 patients (2 had neuroblastoma)
Fazekas, Austria, 2008[378]	Case Report	5 yrs at HSCT	100,0	"intermediate risk"- not further defined	Autologous HSCT (n=1)	Not applicable		
Goldman, USA, 2001[406]	Case Report	2 years at HSCT	100,0	Relapse 6 months after diagnosis Initial stage III Relapse in lungs and abdomen	Autologous HSCT (n=1)	Not applicable	1994-1998	Study included 8 patients with various histologies; only abstracted Wilms.

Table 45. Wilms tumor study characteristics and population (continued)

Study	Design	Median Age (Range)	Sex (M, F%)	Histology, Site, Stage (%)	HSCT (N)	Comparator (N)	Treatment Period	Comment
Dagher, USA, 1998[407]	Case Report	7 years at HSCT	0,100	Recurred in right-sided tumor bed	Autologous HSCT (n=1)	Not applicable		Patient had a left-sided Wilms tumor, FH, stage II at age 9 months and underwent L nephrectomy and CT. At age 6 years, patients developed a right kidney Wilms tumor for which she underwent right nephrectomy, CT and RT. At 7 years of age she had a right-sided recurrence and underwent HSCT.
Hempel, Germany, 1998[404]	Case Report	11 months	100,0	Stage II "medium" malignancy	Autologous HSCT (n=1)	Not applicable		
Maurer, Austria, 1997[405]	Case Report	at diagnosis 8 years	0,100	Initial stage IV with lung metastases UH	Double sequential high-dose chemotherapy and autologous HSCT (n=1)	Not applicable		

Table 45. Wilms tumor study characteristics and population (continued)

Study	Design	Median Age (Range)	Sex (M, F%)	Histology, Site, Stage (%)	HSCT (N)	Comparator (N)	Treatment Period	Comment
Park, Korea, 2006[401]	Case Series	2 yrs (2-3 yrs)	70,30	Autologous HSCT: Initial stage: II n=3 FH n=1 UH n=2 Site of relapse lung n=2 abdomen n=1 Comparator: Initial stage: I n=1 II n=3 III n=1 IV n=2 FH =7 Site of relapse lung n=6 Abdomen n=4 Liver n=1 BM n=1 Bone n=1	Autologous HSCT (n=3)	Chemotherapy +/- RT (n=7)	1994-2004	Comparators were relapsed with at least one risk factor.
Tucci, Brazil, 2007[410]	Case Series	2 years*		Metastases in the liver and lungs.	Autologous HSCT (n=1)	Chemotherapy +/- RT (n=10)		One patient included in the comparator group underwent HSCT. Overall the study included 53 patients. Only abstracted relapsed patients for comparators and one of the relapsed patients had favorable prognostic factors.
Malogolowkin, USA, 2008[403]	Case Series	at diagnosis 0-23 months n=4 24-47 months n=21 48+ n=35	47,53	Initial stage II n=1 III n=39 IV n=20 FH n=56 Focal anaplasia n=3 Diffuse anaplasia n=1	Not applicable	Chemotherapy +/- RT (n=60)	1995-2002	

Table 45. Wilms tumor study characteristics and population (continued)

Study	Design	Median Age (Range)	Sex (M, F%)	Histology, Site, Stage (%)	HSCT (N)	Comparator (N)	Treatment Period	Comment
Abu-Ghosh, USA, 2002[402]	Case Series	at diagnosis 36 months (13-192 months)		High-risk Initial stage: I 18% II 9% III 36% IV 27% V 9% FH 82%, UH 18% Site of relapse: lung 36%, pleura 9%, kidney 18%, kidney and lung 18%, liver 9%	Not applicable	Chemotherapy +/- RT (n=11)	1992-1999	
Brown, USA, 2010[408]	Case Report	At diagnosis 48 months	100,0	Initial stage I n=1	Autologous HSCT (n=1)	Not applicable		Patient treated with chemotherapy, surgical resection, and high-dose chemotherapy with autologous stem-cell transplant in CR3 followed by radiation
Lucas, USA, 2010[409]	Case Report	At diagnosis 12 months	100,0	favorable histology, Wilms - left kidney plus right lung nodules	Allogeneic HSCT (n=1)	Not applicable		

CR = complete remission; CSSK = clear cell sarcoma of the kidney; CT = chemotherapy; FH = favorable histology; LN = lymph node; NR = not reported; RT = radiation;
UH = unfavorable histology
* Included all patients in study.

Table 46 shows the outcomes that were reported across studies.

Table 46. Wilms tumor outcomes reported

Study	OS	EFS (DFS, PFS)	Quality of Life	Treatment-Related Mortality	Second Malignancies	Other Adverse Effects
Fazekas, Austria, 2008[378]	√	NR	NR	√	NR	NR
Spreafico, Italy, 2008[394]	√	√	NR	√	NR	√
Malogolowkin, USA, 2008[403]	√	√	NR	√	√	√
Tucci, Brazil, 2007[410]	√	√	NR	NR	NR	√
Termuhlen, USA, 2006[396]	NR	NR	NR	NR	NR	√
Park, Korea, 2006[401]	√	√	NR	NR	NR	√
Campbell, USA, 2004[395]	√	√	NR	√	NR	√
Valera, Brazil, 2004[399]	NR	NR	NR	NR	NR	√
Kremens, Germany, 2002[392]	√	√	NR	√	NR	√
Abu-Ghosh, USA, 2002[402]	√	√	NR	√	NR	√
Goldman, USA, 2001[406]	NR	NR	NR	√	NR	√
Saarinen-Pihkala, Finland, 1998[393]	NR	√	NR	NR	NR	√
Pein, France, 1998[398]	√	√	NR	√	NR	√
Dagher, USA, 1998[407]	NR	NR	NR	NR	NR	√
Hempel, Germany, 1998[404]	NR	NR	NR	NR	NR	√
Kullendorff, Sweden, 1997[397]	NR	NR	NR	√	NR	NR
Maurer, Austria, 1997[405]	NR	NR	NR	NR	NR	√
Hempel, Germany, 1996[400]	NR	NR	NR	√	NR	√
Brown, USA, 2010[408]	NR	√	NR	NR	NR	√
Lucas, USA, 2010[409]	NR	√	NR	NR	NR	NR

DFS = disease-free survival; EFS = event-free survival; NR = not reported; OS = overall survival; PFS = progression-free survival

Overall Survival

Data on overall survival were reported in fifteen studies (Table 47).[378, 392, 394-398, 400-403, 405-407, 410] No direct comparisons can be made from the published data as there are no comparative studies.

Event-free Survival

Information on event-free survival can be found in Appendix D.

Table 47. Overall survival for treatment (single auto HSCT) and comparison (conventional chemotherapy +/- radiation) groups

Followup	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	Study
1 year	1 yr 86% [73-100] (n=28)	Not applicable	Pein,1998[398]
	Not applicable	1 yr ~73% (n=11)	Abu-Ghosh, 2002[402]
	1 yr 70% [51-88] (n=23)	Not applicable	Kremens, 2002[392]
	1yr 90% [77-100]% (n=20)	Not applicable	Spreafico,2008[394]
	1 yr 100%* (n=7)	Not applicable	Hempel, 1996[400]
	All patients 1 year 75% [33-100]* (n=4) Only Wilms 1 year 100%* (n=3)	Not applicable	Kullendorf, 1997[397]
	median 53+ months (31+-76+) (n=3)	Median 15 months (2-30 months) (n=5)	Park, 2006[401]
	1yr 100% (n=2)	Not applicable	Termuhlen, 2006[396]
	A NED at 12 mos (n=1)	Not applicable	Fazekas, 2008[378]
	A NED at 16+ mos (n=1)	Not applicable	Goldman,2001[406]
	1.8 years (n=1)	Not applicable	Dagher, 1998[407]
2 year	2 yr 60% [41-78] (n=28)	Not applicable	Pein,1998[398]
	2 yr 61% [41-81] (n=23)	Not applicable	Kremens, 2002[392]
	Not applicable	2 yr 64% (n=11)	Abu-Ghosh, 2002[402]
	2 yr 86% [60-100]* (n=7)	Not applicable	Hempel, 1996[400]
	All patients 2 year 75% [33-100]* Only Wilms 2 year 100%* (n=4)	Not applicable	Kullendorf, 1997[397]
	2 yr 100% (n=2)	Not applicable	Termuhlen, 2006[396]
3 year	3yr 60% [41-78] (n=28)	Not applicable	Pein, 1998[398]
	3 yr 61% [41-81] (n=23)	Not applicable	Kremens, 2002[392]
	3yr 55% +/-13% (n=20)	Not applicable	Spreafico,2008[394]
	Not applicable	3 yr 64% (n=11)	Abu-Ghosh, 2002[402]
	Not applicable	3 year 83.3%* (n=10)	Tucci, 2007[410]
4 year	4 yr 50% [29-70] (n=28)	Not applicable	Pein, 1998[398]
	Not applicable	4 yr 48% [33-62] (n=60)	Malogolowkin, 2008[403]
	4 yr 61% [41-81] (n=23)	Not applicable	Kremens, 2002[392]
	Not applicable	4yr 64% (n=11)	Abu-Ghosh, 2002[402]
	4-year 73% (n=13)	Not applicable	Campbell, 2004[395]
	4 yr 100% (n=2)	Not applicable	Termuhlen, 2006[396]
	A NED at 4 yrs (n=1)	Not applicable	Maurer, 1997[405]
5 year	5 yr 50% [29-70]* (n=28)	Not applicable	Pein, 1998[398]
	5 yr 61% [41-81]* (n=23)	Not applicable	Kremens, 2002[392]
	Not applicable	5 yr 64% (n=11)	Abu-Ghosh, 2002[402]
	Not applicable	5 year 43%* (n=10)	Tucci, 2007[410]
	5 yr 100% (n=2)	Not applicable	Termuhlen, 2006[396]
5 year OS range across studies	50%-61% [392, 398]	43-64%[402, 410]	

A = alive; DOD = dead of disease; NED = no evidence of disease

* Survival generated for this review.

Adverse Effects

None of the studies evaluated quality of life. Data on treatment-related mortality was reported in 10 studies (Table 48).[378, 392, 394, 395, 397, 398, 400, 402, 403, 406] Two studies reported a case of serious infection leading to death[394, 403] and one study reported no serious infectious complications.[407] One study reported a secondary malignancy.[403] One study reported a case of mild veno-occlusive disease.[408] There were no reports of other long-term complications.

Ongoing Studies

One Phase II trial is ongoing studying chemotherapy followed by surgery and radiation, with or without HSCT in patients with relapsed or refractory Wilms tumor or clear cell sarcoma of the kidney. The study design is interventional and uses one of three regimens (one of which includes HSCT) depending upon patient risk stratification. Primary outcome measures include unified treatment strategy, improvement of current survival rates, efficacy and toxicity and prognostic variables. Estimated enrollment is 75 (50 for HSCT and 25 for each of the non-HSCT regimens). Estimated final data collection date is November 2008 (NCT00025103).

Table 48. Adverse effects for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups

Outcome	Intervention HSCT (%)	Comparator Chemo (%)	Study
Treatment-related mortality	0	Not applicable	Fazekas, 2008[378]; Spreafico, 2008[394]; Campbell, 2004[395]; Kremens, 2002[392]; Goldman, 2001[406]; Pein, 1998[398]; Kullendorff, 1997[397]; Hempel, 1996[400]
	Not applicable	0	Abu-Ghosh, 2002[402]; Malogolowkin, 2008[403]
Infectious complications	Died of sepsis 4 months after HSCT in CR n=1 (7%)	Not applicable	Spreafico, 2008[394]
	0% (n=1)	Not applicable	Dagher,1998[407]
	Not applicable	Died of influenza B and aspergillus n=1 (2%)	Malogolowkin, 2008[403]
	33% septic (n=1)	Not applicable	Saarinen-Pihkala, Finland, 1998[393]
Secondary malignancies	Not applicable	n=1 MDS (2%)	Malogolowkin, 2008[403]
Other adverse effects	100% (n=1) mild VOD and mucositis	Not applicable	Brown, 2010[408]

MDS = myelodysplastic syndrome; VOD = veno-occlusive disease

Conclusion

Low strength evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for the treatment of high-risk relapsed Wilms tumor.

Rhabdomyosarcoma Systematic Review

Background and Setting

The incidence of rhabdomyosarcoma is 4 to 7 cases per 1 million children age 15 or younger;[411] approximately 350 new cases are diagnosed each year in the United States.[412] The majority of children have an initial presentation of nonmetastatic disease. In this setting conventional treatments have produced at least a 60-70 percent chance of cure.[411] Metastatic rhabdomyosarcoma in comparison is generally a lethal disease, with less than 20 percent of patients being cured from their disease.[411] Despite the development of new chemotherapy options, the prognosis of these patients remains generally poor.

Some centers have used HDC with HSCT in the setting of high-risk rhabdomyosarcoma. High-risk rhabdomyosarcoma includes primary metastatic or stage III or greater disease and relapsed or refractory disease. Patients with relapsed or refractory disease experience 5-year survival of approximately 30 percent.[413] In most series, numbers remain small as the majority of rhabdomyosarcoma cases are cured with conventional treatment; no randomized controlled trials exist.

Data are generally from case series, save two comparative studies[414, 415] with patients who received high-dose chemotherapy and HSCT; case reports are also available. While comparative, the study by McDowell and colleagues[415] is treated here as two single arms. The focus was to treat a subgroup of high-risk patients with sequential HDC and HSCT and compare them to

standard high-risk patients receiving standard chemotherapy. This stratification makes this patient population treated with HSCT not comparable to other treated groups, as they are of generally higher risk than is found in other studies. Prognostic factors identified in prior research were used in identifying those with the poorest prognosis.[366, 416, 417] This study provides outcome data for the stratified high-risk rhabdomyosarcoma group, and tested the hypothesis that the highest risk patients may benefit from sequential HDC and stem-cell rescue. Patients traditionally viewed as high-risk, may not have uniform survival outcomes, and may be further stratified based on prognostic factors. Evidence was evaluated in three groups: studies confined to patients with metastatic disease, studies of mixed tumor stage, and "other" (congenital alveolar, cranial parameningeal disease with metastases, and allogeneic transplantation for metastatic disease).

Evidence Summary

The overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of high-risk rhabdomyosarcoma is shown in Table 49.

The evidence compiled for this review includes two comparative studies,[414, 418] one study comprising two single arms,[415] 15 case series (nine on HSCT[357, 363, 365, 419-424] and six on the comparator conventional chemotherapy[387, 413, 416, 425-427]) and eight case reports on HSCT.[428-435] Two case reports on allogeneic transplantation were also included.[420, 436] The total number of patients abstracted from the 26 studies was 887: 340 patients received HSCT, whereas 547 patients received conventional chemotherapy. Patients with embryonal tumors have a better prognosis than those with alveolar histology. Prognostic factors such as age at diagnosis and location of the metastatic disease may help stratify high-risk patients into two groups, those of standard risk and those of poor risk. Treatment with conventional chemotherapy offers three-year survival of about 39 percent.[416] Treatment with HSCT does not appear to alter the survival for patients with metastatic rhabdomyosarcoma above what is already achieved with conventional chemotherapy.

The effects of HSCT on survival for pediatric patients with high-risk rhabdomyosarcoma of mixed tumor stage and those with congenital alveolar rhabdomyosarcoma, cranial parameningeal rhabdomyosarcoma with metastasis or the use of allogeneic transplantation for metastatic rhabdomyosarcoma is uncertain. No information on quality of life (QOL) was provided, and data on adverse events was sparse and therefore insufficient to make conclusions regarding adverse effects and quality of life. Two ongoing trials focused on treatment for malignant solid tumors are enrolling children with rhabdomyosarcoma. One is focused on the toxicity of killer IG-like receptor mismatched cord blood, and the other is investigating a tumor lysate-pulsed dendritic cell vaccine for immune augmentation after stem-cell transplantation. Future research aimed to further stratify high-risk pediatric patients with nonmetastatic disease will be important as the field moves towards more targeted therapies.

Results

Sixty articles were retrieved for full-text screening, including articles identified from the bibliography of identified articles and articles containing patients with rhabdomyosarcoma identified in another disease search. Twenty-six reports were included in this review, and the remaining 34 articles were excluded. The total number of patients abstracted from the 26 studies was 887: 346 patients received HSCT, whereas 547 patients received conventional chemotherapy.

Table 49. Overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of high-risk rhabdomyosarcoma

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with high-risk **metastatic** rhabdomyosarcoma, what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Outcome of interest is overall survival. The comparator is conventional chemotherapy	There are three comparative studies; one study was comprised of two single arms. Seven case series (four on HSCT and three on the comparator conventional chemotherapy) and three case reports on HSCT. Data from 255 patients treated with HSCT and 429 treated with conventional therapy were abstracted for this review.	The risk of bias in this evidence is high. In our synthesis we incorporated larger studies with adequate descriptions of patient populations with complete reporting of overall survival.	Overall survival data are consistent. Evidence is from the European Collaborative Studies in which patients with similar disease characteristics were assigned to a protocol. A modification to the protocol to include HDC and stem cell rescue offered the opportunity for comparison and showed no difference in survival. While not powered to detect a 10-15% absolute difference the other studies, with some variation show essentially the same survival. Evidence suggests no survival advantage for HSCT over conventional therapy.	The primary outcome, overall survival, is direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons. The best evidence was comparative but the comparison was made with historical controls entered in a previous protocol.	The evidence is precise suggesting no overall survival advantage for HSCT over conventional therapy. While the evidence is qualitative it is unlikely that a clinically important superiority exists for HSCT.	Not applicable due to lack of obvious effect size.	Moderate strength evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for the treatment of high-risk metastatic rhabdomyosarcoma.

Table 49. Overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of high-risk rhabdomyosarcoma (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with high-risk rhabdomyosarcoma, of **mixed tumor stage** what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Outcome of interest is overall survival. The comparator is conventional chemotherapy	There are six case series (five on HSCT and one on the comparator conventional chemotherapy) and one case reports on HSCT. Data from seventy-nine patients treated with HSCT and twenty-seven treated with conventional therapy were abstracted for this review.	The risk of bias in this evidence is high. In our synthesis we incorporated studies containing a mixture of tumor stages. Tumor stage may modify the overall survival within the high-risk category.	Results for overall survival are inconsistent. Five year survival for the three largest studies reporting overall survival range from 12.5 to 57%.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is imprecise. There is uncertainty on whether HSCT is inferior, equivalent or superior to conventional chemotherapy. While no comparator data was available a commonly used estimate is 30% overall survival at 5 years (Pappo, 1999). In these data survival ranged from 12.5 to 57%.	Not applicable due to lack of obvious effect size.	The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of high-risk rhabdomyosarcoma of mixed tumor type is insufficient to draw conclusions.

Table 49. Overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of high-risk rhabdomyosarcoma (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with **congenital alveolar rhabdomyosarcoma, cranial parameningeal rhabdomyosarcoma with metastasis or the use of allogeneic transplantation for metastatic rhabdomyosarcoma**, what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Outcome of interest is overall survival. The comparator is conventional chemotherapy	There are two case reports for congenital alveolar, one case series for cranial parameningeal, and three case studies of allogeneic transplantation for metastatic rhabdomyosarcoma. Data from two patients with congenital alveolar rhabdomyosarcoma and treated with HSCT, four treated with allogeneic HSCT and ninety-one with cranial parameningeal rhabdomyosarcoma treated with conventional therapy were abstracted for this review.	The risk of bias in the evidence for congenital alveolar rhabdomyosarcoma is high. Very few cases of this disease have ever been diagnosed, but the natural history is well known. The risk of bias in the evidence for cranial parameningeal rhabdomyosarcoma and allogeneic transplantation is high.	Consistency cannot be assessed for these diseases as the data is limited to either one case series (cranial parameningeal) or a few case reports (congenital alveolar and allogeneic transplantation) For congenital alveolar rhabdomyosarcoma available evidence may suggest a survival advantage for HSCT over conventional therapy.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is precise for congenital alveolar rhabdomyosarcoma and imprecise for cranial parameningeal rhabdomyosarcoma with metastasis or the use of allogeneic transplantation for metastatic rhabdomyosarcoma.	Not applicable due to lack of obvious effect size.	The body of evidence on overall survival with HSCT compared to conventional therapy for the treatment of pediatric patients with congenital alveolar rhabdomyosarcoma, cranial parameningeal rhabdomyosarcoma with metastasis or the use of allogeneic transplantation for metastatic rhabdomyosarcoma is insufficient to draw conclusions.

Table 50 shows the criteria that were used to select studies for this section.

Table 50. Rhabdomyosarcoma study selection criteria

Study Design	Population	Intervention	Comparators	Outcomes	Followup	Setting
Any study design	Pediatric patients (0-21-yr) with high-risk disease	Single Auto HSCT Tandem Auto HSCT	Chemotherapy +/- RT Chemotherapy +/- RT	OS; EFS (DFS; PFS); long-term adverse events; QOL	All durations of followup	In-patient for HSCT In or out-patient for conventional chemotherapy

Auto = autologous; DFS = disease-free survival; EFS = event-free survival; HSCT = hematopoietic stem-cell transplant; OS = overall survival; PFS = progression-free survival; QOL = quality of life

Table 51 shows the study design and population. Of the included publications, two were comparative studies (McDowell et al.[415] was abstracted as two single arms); one study was comprised of two single arms. There were 15 case series (nine on HSCT[357, 363, 365, 419-424] and six on the comparator conventional chemotherapy[387, 413, 416, 425-427]) and seven case reports on HSCT.[428-435] Two case reports on allo-transplantation were also included.[420, 436] Eight studies were based in Europe,[363, 414, 415, 419, 420, 428, 429, 436] eight in Asia,[357, 421, 422, 430-434] one in the Middle East,[423] and nine in North America.[365, 387, 416, 418, 424-427, 435]

All patients across 18 treatment studies received autologous HSCT as consolidation of primary treatments. Patients in three studies received allogeneic HSCT as consolidation of primary treatments. All patients were considered to have high-risk disease prior to transplant.

For the comparison of tandem to single HSCT, no studies were identified in the search.

All studies were specific to the pediatric age group, with age primarily reported as age at diagnosis; 15 studies reported either mean age or only had one patient. Mean age at diagnosis was approximately 8 years with a range of birth to 17 years. Median or categorical age at diagnosis, reported by 15 studies, was 8 years with a range of 3 to 13.1 years. Across all studies patients were approximately split equally by gender. Studies included patients with diverse histology, approximately 40-50 percent of the patients of alveolar histology, save two studies[419, 424] where 63 percent were of alveolar histology. The majority of the remaining patients had embryonal tumors with a small proportion diagnosed with a tumor not otherwise specified or unknown. Induction regimens varied across and within study (i.e., different chemotherapeutic agents and different (cumulative) dosages). The induction regimen consisted of multiple cycles of chemotherapy with or without radiation and/or surgery.

Conditioning regimens also varied across and within studies. The most common regimens included the following agents: melphalan, thiotepa, busulfan, cyclophosphamide, carboplatin and etoposide, either alone or in combination; MEC (melphalan, VP16, and carboplatin) is a common backbone used alone or in combination with radiation therapy or additional drugs. Treatment periods ranged from 1989 to 2005.

Table 52 shows the pediatric outcomes that were reported across the 26 included studies.

Overall Survival

Data on overall survival were reported in all but two studies[420, 422] (Table 52). Survival data is presented (Table 53). Individual studies varied in their method for calculating overall survival. In general studies of patients with metastatic disease used time since diagnosis, where studies with patients of mixed tumor stage used time from treatment. Similar trends were observed in the 1-, 3-, and 5-year OS across studies. While not direct, comparisons with adequate numbers of participants can be made from both the McDowell[415] and Carli[414] studies.

The study published by McDowell and colleagues[415] stratified patients with metastatic rhabdomyosarcoma into two groups, poor risk and standard risk. Poor-risk patients were identified as those 10 years of age or older with bone or bone marrow involvement.[415] These patients were given sequential HDC and HSCT, while the standard-risk patients (younger than 10 years of age and not bone or bone marrow involvement) were treated with conventional chemotherapy. Patients in the standard risk group had 3 year EFS and OS of 54.92 percent and 62.14 percent, respectively, comparable to rates in other studies. While those in the poor-risk group had 3 year EFS and OS of 16.17 percent and 23.17 percent, respectively, statistically worse than those in the standard-risk group in this study and no improvement on prior studies.

Carli et al.[414] published results from the European Collaborative MMT4-91. Fifty-two patients in complete remission after induction were given HDC and stem-cell rescue. Outcomes were then compared to 44 patients also in complete remission after induction, but went onto receive conventional chemotherapy. No differences in OS were observed.

The data from additional case series and case reports appear consistent with these findings.

Event-free Survival

Information on event-free survival can be found in Appendix D.

Table 51. Rhabdomyosarcoma study characteristics and population

Setting	Study	Design	Median Age	Range	Mean Age	Gender (%)	Histology [Site] (%)	HSCT (N)	Comparator (N)	Treatment Period
Metastatic Autologous HSCT	Carli, Italy, 1999[414]	Comparative	Tx. 60% <10 40% >10 Comp. 7% < 1 61% < 10 32% ≥ 10	NR	NR	NR	Treatment 44% Alveolar 56% Embryonal [Primary extremity, parameningeal, other (75%) genitourinary tract and H&N (25%)] Comparator 30% Alveolar 70% Embryonal or unspecified [Primary extremity parameningeal, other (80%) genitourinary tract and H&N (20%)]	52	44	1989-1996
	McDowell, UK, 2010[415]	Two single arms	high risk 10.6 Standard risk 4.28	high risk 1.7-17.5 Standard risk 0.52-9.93	NR	high risk 56% Male 44% Female Standard risk 60% Male 40% Female Standard risk	high risk 64% Alveolar 22% Embryonal 8% Undifferentiated 6% Unknown [most common primary site Orbit (28%)] Metastatic standard risk 33% Alveolar 57% Embryonal 9% Unspecified or unknown [most common primary site parameningeal (22%) and pelvis (31%)] 71% had Metastatic disease to lung	101	45	1998-2005

Table 51. Rhabdomyosarcoma study characteristics and population (continued)

Setting	Study	Design	Median Age	Range	Mean Age	Gender (%)	Histology [Site] (%)	HSCT (N)	Comparator (N)	Treatment Period
Metastatic Autologous HSCT	Williams, Canada, 2004[418]	retrospective review two single arms	Tx. 4 <10 Comp 7 <10 6 >10	NR	NR	Tx. 25% Male 75% Female Comp 53% Male 47% female	Treatment Embryonal with metastatic disease to lung [Primary H&N, parameningeal, bladder/prostate] Stage IV Comparator 69% Alveolar 23% Embryonal 8% Mixed [Primary Trunk, bladder/prostate, extremity, genitourinary] Stage IV	4	13	1989-1999
	Bisogno, Italy, 2009[419]	prospective single arm	NR	NR	<1 (1) <10 (38) ≥10 (32)	47% Male 53% Female	63% Alveolar 36% Embryonal 1% Not otherwise specified [Primary sites H&N, limbs, abdomen/pelvis]	70	NA	1999-2006
	Navid, USA, 2006[365]	case series	15.5	1.5-18.7	13.1	38% Male 62% Female	Alveolar [various primary sites] Metastatic	8	NA	1996-2000
	Walterhouse, USA, 1999[424]	case series	14	3-17	12.5	37% Male 63% Female	63% Alveolar 25% Embryonal 12% Unknown Stage IV	8	NA	1992-1994
	Moritake, Japan, 1998[433]	case report	NA	NA	10 at diagnosis	Male	Unspecified metastatic to bone marrow [Primary nasal tumor]	1	NA	1994
	Kwan, Hong Kong, 1996[431]	case report	NA	NA	14 years	Female	Alveolar [primary site was left thenar, metastatic to breast] Stage IV	1	NA	NR
	Shaw, Israel, 1996[423]	prospective case series	8 years at diagnosis	4-15	8.8 years at diagnosis	NR	Various primary sites Stage IV	9	NA	NR

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Table 51. Rhabdomyosarcoma study characteristics and population (continued)

Setting	Study	Design	Median Age	Range	Mean Age	Gender (%)	Histology [Site] (%)	HSCT (N)	Comparator (N)	Treatment Period
Metastatic Autologous HSCT	Oue, Japan, 2003[434]	Case report from a case series. Abstracted only one patient receiving a tandem transplant	NA	NA	4.5	Female	Lt. buttock primary site metastatic to lt. femur	1	NA	1991-2001
	Breneman, USA, 2003[416]	Case series	7	0-19	NR	56% Male 44% Female	46% Alveolar 36% Embryonal 3% Undifferentiated [most common 1° site extremity (28%), parameningeal (20%), trunk (20%)] Stage IV Lung most common metastatic site followed by bone marrow and lymph nodes	NA	127	1991-1997
	Pappo, USA, 2001[425]	Case series	10 at diagnosis	0-19	NR	52% Male 48% Female	48% Alveolar 29% Embryonal 4% Undifferentiated 19% Unspecified [most common 1° site retroperitoneum/perineum/trunk (43%), extremity (23%), GU/bladder/prostate (15%), other (19%)] Metastatic	NA	48	1994-1996
	Sandler, USA, 2001[427]	Case series	8.5	0-19	NR	58% Male 42% Female	37% Alveolar 48% Embryonal 15% Unspecified [most common 1° site extremity (31%), H&N (7%) retroperitoneum (18%) other (44%)] Metastatic	NA	152	1988-1991

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Table 51. Rhabdomyosarcoma study characteristics and population (continued)

Setting	Study	Design	Median Age	Range	Mean Age	Gender (%)	Histology [Site] (%)	HSCT (N)	Comparator (N)	Treatment Period
Metastatic Allo Transplant	Doelken, Germany, 2005[436]	Case reports	NA	NA	Pt 1-11.5 Pt 2- 13	M 100%	Alveolar with metastatic disease Stage IV	2	NA	NR
	Donker, Netherlands, 2009[428]	Case study Allo transplant	NA	NA	8 years	Female	Stage IV Metastatic	1	NA	NR
	Misawa, Japan, 2003[432]	Case Study Allo transplant	NA	NA	17 at diagnosis	Female	Alveolar Stage I, group III undifferentiated	1	NA	1997
Mixed tumor stage	Matsubara**, Japan, 2003[421]	Case series	8 at transplant	2-20	9.5	62% Male 38% Female	33% Alveolar 67% Embryonal [Parameningeal most common primary site n=7] Group III/IV at transplant	21	NA	1990-1999
	Scully, USA, 2000[435]	Case report	NA	NA	~5 at trans-plant	Female	Embryonal [Primary site was upper arm] Local recurrence	1	NA	NR
	Hara, Japan, 1998[357]	Case series	3	1-18	6.8	NR	43% Alveolar 57% Embryonal Stage III (2) Stage IV (3) Relapsed (2)	7	NA	1993-1997
	Lucidarme, France, 1998[363]	single arm phase II	NR for our subset	2-17 for the whole study	NR	NR	63% metastatic at transplant Relapsed or Refractory	8	NA	1987-1995
	Sato, Japan, 1998[422]	case series	7 at diagnosis	.7-10 year	5.34 at diagnosis	60% Male 40% Female	60% Embryonal 40% Undifferentiated [Primary retroperitoneum, parameningeal, femur, orbit] Stage III	5	NA	1993-1998
	Koscielniak*, Germany, 1997[420]	retrospective case series	6 at diagnosis	<1-22	NR	NR	61% Alveolar 36% Embryonal 3% Undifferentiated Stage IV	36	NA	1986-1994

Table 51. Rhabdomyosarcoma study characteristics and population (continued)

Setting	Study	Design	Median Age	Range	Mean Age	Gender (%)	Histology [Site] (%)	HSCT (N)	Comparator (N)	Treatment Period
Mixed tumor stage	Van Winkle, USA, 2005[387]	Case series	NR	2.1-20.5	11.3	52% Male 48% Female	37% Alveolar 41% Embryonal 11% Undifferentiated 11% Unknown At recurrence 4% Stage I, 0 Stage II, 11% stage III, 63% Stage IV, 22% unknown	NA	27	1992-1996
Congenital Alveolar RMS	Kuroiwa, Japan, 2009[430]	case report	NA	NA	<1 at transplant		Congenital Alveolar RMS [Primary skin lesions]	1	NA	NR
	Grundy, UK, 2001[429]	case report	NA	NA	Diagnosed at birth	Male	Congenital alveolar RMS [primary right thigh and multiple skin lesions]	1	NA	NR
Cranial Parameningeal	Raney, USA, 2008[426]	case series	5 at diagnosis	<1-19	NR	59% Male 41% Female	15% Alveolar 71% Embryonal 13% Unspecified Cranial parameningeal with metastatic disease	NA	91	1978-1997

NR = not reported

*This paper contains both Allo and Auto transplants as they could not be separated, as well as at least one patient over the age of 21.

** study included one patient who was 22, his survival was similar when compared to a 16 and a 20 year old with similar site of relapse and status at transplant.

Table 52. Rhabdomyosarcoma outcomes reported

Setting	Study	OS	EFS (DFS, PFS)	Quality of Life	Treatment-Related Mortality	Second Malignancies	Other Adverse Effects
Metastatic Auto transplant	Carli, Italy, 1999[414]	√	√	NR	√	NR	√
	McDowell, UK, 2010[415]	√	NR	NR	√	NR	√
	Williams, Canada, 2004[418]	√	√	NR	NR	NR	NR
	Bisogno, Italy, 2009[419]	√	NR	NR	√	NR	√
	Navid, USA, 2006[365]	√	NR	NR	√	NR	√
	Walterhouse, USA, 1999[424]	√	NR	NR	√	NR	NR
	Moritake, Japan, 1998[433]	√	NR	NR	NR	NR	NR
	Kwan, Hong Kong, 1996[431]	√	NR	NR	NR	NR	NR
	Shaw, Israel, 1996[423]	√	NR	NR	√	NR	√
	Oue, Japan, 2003[434]	√	NR	NR	√	NR	NR
	Breneman, USA, 2003[416]	√	√	NR	NR	NR	NR
	Pappo, USA, 2001[425]	√	√	NR	√	NR	NR
	Sandler, USA, 2001[427]	√	√	NR	√	NR	√
Metastatic Allo Transplant	Doelken, Germany, 2005[436]	√	NR	NR	NR	NR	NR
	Donker, Netherlands, 2009[428]	√	NR	NR	NR	NR	NR
	Misawa, Japan, 2003[432]	√	NR	NR	NR	NR	NR
Mixed tumor stage	Matsubara**, Japan, 2003[421]	√	√	NR	NR	√	NR
	Scully, USA, 2000[435]	√	NR	NR	NR	√	NR
	Hara, Japan, 1998[357]	√	NR	NR	√	NR	√
	Lucidarme, France, 1998[363]	√	NR	NR	√	NR	√
	Sato, Japan, 1998[422]	NR	√	NR	NR	NR	NR
	Koscielniak*, Germany, 1997[420]	NR	√	NR	NR	NR	√
	Van Winkle, USA, 2005[387]	√	NR	NR	√	NR	NR
Congenital Alveolar	Kuroiwa, Japan, 2009[430]	√	NR	NR	NR	NR	NR
	Grundy, UK, 2001[429]	√	NR	NR	NR	NR	NR
Cranial Parameningeal with metastatic disease	Raney, USA, 2008[426]	√	√	NR	NR	NR	NR

DFS = disease-free survival; EFS = event-free survival; NR = not reported; OS = overall survival; PFS = progression-free survival

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Table 53. Overall survival for treatment (single auto HSCT) and comparison (conventional chemotherapy +/- radiation) groups

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Metastatic Auto	1 Year	~86% at 1 year[a] (n=52)	~66% at one year[a] (n=44)		Carli, Italy, 1999[414]
		66.7 (35.9, 97.5) at 1 year (n=9)	Not applicable		Shaw, Israel, 1996[b 423]
		50.0 (15.4, 84.6) at 1 year (n=8)	Not applicable		Navid, USA, 2006 [b 365]
		87.5 (64.6, 100) (n=8)	Not applicable		Walterhouse, USA, 1999 [b 424]
		NED 3 months post transplant (n=1)	Not applicable		Kwan, Hong Kong, 1996[431]
		DOD 21 months after transplant (n=1)	Not applicable		Moritake, Japan, 1998[433]
		NED 19 months after diagnosis (n=1)	Not applicable		Oue, Japan, 2003[434]
		Not applicable	~75% at 1 year[a] (n=152)		Sandler, USA, 2001[427]
		Not applicable	~75% at 1 year[a] (n=127)		Breneman, USA, 2003[416]
Mixed tumor stage		37.5% (4, 71.0) at 1 year (n=8)	Not applicable		Lucidarme, France, 1998[b 363]
		57.1 (20.5, 93.8) at 1 years (n=7)	Not applicable		Hara, Japan, 1998 [b 357]
		Not applicable	56 ±10 at 1 year (n=27)		Van Winkle, USA, 2005[387]
Metastatic Allo		DOD at 5.5 months after transplant (n=1)	Not applicable		Misawa, Japan, 2003[432]
Metastatic Auto	3 year	40.0 (25.5-54.7) at 3 years (n=52)	27.7 (13.3-42.1) at 3 years (n=44)	0.2	Carli, Italy, 1999[414]
		23.7 at 3 years (n=101)	62.14 at 3 years (n=45)		McDowell, UK, 2010[415]
		All 35% (13-58) at 3 years HSCT only (n=4) 100% at 3 years	15% (-4-35) at 3 years (n=13)		Williams, Canada, 2004[418]
		42.3% (30.5-53.6) at 3 years (n=70)	Not applicable		Bisogno, Italy, 2009[419]
		53.3 (19.4, 87.3) at 3 years (n=9)	Not applicable		Shaw, Israel, 1996[b 423]
		37.5 (4-71) at 2 years (n=8)	Not applicable		Navid, USA, 2006 [b 365]
		12.5 (0, 35.4) (n=8)	Not applicable		Walterhouse, USA, 1999[b 424]
		Not applicable	~40% at 3 years (n=152)		Sandler, USA, 2001[427]
		Not applicable	39% (30-48) at 3 years (n=127)		Breneman, USA, 2003[416]
Mixed tumor stage		12.5 (0, 35.4) at 3 years (n=8)	Not applicable		Lucidarme, France, 1998[b 363]
		57.1 (20.5, 93.8) at 3 years (n=7)	Not applicable		Hara, Japan, 1998± [357]
		Alive with secondary malignancy at 3 years post transplant (n=1)	Not applicable		Scully, USA, 2000[435]

Table 53. Overall survival for treatment (single auto HSCT) and comparison (conventional chemotherapy +/- radiation) groups (continued)

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Congenital Alveolar	3 year	NED at 46 months after diagnosis (n=1)	Not applicable		Kuroiwa, Japan, 2009[430]
		1 pt DOD at 2 years (n=1)	Not applicable		Grundy, UK, 2001[429]
Metastatic Auto	5 year	~40% at 5 years (n=52)	~26% at 5 years (n=44)		Carli, Italy, 1999[414]
		17.9 at 5 years (n=101)	47.7% at 5 years (n=45)		McDowell, UK, 2010[415]
		12.5 (0, 35.4) (n=8)	Not applicable		Walterhouse, USA, 1999[b 424]
		Not applicable	~34% at 5 years (n=152)		Sandler, USA, 2001[427]
		Not applicable	~25% at 5 years (n=127)		Breneman, USA, 2003[416]
Mixed tumor stage		48% at 5 years (n=21)	Not applicable		Matsubara, Japan, 2003[c 421]
Cranial Parameningeal with metastatic disease		Not applicable	33% (23-43) at 10 years (n=91)		Raney, USA, 2008[426]
Metastatic Allo		1 pt alive in CR at 4 years (n=1)	Not applicable		Donker, Netherlands, 2009[428]
		4.8 months post allo-transplant 1 pt died Approximately 6 years after allo transplant pt. 2 died (pt had a allo- transplant 5 years after the auto transplant) (n=2)	Not applicable		Doelken, Germany, 2005[436]
Metastatic	OS range for 3-5 years for studies with > 20 patients	40-42.3%[414, 419] Survival estimates are measured from the time since diagnosis	27.7-39%[414, 416, 427] Survival estimates are measured from the time since diagnosis		This range does not include the McDowell[415] study as the patients in the treatment arm are not comparable to other studies due to their higher risk category.
Mixed Tumor stage	OS range for 3-5 years for studies with > 5 patients	12.5-57%[357, 363, 421] Survival estimates are measured from the time since treatment	No Comparator		

[a] Estimates preceded by a ~ were estimated from published Kaplan-Meier curves.
[b] Survival curves were constructed using the raw data published in the articles.
[c] Study included one patient who was 22, his survival was similar when compared to a 16- and a 20-year-old with similar site of relapse and status at transplant.

Adverse Effects

None of the studies evaluated quality of life, and serious adverse events were reported by fifteen studies (Table 52). Data on treatment-related mortality was reported in twelve studies (Table 54).[357, 363, 365, 387, 414, 415, 419, 423-425, 427, 434] McDowell reported two cases of treatment-related mortality in the comparator group and there were seven serious adverse events in the treatment group with five resulting in death; however it is unclear how many occurred in 100 days of treatment.[415] Toxic death from sepsis was reported in the treatment group in two studies.[414, 420] Bisogno et al.[419] reported seven of 55 evaluable patients experienced serious infectious complications while Sandler and colleagues[427] reported 40 percent of patients experiencing serious infection with seven leading to death. One study reported a secondary malignancy, myelodysplastic syndrome related to alkylating agents.[435] No treatment related mortality was observed in 11 studies.[363, 421, 422, 424, 429-433, 435, 436] Two studies[416, 426] did not report on adverse events. There were no reports of secondary malignancies, serious hemorrhagic events, irreversible veno-occlusive disease or other long term complications.

Ongoing Research

Twenty children age 21 or younger were to be enrolled in a Phase I study examining the toxicity of killer IG-like receptor mismatched umbilical cord blood for pediatric patients with malignant solid tumors. This study is ongoing and no longer recruiting, and no results have been published.

There are no trials specifically looking at HSCT outcomes in patients with rhabdomyosarcoma; however, ongoing trials are investigating support networks for transplant recipients (NCT00782145), prevention of fungal infection (NCT00079222) and genetic susceptibility (NCT00949052) to secondary malignancy among stem-cell recipients.

Table 54. Adverse effects for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups

Outcome	Intervention (HSCT [%])	Comparator Chemo (%)	Study
Treatment-related mortality	0 [a]	Not applicable	Dolken, 2005[436]; Grundy, 2001[429]; Kurioiwa, 2009[430]; Kwan, 1996[431]; Lucidarme, 1998[363]; Matsubara, 2003[421]; Misawa, 2003[432]; Moritake, 1998[433]; Sato, 1998[422]; Scully, 2000[435]; Walterhouse, 1999[424]
	1.9	2.2	Carli, 1999[414]
	4.3	Not applicable	Bisogno, 2009[419]
	1/7 of RMS patients *one additional patient non-RMS experienced TRM; of all patients 2/28 (7.1%)	Not applicable	Hara, 1998[357]
	Not applicable	5.9% Unclear if these were within 100 days	Sandler, 2001[427]
	5.0% This represents 5 adverse events resulting in death, unclear how many occurred within 100 days of treatment	4.4%	McDowell, 2010[415]

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Table 54. Adverse effects for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups (continued)

Outcome	Intervention (HSCT [%])	Comparator Chemo (%)	Study
Treatment-related mortality	25% Two of eight RMS patients in a study of mixed cancers	Not applicable	Navid, 2006[365]
	8.3 In a mixed tumor study. Neither patient had RMS.	Not applicable	Oue, 2003[434]
	6.6 In a mixed tumor study. Neither patient had RMS.	Not applicable	Shaw, 1996[423]
	Not applicable	6.2%	Pappo, 2001[425]
	Not applicable	0.6 (TRM rate from infection among 336 chemo courses)	Van Winkle, 2005[387]
Secondary malignancies	1 patient in a case report	Not applicable	Scully, 2000[435]
Infectious complications ≥ grade III	12.7	Not applicable	Bisogno, 2009[419]
	Not applicable	4 (8.3%) bacteremia 1 (2.1%) pneumonia	Pappo, 2001[425]
	2.8[b]	Not applicable	Koscielniak, 1997[420]
	Not applicable	40 7 infections lead to death	Sandler, 2001[427]
	4 (50%) Sepsis 1 (13%) Fungal infection	Not applicable	Walterhouse, 1999[424]
Serious hemorrhagic event	NR	NR	
Veno-occlusive disease	NR	NR	
Long-term complications	NR	NR	

HSCT = hematopoietic stem-cell transplantation; NR = not reported

[a] No cases of TRM occurred in these studies.
[b] Unclear if this occurred in first 100 days.

One ongoing open-label nonrandomized study, at the University of Michigan Cancer Center, is investigating a tumor lysate-pulsed dendritic cell vaccine for immune augmentation after stem-cell transplantation for pediatric patients with high-risk solid tumors (NCT00405327). This study is ongoing and no longer recruiting patients, and final data collection for the primary outcome is scheduled for June 2012.

Conclusion

Moderate strength evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for the treatment of high-risk metastatic rhabdomyosarcoma.

The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of high-risk rhabdomyosarcoma of mixed tumor type is insufficient to draw conclusions

The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of congenital alveolar rhabdomyosarcoma, cranial parameningeal rhabdomyosarcoma with metastasis, or the use of allogeneic transplantation for metastatic rhabdomyosarcoma was insufficient to draw conclusions.

Retinoblastoma Systematic Review

Background and Setting

Retinoblastoma is the most common primary intraocular tumor in children, with an incidence of 1 in 15,000 births,[437] and accounts for 4 percent of all childhood cancers. Majority of children present with intraocular disease where conventional treatments have produced at least a 90 percent chance of cure.[438] Patients with trilateral retinoblastoma have an initial diagnosis of intraocular disease, with the subsequent development of a primary intra-cranial primitive neuro-ectodermal tumor and have traditionally had extremely poor prognosis and are included in this review. Extraocular or metastatic retinoblastoma in comparison to intraocular disease is generally lethal specifically when the disease has reached the central nervous system. Despite the development of new chemotherapy options, the prognosis of these patients is generally poor. Some centers have used HDC with HSCT in the setting of extraocular disease. Data from case series and case reports are available. Numbers remain small, as extraocular and trilateral retinoblastoma are rare conditions; no randomized controlled trials exist. Evidence was evaluated in three groups; studies confined to patients with CNS involvement, those with patients without CNS disease and patients with trilateral retinoblastoma.

Evidence Summary

The overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of metastatic retinoblastoma is shown in Table 55.

The evidence compiled for this review includes five case reports[439-443] on HSCT and 15 case series (eight on HSCT[438, 444-450] and five on the comparator conventional chemotherapy[451-455] and two retrospective reviews with data on both HSCT and conventional chemotherapy[456, 457]). The total number of patients abstracted from the 20 studies was 267: 91 patients in 15 studies received HSCT, whereas 176 patients in seven studies received conventional chemotherapy.

Prognostic factors are not well defined except that patients with metastatic disease to the CNS have shorter survival than those with metastatic disease to other areas. Treatment with HSCT does not appear to alter the survival for patients with metastatic retinoblastoma to the CNS. These patients continue to have very poor prognosis. Treatment with HSCT may alter the 5-year survival for patients with metastatic retinoblastoma to sites other than the CNS, but these effects are uncertain. Treatment with HSCT may alter the 5-year survival for patients with trilateral retinoblastoma, but these effects are uncertain. Additional research with more patients is needed to confirm these findings. No information on quality of life was provided and data on

adverse events was sparse and therefore insufficient to make conclusions regarding adverse effects and quality of life. One Phase III multicenter study of multimodal therapy (induction, HDC, and HSCT and/or radiotherapy) for young children with extraocular retinoblastoma is ongoing.

Table 55. Overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of metastatic retinoblastoma

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with **extraocular retinoblastoma with CNS involvement** what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Outcome of interest is overall survival. The comparator is conventional chemotherapy	There are two case reports on HSCT and nine case series (three on HSCT and six on the comparator conventional chemotherapy. Data from 16 patients treated with HSCT and 49 treated with conventional therapy were abstracted for this review.	The risk of bias in this evidence is high as our review consisted of small case series and case reports.	Results for overall survival are of unknown consistency. While in most cases confidence intervals may overlap and clinical heterogeneity exists the data consistently show poor outcome for both HSCT and conventional therapy.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is precise suggesting no overall survival advantage for HSCT over conventional therapy. While the evidence is qualitative it is unlikely that a clinically important superiority exists for HSCT for the treatment of extraocular retinoblastoma with CNS involvement.	Not applicable due to lack of obvious effect size.	Low strength evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for the treatment of **extraocular retinoblastoma with CNS involvement**.

Table 55. Overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of metastatic retinoblastoma (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients **extraocular retinoblastoma without CNS involvement** what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Outcome of interest is overall survival. The comparator is conventional chemotherapy.	There are two case reports on HSCT and ten case series (five on HSCT and four on the comparator conventional chemotherapy and one retrospective review with data on both HSCT and conventional chemotherapy). Data from 41 patients treated with HSCT and 118 treated with conventional therapy were abstracted for this review.	Risk of bias in this evidence is high as our review consisted of small case series and case reports; these reports also included patients with various metastatic sites. Prognostic factors not well defined. The clinical course of disease may be modified by site of metastasis.	Results for overall survival of unknown consistency. While in most cases confidence intervals may overlap and clinical heterogeneity exists the range of results for overall survival are similar for both HSCT and conventional tx. However, some studies report high in the range while others report lower. With small numbers it is impossible to assess consistency.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is imprecise, effects are uncertain. There is uncertainty on whether HSCT is inferior, equivalent or superior to conventional chemotherapy.	Not applicable due to lack of obvious effect size.	The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of **extraocular retinoblastoma without CNS involvement** is insufficient to draw conclusions.

Table 55. Overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of metastatic retinoblastoma (continued)

Key Question	Key Question	Key Question	Key Question	Key Question	Key Question	Key Question	Key Question
For pediatric patients **with trilateral retinoblastoma** what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Outcome of interest is overall survival. The comparator is conventional chemotherapy	There is one case series. Data from thirteen patients treated with HSCT were abstracted for this review. No comparator data was abstracted.	The risk of bias in this evidence is high as our review consisted of one case series with thirteen patients.	Consistency cannot be assessed as the data is limited to one case series.	The outcomes reported are direct. No comparator studies were identified.	The evidence is imprecise, effects are uncertain. There is uncertainty on whether HSCT is inferior, equivalent or superior to conventional chemotherapy.	Not applicable due to lack of obvious effect size.	The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of **trilateral retinoblastoma** is insufficient to draw conclusions.

Results

Forty-one articles were retrieved for full-text screening. Twenty reports were included in this review, and the remaining 21 articles were excluded. The total number of patients abstracted from the twenty studies was 267: 91 patients in 15 studies received HSCT, whereas 176 patients in seven studies received conventional chemotherapy.

Table 56 shows the criteria that were used to select retinoblastoma studies.

Table 56. Retinoblastoma study selection criteria

Study Design	Population	Intervention	Comparators	Outcomes	Followup	Setting
Any study design	Pediatric patients (0-21-yr) with extraocular disease	Single Auto HSCT Tandem Auto HSCT	Chemotherapy +/- RT Chemotherapy +/- RT	OS; EFS (DFS; PFS); long-term adverse events; QOL	All durations of followup	In patient for HSCT. In or out-patient for conventional chemotherapy

Auto = autologous; DFS = disease-free survival; EFS = event-free survival; HSCT = hematopoietic stem-cell transplant; OS = overall survival; PFS = progression-free survival; QOL = quality of life

Table 57 shows the study design and population. Of the included publications, five were case reports on HSCT and 15 were case series (eight on HSCT[438, 444-450] and five on the comparator conventional chemotherapy[451-455] and two retrospective reviews with data on both HSCT and conventional chemotherapy[456, 457]). Five studies were based in Europe,[441, 445, 447, 454, 456] three in Asia,[439, 446, 452] three in South America,[451, 453, 455] and nine in North America.[438, 440, 442-444, 448-450, 457]

All patients across the 15 treatment studies received HSCT as consolidation of primary treatments. Other than the patients with trilateral retinoblastoma[442, 444] all patients had metastatic disease prior to transplant. For the comparison of tandem HSCT to single HSCT; no studies were identified in the search.

All studies were specific to the pediatric age group, with age primarily reported as age at diagnosis; 14 studies reported either mean age or only had one patient. Mean age at diagnosis was 21.8 months with a range of 4 months to 51.8 months. Median age, reported by 13 studies, was 26.3 months with a range of 1 week to 145 months. Patients were approximately split equally by gender. Induction regimens varied across and within study (i.e., different chemotherapeutic agents and different (cumulative) dosages). The induction regimen consisted of multiple cycles of chemotherapy with or without radiation, following primary enucleation.

Conditioning regimens also varied across and within studies. The most common regimens included the following agents; cyclophosphamide, thiotepa, etoposide, carboplatin and etoposide either alone or in combination, ICE (ifosfamide, carboplatin, and etoposide) is a common backbone used alone or in combination with radiation therapy or additional drugs. Treatment periods ranged from 1982 to 2007.

Table 58 shows the outcomes that were reported across studies.

Overall Survival

Data on overall survival were reported in all 20 studies (Table 58). Survival data are presented stratified by if patients were identified as having metastatic spread to the CNS, then by year (Table 59). A study of trilateral retinoblastoma was also separated into its own category. Ten studies presented data for patients with CNS involvement[442, 443, 447, 449, 451, 453-457] and the same ten studies plus nine more [438-441, 445, 446, 448, 450] presented data on patients without CNS

involvement. One study presented data exclusively on trilateral retinoblastoma.[444] The individual studies either did not define overall survival or used different starting points for this variable (i.e., either years from diagnosis or years from first transplant). No direct comparisons can be made from the published data as there are no comparative studies.

Table 57. Retinoblastoma study characteristics and population

Study	Design	Median age	Range	Mean Age	Gender (%)	Histology [Site] (%)	HSCT (N)	Comparator (N)	Treatment Period
Cozza, Italy, 2009[456]	retrospective review case series	41.5 months at diagnosis (n=6)	3-110 months (n=6)	NR	50% Male, 50% Female (n=6)	CSF, Pineal, orbit, bone and bone marrow	HSCT (n=3)	Chemotherapy +/- RT (n=3)	1988-2007
Jubran, USA, 2004[457]	retrospective review case series	11.5 months at diagnosis	2-96 months	23.7 month at diagnosis	NR	distant no CNS involvement	HSCT (n=4)	Chemotherapy +/- RT (n=6)	1991-1999
Dunkel, USA, 2010[444]	case series	8 months at diagnosis	1 week-20 months	NR	NR	suprasellar (n=2) pineal (n=11)	HSCT (n=13)	NA	1997-2005
Dai, Canada, 2008[442]	case report	NR	NR	4 months at diagnosis 12 months at treatment	Female	with CSF involvement	HSCT (n=1)	NA	NR
Matsubara, Japan, 2005[446]	case series	16 months at diagnosis	3-41 months at diagnosis	17.6 months at diagnosis	20% Male 80% Female	distant metastasis	HSCT (n=5)	NA	1986-2000
Taguchi, Japan, 2005[439]	case report	NA	NA	4	Male	maxilla and mandible	HSCT (n=1)	NA	NR
Kremens, Germany, 2003[445]	case series	34 months at diagnosis	20-110 months at diagnosis	51.8 months at diagnosis	NR	bone marrow, extra-ocular tumor	HSCT (n=5)	NA	1992-2001
Rodriguez-Galindo, USA, 2003[448]	case series	30.5 at diagnosis	17-36 months	28.5 age at diagnosis	75% Male 25% Female	distant metastasis no CNS involvement	HSCT (n=4)	NA	NR
Moshfeghi et al. USA, 2002[440]	case report	NA	NA	5	Female	bone marrow, right humerus, both supraorbital bones, and both tibias, ovary	HSCT (n=1)	NA	NR
Hertzberg et al. Germany, 2001[441]	case report	NA	NA	7	Female	lymph nodes, bones and bone marrow	HSCT (n=1)	NA	NR

Table 57. Retinoblastoma study characteristics and population (continued)

Study	Design	Median age	Range	Mean Age	Gender (%)	Histology [Site] (%)	HSCT (N)	Comparator (N)	Treatment Period
Dunkel, USA, 2000[438]	case series	30.5 months at diagnosis	17-44 months	30.5 months at diagnosis	50% Male 50% Female	distant metastasis (BM, Orbit, liver, bone) no CNS involvement	HSCT (n=4)	NA	1993-1996
Namouni, France, 1997[447]	case series	34 months	9-125 months	NR	76% Male 24% Female	cut end of optic nerve (n=5) disruption of ocular globe(n=1) isolated orbital relapse (n=7) various metastases (n=8) CNS/spinal axis (n=4)	HSCT (n=25)	NA	1989-1994
Chang, Taiwan, 2006[452]	case series	26.3 months at diagnosis for all patients*	1.7 months-89 months*	NR	NR	most common sites Orbit (n=7) and CNS (n=7)	NA	Chemotherapy +/- RT (n=15)	1982-2004
Gunduz, Turkey, 2006[454]	case series	NR	13-86	45 months at diagnosis	NR	distant and CNS (n=5) CNS (n=9) distant only (n=4)	NA	Chemotherapy +/- RT (n=18)	1999-2005
Antoneli, Brazil, 2003[451]	case series	32.9 months at diagnosis	2-145	NR	53% Male 47% Female	69 class I/III CCG classification 14 Class IV/V	NA	Chemotherapy +/- RT (n=83)	1987-1991 period 1 1992-2000 period 2
Chantada, Argentina, 1999[453]	case series	24 months	1-7 years	37 months	30% Male 70% Female	Orbit with only one patient with CNS involvement	NA	Chemotherapy +/- RT (n=10) 1 pt dead of parental abuse	1995-1998

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Table 57. Retinoblastoma study characteristics and population (continued)

Study	Design	Median age	Range	Mean Age	Gender (%)	Histology [Site] (%)	HSCT (N)	Comparator (N)	Treatment Period
Schvartzman, Argentina, 1996[455]	case series	Age NR for the subgroup abstracted	NR	NR	NR	Orbital (n=29) intracranial (n=6) hematogenous metastasis (n=6)	NA	Chemotherapy +/- RT (n=41) Stage II(n=29) Stage III (n=6) Stage Iv (n=6)	1987-1993
Dimaras, Canada, 2009[443]	case report	NA	NA	4 months at diagnosis	Male	with CSF involvement	HSCT (n=1)	NA	2001
Dunkel, USA, 2010[449]	case series	24.5 months	4-38 months	22 months at diagnosis	NR	With CNS involvement	HSCT (n=8)	NA	2000-2006
Dunkel, USA, 2010[450]	case series	26 months	1-44 months	25 months at diagnosis	NR	Orbit (n=9), bone (n=11), bone marrow (n=14), liver (n=4)	HSCT (n=15)	NA	1993-2006

NR = not reported

*This age estimate included patients excluded from the report for having intraocular disease.

Table 58. Retinoblastoma outcomes reported

Study	OS	EFS (DFS, PFS)	Quality of Life	Treatment-Related Mortality	Second Malignancies	Other Adverse Effects
Cozza, Italy, 2009[456]	√	NR	NR	NR	NR	NR
Jubran, USA, 2004[457]	√	NR	NR	NR	NR	NR
Dunkel, USA, 2010[444]	√	√	NR	√	NR	√
Dai, Canada, 2008[442]	√	NR	NR	NR	NR	NR
Matsubara, Japan, 2005[446]	√	NR	NR	NR	NR	√
Taguchi, Japan, 2005[439]	√	NR	NR	NR	NR	NR
Kremens, Germany, 2003[445]	√	NR	NR	NR	NR	√
Rodriguez-Galindo, USA, 2003[448]	√	NR	NR	NR	NR	√
Moshfeghi, USA, 2002[440]	√	NR	NR	NR	NR	NR
Hertzberg, Germany, 2001[441]	√	NR	NR	NR	NR	NR
Dunkel, USA, 2000[438]	√	NR	NR	√	NR	√
Namouni, France, 1997[447]	√	√	NR	NR	NR	√
Chang, Taiwan, 2006[452]	√	NR	NR	NR	√	NR
Gunduz, Turkey, 2006[454]	√	NR	NR	NR	NR	NR
Antoneli, Brazil, 2003[451]	√	NR	NR	NR	√	NR
Chantada, Argentina, 1999[453]	√	NR	NR	√	NR	NR
Schvartzman, Argentina, 1996[455]	√	NR	NR	NR	NR	√
Dimaras, Canada, 2009[443]	√	NR	NR	NR	NR	NR
Dunkel, USA, 2010[449]	√	NR	NR	√	NR	NR
Dunkel, USA, 2010[450]	√	√	NR	NR	√	NR

DFS = disease-free survival; EFS = event-free survival; NR = not reported; OS = overall survival; PFS = progression-free survival

Table 59. Overall survival for treatment (single auto HSCT) and comparison (conventional chemotherapy +/- radiation) groups: Retinoblastoma

Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
1 year CNS	50% (0.01-99) at 1 years (n=4)	Not applicable	0.248@	Namouni, 1997± [447]
	50% (0,100) at 1 year (n=2)[b]	Not applicable		Matsubara, 2005[446]
	Not applicable	71.4% (47.8,95.1) at 1 year (n=14)		Gunduz, 2006[454]
	Not applicable	0% at median 2 months (1-3)* (n=4)		Jubran, 2004[457]
	Not applicable	33.3% (0, 86.7) at 1 year (n=3)		Cozza, 2009[456]
	Not applicable	DOD at 3 months (n=1)		Chantada,1999[453]
	Trilateral retinoblastoma with CNS DOD at 32 months (n=1)	Not applicable		Dai, 2008[442]
	50%	Not applicable		Dunkel, 2010[449]

Table 59. Overall survival for treatment (single auto HSCT) and comparison (conventional chemotherapy +/- radiation) groups: Retinoblastoma (continued)

Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
3 Year CNS	25% (0-67.4) at 3 years (n=4)	Not applicable	0.248@	Namouni, 1997± [447]
	50% (0,100) at 3 years (n=2)[b]	Not applicable		Matsubara, 2005[446]
	Not applicable	14.3 (0, 42.9) at 3 years (n=14)		Gunduz, 2006[454]
	0% at 16 months (n=1)	0% at 3 years (n=3)		Cozza, 2009[456]
	NED at 2.7+ years	Not applicable		Dimaras, 2009[443]
	50%	Not applicable		Dunkel, 2010[449]
5 years CNS	25% (0-67.4) at 5 years (n=4)	Not applicable	0.248@	Namouni, 1997± [447]
	0% at 5 year (n=2)[b]	Not applicable		Matsubara, 2005[446]
	Not applicable	0% survival** at 5 years (t1, n=7) 20% survival at 5 years (t2, n=7)	0.003^^ <0.001	Antoneli, 2003[451]
	Not applicable	Stage III (CNS) 0% survival (n=6)		Schvartzman, 1996 # [455]
1 year No CNS	75% (33-100) at 1 year (n=4)	0% at 12 months (n=2)		Jubran, 2004± [457]
	Patients with Trilateral retinoblastoma (n=13) 78% (37-104) at 1 year	Not applicable		Dunkel, 2010[444]
	Disease at cut end of optic nerve or in the ocular globe (n=6) 80% (44.9-100)1 years Bone or Bone marrow disease (n=8) 87.5 (64.6-100) at 1 year	Not applicable	0.248@	Namouni, 1997± [447]
	Bone and bone marrow metastasis (n=4) 100% at 1 year	Not applicable		Rodriguez-Galindo, 2003± [448]
	100% at 1 years (n=2)	Not applicable		Cozza et al. 2009[456]
	DOD at 16 months (n=1)	Not applicable		Moshfeghi, 2002[440]
	DOD at 19 months (n=1)	Not applicable		Taguchi, 2005[439]
	Not applicable	68.6% (32.1 – 100.0) at 1 year (n=8)		Chantada,1999[453]

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Table 59. Overall survival for treatment (single auto HSCT) and comparison (conventional chemotherapy +/- radiation) groups: Retinoblastoma (continued)

Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
3 year No CNS	Patients with trilateral retinoblastoma (n=13) ~38 at 3 years	Not applicable		Dunkel, 2010[444]
	Disease at cut end of optic nerve or in the ocular globe (n=6) 80% (44.9-100) 3 years Bone or bone marrow disease (n=8) 58.3 (22-94.7) at 3 years	Not applicable	0.248@	Namouni, 1997± [447]
	Bone and bone marrow metastasis (n=4) 100% at 3 years	Not applicable		Rodriguez-Galindo, 2003± [448]
	50% (0-100) at 3years (n=4)	Not applicable		Jubran, 2004± [457]
	100% at mean Followup of 86 months (n=3)	Not applicable		Matsubara, 2005[446]
	100% at 3years (n=2)	Not applicable		Cozza et al. 2009[456]
	NED at 4+ years (n=1)	Not applicable		Hertzberg, 2001[441]
	Not applicable	100% at mean 37 months followup (9-62) (n=4)		Gunduz, 2006[454]
5 year No CNS	Bone or bone marrow disease (n=8) 58.3 (22-94.7) at 5 years	Not applicable	0.248@	Namouni, 1997± [447]
	Bone or bone marrow disease (n=4) 100% survival at median follow up of 57 months (46-80)	Not applicable		Dunkel, 2000[438]
	Bone and bone marrow metastasis (n=4) 75% at 5 years[b]	Not applicable		Rodriguez-Galindo, 2003± [448]
	100% at 5 years (n=2)	Not applicable		Cozza et al. 2009[456]
	Not applicable	65.3% at 5 years (t1, n=36) 75.5% at 5 years (t2, n=33)	0.003^^ <0.001	Antoneli, 2003 [451]
	Not applicable	Stage II 85% ± 0.06 (n=29) Stage IV 50% ± 0.20^ (n=6)		Schvartzman, 1996 # [455]
	67% survival (38-85) at 5 years	Not applicable		Dunkel, 2010[450]
	Patients with trilateral retinoblastoma (n=13) 38% (14-63) at 5 years	Not applicable		Dunkel, 2010[444]

Table 59. Overall survival for treatment (single auto HSCT) and comparison (conventional chemotherapy +/- radiation) groups: Retinoblastoma (continued)

Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Overall Survival mixed	~88% at 1 year[c] ~ 60% at 2 years ~57% at 3 years ~52% at 4-5years (n=34)[a]	Not applicable		Namouni, 1997[447]
	Not applicable	39.2 ± 14.7% at 5 years (n=15)		Chang, 2006[452]
5 year OS range in studies with > 1 patients with extraocular retinoblasto-ma with CNS involvement	25%[447]	0-20% [451, 455]		
5 year OS range in studies with > 2 patients with extraocular retinoblasto-ma without CNS involvement not including trilateral retinoblastoma	58.3-100%[447, 448, 450] Dunkel, 2000[d 438]	50-75.5%[451, 455]		
5 year OS range in studies with > 1 patients with trilateral retinoblasto-ma	38% (14-63)[444]	No comparator study identified		

DOD = dead of disease; DOT = dead of toxicity; NED = no evidence of disease
* Only one of these patients was treated.
^ Three of these patients had CNS involvement.
** Two treatment periods are displayed.
^^ P-values are for the comparison of class IV/V (CNS and bone and lymph) to class I/III (non CNS bone or lymph mets).
[a] This includes all patients including those who died prior to treatment.
[b] Two patients developed CNS disease and died.
[c] Estimated preceded by a ~ were estimated from published Kaplan-Meier curves.
± Survival curves were constructed using the raw data published in the articles.
@ Comparison of the three overall survival curves for cut end of optic nerve, bone mets, and CNS disease.
[d] Survival was 100% at a median followup of 57 months (46-80).

Event-free Survival

Information on event-free survival can be found in Appendix D.

Adverse Effects

No studies evaluated quality of life, and adverse effects were only reported by intervention studies. Data on treatment-related mortality was reported in two intervention studies (Table 60). Two patients died from septicemia and multi-organ failure during induction therapy.[444, 449] Two studies reported cases of serious infection, both attributed to *Candida albicans*.[447, 448] One comparator study[451] reported three secondary malignancies (two osteogenic sarcoma, and one nonlymphocytic leukemia) and one intervention study[450] reported three secondary malignancies (osteosarcoma, two occurring in irradiated fields). There were no reports of serious hemorrhagic events, irreversible veno-occlusive disease or other long-term complications among patients treated with HSCT or conventional chemotherapy.

Table 60. Adverse effects for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Retinoblastoma

Outcome	Disease	Intervention HSCT (%)	Comparator Chemo (%)	Study
Treatment related mortality	CNS	0[a]	NA	Dai, 2008[442]; Gunduz, 2006[454]; Matsubara, 2005[446]; Namouni, 1997[447]; Dimaras, 2009[443]
		NA	0[a]	Cozza, 2009[456]; Chantada, 1999[453]; Jubran, 2004[457];
		12.5[b]	NA	Dunkel, 2010[449]
	No CNS	0[a]	NA	Dunkel, 2000[438]; Hertzberg, 2001[441]; Kremens, 2003[445]; Matsubara, 2005[446]; Moshfeghi, 2002[440]; Taguchi, 2005[439]; Dunkel, 2010[450]
		NA	0[a]	Gunduz, 2006[454]; Jubran, 2004[457];
	Trilateral retinoblastoma	7.7[b]	NA	Dunkel, 2010[444]
Secondary malignancies	CNS	NR	NR	
	No CNS		3.6	Antoneli, 2003[451]
		20	NA	Dunkel, 2010[450]
	Trilateral retinoblastoma	NR	NR	
Infectious complications	CNS	4	NR	Namouni, 1997[447]
	No CNS	25	NR	Rodriguez-Galindo, 2003[448]
	Trilateral retinoblastoma	NR	NR	
Serious hemorrhagic event	CNS	NR	NR	There were no reports from any study
	No CNS			
	Trilateral retinoblastoma			
Veno-occlusive disease	CNS	NR	NR	There were no reports from any study
	No CNS			
	Trilateral retinoblastoma			

Table 60. Adverse effects for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Retinoblastoma (continued)

Outcome	Disease	Intervention HSCT (%)	Comparator Chemo (%)	Study
Long-term complications	CNS	NR	NR	There were no reports from any study.
	No CNS			
	Trilateral retinoblastoma			

[a]No cases of TRM occurred in these studies.
[b]Death occurred during induction chemo.

Ongoing Studies

A Phase III multicenter study of multimodal therapy (induction, HDC, and HSCT and/or radiotherapy) for young children with extraocular retinoblastoma was identified (NCT00554788). This trial estimates it will enroll 60 children ages 10 years of age and younger and will be complete in February 2014. Event-free survival is the primary outcome measure.

Twenty children ages 21 or younger were to be enrolled in a Phase I study examining the toxicity of killer IG-like receptor mismatched umbilical cord blood for pediatric patients with malignant solid tumors. This study is ongoing and no longer recruiting, and no results have been published.

Conclusion

Low strength evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for the treatment of extraocular retinoblastoma with CNS involvement.

The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of extraocular retinoblastoma without CNS involvement was insufficient to draw conclusions.

The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of trilateral retinoblastoma without CNS involvement was insufficient to draw conclusions.

Neuroblastoma Systematic Review

Background and Setting

Neuroblastoma is the most common extracranial solid tumor of childhood, and accounts for 8 to 10 percent of all childhood cancers and for approximately 15 percent of cancer deaths in children.[103] At least 40 percent of all children with neuroblastoma are designated as high-risk patients.[103, 104] Despite the development of new treatment options, the prognosis of patients with high-risk neuroblastoma is generally poor; more than half of patients experience disease recurrence and long-term survival with current treatments is about 30 percent.[104]

Many centers have used HDC with HSCT in the setting of high-risk or recurrent disease.[103, 106] Results from randomized controlled trials (RCTs) comparing HDC/HSCT with conventional therapy have shown higher survival rates with HSCT, although higher levels of adverse effects have been reported and overall rates are unsatisfactory.[105, 107, 108] Sequential tandem HSCT has been developed to improve further the outcome of patients with high-risk neuroblastoma.

Evidence Summary

The overall grade of strength of evidence for overall survival in pediatric patients with high-risk neuroblastoma is shown in Table 61.

The evidence compiled for this review includes six observational studies on HSCT, and three RCTs reporting outcomes data on single HSCT. The total number of patients included in the nine studies was 4,044: 682 patients received tandem HSCT, whereas 3,362 patients received single HSCT.

Tandem HSCT results in no significant differences in survival rates than single HSCT. In addition, no significant differences in secondary malignant disease and treatment-related mortality between treatment groups were identified. No information on QOL was provided and data on adverse effects are very limited; no definitive conclusions can be made regarding adverse effects and quality of life.

The ongoing randomized trial by the Children's Oncology Group will address whether tandem HSCT is superior to single HSCT in patients with high-risk neuroblastoma.

Table 61. Overall grade of strength of evidence for overall survival: Neuroblastoma

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/ Conclusion
For pediatric patients with high-risk neuroblastoma, what is the comparative effectiveness and harms of tandem HSCT and single HSCT regarding overall survival? Outcome of interest is overall survival. The comparator is single HSCT.	There are six observational studies on tandem HSCT (three provided comparisons of tandem vs. single HSCT, and three of tandem HSCT. There are three RCTs on single HSCT (vs. conventional therapy).	The risk of bias in this evidence is medium. The EBMT cohort represents the largest cohort of patients in this setting. While this is an uncontrolled design, the risk of bias is mitigated by the similarity of the study patients given well established staging and prognostic factors.	Results for overall survival for tandem HSCT are inconsistent. Recruitment of patients in the EBMT cohort spans over 25 years and includes various treatment regimens and reports similar survival rates. Two more recent case series report higher survival rates. Results for overall survival for single HSCT consistently show improved outcome compared to conventional therapy.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is imprecise, effects are uncertain. There is uncertainty on whether tandem HSCT is inferior, equivalent or superior to single HSCT.	Not applicable due to lack of obvious effect size.	The body of evidence on overall survival with tandem HSCT compared to single HSCT for the treatment of high-risk neuroblastoma was insufficient to draw conclusions.

Results

Eighteen reports describing nine unique studies were included in this review. Data from the European Group for Blood and Marrow Transplantation (EBMT) registry on outcomes for single and tandem HSCT have been reported in two publications.[113, 458] George et al. have reported outcomes of tandem HSCT across four U.S. centers in seven publications.[459-465] Two further studies have been reported in multiple publications; two reports by Sung et al. on tandem HSCT[466, 467] and two reports of the RCT by Matthay et al. on single HSCT.[107, 111] The report with the largest sample size and longest followup period from each of the above series was included in the primary analysis for this review. The total number of patients included in the nine studies was 4,044: 682 patients received tandem HSCT, whereas 3,362 patients received single HSCT.

Table 62 shows the criteria that were used to select studies for this section.

Table 62. Study selection criteria: Neuroblastoma

Study Design	Population	Intervention	Comparators	Outcomes	Time	Setting
Controlled trial, cohort, case-series	Pediatric patients (0-21 yr) with high-risk or relapsed/refractory disease	Tandem (Auto Auto) HSCT	Single (Auto) HSCT	OS; EFS (DFS; PFS); long-term adverse events; QOL	All durations of followup	In-patient

Auto = autologous; DFS = disease-free survival; EFS = event-free survival; HSCT = hematopoietic stem-cell transplant; OS = overall survival; PFS = progression-free survival; QOL = quality of life

Table 63 shows the study design and population. Of the included publications, six were observational studies (three provided comparisons of tandem vs. single HSCT[466, 468, 469]; three of tandem HSCT[459, 462]), and three were RCTs reporting outcomes data on single HSCT.[105, 107, 108, 111] Five were multicenter studies (two reporting on outcomes for tandem HSCT and three trials on single HSCT). Three studies were based in Europe,[105, 108, 113] three in Asia,[466, 468, 469] and three in North America.[107, 459, 462] The EBMT data represents the largest cohort of patients recruited over 28 years (1978–2006).[113]

All patients across eight (of nine) studies received HSCT as consolidation of primary treatments, Eighty percent of patients in the EBMT cohort received HSCT as consolidation therapy; relapse was the indication in another 10 percent while the status prior to HSCT was not specified in a further 10 percent of patients.[113] The vast majority of patients across studies presented with stage IV disease at diagnosis (range: 81 to 100 percent For the EBMT data, the stage was reported only in 53 percent of the cohort but there was a high prevalence for advanced disease with stage IV in more than 90 percent of the reported cases.[113]

Eight studies were specific to the pediatric age group; the EBMT cohort consisted of 2 percent (of 3,421) patients over 18 years of age. Eight studies reported the age of the participants at diagnosis; Sung et al. (2007) reported age at both diagnosis and HSCT.[466] The median age was reported in six studies on tandem HSCT; the remaining three trials on single HSCT reported only the number of cases above and below one year of age. The majority of patients (86 to 97 percent across all studies were over 12 months of age at diagnosis.

All studies used different induction regimens (i.e., different chemotherapeutic agents and different (cumulative) dosages). The induction regimen across studies consisted of multiple cycles (1-10) of chemotherapy followed by surgery for resection of the primary tumor. The

timing of surgery varied during induction and took place at diagnosis or after 2 to 7 cycles of chemotherapy. Tumor-field radiotherapy was used in patients with residual tumor and/or metastatic disease in at least six (of nine) studies: Sung et al. employed radiotherapy in the early study period (diagnosis by December 2003).[466] There was no postoperative radiotherapy in Pritchard et al.; in this latter study, 41 percent of patients randomized to the single HSCT arm received nine or more cycles of induction chemotherapy.[108]

Table 63. Study characteristics and population: Neuroblastoma

Study	Design	Median Age in Months (Range)	Sex (M%)	Histology [Site] (%)	Tandem	Single	Treatment Period
Ladenstein, 2008;1998[113, 458]	Cohort	47 (4-744)	59	NR	455	2,895	1978-2006
Kim, 2007[468]	Case-Series	36 (7-121)	69	NR [Abdomen (89); Other (11)]	9	27	1996-2004
Sung, 2007[466]	Case-Series	36 (13-129); 45.5 (24-140)[a]	NR	Favorable (27); Unfavorable (71); Unknown (2)	52	NA	1997-2005
George, 2006[459]	Case-Series	35 (6-216)	NR	[Adrenal (54); Abdomen (37); Other (9)][b]	82[b]	NA	1994-2002
Hobbie, 2008[462]	Case-series	22 (13-72)	85	NR	13	NA	1997-2001
Sung, 2010[469]	Case-series	36 (13-144)[c] 39 (13-159)[d]	46[c] 50[d]	NR	71	70	2000-2005
Matthay, 2009; 1999[107, 111]	RCT	(0-216)	NR	Favorable (3); Unfavorable (63); Unknown (33)	NA	189	1991-1996
Berthold, 2005[105]	RCT	(0-240)	NR	NR	NA	149	1997-2002
Pritchard, 2005[108]	RCT	(6-240)	50%	[Abdomen (88); Other (12)]	NA	32	1982-1985

M = male; NA = not applicable; NR = not reported; RCT = randomized controlled trial
[a] Age at transplant.
[b] Population characteristics based on 97 study patients.
[c] Tandem HSCT group.
[d] Single HSCT group.

Various conditioning regimens were used across studies. The primary conditioning regimen consisted of carboplatin, etoposide and melphalan. Total body radiation was used as part of the treatment regimen in six studies.[107, 113, 459, 462, 466, 469] In at least four studies, there were also differences in treatment that patients received within the study itself (for example, in external radiotherapy, immunotherapy, and retinoic acid).

Peripheral blood stem cells were used as the sole source of support in six studies,[105, 459, 462, 466, 468, 469] and bone marrow in two studies;[107, 108] the EBMT cohort used peripheral stem cells (56 percent), bone marrow (41 percent) and a combination of both (3 percent) as a source of support after HDC.[113] The median follow-up durations from first transplant across three studies comparing tandem and single HSCT were 2.3 years, 9 years, and 5 years, respectively.[113, 468, 469]

Table 64 shows the outcomes that were reported across nine studies. Of note, the study by Hobbie et al.[462] was a subgroup analysis of George et al.[459] reporting on the long-term adverse

events of tandem HSCT for high-risk disease. For purposes of data analysis and synthesis, these two reports were considered as unique studies; George et al.[459] reported on overall survival (OS), event-free survival (EFS), treatment-related mortality and secondary malignancies, while Hobbie et al.[462] reported on other adverse effects of HSCT.

Table 64. Outcomes reported: Neuroblastoma

Study	OS	EFS (DFS, PFS)	QOL	Treatment-related Mortality	Second Malignancies	Other Adverse Effects
Ladenstein, 2008[113]	√	√	NR	NR	NR	NR
Kim, 2007[468]	√	√	NR	NR	NR	NR
Sung, 2007[466]	√	√	NR	√	√	√
George, 2006[459]	√	√	NR	√	√	√
Hobbie, 2008[462]	NR	NR	NR	NR	NR	√
Matthay, 2009[111]	√	√	NR	√	√	√
Berthold, 2005[105]	√	√	NR	√	√	NR
Pritchard, 2005[108]	√	√	NR	√	NR	√
Sung, 2010[469]	NR	√	NR	√	√	NR

DFS = disease-free survival; EFS = event-free survival; NR = not reported; OS = overall survival; PFS = progression-free survival; QOL = quality of life

Overall Survival

Data on OS were reported in seven (of nine) primary studies (Table 64). Six studies presented 3- and/or 5-year rates and the study by George et al.[459] also presented 7-year rates (Table 65). No significant differences in either the 3-year or 5-year OS between treatment groups were identified in the two comparative studies (Table 65).[113, 468] Multivariate analysis of EBMT data showed significantly better OS rates in patients younger than 2 years of age at diagnosis (Hazard Ratio [HR], 1.6; 95 percent; Confidence Interval [CI], 1.4-1.9; p<0.0001).[113] It should be noted that the individual studies either did not define OS or used different starting points for this variable (i.e., either years from diagnosis or years from first transplant).

Table 65. Overall survival for treatment (tandem HSCT) and comparison (single HSCT) groups: Neuroblastoma

Outcome	Intervention Tandem (%; ± 95% CI; SE) [N]	Comparator Single (%; ± 95% CI; SE) [N]	P Value	Study
3-year rate	66.7 (19.3) [9]	55.1 (13.9) [27]	>0.05	Kim, 2007[468]
	74 (62-82) [82]	Not applicable	NR	George, 2006[459]
	Not applicable	43 (4) [189]	NR	Matthay, 2009[111]
	Not applicable	62 (54-70) [149]	NR	Berthold, 2005[105]
5-year rate	33 (3) [455]	38 (1) [2,895]	0.105	Ladenstein, 2008[113]
	64 (52-74) [82]	Not applicable	NR	George, 2006[459]
	64.3 (14.3) [52]	Not applicable	NR	Sung, 2007[466]
	Not applicable	29 (4) [189]	NR	Matthay, 2009[111]
	Not applicable	47 (30-64) [32]	NR	Pritchard, 2005[108]
7-year rate	54 (38-67) [82]	Not applicable	NR	George, 2006[459]
	Not applicable	~25 [189]	NR	Matthay, 2009[111]
OS range for ≥5 years, studies with >10 pts	33-64	29-47	NR	

CI = confidence interval; N = number of patients; NR = not reported; SE = standard error

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Event-free Survival

Information on event-free survival can be found in Appendix D.

Adverse Effects

None of the studies evaluated quality of life (Table 64). Data on treatment-related mortality were reported in six studies (Table 66). There were 20 (of 197) cases in the tandem group and 36 (of 373) cases in the single HSCT group. Secondary malignancies were reported in five studies (Table 66). There were three (of 212) cases in the tandem group (one synovial cell sarcoma, one myelodysplasia with clonal trisomy 8, and one thyroid cancer); two cases were reported in the George et al.[459] study. The case of thyroid cancer was reported in the 2010 study by Sung et al.[469], and occurred in a patient receiving only the first HSCT. Three (of 408) cases of secondary malignancies were reported in the single HSCT group (two acute myeloblastic leukemias and one follicular carcinoma of the thyroid).

Infectious complications were reported in four studies (Table 66). Sepsis was more prevalent in the single HSCT group (n=219) compared to the tandem group (n=126) (26 vs. 2 percent). All infectious complications were attributed to sepsis in the single HSCT group. Further serious infections in the tandem group included two cases of viral pneumonia and three cases of Epstein-Barr virus and cytomegalovirus, all resulting in toxicity-related deaths. Other reported serious adverse effects included one case of pulmonary hemorrhage in the tandem group and three cases of bleeding in the single HSCT group.

The frequency of veno-occlusive disease was reported across four studies (Table 66).[108, 111, 459, 466] There were nine (of 126) cases in the tandem group and two (of 30) cases in the single HSCT group. Only one study (n=13) by Hobbie et al.[462] reported further long-term complications including developmental delays (i.e., hearing loss, 92 percent), cataracts (54 percent), and growth-hormone deficiency (54 percent) following tandem HSCT.

Table 66. Adverse effects for treatment (tandem HSCT) and comparison (single HSCT) groups: Neuroblastoma

Outcome	Intervention Tandem (%)	Comparator Single (%)	Study
Treatment-related mortality	16	Not applicable	Sung, 2007[466]
	6	Not applicable	George, 2006[459]
	Not applicable	6	Matthay, 2009[111]
	Not applicable	3.3	Berthold, 2005[105]
	Not applicable	7	Pritchard, 2005[108]
	11	13	Sung, 2010[469]
Secondary malignancies	0	Not applicable	Sung, 2007[466]
	2	Not applicable	George, 2006[459]
	Not applicable	1	Matthay, 2009[111]
	Not applicable	1	Berthold, 2005[105]
	1	0	Sung, 2010[469]
Infectious complications	3.8	Not applicable	Sung, 2007[466]
	5	Not applicable	George, 2006[459]
	Not applicable	26	Matthay, 2009[111]
	Not applicable	23	Pritchard, 2005[108]
	2	Not applicable	Sung, 2007[466]

Table 66. Adverse effects for treatment (tandem HSCT) and comparison (single HSCT) groups: Neuroblastoma (continued)

Outcome	Intervention Tandem (%)	Comparator Single (%)	Study
Serious hemorrhagic event	Not applicable	10	Pritchard, 2005[108]
	18	Not applicable	Sung, 2007[466]
Veno-occlusive disease	1	Not applicable	George, 2006[459]
	Not applicable	9	Matthay, 2009[111]
	Not applicable	7	Pritchard, 2005[108]
Long-term complications	(8-92)[a]	Not applicable	Hobbie, 2008[462]

[a]range of late-effects including endocrine, sensory, musculoskeletal, pulmonary, dental, renal, and cardiovascular complications

Ongoing Research

In North America, the Children's Oncology Group is studying, in a randomized fashion, whether tandem HDC/HSCT is superior to a single HDC/HSCT in patients with high-risk neuroblastoma up to 30 years of age. This is an international trial (U.S., Canada, Australia, New Zealand) being undertaken across 142 centers and is currently recruiting patients with an expected enrollment of 495 patients. The primary outcomes of interest include 3-year EFR, response after induction therapy, and incidence rate of local recurrence. The projected completion of accrual is spring 2012 (NCT00567567).[a]

Conclusion

The body of evidence on overall survival with tandem HSCT compared to single HSCT for the treatment of high-risk neuroblastoma was insufficient to draw conclusions.

Germ-Cell Tumors Systematic Review

Background and Setting

Germ cell tumors (GCT) are rare in children younger than 15 years, accounting for approximately 3 percent of cancer cases in this age group.[115] Childhood GCT can be divided into gonadal (ovarian and testicular) and extragonadal (e.g., mediastinal or retroperitoneal) neoplasms.[118] Gonadal GCT (particularly testicular GCT) are much more common among adolescents aged 15 to 19 years, representing approximately 14 percent of cancer diagnoses in this age group.[115] GCTs are highly sensitive to chemotherapy. Cisplatin-based combination chemotherapy, followed by appropriate surgical resection of residual disease, is curative in 80 percent of patients; however, about 20-30 percent of patients may develop recurrent disease.[114, 118, 119] HDC with HSCT has been explored primarily in adults with relapsed testicular GCT through observational studies.[115, 118, 119, 470]

Reports from salvage treatment strategies used in adult recurrent GCT include larger numbers of patients, but the differences between children and adults regarding the location of the primary GCT site, pattern of relapse, and the biology of childhood disease may limit the applicability of adult salvage approaches to children. Sequential tandem HSCT has been developed to improve further the outcome for children with relapsed GCT.

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[a] The projected date was confirmed as personal communication to Hussein Noorani by Dr. Julie Park, Study Chair of the Children's Oncology Group, October 15, 2010.

Evidence Summary

The overall grade of strength of evidence for overall survival in pediatric patients with tandem HSCT compared to single HSCT for the treatment of relapsed germ cell tumors is shown in Table 67. The evidence compiled for this review includes four observational studies.[114, 119, 120, 470] The total number of pediatric patients included in the four studies was 71: 29 patients received tandem HSCT, whereas 42 patients received single HSCT. Tandem HSCT results in no significant differences in survival rates than single HSCT. No information on QOL was provided, and data on adverse effects are very limited; no definitive conclusions can be made regarding adverse effects and QOL. Results to date are based on small observational studies that have focused on adult patients with gonadal disease. Tandem HSCT may be particularly beneficial in patients with more advanced testicular cancer at diagnosis and greater likelihood of exhibiting cisplatin resistance when compared to single HSCT. However, the reports have great variability in patient selection, prior treatments, the choice of the conditioning regimen and variability of doses within the same regimen. Furthermore, many reports have either combined the data from single and tandem transplants or the numbers are very small.

Randomized (prospective) trials focused on young children and adolescents will be needed to determine if tandem HSCT transplants is superior to single HSCT utilizing an optimal conditioning regimen.

Table 67. Overall grade of strength of evidence for overall survival: Germ cell tumor

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/ Conclusion
For pediatric patients with relapsed germ cell tumors, what is the comparative effectiveness and harms of tandem HSCT and single HSCT regarding overall survival? Outcome of interest is overall survival. The comparator is single HSCT.	There are two observational studies on tandem HSCT (one provided comparison of tandem vs. single HSCT, and one of tandem HSCT). There are two observational studies on single HSCT.	The risk of bias in this evidence is high as our review consisted of small cohorts and case series.	Results for overall survival are inconsistent. Confidence intervals overlap and clinical heterogeneity exists between studies.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is imprecise; effects are uncertain. There is uncertainty on whether tandem HSCT is inferior, equivalent or superior to single HSCT.	Not applicable due to lack of obvious effect size.	The body of evidence on overall survival with tandem HSCT compared to single HSCT for the treatment of relapsed pediatric germ cell tumors was insufficient to draw conclusions.

Results

Seventeen articles were retrieved for full-text screening. Four reports were included in this review, and the remaining 13 articles were excluded. The total number of pediatric patients included in the four studies was 71 (of 539): 29 patients received tandem HSCT, whereas 42 patients received single HSCT. Table 68 shows the study selection criteria.

Table 68. Germ cell tumor study selection criteria

Study Design	Population	Intervention	Comparators	Outcomes	Time	Setting
Controlled trial, cohort, case-series	Pediatric patients (0-21-yr) with relapsed disease	Tandem (Auto Auto) HSCT	Single (Auto) HSCT	OS; EFS (DFS; PFS); long-term adverse events; QOL	All durations of followup	In-patient

Auto = autologous; DFS = disease-free survival; EFS = event-free survival; HSCT = hematopoietic stem-cell transplant; OS = overall survival; PFS = progression-free survival; QOL = quality of life

Table 69 shows the study design and population. All four publications were observational studies. Tandem transplants were performed in two (50 percent) studies. Only one study reported outcomes data of tandem versus single HSCT.[119] Two were multicenter studies (Center for International Blood and Marrow Transplant Research [CIBMTR] cohort by Lazarus et al.[119] and a European Group for Blood and Marrow Transplantation [EBMT] cohort by De Giorgi et al.[114] and two were U.S. single-center studies.[120, 470]

Table 69. Germ cell tumor study characteristics and population

Study	Design	Median Age in Years (range)	Sex (M%)	Histology [Site] (%)	Tandem	Single	Treatment Period
Lazarus, 2007[119] [CIBMTR, 2010[471]]	Cohort	19 (15-20)[a] 20 (17-20)[b]	NR	NS (53[a], 67[b]); SM (21[a], 0[b]); CC (16[a],0[b]); EB (5[a],33[b]); Other (5[a],0[b]) [Testes (90[a], 100[b]); Extragonadal (10[a], 0[b])]	12	20	1989-2001
Einhorn, 2007[470]	Case series	20 (17-21)[c]	NR	NS (81); SM (19) [Testes]	17[c]	0	1996-2004
Agarwal, 2009[120]	Case series	NR (0-19)[d]	92	NS (84); SM (16) [Testes (65); Chest/Neck/RP (27); CNS (8)]	0	4[d]	1995-2005
De Giorgi, 2005[114]	Cohort	6.5 (1-18)	56	NG (94); GM (6) [CNS (39); Sacr (39); Retr (17); Med (6)]	0	18	1987-2003

CC = pure choriocarcinoma; CNS = central nervous system; EB = pure embryonal; GM = germinoma; M = male; NG = nongerminoma; NR = not reported; NS = nonseminoma; RP = retroperitoneal; SM = seminoma
[a] Single transplant.
[b] Tandem transplant.
[c] 184 patients in study (median age of 31 yrs (range, 15-58 yrs).
[d] 37 patients in study (median age of 28 yrs (range, 9-59 yrs).

Only one small study by De Giorgi et al.[114] was specific to the pediatric age group; approximately 10 percent of all patients across the remaining three studies were in the pediatric age range (Einhorn, 2007: n=17 [of 184];[470] Lazarus, 2007: n=32 [of 300];[119] Agarwal, 2009: n=4 [of 37][120]). The corresponding authors for the three studies were approached for outcomes data (and if available, patient characteristics) specific to the pediatric age groups.[b] Data on study

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[b] Data from Einhorn et al. (2007) were provided as personal communication to Hussein Noorani by Dr. Lawrence Einhorn, August 11 and September 1, 2010, respectively; data on outcome events from Agarwal et al. (2009) was provided as personal communication to Hussein Noorani by Dr. Rajni Agarwal, August 10, 2010.

variables and outcome events for the pediatric age range (11-20 years) for Lazarus et al.[119] were obtained from the CIBMTR.[471c]

All study patients received HSCT as salvage treatment for relapsed disease. The majority of patients (65-100 percent) across three studies had advanced testicular cancer; the EBMT cohort consisted of pediatric patients with extragonadal GCT.[114] Most patients received a cisplatin-based chemotherapy regimen initially and surgery for residual disease when appropriate. Various conditioning regimens were used across studies. The primary conditioning regimen consisted of carboplatin and etoposide. Peripheral blood stem cells were used as either the sole or primary source of support in all studies.

For the CIBMTR cohort, the tandem and single HSCT groups were comparable for median age, testicular versus abdominal origin, number of chemotherapy regimens prior to HSCT, and year of HSCT (over 50 percent of transplants were performed between 1996 and 1998).[471] The interval from diagnosis to first HSCT for the CIBMTR cohort was 12 (range: 2-34) months for the tandem group and 9 (range: 3-17) months for the single HSCT group. Eighty-three percent and 65 percent of patients had residual cancer at time of HSCT, respectively.[471] There were observed differences in the intensity of the transplant preparative regimen between the two study groups; 58 percent of the tandem group received a regimen containing 3 or more chemotherapeutic agents in contrast to 95 percent in the single HSCT group.[471] In addition, in comparison to the single HSCT group, the tandem group had a greater likelihood of cisplatin-resistance at time of transplantation (58 percent vs. 10 percent), and was more likely to receive blood (83 percent vs. 60 percent) rather than marrow as the stem cell source.[471] Median followup in the CIBMTR cohort was 56 (range: 45-74) months for the tandem group and 59 (range: 13-124) months for the single HSCT group, respectively.[471]

The Einhorn et al.[470] tandem series exhibited more favorable prognostic features compared to the CIBMTR tandem cohort. No patients in this series received more than two chemotherapeutic agents as part of their transplant preparative regimen.[470] Seventy-eight percent of patients exhibited platinum sensitivity and all patients received peripheral-blood stem cells.[470] Median followup in the Einhorn series was comparable to the CIBMTR cohort (48 [range: 14-118] months).[470]

Table 70 shows the pediatric outcomes that were reported across the four studies.

Table 70. Germ cell tumor outcomes reported

Study	OS	EFS (DFS, PFS)	Quality of Life	Treatment-related Mortality	Second Malignancies	Other Adverse Effects
CIBMTR, 2010[471]	√	√	NR	√	NR	√
Einhorn, 2007[470]	√	√	NR	NR	NR	NR
Agarwal, 2009[120]	√	√	NR	√	√	√
De Giorgi, 2005[114]	√	√	NR	√	√	√

DFS = disease-free survival; EFS = event-free survival; NR = not reported; OS = overall survival; PFS = progression-free survival

Overall Survival

Data on OS were reported in all four studies (Table 70). Data were available to compute three-year rates across all studies, and five-year rates for three studies (Table 71). Similar trends were observed between treatment groups in the one-, three-, and five-year OS across studies

(Table 71). For the CIBMTR cohort, five-year survival probability was 36 percent (95 percent confidence interval (CI), 10-69 percent) in the tandem group compared to 49 percent (24-68 percent) in the single HSCT group.[471] OS was defined across three studies as the interval between salvage chemotherapy or transplant and death from any cause.

Table 71. Overall survival for tandem HSCT and comparison (single HSCT) groups: Germ cell tumor

Outcome	Intervention Tandem (%; ± 95% CI) [N]	Comparator Single (%; ± 95% CI) [N]	p Value	Study
1-year rate	67 (34-86) [12]	65 (40-82) [20]	NR	CIBMTR, 2010[471]
	76.5 (59-99.5) [17]	NA		Einhorn, 2007[470]
	NA	67 (45-88) [18]		De Giorgi, 2005[114]
3 year rate	42 (15-67) [12]	49 (24-68) [20]	NR	CIBMTR, 2010[471]
	63 (43-92) [17]	NA		Einhorn, 2007[470]
	NA	50 (7-93) [4]		Agarwal, 2009[120]
	NA	56 (33-78.5) [18]		De Giorgi, 2005[114]
5 year rate	36 (10-59) [12]	49 (24-68) [20]	NR	CIBMTR, 2010[471]
	63 (43-92) [17]	NA		Einhorn, 2007[470]
	NA	49 (25-72) [4]		De Giorgi, 2005[114]
OS range for 5 years for studies with > 10 patients	36-63	49	NA	

CI = confidence interval; N = number of patients; NA = not applicable; NR = not reported

Event-free Survival

Information on event-free survival can be found in Appendix D.

Adverse Effects

None of the studies evaluated quality of life (Table 70). Data on treatment-related mortality was available from three studies (Table 72).[114, 120, 471] There was no reported cases of treatment-related mortality in the two single HSCT series (N=22). For the CIBMTR cohort, cumulative incidence of treatment-related mortality was 10 percent (2-27 percent) at 5 years for the single HSCT group (n=20); none of the 12 patients in the tandem group had treatment-related mortality (Table 72). Relapse/progression incidence, on the other hand, was 64 percent (30–85 percent) for the tandem group up to five years after transplant compared to 41 percent (20–62 percent) for the single HSCT group.[471] Other adverse events were reported in only two single HSCT studies. There were no secondary malignancies (Table 72). Veno-occlusive disease occurred in two (of 18) patients in the EBMT cohort by De Giorgi et al.[114]

Table 72. Adverse effects for tandem HSCT and comparison (single HSCT) groups: Germ cell tumor

Outcome	Intervention Tandem (%)	Comparator Single (%)	Study
Treatment related mortality	Not applicable	0[a]	De Giorgi, 2005 (77240); Agarwal, 2007 (72940)
	0	10	CIBMTR, 2010
Secondary malignancies	Not applicable	0[b]	De Giorgi, 2005 (77240); Agarwal, 2007 (72940)
Veno-occlusive disease	Not applicable	11	De Giorgi, 2005 (77240)
	Not applicable	0	Agarwal, 2007 (72940)

[a] No cases of treatment-related mortality reported in both studies.
[b] No cases of secondary malignancies reported in both studies.

Ongoing Research

Two U.S. nonrandomized studies are underway on tandem transplants. The first is a two-center (M.D. Anderson Cancer Center; Fred Hutchinson Cancer Research Center) Phase II study being undertaken to evaluate if bevacizumab, when given in combination with two cycles of HDC, can help to control GCTs in patients aged 12 to 65 years. The study is currently recruiting patients with an estimated enrollment of 25 participants. The primary outcome of interest is 2-year EFS. The estimated final data collection date for this trial is June 2014. (NCT00936936).

The second study (Phase I/II) is being undertaken at the Children's Memorial Hospital in Chicago to assess the feasibility and toxicity of tandem rescue with peripheral blood cells following HDC as consolidation in pediatric patients with high risk solid tumors, including relapsed GCT. The study is currently recruiting patients with an estimated enrollment of 12 participants. The estimated final data collection date is September 2012 (NCT00179816).

Conclusion

The body of evidence on overall survival with tandem HSCT compared to single HSCT for the treatment of relapsed pediatric germ cell tumors was insufficient to draw conclusions.

Central Nervous System/Embryonal Tumors Systematic Review

Background and Setting

Classification of brain tumors is based on both histopathologic characteristics of the tumor and location in the brain.[122] Central nervous system (CNS) embryonal tumors are the most common malignant brain tumor in childhood. Embryonal tumors of the CNS primarily include medulloblastoma (MB), supratentorial primitive neuroectodermal tumor (PNET), and atypical teratoid/rhabdoid tumor (AT/RT).[122] MBs account for 20 percent of all childhood CNS tumors.[123, 124] The other types of embryonal tumors are rare by comparison.[122]

PNETs are a heterogeneous group of highly malignant neoplasms comprising 3 to 5 percent of all childhood brain tumors, most commonly located in the cerebral cortex and pineal region.[123, 125] AT/RT, on the other hand, comprise approximately 2-3 percent of these tumors with a peak incidence in children less than three years of age, and is associated with characteristic genetic abnormalities.[123, 125, 126] The prognosis for these tumors is worse than for MB, despite identical therapies.[122, 123, 125]

Recurrence of all forms of CNS embryonal tumors is not uncommon, usually occurring within 18 months of treatment; however, recurrent tumors may develop many years after initial treatment.[122] The treatment of these tumors continues to evolve especially in children less than three years of age because of the concern of the deleterious effects of craniospinal radiation on the immature nervous system. Therapeutic approaches have attempted to delay and sometimes avoid the use of radiation, and have included trials investigating different chemotherapy regimens to improve outcome.[122] Many centers have used HDC with HSCT to improve further the outcome for children with CNS embryonal tumors.

Evidence Summary

The overall grade of strength of evidence for overall survival with tandem HSCT compared to single HSCT for the treatment of CNS embryonal tumors is shown in Table 73.

The evidence compiled for this review includes ten observational studies[133, 472-480] and two randomized clinical trials (RCT).[481, 482] Nine studies reported outcomes for HSCT,[133, 473-477, 481, 479, 480] and three studies (including two RCTs) were multi-institutional treatment protocols on CNS embryonal tumors.[478, 481, 482] For HSCT studies, 15 patients received tandem transplant, whereas 132 patients received single HSCT.

Based on the currently available evidence, it is not possible to clarify the role of HSCT (single or tandem procedure), as studies are limited individually by low numbers of patients enrolled and collectively by inconsistencies in the patients' ages. The prognosis and treatment varies depending upon the age of the patient and type of embryonal tumor. Most studies to date have focused on children with newly diagnosed medulloblastoma. Comparison between studies, moreover, remains challenging, given the heterogeneity of these tumors and the varied therapies used across centers.

Table 73. Overall grade of strength of evidence for overall survival: CNS embryonal tumors

Key Question	Study Design	Risk of bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/ Conclusion
For pediatric patients with CNS embryonal tumors, what is the comparative effectiveness and harms of tandem HSCT and single HSCT regarding overall survival? Outcome of interest is overall survival. The comparator is single HSCT.	There are three observational studies on tandem HSCT. There are seven observational studies on single HSCT.	The risk of bias in this evidence is high. There are differences in conditioning regimens and source of stem cell support across studies.	Results for overall survival are of unknown consistency. Studies consist of multiple tumor types. There is variability in prognostic features between studies.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is imprecise, effects are uncertain. There is uncertainty on whether tandem HSCT is inferior, equivalent or superior to single HSCT.	Not applicable due to lack of obvious effect size.	The body of evidence on tandem HSCT compared to single HSCT for the treatment of CNS embryonal tumors was insufficient to draw conclusions.
For pediatric patients with CNS embryonal tumors, what is the comparative effectiveness and harms of single HSCT and conventional therapy regarding overall survival? Outcome of interest is overall survival. The comparator is conventional therapy.	There are five observational studies on single HSCT. There are two RCTs and one observational study on conventional therapy.	The risk of bias in this evidence is high. One RCT was performed earlier in the mid-90s; There are differences in treatment regimens and supportive care across studies.	Results are of unknown consistency. Studies consist of multiple tumor types. There is variability in prognostic features between studies.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is imprecise, effects are uncertain. There is uncertainty on whether single HSCT is inferior, equivalent or superior to conventional chemotherapy.	Not applicable due to lack of obvious effect size.	The body of evidence on single HSCT compared to conventional therapy for the treatment of CNS embryonal tumors was insufficient to draw conclusions.

Results

Twelve reports were included in this review. Table 74 shows the criteria that were used to select studies for this section. For HSCT studies, 15 patients received tandem transplant (MB, n=13; PNET, n=1; AT/RT, n=1), whereas 132 patients received single HSCT (MB, n=61; PNET, n=52; AT/RT, n=19).

Table 74. Study selection criteria: CNS embryonal tumors

Study Design	Population	Intervention	Comparators	Outcomes	Time	Setting
Controlled trial, cohort, case-series	Pediatric patients (0-21-yr) with newly diagnosed disease	Tandem (Auto Auto) HSCT	Single (Auto) HSCT	OS; EFS (DFS; PFS); long-term adverse events; QOL	All durations of followup	In-patient and/or out-patient
		Single (Auto) HSCT	Conventional therapy			

Auto = autologous; DFS = disease-free survival; EFS = event-free survival; HSCT = hematopoietic stem-cell transplant; OS = overall survival; PFS = progression-free survival; QOL = quality of life

Table 75 shows the study design and population. Ten publications were observational studies[133, 472-480] and two were randomized clinical trials (RCTs).[481, 482] Nine studies reported outcomes for HSCT, and three studies (including two RCTs) were multi-institutional treatment protocols on CNS embryonal tumors.[478, 481, 482] Of the nine HSCT studies, tandem transplants were performed in three studies, one of which reported comparative data of tandem vs. single HSCT.[133] Sixty percent of these patients were considered as average-risk (i.e., Chang stage M0 having no metastasis), and 40 percent as high-risk (i.e., Chang stage M1-M4 having metastasis).

All patients across the nine transplant studies received HSCT as consolidation of primary treatments. All studies used different induction regimens (i.e., different chemotherapeutic agents and different (cumulative) dosages). The induction regimen across studies primarily consisted of five cycles of chemotherapy followed by consolidation phase. Various conditioning regimens were used across studies. The conditioning regimen primarily consisted of carboplatin, thiotepa, etoposide, busulfan and/or melphalan. Approximately 30 percent of patients (29-37 percent) also received radiation therapy across these studies. Peripheral blood stem cells were used as the sole source of support in five studies (two on single HSCT and three on tandem HSCT); combination of peripheral blood and bone marrow was used across the remaining four studies.

Data on conventional care were based on results from three multi-institutional treatment protocols on CNS embryonal tumors (one on multiple tumor types which consisted of MB, PNET and AT/RT; and two on MB).[478, 481, 482] The study by Geyer et al.[481] was a RCT from the U.S. Children's Cancer Group (COG) of two multi-agent chemotherapy regimens (with deferred radiotherapy) for children younger than 3 years of age with various malignant brain tumors in a large cohort of patients. Maintenance therapy for all patients in the COG protocol comprised of eight cycles of vincristine, carboplatin and cyclophosphamide; over 40 percent of patients received radiotherapy.[481] Two studies reported on outcomes for MB patients; the RCT by Packer et al.[482] reported on outcomes with radiotherapy and adjuvant chemotherapy for children three years and older with nonmetastatic disease, and the European multicenter study by Taylor et al.[478] reported on outcomes for ages three years and older with metastasis.

Table 76 shows the outcomes that were reported across the 12 studies.

Table 75. Study characteristics and population: CNS embryonal tumors

Study	Design	Median Age in Months (Range)	Sex (M%)	Histology [Tumor Type] (%)	Tandem HSCT	Single HSCT	CC	Rx Period
Sung, 2007[466]	Case series	31 (17-198)	50	M0 (64); M1 (7); M3 (29) [MB (79); PNET (21)]	11	3	NA	1999-2005
Gidwani, 2008[472]	Case report	4	100	M0 [AT/RT (100)]	1	NA	NA	NR
Fangusaro, 2008[473]	Case series	37 (0-120)	51	M0 (82); M1-M3 (18) [PNET (100)]	NA	43	NA	1991-2002
Dhall, 2008[474]	Case series	21 (5-35)	50	M0 (100) [MB (100)]	NA	21	NA	1991-2002
Chi, 2004[475]	Case series	38 (7-119)	76	M1 (19); M2 (9.5); M3 (71) [MB (100)]	NA	21	NA	1997-2003
Gardner, 2008[476]	Case series	35 (4-52)	54	M0 (77); M1 (8); M3 (15) [AT/RT (100)]	NA	13	NA	1992-2002
Perez-Martinez, 2005[477]	Case series	3 (1-14) years	61.5	M1-M4 (NR) [MB (69); PNET (31)]	NA	13	NA	1995-2002
Packer, 2006[482]	RCT	(36-228)	59	M0 (100) [MB (100)]	NA	NA	379	1996-2000
Geyer, 2005[481]	RCT	(0-36)	53	M0 (68); M1+ (32) [MB (44); PNET (22); AT/RT (13) Other (21)]	NA	210	284	1993-1997
Taylor, 2005[478]	Case series	94 (34-197)	29	M2 (19); M3 (81) [MB (100)]	NA	NA	68	1992-2000
Bandopadhayay, 2011[479]	case series	20.5 (3-37)	61	M0 (91); M1 (6); M3 (3) [MB (50); AT/RT (33); PNET (17)]	NA	18	NA	1999-2005
Aihara, 2010[480]	case report	144 (84-156)	100	M3 (100) [MB (100)]	3	NA	NA	NR

AT/RT = atypical teratoid/rhabdoid tumor; CC = conventional care; HSCT = hematopoietic stem-cell transplant; M0 = no evidence of metastasis; M1 = tumor cells found in cerebrospinal fluid (by lumbar puncture and cytology study); M2 = tumor beyond primary site but still in brain; M3 = tumor deposits ("seeds") in spine area that are easily seen on MRI; M4 = tumor spread to areas outside the CNS (outside both brain and spine); M = male; MB = medulloblastoma; NR = not reported; PNET = supratentorial primitive neuroectodermal tumor; RCT = randomized controlled trial

Table 76. Outcomes reported: CNS embryonal tumors

Study	OS	EFS (DFS, PFS)	QOL	Treatment-related Mortality	Second Malignancies	Other Adverse Effects
Sung, 2007[466]	√	√	NR	√	NR	√
Gidwani, 2008[472]	√	√	NR	NR	√	√
Fangusaro, 2008[473]	√	√	NR	√	√	√
Dhall, 2008[474]	√	√	√	√	NR	√
Chi, 2004[475]	√	√	NR	√	NR	NR
Gardner, 2008[476]	√	√	NR	√	NR	√
Perez-Martinez, 2005[477]	NR	√	NR	√	√	√
Packer, 2006[482]	√	√	NR	√	√	√
Geyer, 2005[481]	√	√	NR	√	√	√
Taylor, 2005[478]	√	√	NR	√	NR	√
Bandopadhayay, 2011 [479]	√	NR	NR	√	NR	√
Aihara, 2010[480]	NR	√	NR	√	NR	√

DFS = disease-free survival; EFS = event-free survival; NR = not reported; PFS = progression-free survival; QOL = quality of life

Overall Survival

Data on OS were reported in ten (of 12) studies (Table 76). For comparisons between tandem vs. single HSCT, data were available to compute 2-year rates for two studies, 3-year rates for two studies, and 5-year rates for four studies (Table 77). For Sung et al.[466] (n=14), 2-year survival probability was 82 percent (95 percent confidence interval (CI), 59-100 percent) in the tandem group (MB, n=10; PNET, n=1) compared to 67 percent (13-100 percent) in the single HSCT group (MB, n=1; PNET, n=2). The AT/RT patient reported in Gidwani et al.[472] has remained disease free for two years following tandem HSCT. OS was defined across studies as the interval between diagnosis to death or last followup.

For the conventional-care group of studies, data were available to compute 3-year rates for one study,[478] and 5-year rates for three studies (Table 78).[478, 481, 482] There were no comparative studies between single HSCT vs. conventional care. For Geyer et al.[481] on multiple tumor types, five-year survival probability overall was 43 percent (3 percent) for children under three years of age; for MB, PNET and AT/RT, the corresponding rates were 43 percent (5 percent), 31 percent (7 percent), and 29 percent (9 percent), respectively. Similar rates were observed for MB patients with metastatic disease in the multicenter study by Taylor et al.[478] Packer et al.[482] reported higher survival rates in their cohort of MB patients without metastasis.

Table 77. Overall survival for tandem HSCT and comparison (single HSCT) groups: CNS embryonal tumors

Outcome	Tumor type	Intervention Tandem (%; ± 95% CI; SE) [N]	Comparator Single (%; ± 95% CI; SE) [N]	p Value	Study
2-year	MB-PNET	82 (59-100) [11]	67 (13-100) [3]	NR	Sung, 2007[466]
	AT/RT	[One patient alive without disease]	Not applicable		Gidwani, 2008[472]
	MB AT/RT	Not applicable	50 [4.5] 20 [1.2]*		Bandopadhayay, 2011 [479]
3-year	MB	Not applicable	60 (36-84) [21]		Chi, 2004[475]
	AT/RT	Not applicable	23 (11) [13]		Gardner, 2008[476]
5-year	MB-PNET	82 (59-100) [11]	NA		Sung, 2007[466]
	PNET	Not applicable	49 (33-62) [43]		Fangusaro, 2008[473]
	MB	Not applicable	70 (10) [21]		Dhall, 2008[474]
	MB	50 [4.5]	Not applicable	<.01	Bandopadhayay, 2011 [479]
OS range for 5 years for studies with >10 patients	All	82	49-70	Not applicable	Not applicable

AT/RT = atypical teratoid/rhabdoid tumor; CI = confidence interval; MB = medulloblastoma; N = number of patients; NA = not available; PNET = supratentorial primitive neuro-ectodermal tumors; SE = standard error
*18-month OS.

Table 78. Overall survival for single HSCT and comparison (conventional care) groups: CNS embryonal tumors

Outcome	Tumor type	Intervention Single (%; ± 95% CI; SE) [N]	Comparator CC (%; ± 95% CI; SE) [N]	p Value	Study
3-year	MB	60 (36-84) [21]	Not applicable	NR	Chi, 2004[475]
	AT/RT	23 (11) [13]	Not applicable		Gardner, 2008[476]
	MB	Not applicable	50 (38-62) [68]		Taylor, 2005[478]
5-year	PNET	49 (33-62) [43]	Not applicable		Fangusaro, 2008[473]
	MB	70 (10) [21]	Not applicable		Dhall, 2008[474]
	MB	Not applicable	86 (1.9) [379]		Packer, 2006[482]
	MB-PNET-AT/RT-Other	Not applicable	43 (3) [284] all pts 43 (5) [92] MB 31 (7) [46] PNET 29 (9) [28] Rhabdoid		Geyer, 2005[481]
	MB	Not applicable	44 (32-56) [68]		Taylor, 2005[478]
OS range for 5 years for studies with > 10 patients	All	49-70	43-86	Not applicable	Not applicable

AT/RT = atypical teratoid/rhabdoid tumor; CC = conventional care; CI = confidence interval; MB = medulloblastoma; N = number of patients; NA = not available; PNET = supratentorial primitive neuro-ectodermal tumors; SE = standard error

Adverse Effects

Only one HSCT study on MB patients evaluated quality of life (Table 76).[474] Dhall et al.[474] reported that mean intellectual functioning and QOL for children less than three years of age surviving without radiotherapy (n=4 [of 21]) was within the average range at both followup periods of testing (using the Parent Form of the Child Health Questionnaire [which is a 50-item QOL measure]). Data on treatment-related mortality were reported in 11 studies (Table 79).[133, 474-479, 481-483] There was one (of 15) case (7 percent) in the tandem group, nine (of 132) cases (8 percent) in the single HSCT group, and 71 (of 663) cases (11 percent) in the conventional care group.

Table 79. Adverse effects for treatment (tandem HSCT) and comparison (single HSCT) groups: CNS embryonal tumors

Outcome	Tumor Type	Intervention Tandem (%)	Comparator Single (%)	Study
Treatment-Related Mortality	MB-PNET	18	33	Sung, 2007[466]
	AT/RT	0[a]	NA	Gidwani, 2008[472]
	PNET	NA	5	Fangusaro, 2008[473]
	MB	NA	0	Chi, 2004[475]
	MB	NA	19	Dhall, 2008[474]
	AT/RT	NA	0	Gardner, 2008[476]
	MB-PNET	NA	15	Perez-Martinez, 2005[477]
	AT/RT	0[a]	NA	Gidwani, 2008[472]
	PNET	NA	2	Fangusaro, 2008[473]
	MB-PNET-AT/RT	3	NA	Bandopadhayay, 2011 [479]
Secondary Malignancies	AT/RT	NA	8	Gardner, 2008[476]
	MB-PNET	NA	8	Perez-Martinez, 2005[477]
	MB-PNET	9	0	Sung, 2007[466]
	AT/RT	0	NA	Gidwani, 2008[472]
Infectious Complications	PNET	NA	5	Fangusaro, 2008[473]
	MB	NA	9.5	Dhall, 2008[474]
	AT/RT	NA	8	Gardner, 2008[476]
	MB-PNET	NA	38	Perez-Martinez, 2005[477]
	AT/RT	NA	8	Gardner, 2008[476]
	MB-PNET	NA	15	Perez-Martinez, 2005[477]
	MB-PNET-AT/RT	3	NA	Bandopadhayay, 2011 [479]
Serious Hemorrhagic Events	MB-PNET	NA	8	Perez-Martinez, 2005[477]
Veno-Occlusive Disease		Not reported	Not reported	

AT/RT = atypical teratoid/rhabdoid tumor; MB = medulloblastoma; NA = not applicable; PNET = supratentorial primitive neuro-ectodermal tumors
[a] Case report.

Secondary malignancies were reported in three single HSCT studies476, 477, 483and three studies on conventional care (Table 79 and Table 80).478, 481, 482 Three (of 69) cases (4 percent) of secondary malignancies were reported in the single HSCT group, and 12 (663) cases (2 percent) in the conventional care group. Other adverse events across studies are reported in Table 79 and Table 80, respectively.

Table 80. Adverse effects for treatment (single HSCT) and comparison (conventional care) groups: CNS embryonal tumors

Outcome	Tumor Type	Intervention Single (%)	Comparator CC (%)	Study
Treatment-related Mortality	PNET	5	Not applicable	Fangusaro, 2008[473]
	MB	0	Not applicable	Chi, 2004[475]
	MB	19	Not applicable	Dhall, 2008[474]
	AT/RT	0	Not applicable	Gardner, 2008[476]
	MB-PNET	15	Not applicable	Perez-Martinez, 2005[477]
	MB	Not applicable	14	Packer, 2006[482]
	MB-PNET-AT/RT-Other	Not applicable	6	Geyer, 2005[481]
	MB	0[a]	Not applicable	Aihara, 2010[480]
Secondary Malignancies	PNET	2	Not applicable	Fangusaro, 2008[473]
	AT/RT	8	Not applicable	Gardner, 2008[476]
	MB-PNET	8	Not applicable	Perez-Martinez, 2005[477]
	MB	Not applicable	2	Packer, 2006[482]
	MB	Not applicable	1	Taylor, 2005[478]
	MB-PNET-AT/RT-Other	Not applicable	2	Geyer, 2005[481]
Infectious Complications	PNET	5	Not applicable	Fangusaro, 2008[473]
	MB	9.5	Not applicable	Dhall, 2008[474]
	AT/RT	8	Not applicable	Gardner, 2008[476]
	MB-PNET	38	Not applicable	Perez-Martinez, 2005[477]
	MB	Not applicable	24	Packer, 2006[482]
	MB-PNET-AT/RT-Other	Not applicable	21	Geyer, 2005[481]
Serious Hemorrhagic Events	AT/RT	8	Not applicable	Gardner, 2008[476]
	MB-PNET	15	Not applicable	Perez-Martinez, 2005[477]
	MB-PNET-AT/RT-Other	Not applicable	4	Geyer, 2005[481]
Veno-occlusive Disease	MB-PNET	8	Not applicable	Perez-Martinez, 2005[477]
	MB	Not applicable	1	Taylor, 2005[478]
	MB-PNET-AT/RT-Other	Not applicable	2	Geyer, 2005[481]

AT/RT = atypical teratoid/rhabdoid tumor; CC = conventional care; MB = medulloblastoma; N = number of patients;
PNET = supratentorial primitive neuroectodermal tumors
[a] Case report.

Ongoing Research

In North America, the Children's Hospital of Los Angeles is leading a Phase III trial ("Head Start III") studying combination chemotherapy with or without etoposide followed by single HSCT in treating patients (10 years or younger) with newly diagnosed brain tumors including MB, PNET, and AT/RT. This is an international trial (U.S., Canada, Australia, New Zealand, Switzerland) being undertaken across 37 centers and is currently recruiting patients with an expected enrollment of 120 patients. The primary outcomes of interest include time to tumor progression, disease recurrence or death of any cause, EFS at 2 years and toxicity. The projected completion of accrual is December 2010 (NCT00392886).

The St. Jude Children's Research Hospital is leading a Phase III trial studying two different regimens of radiation therapy when given together with chemotherapy and HSCT (1 to 3 procedures) to see how this regimen works in treating patients (3 years to 21 years) with newly diagnosed MB, PNET, or AT/RT. This is an international trial (U.S., Canada, Australia) being undertaken across nine centers and is currently recruiting patients with an expected enrollment of 342 patients. The primary outcomes of interest include the relationship of protein expression in tumors and PFS up to seven years of followup. The projected completion of accrual is April 2011 (NCT00085202).

In addition to the above studies, there are two trials underway by the Children's Oncology Group (COG). The first trial is open for children aged 3 years or younger at diagnosis with newly diagnosed PNET or high-risk medulloblastoma (NCT00336024). The second trial is a Phase III study for patients under 21 years of age with AT/RT. Both studies are using multi-agent chemotherapy, radiation, and high-dose chemotherapy with hematopoietic stem-cell rescue (NCT00653068)."

Conclusion

The body of evidence on overall survival with tandem HSCT compared to single HSCT for the treatment of CNS embryonal tumors was insufficient to draw conclusions.

The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of CNS embryonal tumors was insufficient to draw conclusions.

Glial Tumor Systematic Review

Background and Setting

Glial tumors comprise a heterogeneous group of neoplasms that are the largest single group of primary brain tumors in children and adolescents and contribute significant morbidity and mortality.[484] The World Health Organization (WHO) classifies glial tumors into four major categories: astrocytic, ependymal, oligodendroglial or mixed gliomas, and choroid plexus tumors. According to SEER data, pediatric age-adjusted incidence rate of primary CNS glial tumors per 100,000 persons was:

- Astrocytoma (excluding pilocytic), 0.411
- Glioblastoma, 0.138
- Ependymoma/anaplastic ependymoma, 0.226
- Choroid plexus tumor, 0.025
- Oligodendroglioma, 0.083
- The age-adjusted mortality rate of brain and other nervous system tumors was 0.65 per 100,000 persons.

Data on glial tumors are primarily from case series, save one comparative study with an historic cohort[485] with patients who received high-dose chemotherapy and HSCT. Case reports were also available. Differences in patient selection, accrual of small numbers of patients with patient data not stratified by tumor type, and differences in conditioning regimens make differences in overall survival between HSCT and conventional chemotherapy difficult to interpret. Although randomized evidence for gross total resection is lacking, retrospective analysis reaffirms the value of surgical resection in prolonging survival.

A greater than 90 percent surgical resection of newly diagnosed malignant gliomas, both anaplastic astrocytoma and glioblastoma multiforme, in childhood and adolescence confers a statistically significant survival advantage when followed by local field irradiation and conventional chemotherapy, or autologous stem-cell rescue.[485] Evidence was evaluated in five groups: anaplastic astrocytoma and glioblastoma multiforme (astrocytic tumors), choroid plexus tumor, ependymoma, and other glial tumor patients. Data for other glial tumors was presented but separate analysis by type was not possible. Patients were classified into newly diagnosed or recurrent/progressive disease due to a poorer overall survival for recurrent/progressive patients.

High-Grade Glioma: Anaplastic Astrocytoma (AA)/Glioblastoma Multiforme (GBM)

The prognosis for patients diagnosed with high-grade glioma is poor. The median survival is less than 1 year, the majority die within two years despite some exceptional survivors.[486] Patients with grade II astrocytoma may survive for 5 or more years while patients with AA often die within 2 or 3 years and frequently show progression to GBM with survival times substantially less than 2 years.[487]

Choroid Plexus Carcinomas

Choroid plexus carcinomas are rare typically occurring among children under 12 years of age with the greatest prevalence among children less than 2 years of age. [488] Choroid plexus tumors account for 1-4 percent of all childhood brain tumors with 25 percent of these patients developing progressive disease. [488] The role of surgery is well established in these tumors. Total resection of the tumor is often limited by tumor vascularity, large tumor size, and the tumor's tendency to invade the brain.[488] The added benefits of radiation and chemotherapy on overall survival after total resection are unclear.[488]

Ependymomas

Ependymomas are significantly more prevalent in infants and young children, than in adults, and account for 6-10 percent of brain tumors in children.[489] Sixty percent of ependymal tumors in children are infratentorial with 40 percent supratentorial. With conventional therapy the estimated 5-year OS and PFS are 50-64 percent and 23-45 percent, respectively.[490] Factors significant in the prognosis of patients are extent of tumor resection and age.[490] Patients with gross total resection have higher survival rates compared to incompletely resected gliomas (67-80 percent and 22-47 percent 5-year OS, respectively), and younger children tend to have a worse prognosis (more aggressive biological behavior of the tumor, avoidance of irradiation, and unacceptable neurotoxicity).[490]

Evidence Summary

The overall grade of strength of evidence for overall survival with HSCT for the treatment of high-risk glial tumors is shown in Table 81. The evidence compiled for this review includes one comparative cohort study of HSCT versus conventional therapy, one noncomparative cohort study, four randomized clinical trials, three Phase II trials, and 30 case series. The total number of patients abstracted was 1012: 215 patients received HSCT and 797 received conventional therapy.

Table 81. Overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of high-risk glial tumors

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with high-risk, **newly diagnosed anaplastic astrocytoma** what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Outcome of interest is overall survival. The comparator was conventional therapy.	Three studies examined overall survival for newly diagnosed anaplastic astrocytoma tumors. All studies were case-series and no studies were comparative between HSCT and conventional therapy. Survival data was available for 30 conventional therapy patients and 11 autologous transplant patients. Patients from Bertolone[491] (N=76) were not included due to grouping of AA and GBM patients and presence in an analysis by Finlay[485] *Patients from Massimo included two oligoastrocytoma patients and nine anaplastic astrocytoma patients.	The risk of bias in this evidence is high. Patient characteristics such as newly diagnosed astrocytoma or recurrent/progressive tumors provide some prognostic information. Data for HSCT patients is limited to only 11 patients.	Results for overall survival are not applicable. One study with N ≥10 is available for HSCT and two for conventional therapy. Studies use several different time points to calculate overall survival. In additional different patient characteristics prohibit direct comparison of patients for all studies.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is imprecise.	Not applicable due to lack of obvious effect size.	The body of evidence on overall survival with HSCT compared to conventional therapy for the treatment of high-risk newly diagnosed anaplastic astrocytoma was insufficient to draw conclusions.

Table 81. Overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of high-risk glial tumors (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with high-risk **recurrent or progressive anaplastic astrocytoma** what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Outcome of interest is overall survival. The comparator was conventional therapy.	Ten studies examined overall survival for recurrent anaplastic astrocytoma tumors. One study was comparative with a historical cohort. The remaining studies were case-series. Survival data was available for 71 conventional therapy patients and 17 autologous transplant patients. *Patients from Bertolone (N=76)[491] were not included due to grouping of AA and GBM patients and presence in an analysis by Finlay[485] *Patients from Gilheeney included 1 anaplastic astrocytoma patient, 1 oligoastrocytoma patient, and 2 GBM patients.[492]	The risk of bias in this evidence is high. Patient characteristics such as newly diagnosed astrocytoma or recurrent/progressive tumors provide some prognostic information. Data for HSCT patients is limited to only 17 patients.	Results for overall survival are consistent One study with N ≥10 is available for HSCT and one for conventional therapy. Studies use several different time points to calculate overall survival. In additional different patient characteristics prohibit direct comparison of patients for all studies.	The outcome reported, overall survival, is direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons. The best evidence was comparative, but the comparison was made with historical controls entered in a previous protocol.	The evidence is precise. While the evidence is qualitative it is likely that an important superiority exists for HSCT compared to conventional therapy for these patients. The results from Finlay et al. with a historic conventional therapy comparison group give 5-year overall survival estimates of 40% for HSCT patients and 0% for conventional therapy . This information is limited due to the HSCT group's small sample size (N=10).	The strength of association is strong. The results from Finlay et al. with a historic conventional therapy comparison group give 5-year overall survival estimates of 40% for HSCT patients and 0% for conventional therapy . This information is limited due to the HSCT group's small sample size (N=10).	Low strength evidence on overall survival suggests a benefit with single HSCT compared to conventional therapy for the treatment of high-risk recurrent or progressive anaplastic astrocytoma.

Table 81. Overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of high-risk glial tumors (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with high-risk **newly diagnosed glioblastoma multiforme** what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Outcome of interest is overall survival. The comparator was conventional therapy.	Five studies examined overall survival for newly diagnosed glioblastoma multiforme. All studies were case-series and no studies were comparative between HSCT and conventional therapy. Survival data was available for 40 conventional therapy patients and 27 autologous transplant patients. *Patients from Bertolone (N=76)[491] were not included due to grouping of AA and GBM patients and presence in an analysis by Finlay.[485]	The risk of bias in this evidence is high. Patient characteristics such as newly diagnosed astrocytoma or recurrent/progressive tumors provide some prognostic information.	Results for overall survival are not applicable. Two studies with N ≥10 are available for HSCT and one for conventional therapy. Studies use several different time points to calculate overall survival. In additional different patient characteristics prohibit direct comparison of patients for all studies. However, newly diagnosed glioblastoma multiforme survival outcomes seem to be similar for both HSCT and conventional therapy.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is imprecise. Survival estimates between groups overlap.	Not applicable due to lack of obvious effect size.	The body of evidence on overall survival with HSCT compared to conventional therapy for the treatment of high-risk newly diagnosed glioblastoma multiforme was insufficient to draw conclusions.

Table 81. Overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of high-risk glial tumors (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with high-risk **recurrent or progressive glioblastoma multiforme** what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Outcome of interest is overall survival. The comparator was conventional therapy.	Nine studies examined overall survival for recurrent/progressive glioblastoma multiforme. One study was comparative with a historical cohort. The remaining studies were case-series. Survival data was available for 35 conventional therapy patients and 22 autologous transplant patients. Patients from Bertolone (N=76)[491] were not included due to grouping of AA and GBM patients and presence in an analysis by Finlay[485] Patients from Gilheeney included 1 anaplastic astrocytoma patient, 1 oligoastrocytoma patient, and 2 GBM patients[492]	The risk of bias in this evidence is high. Patient characteristics such as newly diagnosed glioblastoma multiforme or recurrent/progressive tumors provide some prognostic information.	Results for overall survival are consistent One study with N ≥10 is available for HSCT and one for conventional therapy. Studies use several different time points to calculate overall survival. In additional different patient characteristics prohibit direct comparison of patients for all studies.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons. The best evidence was comparative, but the comparison was made with historical controls entered in a previous protocol.	The evidence is imprecise.	Not applicable due to lack of obvious effect size.	The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of high-risk recurrent glioblastoma multiforme is insufficient to draw conclusions.

Table 81. Overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of high-risk glial tumors (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with **newly diagnosed anaplastic, nonanaplastic, mixed, or unspecified ependymoma**, what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Outcome of interest is overall survival. The comparator was conventional therapy (CT).	Eight studies examined overall survival for **newly diagnosed nonanaplastic, mixed, or unspecified ependymoma** which includes WHO grade II tumors and WHO grade III tumors. Survival data was reported for 329 patients with ependymal tumors who underwent CT and 29 autologous transplant patients. Four studies examined anaplastic ependymoma exclusively. Survival data were reported for 39 patients with anaplastic ependymal tumors who underwent CT and 1 autologous HSCT patient. All were case-series, and no studies were comparative between HSCT and CT.	The risk of bias in this evidence is high. Patient characteristics such as newly diagnosed astrocytoma or recurrent/progressive tumors provide some prognostic information. Studies often mixed anaplastic with non-anaplastic tumors which has been found to be a predictor of patient prognosis in some studies. (Jaing, 2004)	Results for overall survival not applicable. One study with nonanaplastic, mixed, or unspecified ependymoma ≥10 is available for HSCT and 5 for CT. Two CT studies were available for anaplastic ependymoma alone. Studies use different timepoints to calculate OS. Different patient characteristics prohibit direct comparison of patients for all studies. Survival data for newly diagnosed ependymoma treated with HSCT suggest an advantage for CT over HSCT. No comparison can be made for anaplastic disease.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is imprecise for newly diagnosed ependymoma and imprecise for anaplastic ependymoma patients.	Not applicable due to lack of obvious effect size.	The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of newly diagnosed anaplastic, nonanaplastic, mixed, or unspecified ependymoma was insufficient to draw conclusions.

Table 81. Overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of high-risk glial tumors (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with **recurrent/progressive ependymoma**, what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Outcome of interest is overall survival. The comparator was conventional therapy.	Four studies examined overall survival for **recurrent/progressive non-anaplastic, mixed, or unspecified ependymoma** which includes WHO grade II tumors and WHO grade III tumors. Survival data was reported for 23 patients with ependymal tumors who underwent autologous transplant. All studies were case-series, and no studies were comparative between HSCT and conventional therapy.	The risk of bias in this evidence is high. Patient characteristics such as newly diagnosed astrocytoma or recurrent/progressive tumors provide some prognostic information. There were no recurrent ependymoma patients available for comparison in the conventional therapy group. Studies often mixed anaplastic with non-anaplastic tumors which has been found to be a predictor of patient prognosis in some studies. (Jaing, 2004)	Results for overall survival are not applicable. Studies use several different time points to calculate overall survival. In additional different patient characteristics prohibit direct comparison of patients for all studies. No comparison can be made for recurrent disease.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is imprecise.	Not applicable due to lack of obvious effect size.	The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of recurrent ependymoma was insufficient to draw conclusions.

Table 81. Overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of high-risk glial tumors (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with **choroid plexus carcinoma**, what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Outcome of interest is overall survival. The comparator was conventional therapy.	Five studies examined overall survival for choroid plexus tumors. Survival data were reported for 4 patients with choroid plexus carcinoma tumors who underwent autologous transplant and 64 conventional therapy patients.	The risk of bias in this evidence is high. Data is available for only four patients with this tumor type who underwent HSCT in either case reports or a component of a case-series.	Results for overall survival are consistent. Autologous stem cell transplant demonstrated no improvement on overall survival for the four transplanted patients with deaths between 5 and 25 months, and HSCT studies reported 21.5-36% five-year OS.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is imprecise. Survival data for HSCT patients is available only from case reports and does not permit a precise measure of this outcome.	Not applicable due to lack of obvious effect size.	The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of choroid plexus carcinoma was insufficient to draw conclusions.

Table 81. Overall grade of strength of evidence for overall survival and the use of HSCT for the treatment of high-risk glial tumors (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with **other gliomas (oligodendroglioma, pontine glioma, high-grade glioma, brainstem glioma, ganglioma, malignant glioma and other glioma [unspecified])**, what is the comparative effectiveness and harms of HSCT and conventional chemotherapy regarding overall survival? Outcome of interest is overall survival. The comparator was conventional therapy.	Fifteen studies examined overall survival for other glial tumors. Survival data were reported for 2 oligodendroglioma, 40 pontine glioma, 1 ganglioma, and 10 other glioma [unspecified] patients who underwent autologous transplant and 33 brain stem glioma, 19 high-grade glioma, and 28 other glioma [unspecified] conventional therapy patients.	The risk of bias in this evidence is high. Tumors in the other glioma category were poorly characterized by histology and do not allow for direct comparison.	Results for overall survival are not applicable. Consistency cannot be assessed for these diseases as the data is limited to either a few case reports (oligodendroglioma), have no comparative treatment (pontine glioma, ganglioma, brain stem glioma) or are not given a specific histology (other glioma)	Where outcomes were reported, the evidence is indirect. The evidence base utilizes two or more bodies of evidence to make comparisons or there.	The evidence is imprecise. There is uncertainty on whether HSCT is inferior, equivalent or superior to conventional chemotherapy for these conditions.	Not applicable due to lack of obvious effect size.	The body of evidence on overall survival with HSCT compared to conventional therapy for the treatment of other gliomas was insufficient to draw conclusions.

Results

Thirty-eight publications comprising 40 studies were included in this review. The total number of patients abstracted from the 39 studies was 1,012: 215 patients received HSCT, whereas 797 patients received conventional chemotherapy. Study selection criteria are shown in Table 82.

Table 83 shows the study design and population. Of the included publications for HSCT, sixteen were case series,[367, 488, 492-504] two were cohort studies,[485, 490] and one was a Phase II trial.[505] One study, by Finlay et al.[485], compared myeloablative chemotherapy with autologous stem-cell transplant to conventional therapy and used a group of historic controls from a trial by the children's cancer group (CCG-945). All studies were published after 1995 with treatment periods ranging from 1986-2005. Four studies were conducted in France[488, 493, 494, 497], two in Italy[495, 502], one in the U.K.[504], and twelve in the U.S.[132, 367, 485, 490, 496, 498-501, 503, 506]A total of 215 patients were treated with autologous bone marrow transplantation; Two-hundred and two of these were given single autologous stem-cell transplants while 11 patients received tandem or sequential transplant.[367, 504] Due to the small number of patients in each tumor histology (AA 4, GBM 6, BSG 2, EPD 2, CPC 1), and similar survival outcomes to single autologous transplant, these patients were not analyzed separately. Stem cell source varied by study. Six studies treated patients with peripheral blood stem cells,[367, 488, 490, 500, 502, 503] ten studies treated patients with bone marrow transplant, [132, 485, 493-496, 499, 501, 504, 506]and two studies used multiple sources.[497, 498] Eight studies investigated patients with newly diagnosed high-risk disease[488, 490, 494, 495, 498, 500, 503, 504] and the remaining studies contained patients who had recurrent or relapsed disease.[492]

Table 82. Study selection criteria: Glial tumors

Study Design	Population	Intervention	Comparators	Outcomes	Followup	Setting
Any study design	Pediatric patients (0-21-yr) with high-risk or relapsed/refractory disease	Single Auto HSCT Tandem Auto HSCT	Chemotherapy +/- RT Chemotherapy +/- RT	OS; EFS (DFS; PFS); long-term adverse events; QOL	All durations of followup	Inpatient for HSCT; In or outpatient for conventional chemotherapy

Auto = autologous; DFS = disease-free survival; EFS = event-free survival; HSCT = hematopoietic stem-cell transplant; OS = overall survival; PFS = progression-free survival; QOL = quality of life

Conventional therapy included 14 case series,[132, 488, 507-519] one cohort study,[485] two Phase II trials,[505, 520] and four clinical trials.[489, 491, 521, 522] Case reports were excluded as comparators. All studies were published after 1995 with treatment periods ranging from 1986-2005. Four studies were conducted in France[488, 508, 510, 511], two in Germany[520, 522], Italy[509], Taiwan[516], Turkey[507], and the U.K.[512], and ten in the U.S.[485, 489, 491, 505, 513-515, 517, 518, 521] A total of 797 patients were treated with conventional chemotherapy; the vast majority of these patients were given chemotherapy alone (N=458; 57 percent) in 16 studies. Patients received combination radiotherapy in seven studies (N=213; 27 percent), and in four studies patients received radiotherapy alone (N=126; 16 percent). Twelve studies investigated newly diagnosed high-risk patients (60 percent) and the remaining studies contained patients who had recurrent or relapsed disease. Previous treatments included a mix of excision, chemotherapy, and radiotherapy.

All studies were specific to the pediatric age group, with age primarily reported as age at diagnosis or transplant; only one study[520] lacked information about participant's median age. Three studies[495, 499, 517] did not provide information on patient age. Median ages ranged from

under one year of age to 18 years of age. Five studies reported no patient gender[132, 492, 504, 510, 520], but among the remaining studies with five or more patients gender was distributed equally. Studies included patients of diverse histology:

Nineteen HSCT studies (N=215):
- Astrocytoma 31 (14.4 percent)
- Choroid plexus tumor 4 (1.9 percent)
- Ependymoma 70 (32.6 percent)
- High-grade glioma 2 (0.93 percent)
- Glioblastoma multiforme 56 (26.0 percent)
- Oligodendroglioma 4 (1.9 percent)
- Glioma [unspecified] 1 (0.47 percent)
- Pontine glioma [unspecified] 40 (18.6 percent)
- Ganglioma 1 (0.47 percent)

Twenty-one conventional treatment studies (N=797):
- Astroblastoma 1 (0.1 percent)
- Astrocytoma 109 (13.7 percent)
- Brainstem glioma 54 (6.8 percent)
- Choroid plexus tumor 69 (8.6 percent)
- Ependymoma 435 (54.6 percent)
- Ganglioma 1 (0.1 percent)
- Glioblastoma multiforme 80 (10 percent)
- Glioma [unspecified] 14 (1.8 percent)
- Oligodendroglioma 2 (0.3 percent)
- Other 9 (1.1 percent)
- Pontine glioma [unspecified] 0 (0 percent)

Table 83. Study characteristics and population: Glial tumors

Study	Design	Median Age (mo.)	Range	Male (%)	Disease Stage/Category	Histology [Site]%	HSCT (N)	Comparator (N)	Treatment Period
Finlay, 2008[485]	Cohort	133.3	2.4-250	56	NR	GBM 17 (63) AA 10 (37)	27	Not applicable	NR
Shih, 2008[132]	Case-Series	89	5-199	NR	NR	EPD 1(20) AA 2(40) GBM 2(40)	5	Not applicable	1989-2004
Zacharoulis, 2007[490]	Cohort	25	8-107	62	24 M0 (83) 1 M1 (3) 0 M2 4 M3 (14)	EPD: Posterior fossa 22(76) supratentorial 7 (24)	29	Not applicable	1991-1997 (Head Start 1) 1997 - 2002 (Head Start 2)
Thorarins-dottir, 2007[503]	Case-Series	ODG 27 months, Ganglioma 25 months, Anaplastic glioma 18 months , EPD 6 months	Anaplastic glioma: 9-29	ODG 100 Ganglioma 100 Anaplastic glioma 67 EPD 0	All WHO grade III	ODG right frontal 1 (16) Ganglioma temporal 1 (16) Anaplastic glioma 1 c-spine 1 (16) BSG 1 (16) EPD IV ventricle 1 (16)	6	Not applicable	1998 - 2005
Massimino, 2005[502]	Case-Series	120	42-228	33	NR, All high-grade	GBM 10 (48), AA 9(42) Anaplastic ODG 2 (10) spine 2 (10) Posterior fossa 2(10) Supratentorial 17(80)	21	Not applicable	1996- 2003
Ozkaynak, 2004[367]	Case-Series	132	54-216	50	3 progressive (50) 3 recurrent (50)	AA 2 (33) GBM 1 (17) BSG 2 (33) EPD 1 (17)	6	Not applicable	1995-2002
Bouffet, 1997[493]	Case-Series	84	34-204	42	Diffuse pontine glial tumor	At least 2/3rd of tumor had to be in the pons	24	Not applicable	March 1990-?
Grovas, 1999[498]	Case-Series	144	60-216	63	NR, patients with neuraxis dissemination excluded	GBM 11	11	Not applicable	1993-1995
Jakacki, 1999[500]	Case-Series	86	37-151	36	High grade glial tumor or a diffuse pontine tumor	GBM 3 (27), AA 2(18) Pons 6 (55)	11	Not applicable	1997 - 1998
Mason, 1998[506]	PII trial	22	5-144	53	9 low-grade EPD (60) 6 anaplastic (40)	posterior fossa 13 (87) supratentorial 2 (13)	15	Not applicable	1986 - 1993

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Table 83. Study characteristics and population: Glial tumors (continued)

Study	Design	Median Age (mo.)	Range	Male (%)	Disease Stage/Category	Histology [Site]%	HSCT (N)	Comparator (N)	Treatment Period
Dunkel, 1998[496]	Case-Series	95	42-179	70	10 High-grade glial malignancies	PON 10	10	Not applicable	NR
Gururangan 1998[499]	Case-series	AA 23mo CPC 19mo EPD 18mo GBM 24, 4, 11, and 58mo	4-58	AA 0 CPC 100 EPD 0 GBM 50	All tumors were recurrent	EPD 1 GBM 4 AA 1 CPC 1	7	Not applicable	1989-1996
Berger, 1998[488]	Case-Series	27.5	22-33	0	Newly diagnosed 1 metastatic 1 unknown progression	CPC 2	2	Not applicable	1984-1995
Busca, 1997[495]	Case-Series	132 (36-192) years for total group of 11 patients,	NR	46	1 GBM patient was newly diagnosed 5 patients were relapsed.	AA 1 (16) EPD 2 (33) GBM 2(33) ODG 1 (16)	6	Not applicable	1991 - 1996
Bouffet, 1999 [494 493]	Case-Series	72	36-168	60	All high-grade glioma	parieto-occipital 1 (20) BSG 3 (60) thalamus 1 (20)	5	Not applicable	NR
Yule, 1997[504]	Case-Series	120	12-168	NR	NR	anaplastic EPD 1(20%) CPC 1 (20) recurrent GBM 1(20) GBM 1 (20) suprasellar GBM 1(20)	5	Not applicable	1993-1995
Grill, 1996[497]	Case-Series	36	6-180	50	EPD, 2 patients had tumor cells in CSF 3 WHO low-grade tumors 13 WHO high-grade tumors	EPD: Supratentorial 6 (38) Infratentorial 10(62)	16	Not applicable	1988 - 1994

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Table 83. Study characteristics and population: Glial tumors (continued)

Study	Design	Median Age (mo.)	Range	Male (%)	Disease Stage/Category	Histology [Site]%	HSCT (N)	Comparator (N)	Treatment Period
Mahoney, 1996[501]	Case-Series	AA 144 EPD 60 GBM 186 BSG 60	AA: 96-192 EPD: 36-90 GBM:186 BSG: 60	AA 100 EP 33 GBM 100 BSG 0		AA 2 (29) EPD 3(43) GBM 1 (14) BSG 1 (14)	6	Not applicable	1990 - 1993
Gilheeney, 2010[492]	Case-Series	AA 98 GBM 139	AA 89-107 GBM 53-226	NR	NR	NR	4	Not applicable	1999 - 2002
Finlay, 2008[485]	Cohort	133.3	1.2-232	52	NR	GBM 27 (48) AA 29(52)	Not applicable	56	1985-1990
Grundy, 2010[513]	Case-Series	BSG 30 CPC 10 High Grade Glioma 22	BSG: 8.2-36 CPC: 4-34 HGG 4-37	Glioma 69, CPC 93	HGG: AA 7 1 Astroblastoma 2 Anaplastic ODGODG 5 Glioblastoma 3 unknown Diffuse pontine glioma: 1 diffuse AST 1 glioblastoma 1 unclassified 4 Inoperable	HGG 18(45) PON 7 (18) CPC 15(38) HGG metastatic 2 (11) HGG in posterior fossa 2 (11) HGG in supratentorial 17 (89) BSG metastatic 0 BSG 7 (100) CPC metastatic 4 (27) CPC posterior fossa 5(33) CPC supratentorial 10(77)	Not applicable	40	1993 - 2003
Conter, 2009[508]	Case-Series	103	60-204	67	EPD, 13 Grade II (57) 10 Grade III (43)	Supratentorial 4 (17) Infratentorial 20 (83)	Not applicable	24	1996 - 2002

Table 83. Study characteristics and population: Glial tumors (continued)

Study	Design	Median Age (mo.)	Range	Male (%)	Disease Stage/Category	Histology [Site]%	HSCT (N)	Comparator (N)	Treatment Period
Wrede, 2009[522]	RCT	27.6	4-205	50	Histologically confirmed CPC	CPC 29 Metastatic 5 (17) Lateral Ventricle 30 (88) Fourth Ventricle 4(12)	Not applicable	34	2000-2008
Grundy 2007[512]	Case-series	Median Non-metastatic 23.16 Metastatic 16.32	Non-Metastatic: .6-38 Metastatic: 2.88-27	65	All Newly Diagnosed 9 metastatic (10)	89 EPD Metastatic 9 (10) Nonmetastatic 80 (90)	Not applicable	89	1992 - 2003
De Sio, 2006[509]	Case-Series	101	50-235	64	Recurrent/progressive histologically confirmed (except BSG)	EPD 2 (14) AA 3 (21) BSG 8 (57) GBM 1 (7)	Not applicable	14	1998 - 2004
Korones, 2006[518]	Case-Series	108	60-252	77	NR	Glioblastoma 5 (56) AA 2 (22) BSG 2(22)	Not applicable	9	2002 - 2003
Macdonald, 2005[521]	RCT	144	36- 240	48	All patients had histologic verification of high-grade AST	AA 30 (39) GBM variant 40 (53) 6 Other 6 (8) Supratentorial tumor 66 (86.8) Infratentorial tumor 10 (13.2) patients had metastatic disease 5 (7)	Not applicable	76	1993-1998
Jaing, 2004[516]	Case-Series	79	8 - 216	58	EPD, 22 Grade II (47) 24 Grade III (53)	Supratentorial 15 (35) Infratentorial27 (65)	Not applicable	46	1985-2002

Table 83. Study characteristics and population: Glial tumors (continued)

Study	Design	Median Age (mo.)	Range	Male (%)	Disease Stage/Category	Histology [Site]%	HSCT (N)	Comparator (N)	Treatment Period
Bertolone, 2003[491]	RCT	48	<12 - 192	58	NR	AA 11 (61) EPD 3 (17) GBM 2 (11) Anaplastic mixed glioma 1 (6) anaplastic ganglioglioma 1 (6)	Not applicable	18	1985 - 1990
Merchant, 2002[505]	PII trial	36	13.2-275	50	Histologically confirmed EPD w/ no current radio or chemotherapy	differentiated EPD 35(70) anaplastic EPD 19(30)	Not applicable	54	June 1997 - ?
Grill, 2001[511]	Case-Series	27	5-62	55	56 of patients had a high grade tumor (82) 12 had a low-grade tumor (18)	EPD 73 (100)	Not applicable	73	1990 - 1998
Hurwitz, 2001[515]	Case-Series	92.4	4-228	56	Recurrent or progressive disease	AST 4 (9) EPD 13 (29) Malignant Glioma 13 (29) BSG 15(33)	Not applicable	45	1993 - 1998
Horn, 1999[514]	Case-Series	52	8-240	60	EPD, 61 M0 (85) 11 M1-M3 (15)	EPD: WHO II grade 2 51 (61) WHO II grade 3 31 (37) 1 missing Infratentorial 64 (77) Supratentorial 19 (23)	Not applicable	83	1987-1991
Kobrinsky, 1999[517]	Case-Series	NR	NR	55	NR	High grade AST 20 (48) BSG 22 (52)	Not applicable	42	1988 - 1992

Table 83. Study characteristics and population: Glial tumors (continued)

Study	Design	Median Age (mo.)	Range	Male (%)	Disease Stage/Category	Histology [Site]%	HSCT (N)	Comparator (N)	Treatment Period
Doireau, 1999[510]	Case-Series	63	3-132	NR	Relapsed or unresectable intramedullar gliomas	Anaplastic oligo-AST 1 (17) OligoAST 3 (50) AA 1 (17) AST otherwise not specified 1 (17)	Not applicable	6	1992-1998
Robertson, 1998[489]	RCT	84	24-208	53	12 Anaplastic EPD (38)	posterior fossa EPD 21 (66) supratentorial EPD 11 (34)	Not applicable	32	1986 - 1992
Kuhl, 1998[520]	PII trial	NR	36-192	66	19 anaplastic (90) 29% of patients had microscopic tumor cells in CSF	EPD 21	Not applicable	21	1987 - 1991
Berger, 1998[488]	Case-Series	57.5	4-111	55	Newly diagnosed CPC	metastatic 3 (15) nonmetastatic 4 (20) unknown 13 (65)	Not applicable	20	1984-1995
White, 1998[519]	Case-Series	20	3-47	NR	No documented disseminated disease at diagnosis	EPD 14	Not applicable	14	1991 - 1995
Ayan, 1995[507]	Case-Series	150	60 - 180	75	4 Anaplastic (100)	frontal lobe EPD 1(25) parietal-temporal-occipital lobe EPD1 (25) Multiple parenchymal meningeal lesion EPD 1 (25) Temporoparietal lobe EPD 1 (25) CSF cytology positive 1 (25)	Not applicable	4	1990 - 1991

BMT = bone marrow transplant; BSG = brainstem glioma; CPC = choroid plexus carcinoma; EPD = ependymoma; GBM = glioblastoma multiforme; GLI = glioma; HGG = high-grade glioma; M = male; NR = not reported; OAST = oligoAST; ODG = oligodendroglioma; PBSCT = peripheral blood stem cell transplant; PON = Pontine glioma; RCT = randomized clinical trial

Induction regimens varied across and within studies (i.e., different chemotherapeutic agents and different (cumulative) dosages) and consisted of multiple cycles of chemotherapy and/or radiation and/or surgery. Conditioning regimens also varied. The most common regimens included thiotepa, etoposide, carboplatin, cyclophosphamide (with or without mesna), busulfan and carmustine (either alone or in combination with radiation therapy or additional drugs). Table 84 shows the pediatric outcomes that were reported across the 39 included studies.

Overall Survival

Data on overall survival were reported in all but three studies,[505, 515, 518] and calculated from the raw data from the additional studies (Table 84). Survival data are presented by five histologic categories (Table 85). Individual studies varied in their method for calculating overall survival. Fourteen studies examined overall survival for astrocytic gliomas.[123, 132, 367, 485, 491, 492, 495, 500-502, 509, 510, 517, 518] Survival data were reported for 20 patients with astrocytic tumors who underwent autologous transplant and 106 conventional therapy patients. Fourteen studies examined overall survival for glioblastoma multiforme.[123, 132, 367, 485, 491, 492, 495, 498, 500-502, 504, 509, 518] Survival data was reported for 45 patients with glioblastoma multiforme who underwent autologous transplant and 92 conventional therapy patients. Of the noncomparative studies reporting yearly OS, none had HSCT treatment. OS at 5 years ranged from 0 percent in recurrent patients to 25 percent for newly diagnosed patients. One study grouped OS of newly diagnosed AA and GBM patients and stratified by noninfant or infant status. These patients had a 5-year OS of 36±13 for noninfants and 25±15 for infants.

Finlay et al.[485], compared a historic chemotherapy cohort (CCG-945) to astrocytoma and GBM patients receiving HSCT. This study provided 5-year recurrent HSCT and conventional therapy OS estimates of 40 percent and 4 percent for astrocytoma and 12 percent and 0 percent for glioblastoma multiforme respectively. The OS was statistically significantly better for HSCT compared to chemotherapy at p=0.010 and retained this significance when stratified by tumor histology. The authors also found evidence that degree of surgical debulking impacted survival. OS estimates stratified by treatment and degree of debulking minimized the treatment effect and yielding a nonsignificant survival difference of p=0.39 due to the poor prognosis of patients with bulky tumor in both treatment types. However, when the authors looked at HSCT versus chemotherapy treatment among only surgically debulked patients the HSCT patients had a better survival (p=0.017).

Three noncomparative studies reported yearly GBM OS with a 5-year OS estimate for autologous transplant of newly diagnosed GBM of 0-22 percent and newly diagnosed conventional therapy of 22 percent.[498, 502, 521] Data comparing HSCT to conventional therapy was provided by Finlay et al.[485] for recurrent/progressive GBM and AA showed an increase in survival for HSCT. No comparison was made for newly diagnosed AA due to a lack of HSCT studies. Data for newly diagnosed GBM seems to show a similarly poor prognosis for both HSCT and conventional therapy patients.

Seventeen studies examined overall survival for ependymoma[132, 367, 489, 490, 495, 497, 501, 504, 507-509, 511-514, 516, 520] Survival data was reported for 71 patients with ependymal tumors who underwent transplant and 442 conventional therapy patients. No studies were comparative between HSCT and conventional therapy. Five studies reported overall survival with a 5 year overall survival estimates for autologous transplant of recurrent tumor of 10 percent and newly diagnosed of 38 percent.[367, 490, 495, 497, 504] Conventional therapy did not include recurrent disease and found estimates of 35.2 percent to 64 percent for newly diagnosed anaplastic ependymoma

with newly diagnosed nonanaplastic, mixed or unspecified ependymoma estimates of 52-74 percent.[489, 508, 511, 513, 514, 516, 520] One study stratified by metastatic/nonmetastatic disease and obtained a 5-year OS of 33 percent and 59 percent respectively.[512] For patients with newly diagnosed ependymoma, patients treated with HSCT appear to have inferior overall survival when compared to those treated with conventional therapy.

Sixty-four patients with choroid plexus carcinoma were in three conventional therapy studies and four patients with HSCT across three studies reported survival.[488, 499, 504, 513, 522] All HSCT patients died between five and 25 months. A conventional therapy study of 29 patients had survival of 35 percent at last followup (median 25 months, range 3-85 months). Two studies reported 5-year OS of 21.5 and 36 percent.

Event-free Survival

Data on event-free survival can be found in Appendix D.

Table 84. Outcomes reported: Glial tumors

Author, Year	OS	EFS (DFS, PFS)	Quality of Life	Treatment-Related Mortality	Secondary Malignancies	Other Adverse Effects
Finlay, 2008[485]	√	√	NR	√	NR	NR
Shih, 2008[132]	√	√	NR	NR	NR	NR
Zacharoulis, 2007[490]	√	√	NR	√	NR	√
Thorarinsdottir, 2007[503]	√	√	NR	NR	NR	√
Massimino, 2005[502]	√	√	NR	NR	NR	NR
Ozkaynak, 2004[367]	√	NR	NR	NR	NR	NR
Bouffet, 1997[493]	√	√	NR	√	NR	√
Grovas, 1999[498]	√	√	NR	NR	√	√
Jakacki, 1999[500]	√	√	NR	NR	NR	√
Mason, 1998[506]	√	√	NR	√	NR	NR
Dunkel, 1998[496]	√	NR	NR	NR	NR	NR
Gururangan, 1998[499]	√	√	NR	√	NR	NR
Berger, 1998[488]	√	NR	NR	NR	NR	NR
Busca, 1997[495]	√	√	NR	NR	NR	NR
Bouffet, 1999[494]	√	NR	NR	NR	NR	NR
Yule, 1997[504]	√	NR	NR	NR	NR	NR
Grill, 1996[497]	√	√	NR	√	NR	NR
Mahoney, 1996[501]	√	√	NR	√	NR	√
Grundy, 2010[513]	√	√	NR	NR	NR	NR
Conter, 2009[508]	√	√	NR	NR	NR	NR
Wrede, 2009[522]	√	√	NR	NR	NR	NR
Grundy 2007[512]	√	√	NR	√	NR	√
De Sio, 2006[509]	√	√	NR	NR	NR	NR
Korones, 2006[518]	NR	NR	NR	NR	NR	NR
Macdonald, 2005[521]	√	√	NR	NR	NR	√
Jaing, 2004[516]	√	√	NR	NR	NR	NR
Bertolone, 2003[491]	√	√	NR	NR	NR	√
Merchant, 2002[505]	NR	√	NR	NR	NR	NR
Grill, 2001[511]	√	√	NR	NR	NR	NR

Table 84. Outcomes reported: Glial tumors (continued)

Author, Year	OS	EFS (DFS, PFS)	Quality of Life	Treatment-Related Mortality	Secondary Malignancies	Other Adverse Effects
Hurwitz, 2001[515]	NR	√	NR	NR	NR	NR
Horn, 1999[514]	√	√	NR	NR	NR	NR
Kobrinsky, 1999[517]	√	NR	NR	NR	NR	NR
Doireau, 1999[510]	√	√	NR	NR	NR	NR
Robertson, 1998[489]	√	√	NR	NR	NR	NR
Kuhl, 1998[520]	√	√	NR	NR	NR	NR
Berger, 1998[488]	√	NR	NR	NR	NR	NR
White, 1998[519]	√	NR	NR	NR	NR	NR
Ayan, 1995[507]	√	√	NR	NR	NR	NR
Gilheeney, 2010[492]	√	NR	NR	√	NR	NR

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Astrocytoma	1 year	~41 (N=10)	~26 (N=29)	Chemo vs. ABMR unstratified comparison of survival p=.0018 HR 1.9 (1.1-3.1) Chemo versus ABMR comparison stratified by histology: p=.010 Chemo/nonbulky versus ABMR/non-bulky unstratified exact comparison: p=0.017 [hazard ratio=9.1 (95% confidence interval 1.7–47.2) Minimal residual disease status (<3 cm tumor diameter) at time of myeloablative chemotherapy p=.003	Finlay, 2008[485]
		Not applicable	2 AA patients dead at median 7.1 mo (n=2)	Not reported	Shih, 2008[132]
		Not applicable	3 AA dead at median 5mo (4-10mo) (n=3)	Not reported	De Sio, 2006[509]
		Not applicable	1 patient DOD at 4 mo (50%), one patient alive with disease progression at 10+ months (n=2)	Not reported	Korones, 2006[518]
		Not applicable	~46 (n=30)	Not reported	Macdonald, 2005[521]
		Other Glioma ~91 (Anaplastic astrocytoma (N=9) and anaplastic oligodendroglioma (N=2)) (N=11)	Not applicable	OS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse p=.004	Massimino, 2005[502]
		Not applicable	~83 GBM and AA Non-Infants (n=16) ~52 GBM and AA Infants (n=6)	Not reported	Bertolone, 2003[491]
		Not applicable	28±10% (n=35)	Not reported	Kobrinsky, 1999[517]
		2 AA patients dead at 7 and 9 mo (N=2)	Not applicable	Not reported	Jakacki, 1999[500]

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Astrocytoma	3 Year	40±14% (N=10)	7±4% (N=29)	Chemo vs. ABMR unstratified comparison of survival p=.0018 HR 1.9 (1.1-3.1) Chemo versus ABMR comparison stratified by histology: p=.010 Chemo/nonbulky versus ABMR/non-bulky unstratified exact comparison: p=0.017 [hazard ratio=9.1 (95% confidence interval 1.7–47.2) Minimal residual disease status (<3 cm tumor diameter) at time of myeloablative chemotherapy p=.003	Finlay, 2008[485]
		Not applicable	~25 (N=30)	Not reported	Macdonald, 2005[521]
		Other Glioma ~73 (Anaplastic astrocytoma (N=9) and anaplastic oligodendroglioma (N=2)) (N=11)	Not applicable	OS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse P=.004	Massimino, 2005[502]
		Not applicable	~57 GBM and AA Non-Infants (N=16) ~25 GBM and AA Infants (N=6)	Not reported	Bertolone, 2003[491]
		Not applicable	~5 (N=35)	Not reported	Kobrinsky, 1999[517]
		Not applicable	3 OA patients alive median 3 yr.	Not reported	Doireau, 1999[510]
		1 patient died at 15 mo (N=1)	Not applicable	Not reported	Busca, 1997[495]

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Astrocytoma	5 Year	40±14% (N=10)	0-4% (N=29)	Chemo vs. ABMR unstratified comparison of survival p=.0018 HR 1.9 (1.1-3.1) Chemo versus ABMR comparison stratified by histology: p=.010 Chemo/nonbulky vs. ABMR/non-bulky unstratified exact comparison: p=0.017 [hazard ratio=9.1 (95% confidence interval 1.7–47.2) Minimal residual disease status (<3 cm tumor diameter) at time of myeloablative chemotherapy P=.003	Finlay, 2008[485]
		Not applicable	25±8% (N=30)	Not reported	Macdonald, 2005[521]
		Other glioma ~73 (Anaplastic astrocytoma (N=9) and AOA (N=2)) (N=11)	Not applicable	OS for GBM compared to other histotypes (AA and ODG) were worse p=.004	Massimino, 2005[502]
		2 Anaplastic astrocytoma pts. alive with stable disease at follow up of 41 and 80 mo (N=2)	Not applicable	Not reported	Ozkaynak, 2004[367]
		Not applicable	36±13 GBM and AA Non-Infants (N=11) 25±15 GBM and AA Infants (N=6)	Not reported	Bertolone, 2003[491]
		Not applicable	0% (N=35)	Not reported	Kobrinsky, 1999[517]

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Astrocytoma	5 Year	Not applicable	1 AA patient died (car accident) before last FU. 1 AOA patient alive at 5.5 year. 1 Astrocytoma patient with unspecified disease alive at 5.5 years (N=6)	Not reported	Doireau, 1999[510]
		2 AA patients died at 1 mo and 4 mo (N=2)	Not applicable	Not reported	Mahoney, 1996[501]
		50 (N=2) 1 AA patient alive with residual disease at 7.7 years 1 oligoastrocytoma patient DOT at 1 mo	Not applicable	Not reported	Gilheeney, 2010[492]
Glioblastoma multiforme	1 Year	~43% (N=17)	~22% (N=27)	Chemo vs. ABMR unstratified comparison of survival p=.0018 HR 1.9 (1.1-3.1) Chemo versus ABMR comparison stratified by histology: p=.010 Chemo/nonbulky versus ABMR/non-bulky unstratified exact comparison: p=0.017 [hazard ratio=9.1 (95% confidence interval 1.7–47.2) Minimal residual disease status (<3 cm tumor diameter) at time of myeloablative chemotherapy p=.003	Finlay, 2008[485]
		Not applicable	1 patient dead at 4 mo (N=2)	Not reported	Shih, 2008[132]
		Not applicable	1 patient AWD at 12 mo (N=1)	Not reported	De Sio, 2006[509]
		Not applicable	57% (n=7)	Not reported	Korones, 2006[518]
		Not applicable	~45 (N=40)	Not reported	Macdonald, 2005[521]

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Glioblastoma multiforme	1 Year	~90% (N=10)	Not applicable	OS for GBM compared to other histotypes (AA and ODG) were worse p=.004	Massimino, 2005[502]
		1 progressive patient DOD at 1 mo (N=1)	Not applicable	Not reported	Ozkaynak, 2004[367]
		Not applicable	~83 GBM and AA Non-Infants (N=16) ~52 GBM and AA Infants (N=6)	Not reported	Bertolone, 2003[491]
		73±13% (N=11)	Not applicable	Not reported	Grovas, 1999[498]
		1 patient DOD at 6 months, 1 patient had stable disease at last 12 mo FU, 1 patient died of treatment toxicity (N=3)	Not applicable	Not reported	Yule, 1997[504]
		1 patient dead of disease at 7 mo (N=1)	Not applicable	Not reported	Mahoney, 1996[501]
		2 GBM patients DOD at 6 mo and 10 mo (N=2)	Not applicable	Not reported	Gilheeney, 2010[492]

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Glioblastoma multiforme	3 Year	12±6% (N=17)	0% (N=27)	Chemo vs. ABMR unstratified comparison of survival p=.0018 HR 1.9 (1.1-3.1) Chemo versus ABMR comparison stratified by histology: p=.010 Chemo/nonbulky versus ABMR/non-bulky unstratified exact comparison: p=0.017 [hazard ratio=9.1 (95% confidence interval 1.7–47.2) Minimal residual disease status (<3 cm tumor diameter) at time of myeloablative chemotherapy p=.003	Finlay, 2008[485]
		Not applicable	~25%(N=40)	Not reported	Macdonald, 2005[521]
		~30% (N=10)	Not applicable	OS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse p=.004	Massimino, 2005[502]
		Not applicable	~57 GBM and AA Non-Infants (N=16) ~25 GBM and AA Infants (N=6)	Not reported	Bertolone, 2003[491]
		~35% (N=11)	Not applicable	Not reported	Grovas, 1999[498]
		3 pts DOD at median 15 mo (6 – 19 mo) (N=3)	Not applicable	Not reported	Jakacki, 1999[500]
		1 pt alive and progression free at final FU (N=1)	Not applicable	Not reported	Busca, 1997[495]

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Glioblastoma multiforme	5 Year	12±6% (N=17)	0% (N=27)	Chemo vs. ABMR unstratified comparison of survival p=.0018 HR 1.9 (1.1-3.1) Chemo versus ABMR comparison stratified by histology: p=.010 Chemo/nonbulky versus ABMR/non-bulky unstratified exact comparison: p=0.017 [hazard ratio=9.1 (95% confidence interval 1.7–47.2) Minimal residual disease status (<3 cm tumor diameter) at time of myeloablative chemotherapy p=.003	Finlay, 2008[485]
		Not applicable	1 patients dead at 104 mo (N=2)	Not reported	Shih, 2008[132]
		Not applicable	22±7 (N=40)	Not reported	Macdonald, 2005[521]
		0% (N=10)	Not applicable	OS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse p=.004	Massimino, 2005[502]
		Not applicable	36±13 GBM and AA Non-Infants (N=16) 25±15 GBM and AA Infants (N=6)	Not reported	Bertolone, 2003[491]
		~25 (N=11)	Not applicable	Not reported	Grovas, 1999[498]
Anaplastic ependymoma	1 Year	Not applicable	100% (N=12)	Not reported	Robertson, 1998[489]
		1 anaplastic ependymoma patient with tandem autologous treatment DOD at 15 mo (N=1)	Not applicable	Not reported	Yule, 1997[504]
	3 Year	Not applicable	82% (59-100%) (N=12)	Not reported	Robertson, 1998[489]
		Not applicable	Median 33 months (16-35mo) (N=4)	Not reported	Ayan, 1995[507]

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Anaplastic ependymoma	5 Year	Not applicable	35.2±11.0% (N=23)	Not reported	Jaing, 2004[516]
		Not applicable	64% (25-84%) (N=12)	Not reported	Robertson, 1998[489]
Non-anaplastic, mixed, or unspecified ependymoma	1 Year	Not applicable	3 patients dead at 1.4, 2.4, and 3.6 mo (N=3)	Not reported	Shih, 2008[132]
		Not applicable	Metastatic ~89% (N=9) Non-Metastatic ~95% (N=80)	Age< 1 year, p=.18 Female sex, p=.18 Infratentorial, p=.12 WHO gr. III, p=.15 Partial resection (judged by neurosurgeon) p=.07 Partial resection (radiologic review) p=.28 Dose intensity <.8, p=.05 HR=1.6 (1.0-2.7)	Grundy, 2007[512]
		~80% (N=29)	Not applicable	GTR vs. <GTR not significant	Zacharoulis, 2007[490]
		Not applicable	DOD at 2 and 6 mo (N=2)	Not reported	De Sio, 2006[509]
		Not applicable	~96% (N=73)	PF tumor RR 7.9 (1.8 to 35) p=.0004 Postoperative radiologic documented residuum: RR 3.6 (1.7-7.7) p=.0009	Grill, 2001[511]
		Not applicable	95% (85-100%) (N=20)	Not reported	Robertson, 1998[489]
		75 (54-96 95% CI) (N=16)	Not applicable	Not reported	Grill, 1996[497]
		2 patients dead at 7 and 9 months (67%) and one patient alive with progression at 25+ months (N=3)	Not applicable	Not reported	Mahoney, 1996[501]

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Non-anaplastic, mixed, or unspecified ependymoma	3 Year		79% (63.9-95.4) (N=23)	Complete vs. partial resection not significant	Conter, 2009[508]
		Not applicable	Metastatic ~58% (N=9) Non-Metastatic ~80% (N=80)	Age< 1 year, p=.18 Female sex, p=.18 Infratentorial, p=.12 WHO gr. III, p=.15 Partial resection (judged by neurosurgeon) p=.07 Partial resection (radiologic review) p=.28 Dose intensity <.8, p=.05 HR=1.6 (1.0-2.7)	Grundy, 2007[512]
		~62% (N=29)	Not applicable	GTR vs. <GTR not significant	Zacharoulis, 2007[490]
		Not applicable	~68% (N=73)	PF tumor RR 7.9 (1.8 to 35) p=.0004 Postoperative radiologic documented residuum: RR 3.6 (1.7-7.7) p=.0009	Grill, 2001[511]
		Not applicable	65 (44-86%) (N=20)	Not reported	Robertson, 1998[489]
		31 (3-58 95% CI) (N=16)	Not applicable	Not reported	Grill, 1996[497]
	5 Year	Not applicable	74% (57.3-92.3) (N=23)	Complete vs. partial resection NS	Conter, 2009[508]
		Not applicable	Metastatic ~28% (N=80) Nonmetastatic ~ 63 (N=9)	Age< 1 year, p=.18 Female sex, p=.18 Infratentorial, p=.12 WHO gr. III, p=.15 Partial resection (neurosurgeon) p=.07 Partial resection (radiologic review) p=.28 Dose intensity <.8, p=.05 HR=1.6 (1.0-2.7)	Grundy, 2007[512]
		38±10 (N=29)	Not applicable	GTR vs. <GTR NS	Zacharoulis, 2007[490]

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Non-anaplastic, mixed, or unspecified ependymoma	5 Year	2 patients alive NED at last FU 20 mo, 67 mo (N=2)	Not applicable	Not reported	Busca, 1997[495]
		10 (0-29 95% CI) (N=16)	Not applicable	Not reported	Grill, 1996[497]
		Not applicable	52±(38 to 65%) (N=73)	PF tumor RR 7.9 (1.8 to 35) p=.0004 Postoperative radiologic documented residuum: RR 3.6 (1.7-7.7) p=.0009	Grill, 2001[511]
		Not applicable	Grade II 73.7±10.2% (N=20) Complete resection (N=18): 82.1±9.5% Incomplete resection (N=19): 36.8±11.8% Biopsy (N=6): 33.3±19.3% Age <3 years (N=9): 41.7±17.3% Age >3 years (N=34): 57.4±9.1%	Anaplasia p<.001 Surgical Resection p<.001 Age p=.036	Jaing, 2004[516]
		1 patient alive with stable disease at 62 months (N=1)	Not applicable	Not reported	Ozkaynak, 2004[367]
		Not applicable	57.2±5 (N=83)	Age (<=3yr at diagnosis vs. >3 yr) p=.005; HR .04 (.2-.8) Deg. resection (GTR vs. <GTR) p=.01; HR 2.4(1.2-4.9) Histology (grade II vs. III) p=.05; HR 1.9 (.99-3.4)	Horn, 1999[514]
		Not applicable	6 pts DOD at 4.5 mo (N=21)	Not reported	Kuhl, 1998[520]
		Not applicable	53% (31-76%) (N=20)	Not reported	Robertson, 1998[489]
		Not applicable	50.3 (23.1-72.4) (N=15)	Not reported	Grundy, 2010[513]

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Choroid plexus carcinoma (CPC)	1 Year	Not applicable	~82 (N=29)	Tumor Type (Choroid plexus carcinoma vs. choroid plexus paplioma and atypical choroid plexus paplioma) HR 26.4 p=.003	Wrede, 2009[522]
		2 partially resected pts DOD at 21 and 25 mo (N=2)	13 patients DOD at median time 9 mo (range 4-41 mo) (65%) 7 patients Alive and well at median follow up 25 mo (range 3-85 mo) (35%) 1 of 8 gross total resection patients died (12.5%) 11 of 12 partial resection patients died (92%) (N=20)	Not reported	Berger, 1998[488]
		1 patient DOD at 5 months (N=1)	Not applicable	Not reported	Gururangan, 1998[499]
		1 pt dead at 11 mo (N=1)	Not applicable	Not reported	Yule, 1997[504]
		Not applicable	50.3 (23.1-72.4) (N=15)	Not reported	Grundy, 2010[513]
	3 Year	Not applicable	~70 (N=29)	Tumor Type (Choroid plexus carcinoma vs. choroid plexus paplioma and atypical choroid plexus paplioma) HR 26.4 p=.003	Wrede, 2009[522]
		Not applicable	21.5 (5.2-45.0) 3(N=15)	Not reported	Grundy, 2010[513]
	5 Year	Not applicable	36 (9-100) (N=29)	Tumor Type (Choroid plexus carcinoma vs. choroid plexus paplioma and atypical choroid plexus paplioma) HR 26.4 p=.003	Wrede, 2009[522]
		Not applicable	21.5 (5.2-45.6) (N=15)	Not reported	Grundy, 2010[513]

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Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Other glioma	1 Year	1 Oligodendroglioma dead at 8 mo (N=1)	Not applicable	Not reported	Thorarinsdottir, 2007[503]
		Not applicable	Median BSG OS 9mo (3-11) (33%) (N=8)	Not reported	De Sio, 2006[509]
		Not applicable	2 patients w/brainstem glioma DOD at 4 and 8 mo (N=2)	Not reported	Korones, 2006[518]
		Other glioma ~91 (Anaplastic astrocytoma (N=9) and anaplastic oligodendroglioma (N=2)) (N=11)	Not applicable	OS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse P=.004	Massimino, 2005[502]
		Not applicable	Other Glioma ~62 (N=6)	Not reported	Macdonald, 2005[521]
		2 recurrent BSG patient DOD at 4 and 9 mo (N=2)	Not applicable	Not reported	Ozkaynak, 2004[367]
		Pontine ~25 (N=24)	Not applicable	Not reported	Bouffet, 1997[493]
		Not applicable	Brainstem Glioma 9±5 (N=22)	Not reported	Kobrinsky, 1999[517]

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Other glioma	1 Year	1 Pons patient alive at last follow up. 5 patients DOD at median 8 mo (5-14 mo) (N=6)	Not applicable	Not reported	Jakacki, 1999[500]
		Median survival of pontine glioma patients was 4 mo (N=10)	Not applicable	Not reported	Dunkel, 1998[496]
		Median survival of HGG patients was 3 mo (12d-11 mo) (N=13)	Not applicable	Not reported	Bouffet, 1997[493]
		1 oligodendroglioma dead at 10 mo (N=1)	Not applicable	Not reported	Busca, 1997[495]
		Not applicable	1 BSG dead at 2 mo (N=1)	Not reported	Mahoney, 1996[501]
		Not applicable	HGG 57.9 (33.2-76.3) (N=19)	Not reported	Grundy, 2010[513]
	3 Year	Other glioma ~73 (Anaplastic astrocytoma (N=9) and anaplastic oligodendroglioma (N=2)) (N=11)	Not applicable	OS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse p=.004	Massimino, 2005[502]
		Not applicable	3 year OS: Other glioma ~62 (N=6)	Not reported	Macdonald, 2005[521]

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Other glioma	3 Year	Pontine ~0. (N=24)	Not applicable	Not reported	Bouffet, 1997[493]
		Not applicable	Brainstem glioma 0 (N=22)	Not reported	Kobrinsky, 1999[517]
		Not applicable	HGG 40.5 (18.7-61.5) (N=19)	Not reported	Grundy, 2010[513]
	5 Year	1 ganglioma patient dead at 59 mo (N=1)	Not applicable	Not reported	Thorarinsdottir, 2007[503]
		Other glioma ~73 (Anaplastic astrocytoma (N=9) and anaplastic oligodendroglioma (N=2)) (N=11)	Not applicable	OS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse p=.004	Massimino, 2005[502]
		Not applicable	Other glioma ~38 (N=6)	Not reported	Macdonald, 2005[521]
		Not applicable	Malignant glioma 36 ± 10 (N=22)	Not reported	Kuhl, 1998[520]
		Not applicable	HGG 34.7 (14.6-56.0) (N=19)	Not reported	Grundy, 2010[513]

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Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Astrocytoma (summary comparison)	OS Range for 5 years for studies with ≥10 patients	**Newly Diagnosed:** ~73%* (Massimo, 2005 [502]) [*This study included 9 Anaplastic Astrocytoma patients and 2 lower-grade oligodendroglioma patients.] Massimo measured from time of diagnosis	**Newly Diagnosed:** 25% (Macdonald [521] N=30) Macdonald measured from time of study entry to death	Not applicable	Bertolone [491] was not included in this estimate because the study did not differentiate between AA and GBM patients
		Recurrent/Progressive: 40% (Finlay [485] N=17) Measured from time of myeloablative chemotherapy	**Recurrent/Progressive:** 0% (Finlay [485] N=27) Measured from time of recurrence	Not applicable	Bertolone [491] was not included in this estimate because the study did not differentiate between AA and GBM patients

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Glioblastoma multiforme (summary comparison)	5 year OS for all studies with N ≥10 patients	**Newly Diagnosed:** 0-22% (Grovas [498] N=11, Massimo [502] N=10) Grovas measured from time of stem cell rescue Massimo considered OS from date of chemotherapy	**Newly Diagnosed:** 22% (Macdonald [521] N=40) Macdonald measured from time of study entry to death	Not applicable	Bertolone [491] was not included in this estimate because the study did not differentiate between AA and GBM patients
		Recurrent/Progressive: 12% (Finlay [485] N=17) Measured from time of myeloablative chemotherapy	**Recurrent/Progressive:** 0% (Finlay [485] N=27) Measured from time of recurrence	Not applicable	Bertolone [491] was not included in this estimate because the study did not differentiate between AA and GBM patients

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Ependymoma (summary comparison)	5 year OS for studies with N ≥10 patients	**Newly Diagnosed, unspecified anaplastic** 38% (Zacharoulis [490] N=29) Zacharoulis estimated OS from date of diagnosis	**Newly Diagnosed Nonanaplastic, mixed, or unspecified Ependymoma:** 52-74% (Conter [508] N=23, Grill, 2001 [511] N=14, Horn [514] N=83, Jaing [516] N=20, Robertson [489] N=20) Conter and Jaing estimated OS from date of surgery, Grill measured from date of chemotherapy, Robertson measured from date of randomization, and Horn measured from date of diagnosis. Overall, these differing estimates of overall survival approximate date of surgery within 13 weeks. **Newly Diagnosed Anaplastic Ependymoma**: 35.2-64% (Jaing [516] N=23 and Robertson [489] N=12) Jaing used date of surgery for OS calculation and Robertson used date of randomization	Not applicable	Grundy et al. was not included in this estimate because the study stratified by metastasis finding a 5 year OS of 28% for metastatic ependymoma and 63% for nonmetastatic disease and measured the OS from date of surgery.

Table 85. Overall survival for single auto HSCT and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors (continued)

Indication	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P Value	Study
Ependymoma (summary comparison)	5 year OS for studies with N ≥10 patients	No patients alive past 25 months. (Berger [488] N=2, Gururangan [499] N=1, Yule [504] N=1)	21.5-36% (Grundy N=15 and Wrede [522] N=29) Wrede measured OS from date of diagnosis and Grundy used date of surgery	Not applicable	Not applicable
Choroid plexus carcinoma (summary comparison)	5 Year OS All studies	No patients alive past 25 months. (Berger [488] N=2, Gururangan [499] N=1, Yule [504] N=1)	21.5-36% (Grundy N=15 and Wrede [522] N=29) Wrede measured OS from date of diagnosis and Grundy used date of surgery	Not applicable	Not applicable

Adverse Effects

Nine HSCT studies reported adverse events in a patient population of 138 patients composed of 13 anaplastic astrocytoma, three anaplastic glioma, 49 ependymoma, one ganglioma, 30 glioblastoma multiforme, one oligodendroglioma, and 41 pontine tumors (Table 86).[485, 490, 493, 497, 498, 500, 501, 503, 506] The conventional therapy studies reported adverse events for 113 ependymoma patients, 30 anaplastic astrocytoma patients, 40 glioblastoma multiforme patients, 18 high-grade glioma patients, seven pontine tumor patients and 15 choroid plexus tumor patients.[508, 512, 513, 521] Overall, the level of adverse event reporting for both HSCT and conventional therapy may be underreported. Many studies included tumor types not relevant to this report in their design, and the authors in most instances did not give data on a tumor group or per patient basis when discussing adverse events.

Table 86. Adverse effects for single auto HSCT and comparison (conventional chemotherapy +/- radiation) group: Glial tumors

Outcome	HSCT (%)	Conventional Therapy (%)	Study
Treatment related mortality	5 toxic deaths in HSCT group (19%)	Not applicable	Finlay, 2008[485]
	3 toxic deaths (10%)	Not applicable	Zacharoulis, 2007[490]
	Not applicable	1 patient died preoperatively (1%)	Grundy, 2007[512]
	Not applicable	3 (4%)	Macdonald, 2005[521]
	1 hVOD (3%) 1 toxic exfoliative dermatitis with acute renal failure (3%) S1 aspergillus fumigatus pneumonia (3%)	Not applicable	Bouffet, 1997[493]
	2 (18%)	Not applicable	Grovas, 1999[498]
	5 toxic mortality (33%)	Not applicable	Mason, 1998[506]
	1 (6%)	Not applicable	Grill, 1996[497]
	4 (21%)	Not applicable	Mahoney, 1996[501]
Secondary malignancies	1 lymphoblastic non-Hodgkin's lymphoma at 3.5 yr (9%)	Not applicable	Grovas, 1999[498]

Table 86. Adverse effects for single auto HSCT and comparison (conventional chemotherapy +/- radiation) group: Glial tumors (continued)

Outcome	HSCT (%)	Conventional Therapy (%)	Study
Infectious complications ≥ grade III	# Gram positive bacterium per patient: Oligodendroglimoma 2 Ganglioma 3 Anaplastic glioma 0, 1, 2 Ependymoma 4	Not applicable	Thorarinsdottir, 2007[503]
	3 cases of sepsis leading to toxic morality (10%)	Not applicable	Zacharoulis, 2007[490]
	Not applicable	6 Grade 3 or 4 infectious complication (8.6%) 1 patient died due to infection (group not given) (1.4%)	Macdonald, 2005[521]
	1 Aspergillus fumigatus (6%) 1 cytomegalovirus (6%)	Not applicable	Bouffet, 1997[493]
	gram-positive sepsis (9%)	Not applicable	Grovas, 1999[498]
	7 infection (37%) 1 fungal infection (5%)	Not applicable	Mahoney, 1996[501]
	2 patients had interstitial pneumonia which resolved with treatment (17%)	Not applicable	Jakacki, 1999[500]
Serious hemorrhagic event	Not applicable	2 patients died of serious hemorrhagic events (group not given)	Macdonald, 2005[521]
Veno-occlusive disease	4 mild-severe hVOD (11%) 1 fatal hVOD (3%)	Not applicable	Bouffet, 1997[493]
	1 Fatal hVOD at 2.9 mo (9%)	Not applicable	Grovas, 1999[498]
Long-term complications	Not applicable	5 children required special needs education	Grundy, 2010[513]
	Not applicable	2 Mild retardation (13%) 2 Severe retardation (13%) Two patients were placed in a special school, and two were ≥ 2 years behind at school 5 Diplopia (32%) Severe decrease of visual acuity 1 (6%)	Conter, 2009[508]
	1 ODG pt had decreased neurologic responsiveness/ blindness (100%) 1 GG pt had ADD (100%) 1 AG patient had Gr 2 L hemiparesis (33%) 1 AG pt had Ataxia (33%) 1 EPD pt had hypotonia/multiple neuropathies G 2-4 hearing loss/poor speech (100%)	Not applicable	Thorarinsdottir, 2007[503]
	1 right atrial mural thrombosis leading to death at 3.4 mo (9%)	Not applicable	Grovas, 1999[498]

Ongoing Research

Six trials were identified with currently unpublished results (Table 87). One trial was completed, two were ongoing, and three were recruiting participants. Anaplastic astrocytoma was investigated in four studies, brainstem glioma in one study, choroid plexus carcinoma in two studies, ependymoma in three studies, and glioblastoma multiforme in four studies. The estimated total enrollment of these trials is 363 participants, but with the exception of two studies, nonpediatric patients will also be enrolled. All studies include overall survival or event-free survival as outcomes relevant to this report.

Table 87. Ongoing trials: Glial tumors

Trial Name (Estimated Enrollment)	Status	Indication Relevant Tumor Types	Patient Population
Chemotherapy Plus Peripheral Stem Cell Transplantation in Treating Infants With Malignant Brain or Spinal Cord Tumors (n=83)	Completed	Newly Diagnosed: EPD, AA, CPC	up to 2 years
Stem Cell Transplant for High Risk Central Nervous System (CNS) Tumors (n=50)	Ongoing	Newly Diagnosed: GBM, AA	18 mo - 25 years
Chemotherapy Followed by Bone Marrow or Peripheral Stem Cell Transplantation in Treating Patients With Glioblastoma Multiforme or Brain Stem Tumors (n=60)	Ongoing, no recruitment	Nonprogressive: GBM	6-60 years
Busulfan, Melphalan, Topotecan Hydrochloride, and a Stem Cell Transplant in Treating Patients With Newly Diagnosed or Relapsed Solid Tumor (n=20)	Recruiting	Progressive/ Recurrent CNS: EPD, AA, BSG	6-40 years
Phase III Pilot Study of Induction Chemotherapy Followed by Consolidation Myeloablative Chemotherapy Comprising Thiotepa and Carboplatin With or Without Etoposide and Autologous Hematopoietic Stem Cell Rescue in Pediatric Patients With Previously Untreated Malignant Brain Tumors(n=120)	Recruiting	Newly diagnosed: CNS Tumors: GBM, HGG, CPC, EPD, AA	Less than 10 years
Temozolomide, Carmustine, O6-Benzylguanine, Radiation Therapy, and an Autologous Stem Cell Transplant in Treating Patients With Newly Diagnosed Glioblastoma Multiforme or Gliosarcoma (n=30)	Recruiting	Newly diagnosed: GBM	18+ years

AA = anaplastic astrocytoma; BSG = brainstem glioma; CNS = central nervous system; CPC = choroid plexus carcinoma; EPD = ependymoma; GBM = glioblastoma multiforme; HGG = high-grade glioma; OAST = oligoastrocytoma; ODG = oligodendroglioma; REC = recurrent

Conclusions

Low strength evidence on overall survival suggests a benefit with single HSCT compared to conventional therapy for the treatment of:

- High-risk recurrent or progressive anaplastic astrocytoma
- High-risk recurrent glioblastoma multiforme.

Low strength evidence on overall survival suggests a harm due to higher treatment-related mortality with single HSCT compared to conventional chemotherapy for the treatment of nonanaplastic mixed or unspecified ependymoma.

The body of evidence on overall survival with single HSCT compared to conventional therapy was insufficient to draw conclusions for treatment of:

- High-risk newly diagnosed anaplastic astrocytoma
- High-risk newly diagnosed glioblastoma multiforme
- Newly diagnosed anaplastic, nonanaplastic, mixed, or unspecified ependymoma

- Recurrent ependymoma
- Choroid plexus carcinoma
- Other gliomas.

Systematic Reviews: Nonmalignant Disease

Inherited Metabolic Diseases Systematic Review

Background and Setting
Inherited metabolic diseases (IMD), also known as inborn errors of metabolism, are rare genetic diseases of biochemistry. IMDs are caused by defects of enzymes which result in the accumulation of substrates in tissues and organs. As substrates accumulate, progressive damage to the skeletal structure, connective tissues, organs, and in more severe disorders, the central nervous system occurs. Symptoms and the severity range widely among the IMDs. Many of the diseases are characterized by a rapid deterioration and have a life expectancy of a few years, while some of the IMDs have a slower course and patients may live into adulthood. While each condition is rare, the collection of these diseases has caused significant morbidity and mortality. Estimates of cumulative incidence for IMDs range from 1 in 1500 to 1 in 5,000 live births.[270, 523, 524]

In this report, IMDs will be discussed in three sections: 1) diseases with rapid progression of symptoms and life expectancies of 10 years or less, 2) diseases with slower progression of symptoms and life expectancies of more than 10 years, and 3) diseases with two different forms, one form which has a rapid progression of symptoms and one form which has a slow progression of symptoms. For diseases that have a rapid progression of symptoms, the expected outcome following HSCT is prolonged life expectancy. For diseases with a slow progression of symptoms, the expected outcomes following HSCT are improvements in neurocognitive and neurodevelopmental functioning.

The diseases with rapid progression of symptoms that were systematically reviewed include: Wolman disease, Gaucher disease Type II, Niemann-Pick Type A, mucolipidosis II (I-cell disease), cystinosis, and infantile free sialic acid disease. The diseases with slow progression of symptoms that were systematically reviewed are mucopolysaccharidosis II (Hunter's disease), mucopolysaccharidosis III (Sanfilippo disease), mucopolysaccharidosis IV (Morquio syndrome), Fabry's disease, Gaucher disease Type III, aspartylglucosaminuria, β-mannosidosis, mucolipidosis III, mucolipidosis IV, Niemann-Pick Type C, glycogen storage disease Type 2 (Pompe disease), Salla disease, and adrenomyeloneuropathy. Diseases with forms that progress rapidly and forms that progress slowly and that were systematically reviewed are Farber's disease, GM_1 gangliosidosis, Tay-Sachs disease, Sandhoff's disease, ceroid lipofuscinosis, and galactosialidosis.

Evidence Summary

Diseases With Rapid Progression
The overall grade of strength of evidence for overall survival with the use of HSCT for the treatment of inherited metabolic diseases with rapid progression is shown in Table 88.

Diseases With Slow Progression

The overall grade of strength of evidence for stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with slow progression is shown in Table 89.

Diseases With Forms That Progress Rapidly and Slowly

The overall grade of strength of evidence for overall survival and stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with rapid progression and slow progression forms is shown in Table 90.

Table 88. Overall grade of strength of evidence for overall survival with the use of HSCT for the treatment of inherited metabolic diseases with rapid progression

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **Wolman's disease** compared to symptom management and natural progression of disease? Key outcomes are overall survival.	2 case reports and 2 case series	High	The evidence is consistent.	The outcomes reported are direct.	The evidence is precise suggesting an overall survival advantage for HSCT over conventional therapy. While the evidence is qualitative it is unlikely that the prognosis would change without HSCT treatment.	The strength of association is strong.	High strength evidence on overall survival suggests a benefit with single HSCT compared to conventional management of Wolman's disease. 4 survived treatment, with followups of 0.3-11 yrs; 3 long-term survivors (4-11 yrs) highly functional and attending school. 2 TRM deaths 1 death from disease progression
What is the comparative effectiveness and harms of HSCT in the treatment of **Gaucher disease Type II** compared to symptom management and natural progression of disease? Key outcomes are overall survival.	0 studies found	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Insufficient evidence
What is the comparative effectiveness and harms of HSCT in the treatment of **Niemann-Pick Type A** compared to symptom management and natural progression of disease? Key outcomes are overall survival.	1 case report and 1 case series	High	The evidence is consistent.	The outcomes reported are direct.	The evidence is imprecise.	Not applicable due to lack of obvious effect size.	Low strength evidence on overall survival suggests no benefit with single HSCT compared to symptom management for Niemann-Pick Type A. 2 pts dead at 2 yrs followup from disease progression 1 pt alive at 2.7 yrs followup, with neurocognitive and neurodevelopmental decline.

Table 88. Overall grade of strength of evidence for overall survival with the use of HSCT for the treatment of inherited metabolic diseases with rapid progression (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **mucolipidosis II (I-cell disease)** compared to symptom management and natural progression of disease? Key outcomes are overall survival.	3 case reports	High	The evidence is inconsistent.	The outcomes reported are direct.	The evidence is imprecise.	Not applicable due to lack of obvious effect size.	The body of evidence on overall survival with single HSCT compared to symptom management for mucolipidosis II (I-cell disease) is insufficient to draw conclusions. 1 pt died of progressive disease 5.6 yrs post-transplant. 1 pt alive 5 yrs post-transplant, mildly to moderately impaired mentally and physically 1 pt alive 2 yrs post, with unknown mental and physical outcomes
What is the comparative effectiveness and harms of HSCT in the treatment of **cystinosis** compared to symptom management and natural progression of disease? Key outcomes are overall survival.	0 studies found	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Insufficient evidence
What is the comparative effectiveness and harms of HSCT in the treatment of **infantile free sialic acid disease** compared to symptom management and natural progression of disease? Key outcomes are overall survival.	0 studies found	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Insufficient evidence

TRM = treatment-related mortality

Table 89. Overall grade of strength of evidence for stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with slow progression

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **MPS II (Hunter's disease)** compared to symptom management, ERT, and the natural history of disease? Key outcomes are neurocognitive and neurodevelopmental symptoms.	8 case reports and 6 case series	High	The evidence is consistent for the severe form. Evidence is inconsistent for the attenuated form.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	For neurodevelopmental symptoms, the evidence is precise for both the severe and attenuated form, suggesting outcomes with HSCT are equal to ERT. For neurocognitive symptoms, the evidence is precise for the severe form, suggesting HSCT does not provide a benefit. For neurocognitive symptoms, the evidence is imprecise for the attenuated form, suggesting an advantage of HSCT over ERT.	For neurodevelopmental symptoms, the strength of association is not applicable as no effect size is obvious compared to ERT. For neurocognitive symptoms in the severe form, this is not applicable due to lack of obvious effect size. For neurocognitive symptoms in the attenuated form, the strength of association is weak.	Low strength evidence on neurodevelopmental outcomes suggests equivalent benefit with single HSCT compared to ERT for severe and attenuated forms of MPS II (Hunter's disease). Low strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared to symptom management/natural history for the severe MPS II. Low strength evidence on neurocognitive outcomes suggests benefit with single HSCT compared to ERT for attenuated MPS II. 7 TRM deaths out of 32 pts undergoing HSCT. 7 of 8 with severe form showed neurocognitive decline. Among 6 with attenuated form, 4 stable neurocognitively, 2 declining. ERT* trials on pts with attenuated form only. No neurocognitive outcomes reported. Improvements in neurodevelopmental symptoms were reported.

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Table 89. Overall grade of strength of evidence for stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with slow progression (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **MPS III (Sanfilippo disease)** compared to symptom management and natural history of the disease? Key outcomes are neurocognitive and neurodevelopmental symptoms.	1 case reports and 4 case series	High	Evidence is inconsistent.	The outcomes reported are direct.	The evidence is imprecise.	Not applicable due to lack of obvious effect size.	Low strength evidence on neurocognitive and neurodevelopmental outcomes suggests no benefit with single HSCT compared to symptom management for MPS III (Sanfilippo disease). 1 pt died 5 mos post-HSCT of pneumonia 1 pt alive at unspecified followup, 7 pts alive at 2.4-14.0 yrs No followup details in 1 pt, 1 pt stable, 6 pts declining neurocognitively and neurodevelopmentally, though 2 of 6 are declining slower than untreated siblings.
What is the comparative effectiveness and harms of HSCT in the treatment of **MPS IV (Morquio syndrome)** compared to symptom management and natural history of the disease? Key outcomes are neurocognitive and neurodevelopmental symptoms.	2 case reports	High	Not applicable	The outcomes reported are direct.	The evidence is imprecise.	Not applicable due to lack of obvious effect size.	The body of evidence on neurocognitive and neurodevelopmental outcomes with single HSCT compared to symptom management for MPS IV (Morquio syndrome) is insufficient to draw conclusions. No followup data provided for 1 pt who was transplanted at 15 yrs of age. Only cardiac followup on 2nd pt, and no cardiac improvement reported.

Table 89. Overall grade of strength of evidence for stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with slow progression (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **Fabry's disease** compared to symptom management and the natural history of the disease? Key outcomes are neurocognitive and neurodevelopmental symptoms.	0 studies found	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Insufficient evidence

Table 89. Overall grade of strength of evidence for stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with slow progression (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **Gaucher Type III** compared to symptom management, ERT, substrate reduction therapy, and the natural history of the disease? Key outcomes are neurocognitive and neurodevelopmental symptoms.	2 case reports and 2 case series	High	Evidence for neurocognitive outcomes with HSCT is consistent.	The outcomes reported are direct. The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence on neurocognitive score stabilization with HSCT is precise.	Not applicable due to lack of obvious effect size.	Low strength evidence on neurocognitive and neurodevelopmental outcomes suggests no benefit with single HSCT compared to ERT for Gaucher Type III disease. 1 TRM death out of 8 undergoing HSCT. 5 out of 8 pts treated with HSCT showed stable neurocognitive scores. All pts with HSCT had improved growth, but no improvement in skeletal symptoms. 2 pts treated with HSCT followed by ERT*, alive at 19-21 yrs, with borderline mental retardation. Among 23 pts treated with ERT alone, 1 died of liver biopsy, the remaining are alive at 0.4-5 yrs followup. Neurocognitive scores are stable in 7 of 9 pts. Growth improved, but no change in skeletal symptoms. In an RCT with 30 pts, comparing ERT alone and ERT with substrate reduction therapy, there was no difference between the 2 grps in neurocognitive scores.

Table 89. Overall grade of strength of evidence for stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with slow progression (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **aspartylglucosaminuria** compared to symptom management and natural history of the disease? Key outcomes are neurocognitive and neurodevelopmental symptoms.	1 case report and 3 case series	High	Evidence is consistent.	The outcomes reported are direct.	The evidence is imprecise.	Not applicable due to lack of obvious effect size.	The body of evidence on neurocognitive and neurodevelopmental outcomes with single HSCT compared to symptom management of aspartylglucosaminuria is insufficient to draw conclusions. All 10 pts alive at followups from 0.3-7.6 yrs. Improved concentration reported in 2 pts, development stabilized at 5 yrs of age in 2 pts whose real ages were 15 and 11. Studies may not have long enough followups to see real effect of HSCT since rapid decline in this disease occurs during adolescence.
What is the comparative effectiveness and harms of HSCT in the treatment of **ß-mannosidosis** compared to symptom management and natural history of the disease? Key outcomes are neurocognitive and neurodevelopmental symptoms.	0 studies found	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Insufficient evidence

Table 89. Overall grade of strength of evidence for stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with slow progression (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **mucolipidosis III** compared to symptom management and natural history of the disease? Key outcomes are neurocognitive and neurodevelopmental symptoms.	0 studies found	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Insufficient evidence
What is the comparative effectiveness and harms of HSCT in the treatment of **mucolipidosis IV** compared to symptom management and natural history of the disease? Key outcomes are neurocognitive and neurodevelopmental symptoms.	0 studies found	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Insufficient evidence

Table 89. Overall grade of strength of evidence for stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with slow progression (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **Niemann-Pick Type C** compared to symptom management, substrate reduction therapy, and the natural history of the disease? Key outcomes are neurocognitive and neurodevelopmental symptoms.	2 case reports	High	Not applicable	The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is imprecise.	Not applicable due to lack of obvious effect size.	The body of evidence on neurocognitive and neurodevelopmental outcomes with single HSCT compared to symptom management or natural history of Niemann-Pick Type C disease is insufficient to draw conclusions . 1 pt alive at 0.8 yrs followup, with slowly decreasing developmental age measurements. Pt became bedridden during conditioning phase and never improved. 1 pt alive at 1.7 yrs followup, developing normally, except for delayed speech. Studies of substrate reduction therapy versus symptom management present combined adult and pediatric data. Substrate reduction therapy may stabilize ambulation in these pts.

Table 89. Overall grade of strength of evidence for stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with slow progression (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **glycogen storage disease Type 2 (Pompe disease)** compared to symptom management and natural history of the disease? Key outcomes are neurocognitive and neurodevelopmental symptoms.	0 studies found	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Insufficient evidence
What is the comparative effectiveness and harms of HSCT in the treatment of **Salla disease** compared to symptom management and natural history of the disease? Key outcomes are neurocognitive and neurodevelopmental symptoms.	0 studies found	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Insufficient evidence

Table 89. Overall grade of strength of evidence for stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with slow progression (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **adrenomyeloneuropathy** compared to symptom management and the natural history of the disease? Key outcomes are neurocognitive and neurodevelopmental symptoms.	0 studies found	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Insufficient evidence A single report of HSCT on an adrenomyeloneuropathy was found on an adult patient, but no pediatric cases were found.

ERT = enzyme replacement therapy; TRM = treatment-related mortality

Table 90. Overall grade of strength of evidence for overall survival and stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with rapid progression and slow progression form

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **Farber's disease** compared to symptom management and the natural history of the disease? Key outcomes are overall survival for the rapidly progressive form and neurocognitive and neurodevelopmental outcomes for the slowly progressive form.	**Rapid progression:** Type 1: 1 case report and 1 case series **Slow progression:** Type 2/3: 2 case series	**Rapid progression:** High **Slow progression:** High	**Rapid progression:** The evidence is inconsistent **Slow progression:** The evidence is consistent.	The outcomes reported are direct.	**Rapid progression:** The evidence is imprecise. **Slow progression:** Precise	**Rapid progression:** Not applicable for Type I Farber's disease. **Slow progression:** The strength of association is strong for Type 2/3 Farber's disease.	The body of evidence on overall survival with single HSCT compared to symptom management or natural history of the Type 1 form of Farber's disease is insufficient to draw conclusions. High strength evidence on number of subcutaneous nodules and number of joints with limited range of motion suggests a benefit with single HSCT compared to symptom management and the natural history of the Type 2/3 form of Farber's disease. 1 pt with Type 1 alive at 2.3 yrs followup with neurocognitive and neurodevelopmental decline. 1 pt with Type 1 dead at 6 mos post-HSCT from disease progression. All 5 pts with Type 2/3 alive at 0.7-1.3 yrs followup, with reduction in number of subcutaneous nodules and number of joints with limited range of motion.

Table 90. Overall grade of strength of evidence for overall survival and stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with rapid progression and slow progression form (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **GM$_1$ gangliosidosis** compared to symptom management and natural history of the disease? Key outcomes are overall survival for the rapidly progressive form and neurocognitive and neurodevelopmental outcomes for the slowly progressive form.	**Rapid progression:** infantile form: 0 studies found **Slow progression:** juvenile form: 1 case report	**Rapid progression:** Not applicable **Slow progression:** High	**Rapid progression:** Not applicable **Slow progression:** Not applicable	The outcomes reported are direct.	**Rapid progression:** Not applicable **Slow progression:** Not applicable	**Rapid progression:** Not applicable **Slow progression:** Not applicable	Insufficient evidence for the infantile form of this disease. Insufficient evidence for the juvenile form of this disease. 1 pt alive at 7 yrs followup. Pt is wheelchair bound and has lost all language skills.

Table 90. Overall grade of strength of evidence for overall survival and stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with rapid progression and slow progression form (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **Tay-Sachs disease** compared to symptom management, substrate reduction therapy, and the natural history of the disease? Key outcomes are overall survival for the rapidly progressive form and neurocognitive and neurodevelopmental outcomes for the slowly progressive form.	**Rapid progression:** infantile form: 0 studies found **Slow progression:** juvenile form: 1 case report **Unspecified progression:** 1 case report and 1 case series	**Rapid progression:** Not applicable **Slow progression:** High **Unspecified progression:** High	**Rapid progression:** Not applicable **Slow progression:** Not applicable **Unspecified progression:** Not applicable	The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	**Rapid progression:** Not applicable **Slow progression:** Not applicable **Unspecified progression:** Not applicable	**Rapid progression:** Not applicable **Slow progression:** Not applicable **Unspecified progression:** Not applicable	Insufficient evidence for the infantile form of this disease. Insufficient evidence for the juvenile form of this disease. Insufficient evidence for the unspecified progression form of this disease. 1 pt with the juvenile form is alive at 2 yrs followup. Neurocognitive and neurodevelopmental decline is similar to untreated sibling. 2 pts with the juvenile form received substrate reduction therapy and were alive at 2 yrs followup. Both have declined neurocognitively and neurodevelopmentally. 1 pt with unspecified progression died 4.6 yrs post-HSCT of disease progression and the 2nd pt with unspecified progression was alive at 1.7 yrs post-transplant, but had regressed to a vegetative state.

Table 90. Overall grade of strength of evidence for overall survival and stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with rapid progression and slow progression form (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **ceroid lipofuscinosis** compared to symptom management and the natural history of the disease? Key outcomes are overall survival for the rapidly progressive form and neurocognitive and neurodevelopmental outcomes for the slowly progressive form.	**Rapid progression:** infantile form: 1 case series **Slow progression:** juvenile form: 0 studies found	**Rapid progression:** High **Slow progression:** Not applicable	**Rapid progression:** Consistent **Slow progression:** Not applicable	The outcomes reported are direct.	**Rapid progression:** The evidence is precise. **Slow progression:** Not applicable	**Rapid progression (infantile):** Not applicable due to lack of obvious effect size. **Slow progression:** Not applicable	Low strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared to symptom management and the natural history of the disease for the infantile form of ceroid lipofuscinosis. Insufficient evidence for the juvenile form of this disease. All 3 pts in case series are alive at 2-4 yrs followup. All 3 pts have neurocognitive decline, and are hypotonic and spastic.
What is the comparative effectiveness and harms of HSCT in the treatment of **galactosialidosis** compared to symptom management and the natural history of the disease? Key outcomes are overall survival for the rapidly progressive form and neurocognitive and neurodevelopmental outcomes for the slowly progressive form.	**Unspecified progression:** 1 case report	High	Not applicable	The outcomes reported are direct.	The evidence is imprecise.	Not applicable	The body of evidence on overall survival, neurocognitive and neurodevelopmental outcomes with HSCT compared to symptom management for galactosialidosis is insufficient to draw conclusions. This single case was part of a case series with several different diseases. Results were cumulative across all diseases and no data was available for the single galactosialidosis case [525]

Table 90. Overall grade of strength of evidence for overall survival and stabilization of neurocognitive and neurodevelopmental symptoms with the use of HSCT for the treatment of inherited metabolic diseases with rapid progression and slow progression form (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
What is the comparative effectiveness and harms of HSCT in the treatment of **Sandhoff's disease** compared to symptom management, substrate reduction therapy, and the natural history of the disease? Key outcomes are overall survival for the rapidly progressive form and neurocognitive and neurodevelopmental outcomes for the slowly progressive form.	**Unspecified progression:** 1 case report	High	Not applicable	The comparisons are indirect as the evidence base utilizes two or more bodies of evidence to make comparisons.	The evidence is imprecise.	Not applicable	The body of evidence on overall survival, neurocognitive and neurodevelopmental outcomes with HSCT compared to symptom management, substrate reduction therapy, and the natural history of the disease for Sandhoff's disease is insufficient to draw conclusions. The single case report was part of a case series with several diseases. The form of the disease was not specified and there were no neurocognitive or neurodevelopmental outcomes reported. 3 pts with the juvenile form received substrate reduction therapy and were alive at 2 yrs followup. They were stable neurocognitively, but 2 developed gait disturbance and 1 is wheelchair bound.

Results

Table 91 shows the criteria that were used to select studies for this section.

Table 91. Study selection criteria: Inherited metabolic diseases

Study Design	Population	Intervention	Comparators	Outcomes	Followup	Setting
Controlled trials, case series, case reports from 1992-present	Pediatric patients (0-21-yr)	HSCT	symptom management, ERT, substrate reduction therapy	enzyme activity, neuro-cognitive and neuro-developmental measurements	All durations of followup	In-patient, out-patient

ERT = enzyme replacement therapy; HSCT = hematopoietic stem cell transplant

Diseases With Rapid Progression

Wolman Disease

Wolman disease is a rare autosomal recessive disorder characterized by a deficiency of lysosomal acid lipase which causes an accumulation of cholesterol esters and triglycerides in the spleen, liver, adrenal glands, bone marrow, small intestines, and lymph nodes.[261] Fewer than 80 cases have been identified. Symptoms appear immediately, within the first week of life, and include failure to thrive, jaundice, anemia, relentless vomiting, abdominal distention, steatorrhea, and hepatosplenomegaly. Because of the failure to absorb nutrients, severe malnutrition occurs and life expectancy is less than 6 months.[526] Several patients with Wolman disease have undergone HSCT (Table 92).[527-530]

Refer to Appendix E Table E1 for details of neurocognitive and neurodevelopmental outcomes. In summary, two patients died of treatment-related mortality, one at 2.5 months post-transplant and one at 8 months post-transplant and one died from the natural progression of the disease.[527] Three (of 4) patients who survived HSCT are long-term survivors, with followup from 4 to 11 years. They are highly functional in language skills, and social and behavioral skills. One attends regular school and two attend special schools.[529, 531]

The case report of the patient with Wolman disease who underwent HSCT reported growth in height, weight and head circumference.[529] Of the three surviving Wolman disease patients in the case series, one showed improvement in motor skills and another is reported to have average gross motor skills and below average fine motor skills[531]

Evidence for this rapidly progressing disease which has a life expectancy of 6 months, consists of two case reports and two case series. A total of seven patients with Wolman disease have undergone HSCT. Two died from the procedure and 1 died from disease progression. Four have survived and have been followed for 0.3 to 11 years, with normal or near normal functioning. For three patients who have survived long-term followup from 4 to 11 years, HSCT altered the course of Wolman disease.

Table 92. Study characteristics and population for Wolman disease

Study	Design	Median Age in Years (Range) at Treatment	Sex (M%)	Treatment, Year	Followup Period (yrs)	Enzyme Activity	Neuro-cognitive Outcomes	Neuro-developmental Outcomes	Adverse Effects
Gramatges, US, 2009[527]	case report	0.2	0	HSCT, NR	0.2	√	NR	NR	√
Tolar, US, 2009[531]	case series (n=4)	4.5 (0.2-2.1)	50	HSCT, NR	(0.2-11.0)	√	√	√	√
Stein, Israel, 2007[529]	case report	0.25	0	HSCT, NR	4.0	√	√	√	√
Styczynski, 2011[530]	Case series (n=1)	16	0	HSCT, NR	0.3	NR	NR	NR	√

Gaucher Disease Type II

Gaucher disease is caused by a deficiency in the enzyme glucocerebrosidase, which leads to an accumulation of glucosylceramide in the spleen, liver, lungs, bone marrow, and sometimes the brain.[261] There are three types of Gaucher disease. Gaucher Type I is discussed in the Narrative Review section of this report. Gaucher Type III is discussed in this Systematic Review section under diseases with slow progression.

Type II is the acute neuronopathic form, exhibiting hepatosplenomegaly as early as three months of age. There is severe central nervous system involvement and death occurs within two years of life. There is no effective treatment for Type II because of the rapid progression of symptoms and neurological involvement. No HSCT and Gaucher Type II studies were found in the literature.

Niemann-Pick Disease Type A

Niemann-Pick disease is characterized by the accumulation of lipids in the spleen, liver, lungs, bone marrow, and the brain. There are three types of this disease. Type A occurs most frequently in the Ashkenazi Jewish population (1 in 40,000), while the frequency of Type A and B in the general population is estimated to be 1 in 250,000.[532] Type B is discussed in the Narrative Review section of this report. Type C is discussed under the heading "Other Lipidoses" within this Systematic Review.

Type A is the most severe form, occurring in infants and characterized by jaundice, an enlarged liver, and brain damage, with life expectancy of 3 years.[261] Reports of HSCT on 3 Type A patients have been found in the literature (Table 93).

Table 93. Study characteristics and population for Niemann-Pick Type A

Study	Design	Median Age in Years (Range) at Treatment	Sex (M%)	Treatment, Year	Followup Period (yrs)	Enzyme Activity	Neuro-cognitive Outcomes	Neuro-developmental Outcomes	Adverse Effects
Morel, Canada, 2007[533]	case report	2.5	0	HSCT, NR	2.7	√	√	√	√
Bayever, US, 1995 [534]	case series (n=2)	7 mos (4-10 mos)	100	HSCT, NR	2.0	√	√	√	√

Refer to Appendix E Table E1 for details of neurocognitive and neurodevelopmental outcomes. In summary, a case report of a patient with Niemann-Pick Type A who underwent HSCT at 3 months of age, showed initial normal neurocognitive and neurodevelopmental progress, followed by brain atrophy at 0.6 years post-transplant, and the onset of seizure disorders and developmental delays by 1.7 years post-transplant.[533] At the time of the report, the patient was alive at 2.7 years' followup. Two patients receiving HSCT continued to decline neurocognitively and neurodevelopmentally, and died 2 years post-transplant, from natural progression of disease.[534] Autopsy of one patient showed very little enzyme present in target tissues of brain and liver.[534]

Evidence for Niemann-Pick Type A, which has a life expectancy of 3 years, consists of 1 case report and 1 case series.[533, 534] HSCT did not prevent neurocognitive and neurodevelopmental decline in these patients. Based on these reports, HSCT does not show a benefit for Niemann-Pick Type A.

Mucolipidosis II (I-cell Disease)

Mucolipidosis II is an autosomal recessive disorder caused by a defective enzyme, N-acetylglucosamine-1-phosphotransferase, which is instrumental in the transport of enzymes. This defect causes a deficiency of lysosomal enzymes in fibroblasts, and an excess of lysosomal enzymes in tissues and extracellular fluids.[535] This is a rare, panethnic disorder with an estimated frequency of 1 in 640,000 live births.[524]

The skeletal system is most severely affected. Death from progressive psychomotor retardation, pneumonia, or congestive heart failure usually occurs in early childhood. Symptom management of this disease includes antibiotics for respiratory infections and nutritional supplements.

There are reports of four cases of mucolipidosis II undergoing HSCT (Table 94).[536-538] One mucolipidosis II patient was included in the retrospective study of 81 patients in the Japan Marrow Donor Program. The patient failed to engraft and no further information on that case could be separated from the aggregate data in that study.[525]

Table 94. Study characteristics and population for mucolipidosis II

Study	Design	Median Age, Yrs (Range) at Treatment	Sex (M%)	Treatment, Year	Followup Period (yrs)	Enzyme Activity	Neuro-cognitive Outcomes	Neuro-developmental Outcomes	Adverse Effects
Li, China, 2004[536]	case series (n=1)*	1.0	0	HSCT, 1999-2003 (for series)	2.0 (for series)	NR	NR	NR	√
Grewal, US, 2003[537]	case report	1.6	0	HSCT, NR	5.0	√	√	√	√
Imaizumi, Japan, 1994[538]	case series (n=1)*	0.7	0	HSCT, NR	5.6	√	√	√	√

*This case series combined several diseases in one study and only 1 pt in the series had this disease.

Refer to Appendix E Table E1 for details of neurocognitive and neurodevelopmental outcomes. In summary, one patient in a case series of combined diseases, did not have neurocognitive or neurodevelopmental followup, only adverse events reported.[536] The patient experienced infectious complications, grade 2 skin aGVHD, and skin cGVHD. The patient was alive at last followup, which had a median of 2 years for the case series.[536] One patient with delayed language skills continued to develop neurocognitively after HSCT, although abilities remained below real age. The patient's gross motor skills remained at level of a 1.5 year-old and fine motor skills were slowly developing through 5-years of followup.[537] At the time of the report, the patient was alive at 5 years' followup. One patient with severe psychomotor retardation prior to HSCT gained developmental milestones of a 4- to 8-month old. The patient had no change in joint contractures and skeletal symptoms and died of disease progression at 5.6 years post-transplant.[538]

There was mention in one of the discussion sections[537] of a personal communication with another physician who reportedly used HSCT to treat a patient with mucolipidosis II and that at 1 year post-transplant, the patient showed improvement in development and growth retardation. To our knowledge, this case has not been published.

Evidence for this disease which has a life expectancy of less than 1 decade, consists of three case reports. One patient died at 5.6 years post-transplant of disease progression, one is alive at 2 years' followup but with unknown neurological status, and the other patient was reported as showing progress neurocognitively, although below real age levels, and attends a special school. Based on these three patients with differing outcomes, there is uncertainty as to the benefit of HSCT for I-cell disease.

Cystinosis

Cystinosis is a rare autosomal recessive disease caused by a defect in cystinosin, which is needed to transport cystine out of lysosomes, which then results in the accumulation of cystine crystals in most major organs of the body.[539] The incidence is estimated at 1 in 100,000-200,000, although the incidence in French Canadians may be higher.[540] There are three types of cystinosis: classic nephropathic cystinosis, a rare adolescent form, and a mild adult-onset form.

Symptoms in the classic form present in the first year of life. Progressive renal damage and end stage renal failure is the usual cause of death, commonly within the first decade of life.[539] The adolescent form of the disease is milder with a slower progression to renal failure. The adult form is benign, with no renal involvement.[540] Renal transplant, oral cysteamine therapy, cysteamine eyedrops, and dialysis have prolonged survival into adulthood for patients with the nephropathic form.[539] No studies of HSCT to treat cystinosis were found in the literature.

Infantile Sialic Acid Storage Disease

Infantile free sialic acid storage disease (ISSD) is a rare autosomal disorder caused by the accumulation of free sialic acid in lysosomes, due to a defect in the lysosomal membrane transport system.[541] More than 27 ISSD cases have been reported. Dysmyelination of the brain occurs in ISSD. Symptoms present at birth and life expectancy is about a year, with cause of death commonly from respiratory infections.[542] Disease management is symptom specific. No studies of HSCT to treat ISSD were found in the literature.

Diseases With Slow Progression

Hunter Syndrome (Mucopolysaccharidosis Type II)

Hunter Syndrome is a rare X-linked recessive disorder caused by a deficiency of the enzyme iduronate sulfatase, needed to degrade heparin sulfate and dermatan sulfate. The disease is panethnic, with an estimated incidence in Europe between 1 in 110,000–300,000; a higher incidence of 1 in 34,000 has been noted in the Jewish population living in Israel.[543]

There are two clinical forms of the disease, severe and attenuated. Onset of symptoms in the severe form occur at age 2 to 4 years. Survival can be expected into the second decade of life. Cause of death is usually heart disease, from valvular, myocardial, and ischemic factors.[263] In the attenuated form, symptoms begin later in life, with minimal to no CNS involvement. Survival can extend into the fifth to sixth decade of life.[263]

Treatment is symptom specific: developmental, occupational, and physical therapy; shunting for hydrocephalus; tonsillectomy and adenoidectomy; positive pressure ventilation; carpal tunnel release; cardiac valve replacement; inguinal hernia repair; and hip replacement.[544] HSCT has been attempted in MPS II patients, with both the severe (n=8) and attenuated forms (n=10), in attempts to slow or stop the progression of the disease (Table 95). An enzyme replacement therapy, Elaprase®, was approved by the FDA in 2006 for treatment of MPS II, following clinical trials which proved efficacy in patients with the attenuated form of the disease, aged 5-31 years.

Refer to Appendix E Table E2 for details of neurocognitive and neurodevelopmental outcomes. In summary, among 32 patients undergoing HSCT, seven died of the treatment. In eight MPS II patients with the severe form, five showed decreases in neurocognitive scores[545-547] and one showed stable scores.[548] In 10 MPS II patients with the attenuated form, there are neurocognitive test scores for 6 patients. Four showed stable scores and two showed slight decreases in their neurocognitive scores.[538, 545, 549, 550] Among the three case series and two case reports that did not specify if patients had the severe or attenuated form, there was neurocognitive information on three patients[549]: two patients showed neurocognitive decline and one patient was stable and attends a special school.

Of 32 MPS II patients undergoing HSCT, there was followup neurodevelopmental information for 19 patients. Improvements in joint stiffness were reported in 14 of the 19 patients,[538, 545, 548, 551-553] and one patient showed improvement in both fine and gross motor skills.[548]

The two clinical trials of enzyme-replacement therapy for MPS II patients reported pre- and post-treatment measurements for 6-minute walk tests.[548, 554, 555] The 1-year followup in the Phase II/III trial (N=96) showed improvements in distance walked by the ERT weekly group (p=0.01) and the enzyme-replacement therapy every other week group (p=0.07) compared to the placebo group. The open label extension (n=12) reported that 8 patients improved and 4 experienced no change in walk test results after 1 year of followup.

Table 95. Study characteristics and population for mucopolysaccharidosis II (Hunter disease)

Study	Design	Median Age in Years (Range) at Treatment	Sex (M%)	Treatment, Year	Followup Period (yrs)	Enzyme Activity	Neuro-cognitive Outcomes	Neuro-developmental Outcomes	Adverse Effects
Guffon, France, 2009[545]	case series (N=8)	4.6 (3.0-16.3)	100	HSCT, 1990-2000	5.0-14.0	√	√	√	√
Page, US, 2008[556]	case series (n=2)	≤0.25	100	HSCT, 1998-2007	NR	NR	NR	NR	√
Tokimasa, Japan, 2008[557]	case series (n=1)*	5.8	100	HSCT, 2005	0.8	NR	NR	NR	√
Seto, Japan, 2001[558]	case series (n=3)	6.0 (2.0-9.0)	100	3 HSCT, NR, 7 not treated	7.0	NR	√	NR	NR
Takahashi, Japan, 2001[547]	comparative study (n=1)	4.7	100	1 HSCT, 2 not treated, NR	1.1	√	√	NR	NR
Mullen, US, 2000[559]	case report	0.8	100	HSCT, NR	2.2	√	√	√	√
Coppa, Italy, 1999[551]	case report	3.0	100	HSCT, 1995	4.0	√	√	√	√
Vellodi, England, 1999[549]	case series (N=9)	1.7 (0.8-5.1)	100	HSCT, 1982-1991	7-14	√	√	√	√
Li, US, 1996[548]	case report	5.0	100	HSCT, NR	5.0	√	√	√	NR
McKinnis, US, 1996[546]	case report	2.4	100	HSCT, 1988	5.6	√	√	√	√
Coppa, Italy, 1995, [550]	case report	2.8	100	HSCT, 1992	2	√	√	√	NR
Hooger-brugge, Netherlands, 1995[553]	case series (n=1)*	5.5	100	HSCT, NR	1.4	NR	NR	√	NR
Bergstrom, US, 1994[552]	case report	14.0	100	HSCT, NR	3	√	√	√	√
Imaizumi, Japan, 1994[538]	case series, (n=1)*	9.8	100	HSCT, NR	9.8	√	√	√	√
Muenzer, US, 2007[554]	open label ex-tension (N=9)	6.0-20.0	100	ERT, NR	1.0	√	NR	√	√
Muenzer, US, 2006[555]	RCT (N=64)	5.4-30.9	100	ERT, NR	1.0	√	NR	√	√

*This case series combined several diseases in one study and only 1 pt in the series had this disease.

Evidence for the attenuated form of this disease with a life expectancy into adulthood, consists of three case reports and three case series. HSCT showed stabilization of cognitive skills in four of six patients. Though the numbers are small, HSCT may benefit MPS II patients with the attenuated form.

Evidence for the severe form of this disease with life expectancy into the second decade of life, consists of three case reports and one case series. Neurocognitive decline continued in seven of eight patients. Though the numbers are small, HSCT does not appear to benefit MPS II patients with the severe form.

Sanfilippo Syndrome (Mucopolysaccharidosis Type III)

Sanfilippo Syndrome is an autosomal recessive disorder, with an incidence of 1 in 70,000 births.[560] There are four types of Sanfilippo Syndrome, differentiated by the specific enzyme deficiency needed to break down heparan sulfate (Type A: heparan sulfate sulfatase, Type B: N-acetyl-o-glucosaminidase, Type C: Acetyl CoA: o-glucosaminide N-acetyltransferase, and Type D: N-acetyl-o-glucosamine-6-sulfate sulfatase).

Type A is the most severe form. Unlike most mucopolysaccharidoses, Sanfilippo disease has milder somatic symptoms, but severe progressive CNS involvement.[263] Initial clinical symptoms occur slowly from 1-6 years of age. Mental deterioration is progressive and severe by ages 6 to 10 years.[560] Life expectancy is from 12-20 years, with cause of death primarily caused by cardiopulmonary arrest due to airway obstruction and/or pulmonary infection.[263] Symptom management of this disease includes anticonvulsants and sedative medications to improve sleep quality. HSCT has been attempted in several MPS III patients (Table 96).[553, 561-564]

Table 96. Study characteristics and population for mucopolysaccharidosis III (Sanfilippo disease)

Study	Design	Median Age, Yrs (Range) at Treatment	Sex (M%)	Treatment, Year	Followup Period (yrs)	Enzyme Activity	Neuro-cognitive Outcomes	Neuro-developmental Outcomes	Adverse Effects
Ringden, Sweden, 2006[561]	case series (n=2)	NR	NR	HSCT, NR	0.4-14.0 (whole series)	NR	NR	NR	√
Lange, Brazil, 2006[562]	case series (n=1)*	6.0	0	HSCT, 1988-2000 (whole series)	3.3-14.2 (whole series)	NR	√	NR	√
Sivakumar, England, 1999[563]	comparative study (n=1)	0.6	100	1 HSCT, 1 not treated, NR	7.4	√	√	√	√
Hooger-brugge, Netherlands, 1995[553]	case series (n=3)	2.1 (1.7-4.7)	NR	HSCT, NR	2.4-7.2	NR	√	NR	NR
Vellodi, England, 1992[564]	case series (N=2)	1.5 (twins)	0	HSCT, NR	9.0	√	√	√	√

*This case series combined several diseases in one study and only 1 pt in the series had this disease.

Refer to Appendix E Table E2 for details of neurocognitive and neurodevelopmental outcomes. In summary, one patient died 5 months post-transplant of pneumonia.[561] Of nine MPS III patients undergoing HSCT, there is neurocognitive followup information on six patients. There was a continuing deterioration in six patients[553, 563, 564] and no significant improvement reported in one patient.[562]

There is neurodevelopmental information for three of the nine MPS III patients undergoing HSCT.[563, 564] One patient experienced a slow and continuous decline in skeletal and muscular symptoms and was wheelchair-bound by 7.4 years after the transplant. This patient experienced the same physical deterioration as his untreated sibling.[563] Twins experienced less neurodevelopmental decline compared to untreated brothers who were wheelchair-bound by the time they reached the age of the twins.[564]

Evidence for this disease with a life expectancy into the second decade consists of two case reports and two case series.[553, 561, 562, 564] HSCT did not alter the neurocognitive decline but may have had some effect on the neurodevelopmental decline in two patients. Although the numbers are small, HSCT does not appear to benefit MPS III.

Morquio Syndrome (Mucopolysaccharidosis Type IV)

Morquio Syndrome is an autosomal recessive disorder with an estimated incidence of 1 in 200,000 births.[565] There are two types, differentiated by which enzyme needed to degrade keratin sulfate is deficient (Type A: N-acetylgalactosamine 6-sulfatase, and Type B: β-galactosidase). Type A is the more severe form. Onset of symptoms occurs around 2 years of age. In most cases, normal intelligence is preserved.[263] Life expectancy can extend into the third or fourth decade of life with the more severe form, while those with the milder form have been reported to live decades longer.[264] Common causes of death include myelopathy, restrictive chest wall movement, and valvular heart disease.[565] Spinal fusion to stabilize the upper cervical spine and prevent irreversible spinal cord injury can be a life-saving treatment for MPS IV patients. HSCT has been attempted on two MPS IV patients (Table 97).[558, 566]

Table 97. Study characteristics and population for mucopolysaccharidosis IV (Morquio syndrome)

Study	Design	Median Age, Yrs (Range) at Treatment	Sex (M%)	Treatment, Year	Followup Period (yrs)	Enzyme Activity	Neuro-cognitive Outcomes	Neuro-developmental Outcomes	Adverse Effects
Seto, Japan, 2001[558]	case series (n=1)*	15.0	100	HSCT, NR	7.0	NR	NR	NR	NR
Gatzoulis, England, 1995[566]	case series (n=1)*	5.25	100	HSCT, NR	2.5 (mean for series)	NR	NR	NR	NR

*This case series combined several diseases in one study and only 1 pt in the series had this disease.

Refer to Appendix E Table E2 for details of neurocognitive and neurodevelopmental outcomes. In summary, one patient was 15 years old at the time of transplant and a pretransplant MRI showed no pathological findings in the brain or spinal cord. The patient had mild bone deformities at the time of transplant, and there was no followup for this patient.[558] From echocardiograph, aortic stenosis and left ventricular dilatation were detected in one patient prior to HSCT. There was no change in cardiac symptoms after HSCT.[566]

Evidence for this disease with a life expectancy that varies from adolescence into adulthood, is based on two cases of HSCT found in the literature. The reports did not provide any post transplant neurocognitive or neurodevelopmental followup data.

Fabry Disease

Fabry disease is an X-linked recessive disorder characterized by decreased activity of α-galactosidase A. The prevalence is estimated at 1/40,000-60,000 males.[526] The onset of symptoms and the severity of the disease vary widely. Males may exhibit symptoms in childhood or adolescence, or remain asymptomatic into adulthood. Female carriers may be asymptomatic or have symptoms as severe as affected males.[526] Pain episodes, called Fabry pain crises, consist of burning, tingling, and numbness in the hands and feet, and can last several hours to days.[261] Decline in kidney function in early adulthood is the main cause of premature death in Fabry disease. Cardiovascular disease is also a cause of premature death, with hypertension, mitral valve prolapse, or congestive heart failure occurring.[261]

Renal transplantation and long-term hemodialysis have prolonged life in Fabry's disease patients, and enzyme-replacement therapy using recombinant alpha-galatosidase has been shown to be safe and effective.[261]

Gaucher Disease Type III

Gaucher disease is caused by a deficiency in the enzyme glucocerebrosidase, which leads to an accumulation of glucosylceramide in the spleen, liver, lungs, bone marrow, and sometimes the brain.[261] There are three types of Gaucher disease. Gaucher Type I is discussed in the Narrative Review section. Gaucher Type II is discussed in the Systematic Review under diseases with rapid progression.

Gaucher Type III is the subacute neuronopathic form, usually beginning later in childhood or adolescence, with loss of muscle coordination and cognitive deterioration progressing more slowly than in Type II.[261] Gaucher Type III patients may live into adulthood. Enzyme replacement therapy can be used to alleviate severe visceral symptoms, but is not effective in altering the neurologic progression of the disease.[261] Combinations of enzyme replacement therapy using recombinant imiglucerase or velaglucerase, substrate reduction therapy using miglustat, and HSCT have been attempted in Type III Gaucher patients (Table 98).

Table 98. Study characteristics and population for Gaucher Type III

Study	Design	Median Age in Years (range) at Treatment	Sex (M%)	Treatment, Year	Followup Period (yrs)	Enzyme Activity	Neuro-cognitive Outcomes	Neuro-developmental Outcomes	Adverse Effects
Goker-Alpan, US, 2008[567]	case series, N=32	1.3*	53	HSCT followed by ERT (n=2), NR; ERT only (n=30), NR	3-33	NR	√	NR	NR
Chen, Taiwan, 2007[568]	case report	5.8	0	HSCT, 2004	1.5	√	√	√	√
Ringden, Sweden, 1995[303]	case series, N=6	2.5	67	HSCT	5-11	√	√	√	√
Tsai, US, 1992[569]	case report	2.0	0	HSCT	2	√	√	√	√
Schiffman, Netherlands 2008[570]	Randomized control-led trial (N=30)	substrate reduction therapy (n=21), mean: 10.4 no treatment (n=9) mean: 9.9	substrate reduction therapy (n=21): 48 no treatment (n=9): 22	Substrate reduction therapy in combination with ERT, NR	2.0	NR	√	√	NR
El-Beshlawy, Egypt, 2006[571]	case series (n=11)	mean: 6.14 range (1-16), this data is on the whole study population of 22 pts, which includes 11 with Gaucher Type I	NR	ERT, NR	0.4-2.2	√	NR	√	√
Chan, Malaysia, 2002[572]	case report	7.6	0	ERT, 1996-1998	4.5	NR	√	√	NR
Banjar, Saudi Arabia, 1998[573]	case series (n=3)	2.8 (2.0-3.0)	33	ERT, NR	2.5-3.5	NR	NR	√	NR
Schiffmann, Netherlands, 1997[574]	case series (N=5)	7.5 (3.5-8.5)	80	ERT, NR	up to 5 yrs	√	√	NR	NR
Erikson, Sweden, 1995[575]	case series (n=3)	4.8 (3.8-13.7)	33	ERT, NR	2.3 yrs	√	√	√	NR

* Age at diagnosis.

Refer to Appendix E Table E2 for details of neurocognitive and neurodevelopmental outcomes. In summary, among eight patients undergoing HSCT (two case reports and one case series of 6 patients), five showed stable neurocognitive scores.[561, 569] All eight patients showed improved growth, although skeletal symptoms persisted.[561, 568, 569] A case series that included two patients that had HSCT followed by enzyme-replacement therapy, report only followup data.[567] Both patients have borderline mental retardation at last followup, but the mental status prior to HSCT and enzyme-replacement therapy is not specified.

Of 23 Gaucher Type III patients treated with enzyme-replacement therapy, neurocognitive followup is available on nine patients. Seven of the nine patients showed stable neurocognitive function,[574, 575] one deteriorated clinically,[574] and one who was showing improvement following enzyme-replacement therapy, deteriorated when therapy was discontinued.[572] Enzyme-replacement therapy improves growth, but cannot change skeletal deformities. In the enzyme-replacement therapy case series of 11 patients for which grading severity of marrow involvement was provided, one worsened, five remained constant, and five experienced complete improvement.[571] In a 2-year randomized controlled trial of substrate reduction therapy (miglustat) with enzyme-replacement therapy (imiglucerase; n=21) compared to enzyme-replacement therapy alone (n=9), there was no significant difference between study groups using several neurocognitive measurements.[570]

Evidence for HSCT for the treatment of Gaucher Type III which has a life expectancy extending into adulthood, consists of two case reports and two case series. In one case series, HSCT was followed by enzyme-replacement therapy. Among the patients who were treated with HSCT only, five of eight had stable neurocognitive scores at last followup. Among patients treated with enzyme-replacement therapy only, seven of nine had stable neurocognitive scores at last followup. Patients undergoing HSCT and patients treated with enzyme-replacement therapy have shown improved growth, although skeletal symptoms persist. HSCT appears to have a similar benefit compared to enzyme-replacement therapy.

Aspartylglucosaminuria

Aspartylglucosaminuria is a rare autosomal recessive disease characterized by a deficiency in the enzyme aspartylglucosaminidase, leading to an accumulation of glycoproteins in the liver, spleen, and thyroid. There is a higher prevalence of this disease in Finland, where the carrier frequency is estimated to be 1 in 36[576] and the estimated incidence of the disease is 1 in 35,000. The estimated incidence outside of Finland is 1 in 2,000,000 births.

In the first year of life, recurrent infections, diarrhea, and hernia may occur. During adolescence, the intellectual disabilities worsen. The central nervous system is affected. Survival to mid-adulthood is expected, with most deaths attributed to pneumonia or other pulmonary complications.[576] Anticonvulsant medications have been used to control seizures. HSCT has been attempted as a potential treatment of this disease (Table 99).

Table 99. Study characteristics and population for aspartylglucosaminuria

Study	Design	Median Age in Years (Range) at Treatment	Sex (M%)	Treatment, Year	Followup Period (yrs)	Enzyme Activity	Neuro-cognitive Outcomes	Neuro-developmental Outcomes	Adverse Effects
Malm, Sweden, 2004[577]	case series (N=2)	8.1 (5.8-10.4)	50	HSCT, 1996	5.0	√	√	√	√
Arvio, Finland, 2001[578]	comparative study (n=5)	2.75 (1.6-5.5)	40	HSCT, 1991-1997	1.0-7.6	NR	√	√	√
Autti, Finland, 1999[579]	comparative study (n=2)	2.3 (2.0-2.6)	100	HSCT, NR	4.0-7.0	√	√	NR	NR
Laitinen, Finland, 1997[580]	case report	1.5	100	HSCT, NR	0.33	√	NR	NR	NR

Refer to Appendix E Table E2 for details of neurocognitive and neurodevelopmental outcomes. In summary, there were no reports of treatment-related mortality in the 10 patients undergoing HSCT. Of 10 patients with aspartylglucosaminuria undergoing HSCT, there is neurocognitive followup on nine. Two patients have improved concentration and cooperation.[579] Two patients have stabilized developmentally at 5 years of age (real ages 15 and 11 years), and can speak in sentences and understand words in two languages.[577] Five patients had, on average, lower developmental ages compared to 12 untreated patients, but direct comparisons may not be appropriate because the severity of disease differs widely in this disease. Two of the five transplanted patients were more severely retarded than any of the nontransplanted patients, potentially skewing the average age differential higher in the transplanted group.[578]

Evidence for aspartylglucosaminuria which has a life expectancy into mid-adulthood, consists of one case report and three case series, with a total of 10 transplants. Neurocognitive and neurodevelopmental measurements did not show clear improvements following HSCT. Small numbers in studies, and differences in severity of disease make interpretations of results difficult.

ß-Mannosidosis

ß-mannosidosis is a rare autosomal recessive disorder caused by a deficiency in the enzyme ß-mannosidase, resulting in the accumulation of oligosaccharides in lysosomes. Twenty cases have been identified worldwide, but the incidence may be higher because people with milder symptoms may never be diagnosed.

The onset of symptoms varies from infancy to adolescence, and the severity of symptoms varies from relatively mild to moderately severe.[581] Mental retardation is present in all individuals with this disease. There is no cure for ß-mannosidosis and treatment is symptom-specific.

No reports of HSCT for ß-mannosidosis patients have been found.

Mucolipidosis III (Pseudo-Hurler Polydystrophy)

Mucolipidosis III is a rare autosomal recessive disorder caused by a deficiency of the enzyme, N-acetylglucosamine-1-phosphotransferase. A defect of this enzyme affects the function of all lysosomal enzymes, which in turn causes the accumulation of a variety of substrates.[535]

Symptoms present between the ages of 4 to 5 years and include joint stiffness and short stature. Survival to adulthood is expected. There is no cure and treatment is symptom-specific, and may include: low-impact physical therapy for stiff joints, myringotomy tube placement for recurrent otitis media, tendon release for carpal tunnel syndrome, bilateral hip replacement for older adolescents with milder disease, and monthly bisphosphonate pamidronate IV for bone pain associated with osteoporosis.

No reports of HSCT for mucolipidosis III have been found.

Mucolipidosis IV

Mucolipidosis IV is a rare autosomal recessive disorder caused by a defect in the protein mucolipin-1, which is needed in the transport of lipids and proteins. This defect results in the build-up of lipids and proteins in lysosomes, affecting the development and maintenance of the brain and retinas.[582] An estimated 1 in 40,000 have mucolipidosis IV, with 70 percent having Ashkenazi Jewish ancestry.

There is a severe and more common form called typical mucolipidosis IV (about 95 percent) and a milder form called atypical mucolipidosis IV. In the severe form, mental and motor developmental delays occur within the first year of life. Most are unable to walk independently. Those with the milder form have less severe psychomotor and ophthalmic symptoms, and may be ambulatory. Life expectancy extends to adulthood, though a shorter life span is expected.[582]

Treatment is symptom-specific and may include: physical therapy for spasticity and ataxia, antiepileptic drugs, topical lubricating eyedrops, artificial tears, gels, or ointments for ocular irritation, and surgery for strabismus.

There are no reports of HSCT attempted in patients with mucolipidosis IV.

Niemann-Pick Disease C

Niemann-Pick disease is characterized by the accumulation of lipids in the spleen, liver, lungs, bone marrow, and the brain. There are three types of this disease. Type A is discussed in the "Sphingolipidoses" section of this Systematic Review and Type B is discussed in the Narrative Review section. The incidence of Type C is estimated to be 1 in 150,000 and is most common in Nova Scotia among those of French-Acadian descent.[523]

Prolonged neonatal jaundice may occur, with no other symptoms until 1-2 years later or potentially until teen or adult years, when the disease develops a slow, progressive neurodegenerative course.[261] Death may occur in the late second or third decade of life, commonly from aspiration pneumonia. Management of this disease is symptom-specific for seizures, dystonia, and cataplexy, and may include chest physical therapy with aggressive bronchodilation and antibiotics for recurrent infections and seizure management. A randomized controlled study using substrate reduction therapy versus standard care has been conducted, and there are two case reports of HSCT to treat this disease (Table 100).

Table 100. Study characteristics and population for Niemann-Pick Type C

Study	Design	Median Age in Years (Range) at Treatment	Sex (M%)	Treatment, Year	Followup Period (yrs)	Enzyme Activity	Neuro-cognitive Outcomes	Neuro-developmental Outcomes	Adverse Effects
Bonney, England, 2009[583]	case report	1.3	100	HSCT, NR	1.7	NR	√	√	√
Hsu, Taiwan, 1999[584]	case report	2.5	0	HSCT, NR	0.8	NR	√	√	√
Patterson, US, 2010[585]	open label extension (n=12)	Mean: 7.2 (4-11)	42	substrate reduction therapy, 2002-2004	2.0	NR	NR	NR	√
Pineda, Spain, 2009[586]	retrospective cohort (n=66)*	Mean: 12.8 (0.6-43.0)	47	substrate reduction therapy, NR	5.0	NR	√	√	NR
Pacior-kowski, US, 2008[587]	case report	1.6	0	substrate reduction therapy, NR	1.0	NR	√	√	√
Patterson, US, 2007[588]	RCT (n=12)*	Mean: 7.2 (4-11)	42	substrate reduction therapy, 2002-2004	1.0	NR	√	√	√

*Cannot separate adult and pediatric data in these studies.

Refer to Appendix E Table E2 for details of neurocognitive and neurodevelopmental outcomes. In summary, results from one case report of a patient with Niemann-Pick Type C undergoing HSCT showed that the transplant did not stop a progressive decline in developmental age, and an MRI confirmed brain atrophy. The patient became bedridden during the conditioning phase of the treatment. She never recovered developmentally following the transplant.[584] The second case of HSCT showed a resolution of lung disease in the patient, and normal neurocognitive and neurodevelopmental progress, except for delayed speech.[583] An abstract referenced in the most recent report of HSCT[583] describes the resolution of lung disease in a Niemann-Pick Type C transplanted patient at 2 months post-transplant, but the patient died 3 months post-transplant of an adenovirus pulmonary infection.

Results from the randomized, controlled trial comparing substrate reduction therapy to routine symptom management and the retrospective cohort of substrate reduction therapy for Niemann-Pick Type C combined data for pediatric and adult patients.[586, 588] The randomized, controlled trial did not find a significant difference in the mini-mental status examination (p=0.165) but found significantly improved ambulatory indexes in the treated group[588] and the cohort study reported majority stable or improved scores in ambulation.[586] The open-label extension study, which focused on pediatric patients, reported that eight of ten patients were stable in ambulation.[585]

Evidence for HSCT and Niemann-Pick Type C which has a life expectancy into the second to third decade, consists of two case reports. HSCT for one patient was not successful in stopping the neurocognitive and neurodevelopmental decline. One HSCT patient is developing normally at 1.7 years post-transplant. Based on two case reports, it is unclear if HSCT provides a benefit in the treatment of Niemann-Pick Type C.

Glycogen Storage Disease Type 2 (Pompe Disease)

Pompe disease is an autosomal recessive disorder caused by a deficiency in acid maltase, which results in the accumulation of lysosomal glycogen in tissues and cells. Cardiac, skeletal, and smooth muscle cells are the most seriously affected.[589] The incidence is estimated at 1 in 40,000 live births. Age of onset and severity of symptoms varies among patients.

In infantile-onset Pompe disease, symptoms begin within the first few months of life and life expectancy is less than one year, with cause of death usually from cardiorespiratory failure or respiratory infection. The juvenile and adult-onset forms of the disease have either no or less severe cardiac involvement. Life expectancy ranges from early childhood to late adulthood, depending on the rate of disease progression. Respiratory failure is the most common cause of death.[589] Several clinical trials of enzyme-replacement therapy in patients with infantile-onset Pompe disease have shown promising cardiac responses and variable skeletal responses to the treatment.[590, 591]

There have been no reports of HSCT in the treatment of Pompe disease.

Salla Disease

Salla disease is a type of sialic acid storage disease, which is a rare autosomal disorder caused by the accumulation of free sialic acid in lysosomes, due to a defect in the lysosomal membrane transport system.541 Salla disease is autosomal recessive. One hundred twenty Salla disease cases have been reported. Patients appear normal at birth, then develop psychomotor delay and ataxia during infancy, as dysmyelination of the brain occurs. Life expectancy is slightly reduced.541 Disease management is symptom-specific.

There are no reports of HSCT used to treat Salla disease.

Adrenomyeloneuropathy

Adrenomyeloneuropathy is a variant of the X-linked recessive disorder, adrenoleukodystrophy, which is discussed in the Narrative Review section of this report. These disorders are caused by the accumulation of very long chain fatty acids in the brain and adrenal cortex, due to a deficiency in the enzyme that breaks down fatty acids.[592] About 40 percent of males with adrenoleukodystrophy develop adrenomyeloneuropathy, which presents in their late twenties as a chronic disorder of the spinal cord and peripheral nerves.[593] The severity of symptoms varies greatly, even within one family. Depending on the severity of symptoms, life expectancy can reach late adulthood, though ambulation with a cane or walker may be necessary. HSCT has been shown to prevent the progression of symptoms in adrenoleukodystrophy if performed prior to the development of neurological symptoms.

A single case of HSCT for a 39-year-old male with adrenomyeloneuropathy was found in the literature.[561] No pediatric cases treated with HSCT have been reported.

Diseases With Forms That Progress Rapidly and Slowly

Farber Disease

Farber disease is an autosomal recessive disorder characterized by a deficiency in ceramidase, resulting in the accumulation of ceramide in various tissues, the central nervous system, and most notably the joints. Fifty cases of this disease have been reported in the literature.[594]

Symptoms can begin in the first few weeks of life.[261] Nodules forming on the vocal cords cause hoarseness and breathing difficulties, which sometimes require the insertion of a breathing tube. Life expectancy in Type 1, the more severe form which has central nervous system involvement, is 2 years of age with progressive neurological deterioration as cause of death. Patients with the milder form, Type 2/3 with either no or mild central nervous system symptoms, can live to their teenage years with chronic respiratory failure as the most common cause of death.[595]

Physical therapy or surgery may provide relief of contractures, and surgery to remove nodules, granulomas, and possibly enlarged lymph nodes may be recommended. Hematopoietic stem-cell transplantation has been attempted in two patients with Type 1 Farber and in five patients with Type 2/3 Farber (Table 101).

Table 101. Study characteristics and population for Farber's disease

Study	Design	Median Age in Years (Range) at Treatment	Sex (M%)	Treatment, Year	Followup Period (yrs)	Enzyme Activity	Neuro-cognitive Outcomes	Neuro-developmental Outcomes	Adverse Effects
Ehlert, Germany, 2006[596]	case series (n=3)	3.8 (2.0-3.9)	33	HSCT, NR	0.5-1.2	NR	NR	√	√
Vormoor, Germany, 2004[597]	case series (n=2)	3.9 (3.8-3.9)	50	HSCT, NR	0.9-1.2	NR	NR	√	√
Yeager, US, 2000[598]	case report	0.8	0	HSCT, NR	2.3	√	√	√	√
Hoogerbrugge, Netherlands, 1995[553]	case series (n=1)*	1.5	NR	HSCT, NR	0.5	NR	√	√	NR

*This case series combined several diseases in one study and only 1 pt in the series had this disease.

Refer to Appendix E, Table E3 for details of neurocognitive and neurodevelopmental outcomes. In summary, no treatment-related mortality was reported in the seven patients with Farber disease undergoing HSCT. There is neurocognitive followup on the two patients with Type 1 Farber disease with CNS involvement. In one patient at the time of transplant, her developmental age was equivalent to her real age. After 1.4 years followup, at age 2.1 years, her developmental age had deteriorated to 0.6 years.[598] The second Type I patient had mental regression prior to the transplant, which worsened following the transplant. This patient died 6 months post-transplant of disease progression.[553] No neurocognitive followup was provided for the five Farber disease patients who had Type 2 disease, which has little or no CNS involvement.

The five patients reported in the case series on Farber Type 2/3 had nodule and joint inflammation. HSCT was successful in reducing the number of subcutaneous nodules and reducing the number of joints with limited range of motion in five of five patients.[596, 597]

Evidence for Type 1 Farber disease with CNS involvement and a life expectancy of 2 years, consists of one case report and one case series. HSCT did not stop the neurocognitive deterioration in these patients. Evidence for Type 2 Farber disease without CNS involvement and a life expectancy extending into the second decade, consists of two case series. In all five patients with Farber Type 2/3 undergoing HSCT, both the number of subcutaneous nodules and the number of joints with limited range of motion were reduced. Based on these five patients, HSCT appears to improve the quality of life of patients with Farber Type 2/3.

GM1 Gangliosidosis

GM_1 gangliosidosis is an autosomal recessive disorder caused by a deficiency in ß-galactosidase. There are three subtypes, classified by age at presentation: infantile (type 1), juvenile (type 2), and adult (type 3). Estimated incidence is 1 in 100,000-200,000 live births.[599] The infantile form, which can present as early as six months, is characterized by overall developmental retardation and generalized seizures. Survival is 2-4 years, with death most commonly due to aspiration pneumonia. Symptoms in the juvenile form begin around 1 year and are primarily neurological. Progression of this form of the disease is slow, and survival through the fourth decade of life is possible. The adult form is a slowly progressive disease characterized by spasticity, ataxia, dysarthria, and loss of cognitive function.[600]

Research in the areas of enzyme replacement therapy and gene therapy for this disease are ongoing, but have not advanced to human trials.[599] A case report describes the use of HSCT to treat a patient with the juvenile form of the disease (Table 102).

Table 102. Study characteristics and population for GM$_1$ gangliosidosis

Study	Design	Median Age in Years (Range) at Treatment	Sex (M%)	Treatment, Year	Followup Period (yrs)	Enzyme Activity	Neuro-cognitive Outcomes	Neuro-developmental Outcomes	Adverse Effects
Shield, England, 2005[601]	case report	0.6	100	HSCT, NR	7	√	√	√	NR

Refer to Appendix E, Table E3 for details of neurocognitive and neurodevelopmental outcomes. In summary, a case report of a patient with GM_1 gangliosidosis juvenile form describes a slow deterioration in neurocognitive and neurodevelopmental measurements.[601]

There have been no reports of HSCT for the infantile form of GM_1 gangliosidosis, which has a life expectancy of 2 to 4 years. Evidence for the juvenile form of GM_1 gangliosidosis, which has a life expectancy extending into the second through fourth decade, consists of 1 case report. Based on this case report, HSCT did not alter the course of the disease.

Tay-Sachs Disease

Tay-Sachs disease is an autosomal recessive disorder caused by a deficiency in the isoenzyme hexosaminidase A, resulting in the accumulation of GM_2 ganglioside in the brain. The Ashkenazi Jewish population is most at risk, with a carrier rate estimated at 1 in 30.[600] There are infantile-, juvenile-, and adult-onset forms of the disease. In the infantile form, patients have no hexosaminidase A enzyme and in the juvenile and adult forms, patients have low levels of hexosaminidase A enzyme. The infantile form is the most severe, and other than a marked startle reaction to noise, infants appear normal until about 6 months of age when developmental delays begin. Life expectancy is 4 to 5 years, with aspiration or bronchopneumonia the most common causes of death.[261] The juvenile and adult forms are rare and symptoms are less severe.

Anticonvulsant medication to control seizures, proper hydration to keep airways open, and feeding tubes to provide nutritional supplements have been recommended. HSCT, substrate reduction therapy, and a combination of both, have been attempted on several Tay-Sachs disease patients (Table 103).

Table 103. Study characteristics and population for Tay-Sachs disease

Study	Design	Median Age in Years (Range) at Treatment	Sex (M%)	Treatment, Year	Followup Period (yrs)	Enzyme Activity	Neuro-cognitive Outcomes	Neuro-developmental Outcomes	Adverse Effects
Page, US, 2008[556]	case series (n=1)*	0.06	NR	HSCT, 1998-2007 for whole series	4.6	NR	NR	NR	√
Hooger-brugge, Nether-lands,1995[553]	case series (n=1)*	1.1	NR	HSCT, NR	1.7	NR	√	√	NR
Jacobs, Nether-lands, 2005[602]	case report	3.8	0	HSCT, with substrate reduction therapy added at 2 yrs post-HSCT, NR	2.0	√	√	√	NR
Maegawa, Canada, 2009[603]	single arm (n=2)	13.1 (10.1-16.0)	0	substrate reduction therapy, NR	2.0	NR	√	√	√

*This case series combined several diseases in one study and only 1 pt in the series had this disease.

Refer to Appendix E, Table E3 for details of neurocognitive and neurodevelopmental outcomes. Two case series of HSCT to treat several different diseases included one patient with Tay-Sachs in each series (disease form not specified). One patient died at 4.6 years post-transplant of a possible infection.[556] The other patient had psychomotor retardation at the time of transplant and further regressed to a vegetative state at 1.7 years' followup.[553]

The case report[602] was of a patient with the juvenile form of Tay-Sachs. In the case report, brain MRI, EEG, and neuropsychological tests showed neurological deterioration at 1.5 years post-transplant. At that time, substrate reduction therapy was initiated, but was not successful in stopping the deterioration. Neurodevelopmental followup in this case report showed motor skills deteriorating by 0.5 years post-transplant in this patient; her deterioration was comparable to her untreated sister's.

Among the two patients with the juvenile form who were treated with substrate reduction therapy,[603] one who had mild cognitive impairment pretreatment experienced an acute psychotic event at 1.3 years post-treatment, and one who had severe cognitive impairment pretreatment had increased spasticity and seizures post-treatment. The 2 Tay-Sachs disease patients with the juvenile form of the disease who were treated with substrate reduction therapy, continued to have neurodevelopmental decline following the treatment.

Evidence for the juvenile form of Tay-Sachs disease which has a life expectancy of 15 years, consists of one case report. The patient continued to show neurocognitive and neurodevelopmental decline similar to what was experienced in the untreated sibling. Based on this case report, HSCT does not show a benefit in the treatment of the juvenile form of Tay-Sachs disease.

Ceroid Lipofuscinosis

Neuronal ceroid lipofuscinoses are autosomal recessive disorders which are the most common class of neurodegenerative diseases in children.[600] A defect in the enzyme that degrades fatty acylated proteins causes the storage of autofluorescent lipopigments in lysosomes.[604] Worldwide incidence of this disease is estimated at 1 in 20,000-100,000, but the incidence is higher in Finland.[600]

Depending on which gene is affected, symptoms may begin during early infancy, late infancy, or during juvenile years. Symptoms develop by the end of age 1 in the early infantile form with life expectancy from 6 to 13 years. In the late infantile form, symptoms begin from 2 to 4 years of age, with a life expectancy extending from 6 to 40 years. In the juvenile form, symptoms begin between 5 to 10 years of age with a life expectancy from teens to thirties.[600]

There is no cure for these disorders and treatment is symptom-specific: antiepileptic drugs and benzodiazepines for seizures, anxiety, and spasticity, gastric tubes for swallowing problems, and antidepressants and antipsychotic agents for patients with the juvenile form. HSCT has been performed in several patients with the early infantile form of the disease (Table 104).

Table 104. Study characteristics and population for ceroid lipofucinosis

Study	Design	Median Age in Years (Range) at Treatment	Sex (M%)	Treatment, Year	Followup Period (yrs)	Enzyme Activity	Neuro-cognitive Outcomes	Neuro-developmental Outcomes	Adverse Effects
Lonnqvist, Finland, 2001[605]	case series (n=3)	0.3 (0.3-0.6)	33.3	HSCT, 1996-1998	2-4	√	√	√	NR

Refer to Appendix E, Table E3 for details of neurocognitive and neurodevelopmental outcomes. Neurocognitive decline continued in three of three patients with ceroid lipofuscinosis with the infantile form undergoing HSCT, as measured by cerebral cortical atrophy and periventricular white matter hyperintensity. HSCT did not prevent the neurodevelopmental decline in the three patients with infantile ceroid lipofuscinosis. By followup of 2 to 4 years, all three were hypotonic and spastic.

Evidence for this disease which has a life expectancy of 6-13 years, consists of one case series of three patients. The procedure was unable to stop the neurocognitive and neurodevelopmental decline in all three patients. Based on this case series, HSCT does not show a benefit of HSCT for the treatment of infantile ceroid lipofuscinosis.

Galactosialidosis

Galactosialidosis is a rare autosomal recessive condition in which there is a deficiency of two lysosomal enzymes, neuraminidase and β-galactosidase. This enzyme deficiency causes the accumulation of oligosaccharides in many tissues such as the liver, bone marrow, and brain.[576] There are three forms which differ by age of onset of symptoms and symptom severity. One-hundred cases have been reported, with 60 percent of the juvenile/adult forms in patients of Japanese descent.[606]

In the early infantile form, fluid accumulation begins before birth. Life expectancy does not extend beyond late infancy, with kidney failure or cardiomegaly as common causes of death. Symptoms in the late infantile form of the disease are similar to those in the early infantile form, though less severe and the onset is later in the first year of life. Life expectancy can extend into the second decade of life, depending on severity of symptoms. The juvenile/adult form of the disease is least severe, with symptoms first occurring usually in the teen years. There is no cure for galactosialidosis and treatment is symptom specific.

A retrospective study of 81 patients in the Japan Marrow Donor Program who underwent unrelated bone marrow transplantations for immunodeficiency and metabolic diseases reported a single case of galactosialidosis within its study population.[525] The form of galactosialidosis was not specified in the report. Outcomes were cumulative overall and event-free survival, and cumulative acute and chronic graft-versus-host disease. Engraftment occurred in the galactosialidosis case, but no other information on that case could be separated from the aggregate data.

Sandhoff's Disease

Sandhoff's disease is caused by a deficiency in both hexosaminidase A and B, resulting in the accumulation of GM_2 ganglioside in lysosomes. Symptoms are similar to those in Tay-Sachs disease, presenting at about 6 months of age. Life expectancy is 3 years of age.[600] Symptom management includes anticonvulsant medication to control seizures, and proper hydration and nutrition to keep airways open.

A case of a patient with Sandhoff's disease undergoing HSCT is reported in the literature, but the form of the disease is not specified (Table 105). There is also a single arm study reporting the use of substrate reduction therapy in 3 patients with Sandhoff's disease (juvenile form).

Table 105. Study characteristics and population for Sandhoff's disease

Study	Design	Median Age in Years (Range) at Treatment	Sex (M%)	Treatment, Year	Followup Period (yrs)	Enzyme Activity	Neuro-cognitive Outcomes	Neuro-developmental Outcomes	Adverse Effects
Ringden, Sweden, 2006[561]	case series (n=1)*	NR	NR	HSCT, NR	0.4-14 (for whole series)	NR	NR	NR	√
Maegawa, Canada, 2009[603]	single arm (n=3)	18 (8.7-20.1)	67	Substrate reduction therapy, NR	2.0	NR	√	√	√

*This case series combined several diseases in one study and only 1 pt in the series had this disease.

Refer to Appendix E, Table E3 for details of neurocognitive and neurodevelopmental outcomes. In summary, there is no neurocognitive or neurodevelopmental information in the patient with Sandhoff's disease (form unspecified) who underwent HSCT. The three patients with Sandhoff's disease who were treated with substrate reduction therapy experienced stable neurocognitive scores, but neurodevelopmental decline occurred.[603] One became wheelchair dependent by 1.8 years post-treatment, and two had gait disturbance.

Evidence for Sandhoff's disease consists of one case report. The report did not specify if the patient had the infantile form or the juvenile form of the disease. No neurocognitive or neurodevelopmental followup information on the single Sandhoff's disease patient was provided; no conclusions on effectiveness can be made.

Adverse Effects

Table 106 summarizes the adverse effects reported in patients undergoing HSCT for inherited metabolic disorders.

Ongoing Research

"Stem Cell Transplantation for Inborn Errors of Metabolism," a study sponsored by the Masonic Cancer Center of the University of Minnesota, is ongoing and no longer recruiting. The study is comparing patients treated by bone marrow, peripheral blood, or umbilical cord blood transplantation after March 2001 with historical controls. Outcomes to be measured include: survival, change in neuropsychometric function, rate of donor cell engraftment, rate of graft-versus-host disease, and toxicity of HSCT therapy. Patients with the following diseases were eligible to participate in the study: adrenoleukodystrophy, metachromatic leukodystrophy, globoid cell leukodystrophy, Gaucher disease, fucosidosis, Wolman's disease, Niemann-Pick disease, Batten disease, GM_1 gangliosidosis, Tay-Sachs disease, and Sandhoff disease. The study began in January 1995 and the estimated study completion date was June 2010.

Table 106. Adverse effects for treatment (HSCT) in IMD patients

Progression of Disease	Adverse Effect	Description	Disease	Study
Rapid	Treatment-related mortality	- unknown cause, probable infection at 4.6 yrs post	Tay-Sachs	Page, 2008[556]
		2 of 4 pts in study: - pt 2: at 2.5 mos post, hepatorenal failure, pulmonary failure, coagulopathy, sepsis - pt 3: at 8 mos post, sepsis and liver	Wolman disease	Tolar, 2009[531]
	aGVHD	- grade 3 skin and liver in 2 of 4 pts - grade 3 skin in 1 of 4 pts	Wolman disease	Tolar, 2009[531]
		-grade 3 skin and gut in 1 of 1 pt	Wolman disease	Styczynski, 2011[530]
		- grade 2 in 1 of 1 pt	Tay-Sachs	Page, 2008[556]
		- skin rash in 1 of 1 pt	Niemann-Pick Type A	Morel, 2007[533]
		- mild skin rash in 1 of 1 pt	Wolman disease	Stein, 2007[529]
		- grade 2, skin in 1 of 1 pt	Mucolipidosis II	Li, 2004 [536]
		- grade 2, gastrointestinal	Mucolipidosis II	Grewal, 2003[537]
		- moderately severe diarrhea in 1 of 2 pts	Niemann-Pick Type A	Bayever,1995 [534]
	cGVHD	- skin, in 1 of 1 pt	Mucolipidosis II	Li, 2004[536]
		- gastrointestinal, in 1 of 2 pts	Niemann-Pick Type A	Bayever, 1995[534]
	Infectious complications	- candida parapsilosis sepsis in 1/1 pt	Wolman disease	Gramatges, 2009[527]
		- sepsis in 2 of 4 pts	Wolman disease	Tolar, 2009[531]
		- cytomegalovirus and anigenemia in 1 of 1 pt	Wolman disease	Stein, 2007[529]
		- coagulase-negative staphylococcus septicemia in 1 of 1 pt	Mucolipidosis II	Li, 2004 [536]
Slow	Treatment-related mortality	- single pt had post-tx lymphoproliferative disease at 0.8 yrs post-HSCT	MPS II	Tokimasa 2008[557]
		- 4 of 9 pts died <100 days post-HSCT, 2 from sepsis and 2 from aGVHD - 1 pt died 4 yrs post-HSCT from tx-related obliterative bronchiolitis - 1 pt died of GVHD, at an unknown followup time	MPS II	Vellodi 1999[549]
		- 1 of 2 died mos post-HSCT of pneumonia	MPS III	Ringden, 2006[561]
		- 1 of 1 pt died of S. pneumonia sepsis at 2 yrs post	Gaucher Type III	Tsai, 1992[569]

Table 106. Adverse effects for treatment (HSCT) in IMD patients (continued)

Progression of Disease	Adverse Effect	Description	Disease	Study
Slow	aGVHD	- grade 1 skin in 1 of 1 pt	Niemann-Pick Type C	Bonney, 2009[583]
		- grade 1 in 1 of 1 pt	MPS II	Tokimasa 2008[557]
		- Grade 3 skin and Grade 2 gastrointestinal aGVHD at 2 wks post-HSCT and a skin rash at 17 wks post-HSCT in 1 of 1 pt	MPS II	Mullen 2000[559]
		- moderate aGVHD in 1 of 3 surviving pts	MPS II	Vellodi 1999[549]
		- grade 1 in 1 of 2 pts - grade 2 in 1 of 2 pts	Farber's disease, Type 2/3	Vormoor, 2004[597]
		- grade 1 in 1 of 3 pts - grade 2 in 2 of 3 pts	Farber's disease, Type 2/3	Ehlert, 2006[596]
		- Gr 1 mild skin rash in 1 of 1 pt	Gaucher Type III	Chen, 2007[568]
		- severe skin, gastrointestinal, and liver aGVHD in 1 of 2 pts - grade 1 skin aGVHD in 1 of 2 pts	aspartylglucosa-minuria	Malm, 2004[577]
		- grade 1 in 1 of 1 pt	Niemann-Pick Type C	Hsu, 1999[584]
		- severe in 2 of 2 pts	MPS III	Vellodi, 1992[564]
	cGVHD	- severe hemolytic anemia at 9 mos post in 1 of 1 pt	MPS II	Mullen 2000[559]
		- severe in 2 of 2 pts	MPS III	Vellodi, 1992([564]
	Infectious complications	- septicemia (MRSA) in 1 of 1 pt	MPS II	Tokimasa 2008[557]
		- 2 episodes of gram-positive bacteremia, one of limited gastrointestinal bleeding while thrombocytopenic, and one mucositis requiring parenteral nutrition for several wks in 1 of 1 pt	MPS II	Mullen 2000[559]
		- rotavirus gastroenteritis leading to severe hypoalbuminanemia and cerebral edema in 1 of 3 surviving pts	MPS II	Vellodi 1999[549]
		- grade 2 mucositis in 1 of 2 pts - grade 3 mucositis in 1 of 2 pts	Farber's disease, Type 2/3	Vormoor, 2004[597]
		- cytomegalovirus in 2 of 3 pts - mucositis in 2 of 3 pts - clostridium difficile enteritis in 1 of 3 pts	Farber's disease, Type 2/3	Ehlert, 2006[596]
		staphylococcus epidermis sepsis in 1 of 1 pt	Gaucher Type III	Chen, 2007[568]
		- herpetic keratitis in 1 of 5 pts - pneumonia in 1 of 5 pts	aspartylglucosaminuria	Arvio, 2001[578]
		- sepsis in 2 of 2 pts	MPS III	Vellodi A, 1992[564]
	Seizures	- generalized tonic-clonic seizure occurred 3 days prior to transplant, attributed to conditioning regimen (busulfan)	Niemann-Pick Type C	Hsu, 1999[584]

Conclusions

Rapidly Progressive Diseases
- High strength evidence on overall survival suggests a benefit with single HSCT compared to conventional management for Wolman's disease.
- Low strength evidence on overall survival suggests no benefit with single HSCT compared to symptom management or disease natural history for Niemann-Pick Type A.
- The body of evidence on overall survival with single HSCT compared to symptom management is insufficient to draw conclusions for mucolipidosis II (I-cell disease), Gaucher disease type II, cystinosis and infantile free sialic acid disease.

Slowly Progressive Diseases
- Low strength evidence on neurodevelopmental outcomes suggests a benefit with single HSCT compared to enzyme replacement therapy for the attenuated and severe forms of MPS II (Hunter's disease).
- Low strength evidence on neurocognitive outcomes suggests a benefit with single HSCT compared to enzyme replacement therapy for the attenuated form of MPS II (Hunter's disease).
- Low strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared to enzyme replacement therapy for the severe form of MPS II (Hunter's disease).
- Low strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared to enzyme replacement therapy for Gaucher Type III.
- Low strength evidence on neurocognitive or neurodevelopmental outcomes suggests no benefit with single HSCT compared to symptom management, substrate reduction therapy or disease natural history for MPS III (Sanfilippo).
- The body of evidence on neurocognitive or neurodevelopmental outcomes with single HSCT compared to symptom management and/or disease natural history is insufficient to draw conclusions for Niemann-Pick type C, MPS IV (Morquio syndrome), aspartylglucosaminuria, Fabry's disease, β-mannosidosis, mucolipidosis III or IV, glycogen storage disease type II (Pompe disease), Salla disease, and adrenomyeloneuropathy.

Disease With Both Rapidly and Slowly Progressive Forms
- High strength evidence on number of subcutaneous nodules and number of joints with limited range of motion suggests a benefit with single HSCT compared to symptom management or disease natural history for Farber's disease Type 2/3.
- Low strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared to symptom management or disease natural history for infantile ceroid lipofuscinosis.
- The body of evidence on overall survival and/or neurocognitive and neurodevelopmental outcomes with single HSCT compared to symptom management and or disease natural history is insufficient to draw conclusions for galactosialidosis (type unspecified) and Sandhoff disease (type unspecified), Farber's disease type I, infantile and juvenile forms

of GM_1, infantile and juvenile forms of Tay-Sachs, infantile GM_1 gangliosidosis, and juvenile ceroid lipofuscinosis.

Autoimmune Diseases Systematic Review

Type 1 Diabetes Mellitus

Background and Setting

Type 1 diabetes mellitus (DM1) is a T-cell mediated autoimmune disease characterized by selective, relentless and irreversible destruction of insulin-producing pancreatic beta-cells.[607] DM1 is the most common autoimmune disorder in childhood, with an estimated incidence of 15,000 newly diagnosed cases in the U.S. annually based on 2002-2003 data.[608] The disease typically is clinically diagnosed after approximately 60 to 80 percent of beta-cell mass has been destroyed.[609] At this stage of disease, exogenous insulin treatment is required to maintain glucose homeostasis and survival. While DM1 comprises 5-10 percent of all diabetic causes, it is ultimately associated with a high frequency of vascular-related complications, including heart disease, stroke, blindness, and renal disease, with highly compromised quality of life and life expectancy.[610]

According to the U.S. Centers for Disease Control and Prevention, diabetes was the seventh leading cause of death listed on U.S. death certificates in 2006. Intensive insulin therapy (IIT) represents the gold standard treatment for DM1, to maintain tight control of blood glucose levels, as reflected by levels of HbA1C. IIT is delivered by multiple daily injections or by continuous subcutaneous infusion. Both methods have been shown to decrease the risk of diabetic retinopathy, nephropathy, and neuropathy by 39 to 90 percent and reduce their rate of progression by 39 to 60 percent when compared to standard insulin therapy with 1 to 2 injections daily.[611] However, IIT is complicated by lack of patient acceptance and compliance, cannot fully prevent diabetic complications, and is associated with increased risk of severe hypoglycemia compared to standard therapy.

While DM1 does not typically develop into a fulminant, life-threatening form, it is a relentlessly progressive disorder despite IIT. The natural history may be transiently altered, but not halted, by coadministration of IIT and immune modulating therapies that include cyclosporine, azathioprine, prednisone, etanercept, and antithymocyte globulin (ATG).[607] These approaches may induce a slower decline or some initial improvement in C-peptide levels, which directly reflect beta-cell mass and endogenous insulin production. However, the majority of patients continue to require increasing amounts of exogenous insulin. Furthermore, the toxic effects of immune suppressants, concerns about potential risks associated with immune suppression, and the need for continuous treatment in an otherwise healthy young population limit the use of these agents in conjunction with IIT.

For these reasons, based on a theory of possible reconstitution of immune tolerance after "immunologic reset," nonmyeloablative autologous HSCT has been investigated as a way to effect an intense, but brief, immune suppression and preserve islet cell mass in children with newly diagnosed DM1. It is hypothesized that early intervention with HSCT will prevent the development of DM1-associated complications, improve quality of life, and ultimately increase life expectancy in this population. The effects of HSCT on insulin use and C-peptide levels will be compared to those parameters in children treated with IIT, in the context of adverse events associated with HSCT and IIT.

Evidence Summary

The overall grade of the strength of evidence for insulin independence and the use of HSCT for the treatment of autoimmune type I juvenile diabetes mellitus is shown in Table 107.

Evidence compiled for this review includes one prospective Phase I/II study of autologous HSCT (n=18 pediatric patients) that reported pre- and post-HSCT data on C-peptide levels and daily insulin use. Comparator data were obtained from the IIT control arms of two studies (total n=35) in newly diagnosed pediatric DM1 patients.

In the HSCT study, among 18 pediatric patients, the majority (89 percent) became free from insulin, either continuously (63 percent) or transiently (37 percent). Insulin independence was maintained for 7 to 52 months at total followup that ranged from 9 to 56 months. Among the 6 patients who resumed insulin, daily doses were lower than prior to HSCT. There was no treatment-related mortality in the HSCT study.

Table 107. Overall grade of strength of evidence for insulin independence and the use of HSCT for the treatment of autoimmune Type I diabetes mellitus

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/ Conclusion
For pediatric patients with newly diagnosed (within 4 weeks) autoimmune type 1 diabetes mellitus (DM1) what are the comparative effectiveness and harms of autologous HSCT and intensive insulin therapy (IIT). Outcomes of interest include long-term insulin independence, metabolic control, treatment-related mortality, and other long-term benefits and harms. Insulin independence is the key outcome of interest. Nonmyeloablative autologous HSCT is compared to IIT.	One Phase I/II prospective observational study (n=18) is available on the benefits and harms associated autologous HSCT using nonmyeloablative conditioning. For IIT, evidence was derived from the arms of two studies that compared IIT to conventional therapy in similar populations. One was an RCT and one an observational study.	The risk of bias is high.	The consistency of the evidence on long-term benefits and harms is unknown. The evidence is consistent in showing that an extended insulin-free interval can be achieved with autologous HSCT in children with newly diagnosed DM1.	Insulin independence in the short term can be considered a health outcome in itself. There is direct evidence that a prolonged interval of insulin independence can be achieved with autologous HSCT. There is indirect evidence for comparison of long-term benefits and harms between HSCT and IIT.	The precision of the evidence for long-term benefits and harms of HSCT is unknown. The evidence that an extended interval of insulin independence can be achieved with autologous HSCT is precise.	Not applicable due to lack of obvious effect size for adverse events including TRM. Strong strength of association for achieving an extended period of insulin independence following HSCT (16 of 18, 89%), averaging 31 months (range 14-52 months)	The overall body of evidence is insufficient to draw conclusions on long-term benefits or harms with single autologous HSCT in patients with newly diagnosed type I juvenile diabetes. Although the overall body of evidence is insufficient to come to conclusions about the relative balance of benefits (e.g., increased overall survival) or harms (treatment-related mortality, secondary malignancies), moderate strength evidence suggests that an extended interval of insulin independence can be achieved with single autologous HSCT in patients with newly diagnosed type I juvenile diabetes.

Results

The electronic literature search identified 15 citations relevant to HSCT and DM1, from which seven were retrieved for full-text screening, including those found in examination of the bibliographies of retrieved articles. A total of three reports were included in this review.[612-614]

Table 108 shows the criteria that were used to select studies for this section.

Table 108. Study selection criteria: Type I DM

Study Design	Population	Intervention	Comparator	Outcomes	Followup	Setting
Any study design	Pediatric patients (0-21 yrs) with newly diagnosed DM1 (within 6 weeks prior to study entry)	Nonmyeloablative autologous HSCT	Intensive insulin therapy	Serum C-peptide levels, HbA1C and daily insulin requirement pre- and post-HSCT	All durations of followup	In- or out-patient

Table 109 shows the characteristics of one Phase I/II study of HSCT,[612] and the IIT control arms of two randomized trials that compared IIT with IIT plus an immunosuppressant agent.[613, 614] All three studies included pediatric patients with DM1 who had been clinically diagnosed within 6 weeks prior to study entry.

In the HSCT study, peripheral blood hematopoietic stem cells were mobilized with cyclophosphamide (2 g/m^2) and granulocyte colony-stimulating factor (10 µg/kg daily).[612] Patients were conditioned with a nonmyeloablative regimen comprising cyclophosphamide (50 mg/kg daily for 4 days) and rabbit antithymocyte globulin (0.5 mg/kg daily for 1 day, then 1 mg/kg daily for 4 days) prior to stem cell infusion. The IIT studies utilized 3 to 4 injections of short- or intermediate-acting insulin, with blood glucose levels monitored and maintained as near to normal as possible.[613, 614]

Table 109. Type 1 juvenile diabetes mellitus study characteristics and population

Study	Design	Age Range (yrs)	Mean Age (yrs)	Sex M (%)	Disease Stage	HSCT (N)	Comparator (N)	Treatment Period
Couri et al. 2009[612]	Prospective phase I/II	13-21	16	67	Newly diagnosed	18	Not applicable	11/2003-04/2008
Crino et al. 2005[613]	Retrospective	NR	14	NR	Newly diagnosed	Not applicable	27	NR
Mastrandrea et al. 2009[614]	Randomized, double-blind	8-18	12	38	Newly diagnosed	Not applicable	8	10/2002-10/2007

Table 110 shows the outcomes that were reported across the studies included in this report.

Table 110. Outcomes reported: Type I DM

Study	Δ C-peptide Level*	Δ Daily Insulin Requirement	Δ HbA1c*	Treatment-Related Mortality	Other Adverse Effects
Couri et al. 2009[612]	√	√	√	√	√
Crino et al. 2005[613]	√	√	√	NR	√
Mastrandrea et al. 2009[614]	√	√	√	NR	√

* See Appendix F for data

Insulin Requirements

Daily pretransplant insulin use ranged from 0.13 to 0.59 IU/kg in the HSCT study.[612] Insulin was suspended in 16 of 18 (89 percent) pediatric patients following HSCT.[612] Among the 16 who became insulin-independent, 10 were reported continuously free for an average of 31 months (range: 14-52 months) at followup times that ranged from 9 to 56 months. Patients who ultimately resumed insulin remained free from its use for about 15 months (range 7 to 47 months), at followup times that ranged from 9 to 58 months. However, daily insulin doses after exogenous treatment was resumed were relatively small, ranging from 0.1 to 0.3 IU/kg, compared to premobilization doses that ranged from 0.13 to 0.44 IU/kg, maintaining good glucose control.

In one IIT study, daily insulin use averaged 0.91 ± 0.28 IU/kg at study entry, with no significant change at 12 or 24 months (0.61 ± 0.28 and 0.70 ± 0.24 IU/kg, respectively).[613] In the second IIT study, average daily insulin use at 6 months was reported to have increased by 23 percent from that at baseline ($p<0.05$) but the dose was not specified.[614] No patients became insulin independent in either study.

Adverse Events

No treatment-related mortality was reported in the HSCT study.[612] One post-conditioning case of bilateral pneumonia was reported that responded quickly to intravenous broad-spectrum antibiotics. With long-term followup, six cases of oligospermia were reported, and one case of leukopenia. The majority of adverse effects in the HSCT study were mild and included nausea, vomiting, fever, and alopecia.

No severe adverse effects were reported with IIT in either study.[613, 614]

Ongoing Research

According to the website ClinicalTrials.gov, five clinical studies are recruiting pediatric patients, as shown in Table 111. None of these originates in the U.S. Of the ongoing trials, only one offers a comparison between autologous mesenchymal stem cells and placebo (NCT01157403).

Table 111. Ongoing clinical trials of HSCT in DM1

Study Title	Phase	Intervention	NCT ID
Autologous Transplantation of Mesenchymal Stem Cells for Treatment of Patients with Inset of Type 1 Diabetes	II/III	Autologous	01157403
Autologous Hematopoietic Stem Cell Transplantation for Early Onset Type 1 Diabetes	II	Autologous	00807651
Hematopoietic Stem Cell Transplantation in Type 1 Diabetes Mellitus	I/II	Autologous	01121029
Safety and Efficacy of Autologous Stem Cell Transplantation for Early Onset Type 1 Diabetes Mellitus	I/II	Autologous	00315133
Safety and Efficacy of Autologous Adipose-Derived Stem Cell Transplantation in Patients with Type 1 Diabetes	I/II	Autologous	00703599

Conclusion

The overall body of evidence is insufficient to draw conclusions on long-term benefits or harms with single autologous HSCT in patients with newly diagnosed type I juvenile diabetes.

Moderate strength evidence suggests that an extended interval of insulin independence can be achieved with single autologous HSCT in patients with newly diagnosed type I juvenile diabetes.

Systemic Lupus Erythematosus

Background and Setting

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is associated with inflammation and eventual organ damage.[607] It may involve any organ system, with a wide range of disease severity. The exact cause of SLE is unknown. Diagnosis of SLE is the same regardless of age at onset, and is based on a combination of laboratory and clinical criteria. SLE is likely if four of the 11 revised American College of Rheumatology (ACR) criteria are present in a patient simultaneously or over time.[615]

SLE is rare in childhood, with an estimated incidence of 10 to 20 per 100,000 children, with some variation depending on ethnicity. Juvenile-onset SLE (prior to age 18 years) accounts for 15 to 20 percent of cases,[616] which in general have a more severe presentation, faster development of organ damage, and a higher disease burden over a lifetime. For all age groups, 5-year survival rates have improved with advances in management of organ damage and complications, from 59 to 93 percent in the 1980s to 94 to 100 percent by the late 1990s.[617] Patients aged younger than 24 years have the highest rate of SLE-related all-cause mortality, about 8-fold greater than the average for all SLE cases.[618]

The clinical course of SLE is marked by the alternation of periods of active disease and quiescence. However, children and adolescents with SLE enter adult life with considerable morbidity, secondary to sequelae of disease activity, side effects of medications, and comorbid conditions. The most common symptoms of SLE include fever, rash, fatigue, weight loss, arthritis, and renal disease.[619] Lupus nephritis is one of the main clinical presentations of pediatric SLE, and it determines the course of illness as the major threat to long-term survival. Other major manifestations include neuropsychiatric, cardiac, and lung.

SLE has no known cure. Depending on severity, it is often treated with high-dose corticosteroids and immune suppressants, which are responsible for much of the permanent organ damage observed in these patients. Other treatments include hydroxychloroquine, cyclophosphamide, cyclosporine A, mycophenolate mofetil, azathioprine, nonsteroidal anti-inflammatory drugs (NSAIDs), rituximab, and abatacept.[607] Only three agents have received U.S. Food and Drug Administration marketing approval for SLE: corticosteroids, hydroxychloroquine, and aspirin.

Autologous HSCT has been used to treat a small number of pediatric SLE cases, all of which have been severe, life-threatening, and refractory to nearly all drug therapies, with a dismal prognosis. Accordingly, this systematic review will present only results from HSCT reports, with the comparison being usual care.

Evidence Summary

The overall grade of strength of evidence for drug-free clinical remission and the use of HSCT for the treatment of severe, refractory systemic lupus erythematosus is shown in Table 112.

Table 112. Overall grade of strength of evidence for drug-free clinical remission and the use of HSCT for the treatment of severe, refractory systemic lupus erythematosus

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with severe, refractory systemic lupus erythematosus (SLE) what are the effectiveness and harms of autologous HSCT and drug therapies? Outcomes of interest include long-term drug-free clinical remission, TRM, and other long-term benefits and harms. All patients in these studies had severe, refractory disease, with dismal prognosis, so the comparator is usual care and natural history.	There are 7 reports on autologous HSCT (total n = 17); the largest, a phase I/II study, contains information on 9 pediatric patients.	The risk of bias is high.	The consistency of the evidence on long-term benefits and harms is unknown. The evidence is consistent in showing an extended drug-free interval and clinical remission can be achieved with autologous HSCT.	Drug-free clinical remission of severe, refractory SLE in the short-term is considered a health outcome. There is direct evidence that an extended drug-free clinical remission can be achieved with autologous HSCT. The evidence comparing usual care is indirect.	The precision of the evidence for long-term benefits and harms is unknown. The evidence that an extended drug-free clinical remission can be achieved with autologous HSCT is precise. The precision of the evidence comparing usual care is unknown.	Not applicable due to lack of obvious effect size for adverse events including TRM. Strong strength of association for achieving an extended period of drug-free clinical remission following HSCT (12 of 17, 71%), ranging in duration from 4 to 66 months.	The overall body of evidence is insufficient to draw conclusions on long-term benefits or harms with single autologous HSCT for the treatment of severe, refractory SLE in children. Although the overall body of evidence is insufficient to come to conclusions about the relative balance of benefits (e.g., increased overall survival) or harms (treatment-related mortality, secondary malignancies), moderate strength evidence suggests that an extended drug-free clinical remission can be achieved with single autologous HSCT for the treatment of severe, refractory SLE in children.

Overall, 12 of 17 (71 percent) SLE patients treated with autologous HSCT entered a state of complete drug-free remission, for periods that ranged from about 4 months[620] to 66 months.[621] The former reflects the followup time at preparation of the paper. In the largest series (n=9), patients experienced complete drug-free remission for a median 24 months, and a range of 12 to 66 months.[621]

Three studies reported SLE Disease Activity Index (DAI) score changes pre- and post-HSCT.[621-624] Patients who underwent autologous HSCT and experienced a complete drug-free remission had substantial reduction in their SLEDAI scores. In one study, two of four patients succumbed to treatment-related mortality, one at 63 days from multiorgan failure, the other on day 15 due to multiple causes.[623]

Results

A total of seven reports were included in this review. Table 113 shows the criteria that were used to select studies for this section.

Table 113. Study selection criteria: SLE

Study Design	Population	Intervention	Comparator	Outcomes	Followup	Setting
Any study design	Pediatric patients (0-21 yrs) with severe, refractory systemic lupus erythematosus (SLE)	Autologous HSCT	None applicable	Survival, drug-free remission post-HSCT, HSCT-related adverse events	All durations of followup	In-patient

Table 114 shows the characteristics of studies of autologous HSCT in 17 patients (16 female) aged 13-21 years with SLE. All had severe, life-threatening SLE that was refractory to most first- and second-line drugs, variously including corticosteroids, pulsed cyclophosphamide, 6-mercaptopurine, azathioprine, plasmapheresis, and hydroxychloroquine. Although rituximab and abatacept have been studied in adults with SLE, we did not identify any studies of those agents in the pediatric setting. Outcomes reported are included in Table 115.

Five studies used only peripheral blood stem cells.[620-622, 625, 626] One used bone marrow cells;[624] and, one used both sources.[623] Conditioning regimens typically included cyclophosphamide plus ATG; two studies included total-body irradiation,[624, 626] and one used modified BEAM regimens with ATG.[623]

Table 114. Systemic lupus erythematosus study characteristics and population

Study	Design	Age Range (yrs)	Mean Age (yrs)	Sex F (%)	Disease Stage	HSCT (N)	Comparator (N)	Treatment Period
Statkute, 2005[621]	Case series	15-21	19	100	Severe, refractory, including WHO class III/IV renal, cardiac, CNS, and pulmonary involvement	9	N/A	04/1997-08/2004
Chen, 2005[622]	Case reports	13, 18	NR	100	Severe, refractory, including WHO class III/IV nephritis	2	NA	1996, 2001
Lisukov, 2004[623]	Case series	15-21	19	100	Severe, refractory, with SLEDAI score ranging from 6-30, with WHO class III/IV nephritis, CNS, cardiac, pulmonary and life-threatening cytopenias	4	NA	1998-2003
Brunner, 2002[625]	Case report	18	NR	100	Severe, refractory, with WHO class IV nephritis, cutaneous vasculitis, pneumonitis, with mechanical ventilation	1	NA	2000
Musso, 2001[620]	Case reports	17, 20	NR	100	Severe, life-threatening, refractory	2	NA	NR
Wulffraat, 2001[624]	Case reports	14, 14	NR	50	Severe, life-threatening, refractory, with WHO class IV nephritis, hemorrhagic pneumonitis, pancytopenia, vasculitis, polyarthritis	2	NA	NR
Trysberg, 2000[626]	Case report	18	NR	100	Severe, progressive life-threatening, refractory CNS lupus	1	NA	1998

Table 115. Outcomes reported: SLE

Study	Complete Drug-Free Remission (%)	SLEDAI Score (pre-post)	TRM	Other Adverse Effects
Statkute, 2005[621]	√	NR	√	√
Chen, 2005[622]	√	√	√	√
Lisukov 2004[623]	√	√	√	NR
Brunner, 2002[625]	√	NR	NR	√
Musso, 2001[620]	√	NR	√	√
Wulffraat, 2001[624]	√	√	√	√
Trysberg, 2000[626]	NR	NR	√	√

Complete Drug-Free Remission

Table 116 shows the proportions of patients with severe, refractory SLE who entered a state of complete drug-free remission following intense immune suppression and autologous HSCT. Overall, 12 of 17 (71 percent) entered a state of complete drug-free remission, for periods that ranged from about 4 months[620] to 66 months.[621] The former reflects the followup time at preparation of the paper. In the largest series, patients experienced complete drug-free remission for a median 24 months, and a range of 12 to 66 months.[621]

Table 116. Complete drug-free remission in patients with SLE undergoing autologous HSCT

Complete Drug-Free Remission (%)	Duration of Complete Drug-Free Remission (Months)	Study
78 (n=9)	Median 24 (rng 12-66)	Statkute, 2005[621]
2 of 2	9, 44	Chen, 2005[622]
25 (n=4)	>60	Lisukov, 2004[623]
1 of 1	21	Brunner, 2002[625]
2 of 2	>30, >3.8	Musso, 2001[620]
2 of 2	12, 18	Wulffraat, 2001[624]
NR	NR	Trysberg, 2000[626]

Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) Score

Three studies reported SLEDAI score changes pre- and post-HSCT,[622-624] as shown in Table 117. In studies that reported this outcome, patients who underwent autologous HSCT and experienced a complete drug-free remission had substantial reduction in their SLEDAI scores.

Table 117. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) Score

Pre-HSCT SLEDAI Score (Mean ± SD)	Post-HSCT SLEDAI Score	Study
NR	NR	Statkute, 2005[621]
6, 12	0, 0	Chen, 2005[622]
19 ± 10	<3	Lisukov, 2004[623]
NR	NR	Brunner, 2002[625]
NR	NR	Musso, 2001[620]
20, 27	0, 8	Wulffraat, 2001[624]
NR	NR	Trysberg, 2000[626]

Mortality and Other Serious Adverse Events Associated With Autologous HSCT

As shown in Table 115, six studies reported information on treatment-related mortality among autologous HSCT recipients.[620-624, 626] In one study, 2 of 4 patients succumbed to treatment-related mortality, one at 63 days from multiorgan failure, the other on day 15 due to multiple causes.[623] Other than those mentioned, all other adverse effects of the autologous HSCT conditioning regimens were reported by the authors to be mild to moderate and without clinical sequelae.

Ongoing Research

According to the Web site ClinicalTrials.gov, two clinical studies are recruiting pediatric patients, as shown in Table 118.

Table 118. Ongoing clinical trials of HSCT in SLE

Study Title	Phase	Intervention	NCT ID
Cyclophosphamide and rATG/Rituximab in Patients With Systemic Lupus Erythematosus	II	Autologous HSCT	NCT00278538
Mesenchymal Stem Cells Transplantation for Refractory Systemic Lupus Erythematosus (SLE)	I/II	Allogeneic HSCT	NCT00698191

Conclusion

The overall body of evidence is insufficient to draw conclusions on long-term benefits or harms with single autologous HSCT for the treatment of severe, refractory SLE in children.

Moderate strength evidence suggests that an extended drug-free clinical remission can be achieved with single autologous HSCT for the treatment of severe, refractory SLE in children.

Juvenile Idiopathic Arthritis (JIA)

Background and Setting

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic condition in children, with a prevalence of between 16 and 150 per 100,000.[607] It is defined as persistent arthritis in one or more joints in a child or adolescent less than 16 years old, after excluding other causes. According to the current International League of Association of Rheumatologists (ILAR) the term JIA refers to seven different disease categories: systemic, persistent oligoarticular, extended oligoarticular, polyarticular rheumatoid factor (RF) negative, polyarticular RF positive, enthesitis-related arthritis, and psoriatic.[627]

While the cause of JIA is not defined, evidence suggests altered immune system function, particularly T-cell regulation, has a major role in the pathogenesis of joint damage and disease progression.[628, 629] JIA subtypes vary by the number of joints involved, and by age of onset. The most common form is the early onset (before age 6 years) oligo- or mono-articular JIA, with 1 to 4 asymmetrical joints affected, a high frequency of positive antinuclear antibodies (ANA), and high risk (30 percent) of chronic uveitis. These forms have generally good prognosis, and may be managed with intra-articular steroids and physiotherapy.[627]

At the other end of the spectrum, systemic-onset JIA is distinct from other JIA subtypes, with a systemic inflammatory component. While about 50 percent of cases will have a waxing and waning course, with favorable long-term prognosis, the other 50 percent will have an unremitting course with polyarthritis; prolongation of active systemic illness past 6 months is a particularly bad prognostic sign.[607] Despite current treatment that includes methotrexate, corticosteroids,

biological response modifiers (blocking agents of TNF-alpha, IL-1, IL-6) or blockers of costimulatory immune cell-surface molecules (e.g., CD28 or CD20),and other immune suppressants, most children with systemic polyarticular JIA do not achieve long-term clinical remission.[607, 627] More than one-third will have ongoing active disease into adulthood, with sequelae secondary to chronic inflammation. Those who do not respond to early use of antirheumatic agents will experience considerable morbidity from joint damage, osteoporosis, growth retardation, psychosocial morbidity, reduced quality of life and educational and employment disadvantage.[627]

Autologous HSCT has been used to treat a small number of pediatric JIA cases, all of which have been severe, progressive and refractory to standard drug therapies. Accordingly, this systematic review will present only results from HSCT reports, compared to usual care and the disease course.

Evidence Summary

The overall grade of strength of evidence for drug-free clinical remission and the use of HSCT for the treatment of severe, refractory juvenile idiopathic arthritis is shown in Table 119.

Overall the evidence signals that autologous HSCT following chemotherapy-induced immune suppression may be associated with prolonged resolution of JIA into a drug-free, much-improved state. Among all cases reported, 21 of 43 (56 percent) achieved extended drug-free remission for 3 to 60 months. In the largest series, drug-free remission was reported in 53 percent, with a median duration of 29 months. There were four cases of treatment-related mortality, with no other reports of long-term benefits and harms.

Table 119. Overall grade of strength of evidence for drug-free clinical remission and the use of HSCT for the treatment of severe, refractory juvenile idiopathic arthritis

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with severe, refractory juvenile idiopathic arthritis (JIA) what is the comparative effectiveness and harms of autologous HSCT and drug therapies? All patients in these studies had severe, refractory disease, with very poor prognosis, so the comparator is usual care and natural history. Outcomes of interest include extended, drug-free clinical remission, TRM, and other long-term benefits and harms.	There are 4 single-arm and case reports (total n = 43). The largest, a registry report, contains information on 34 pediatric patients.	The risk of bias is high.	The consistency of the evidence on long-term benefits and harms is unknown. The evidence is consistent in showing an extended drug-free interval and clinical remission can be achieved with autologous HSCT.	Drug-free clinical remission of severe, refractory JIA in the short-term is considered a health outcome. There is direct evidence that an extended drug-free clinical remission can be achieved with autologous HSCT. The evidence comparing usual care is indirect.	The precision of the evidence for long-term benefits and harms is unknown. The evidence that an extended drug-free clinical remission can be achieved with autologous HSCT is precise. The precision of the evidence comparing usual care is unknown.	Not applicable due to lack of obvious effect size for adverse events including TRM. Strong strength of association for achieving an extended period of drug-free clinical remission following HSCT (24 of 43, 56%),averaging 30 months duration (range 6 to 60 months).	The overall body of evidence is insufficient to draw conclusions on long-term benefits or harms with single autologous HSCT for the treatment of severe, refractory JIA in children. Although the overall body of evidence is insufficient to come to conclusions about the relative balance of benefits (e.g., increased overall survival) or harms (treatment-related mortality, secondary malignancies), moderate strength evidence suggests that an extended drug-free clinical remission can be achieved with single autologous HSCT for the treatment of severe, refractory JIA in children.

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Results

A total of four reports were included in this review.[630-633] Table 120 shows the criteria that were used to select studies for this section.

Table 120. Study selection criteria: JIA

Study Design	Population	Intervention	Comparator	Outcomes	Followup	Setting
Any study design	Pediatric patients (0-21 yrs) with severe, refractory progressive juvenile idiopathic arthritis (JIA)	Autologous HSCT	None applicable	Survival, drug-free remission post-HSCT, HSCT-related adverse events	All durations of followup	In-patient

Table 121 presents the study characteristics and populations of 4 reports on the use of autologous HSCT treatment in patients with JIA. All patients had severe, refractory illness, mostly systemic (79 percent) but also polyarticular (21 percent). The largest experience is from the registry of the EBMT, which reports on 34 of 41 total patients who had received autologous HSCT at nine European centers.[630] Four cases were treated in Japan[631, 632] and five were from Italy.[633] Patients ranged in age from 3 to 21 years, with 49 percent females and 51 percent males.

Among 43 cases, 26 (60 percent) used bone-marrow stem cells, 12 (28 percent) used peripheral-blood stem cells, and the stem-cell source was not identified for five.[633] Various conditioning regimens were reported, typically involving cyclophosphamide and ATG.

Table 121. Juvenile idiopathic arthritis study characteristics and population

Study	Design	Age Range (yrs)	Mean Age (yrs)	Sex F (%)	Disease Stage	HSCT (N)	Comparator (N)	Treatment Period
De Kleer, 2004[630]	Registry report	4-18	9	44	Severe, refractory systemic (n=29) or polyarticular (n=5)	34	NA	Since 1997
Kishimoto, 2003[631]	Case reports	3-21	12	67	Severe, refractory systemic disease	3	NA	NR
Nakagawa, 2001[632]	Case report	15	NA	Male	Severe, refractory systemic disease	1	NA	1999
Rabusin, 2000[633]	Case series	9-20	15	80	Severe, refractory systemic (n=1) and systemic polyarticular (n=4)	5	NA	NR

Table 122 shows outcomes that were reported in the four studies in this systematic review. Complete drug-free remission is the key outcome, which is generally defined as disappearance of signs and symptoms of JIA and cessation of antirheumatic agents.

Table 122. Outcomes reported: JIA

Study	Complete Drug-Free Remission (%)	TRM and Other Adverse Events
De Kleer, 2004[630]	√	√
Kishimoto, 2003[631]	√	√
Nakagawa, 2001[632]	√	√
Rabusin, 2000[633]	√	√

Complete Drug-free Remission

Overall, 56 percent of patients in these reports achieved a complete drug-free remission following autologous HSCT (Table 123). In the largest study, a complete drug-free response was achieved in 53 percent of cases, for an average duration of about 2.5 years, although some patients maintained this response for 60 months.[630] In the Rabusin series, four of five (80 percent) patients achieved a complete drug-free response at 3 months' followup, with a relapse in one at 6 months, and ultimately relapse in the other three at 8, 12, and 18 months.[633] One patient in the Kishimoto study had disease flares at 11 and 23 months followup, but became medication-free and asymptomatic at 39 months followup.[631]

Table 123. Complete drug-free remission in patients with JIA undergoing autologous HSCT

Complete Drug-Free Remission (%)	Duration of Complete Drug-Free Remission (Months)	Study
53 (n=34)	29 ± 12 (rng 21-60)	De Kleer, 2004[630]
67 (n=3)	10, 35	Kishimoto, 2003[631]
1 of 1	15	Nakagawa, 2001[632]
80 (n=5)	11 ± 5 (rng 6-18)	Rabusin, 2000[633]

Overall Survival

One study reported Kaplan-Meier overall survival of about 79 percent at 5 years' followup.[630]

Treatment-related Mortality and Other Adverse Events

Overall, treatment-related mortality was reported in 4 of 43 (9 percent) compiled cases in this review. In the EBMT experience, treatment-related mortality was reported in 3 of 34 cases (9 percent), attributed to macrophage-activation syndrome.[630] In another study, one patient who had an uncontrollable disease flare after autologous HSCT underwent a subsequent cord-blood allogeneic HSCT, but developed a CMV infection and died 48 days after allogeneic HSCT.[631] No treatment-related mortality was reported in the other two studies.[632, 633]

Ongoing Research

According to ClinicalTrials.gov, there are no clinical trials of HSCT actively recruiting patients with JIA.

Conclusion

The overall body of evidence is insufficient to draw conclusions on long-term benefits or harms with single autologous HSCT for the treatment of severe, refractory JIA in children.

Moderate strength evidence suggests that an extended drug-free clinical remission can be achieved with single autologous HSCT for the treatment of severe, refractory JIA in children.

Systemic Sclerosis

Background and Setting

Systemic sclerosis is a generalized, highly heterogeneous autoimmune disorder characterized by diffuse, disabling skin thickening combined with fibrotic changes in many organs, in particular the heart and lung, ultimately resulting in end-stage failure.[634]

Systemic sclerosis is a rare disease. It is diagnosed in approximately 67 male patients and 265 female patients per 100,000 people each year in the U.S. Systemic sclerosis usually appears in women aged 30 to 40 years, and it occurs in slightly older men. In approximately 85 percent of cases, systemic sclerosis develops in individuals aged 20 to 60 years. Cases also are observed in children and in the elderly population. Immunologic mechanisms and heredity (certain HLA subtypes) play a role in etiology. Systemic sclerosis-like syndromes can result from exposure to vinyl chloride, bleomycin, pentazocine, epoxy and aromatic hydrocarbons, contaminated rapeseed oil, or L-tryptophan.

Systemic sclerosis pathophysiology involves vascular damage and activation of fibroblasts; collagen and other extracellular proteins in various tissues are overproduced. The disease varies in severity and progression, ranging from generalized skin thickening with rapidly progressive and often fatal visceral involvement, primarily end-stage organ failure.[635-637] The course depends on the type of systemic sclerosis but is often unpredictable. Typically, progression is slow. Overall, 5- and 10-year survival is about 20 to 80 percent and 15 to 65 percent, respectively, according to the major organ affected at diagnosis.[638-640] Patients with diffuse skin disease eventually develop visceral complications, which are the usual causes of death. Prognosis is poor if cardiac, pulmonary, or renal manifestations are present early. Heart failure may be intractable. Acute renal insufficiency, if untreated, progresses rapidly and causes death within months.

Results from Phase II open studies suggest intravenous pulse cyclophosphamide therapy may improve skin score and pulmonary function.[641-643] However, no treatment has been shown definitively to halt disease progression. Autologous HSCT has been used to treat a small number of pediatric systemic sclerosis cases, all of which have been severe, progressive and refractory. Accordingly, this systematic review will present only results from HSCT reports, compared to usual care and the disease course.

Evidence Summary

The overall grade of strength of evidence for drug-free clinical remission and the use of HSCT for the treatment of severe, refractory systemic sclerosis is shown in Table 124.

Systemic sclerosis is very rare in children, with one registry report comprising the sole source of published evidence on the use of autologous HSCT in this setting. There are no proven therapies for advanced, progressive systemic sclerosis with visceral involvement, which has a dismal prognosis. In this context, that four of five patients (80 percent) entered a state of complete clinical remission, with the other one in partial remission, signals that autologous HSCT following chemotherapy-induced immune suppression may be associated with these results.

Table 124. Overall grade of strength of evidence for drug-free clinical remission and the use of HSCT for the treatment of severe, refractory systemic sclerosis

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with severe, refractory systemic sclerosis (SSc) what is the comparative effectiveness and harms of autologous HSCT and drug therapies? All patients in these studies had severe, refractory disease, with very poor prognosis, so the comparator is usual care and natural history. Outcomes of interest include extended, drug-free clinical remission, TRM, and other long-term benefits and harms.	There is one report from the EBMT/EULAR registry, with a total of 5 pediatric patients.	The risk of bias is high.	The consistency of the evidence on long-term benefits and harms is unknown. The evidence is consistent in showing a drug-free clinical remission can be achieved with autologous HSCT.	Drug-free clinical remission of severe, progressive SSc in the short-term is considered a health outcome. There is direct evidence that a drug-free clinical remission can be achieved with autologous HSCT. The evidence comparing usual care is indirect.	The precision of the evidence on long-term benefits and harms is unknown. The evidence that a drug-free clinical remission can be achieved with autologous HSCT is precise. The precision of the evidence comparing usual care is unknown.	Not applicable due to lack of obvious effect size for adverse events including TRM. Strong strength of association for achieving an extended period of drug-free clinical remission following HSCT (4 of 5, 80%). The duration of remission was not reported.	The overall body of evidence is insufficient to draw conclusions on long-term benefits or harms with single autologous HSCT for the treatment of severe, refractory SSc in children. Although the overall body of evidence is insufficient to come to conclusions about the relative balance of benefits (e.g., increased overall survival) or harms (treatment-related mortality, secondary malignancies), moderate strength evidence suggests that a drug-free clinical remission can be achieved with single autologous HSCT for the treatment of severe, refractory SSc in children.

Results

One report was included in this review. Table 125 shows the criteria that were used to select studies for this section.

Table 125. Study selection criteria: Systemic sclerosis

Study Design	Population	Intervention	Comparator	Outcomes	Followup	Setting
Any study design	Pediatric patients (0-21 yrs) with severe, progressive systemic sclerosis (SSc)	Autologous HSCT	None applicable	Survival, drug-free remission post-HSCT, HSCT-related adverse events	All durations of followup	In-patient

Table 126 shows the study and patient characteristics of one report on the use of autologous HSCT in pediatric systemic sclerosis patients.[644] This registry report provides details on 5 children age 9 to 17 years, all of whom had lung disease at inclusion and systemic sclerosis (4 diffuse, 1 limited). Disease had been diagnosed within 62 months (range: 26-85 months) before HSCT. They all received the same mobilization regimen comprising cyclophosphamide and G-CSF plus cell selection before transplantation with either CD34+ selection alone (n=3) or CD34+/4+/8+ (n=2). Different conditioning regimens were used, comprising cyclophosphamide plus antiCD52 (CAMPATH 1) (n=3), cyclophosphamide plus TBI plus ATG (n=1), or cyclophosphamide alone (n=1).

Table 126. Systemic sclerosis study characteristics and population

Study	Design	Age Range (yrs)	Mean Age (yrs)	Sex F (%)	Disease Stage	HSCT (N)	Comparator (N)	Treatment Period
Farge, 2004[644]	Registry report	9-17	12	80	Refractory, severe, with early visceral involvement	5	NA	1996-2002

Only scant details on pediatric patients are available in the registry report. All five children were reported alive after a median duration of about 38 months (range: 14-68 months). Four (80 percent) entered complete remission, with one partial remission. Disease ultimately progressed in one patient, and one relapsed about 9 months after experiencing a complete remission. One 19-year-old patient, not included in the group of five reported above, succumbed to diffuse alveolar hemorrhage 11 days post-transplant.

Ongoing Research

According to ClinicalTrials.gov, one Phase I/II study in China is actively recruiting individuals with systemic sclerosis to undergo HSCT with allogeneic mesenchymal stem cells (NCT00962923). A pilot study of total body irradiation in combination with cyclophosphamide, antithymocyte globulin, and autologous CD34-selected peripheral blood stem cell transplantation in children with refractory autoimmune disorders is active but not recruiting (NCT00010335).

Conclusion

The overall body of evidence is insufficient to draw conclusions on long-term benefits or harms with single autologous HSCT for the treatment of severe, refractory systemic sclerosis in children.

Moderate strength evidence suggests that an extended drug-free clinical remission can be achieved with single autologous HSCT for the treatment of severe, refractory systemic sclerosis in children.

Multiple Sclerosis

Background and Setting

Multiple sclerosis (MS) is a CNS demyelinating disease with an autoimmune etiology.[645] It is characterized by the presence of inflammatory, demyelinating lesions scattered throughout the CNS at different sites and at different times. Clinical features secondary to the CNS lesions include loss of sensation, muscle weakness, visual loss, incoordination, cognitive impairment, fatigue, pain, and bladder and bowel disturbance.[645]

Pediatric MS is diagnosed after two clinical episodes of CNS demyelination that are separated by at least 30 days.[646] In adults, three of the following four features are required: nine or more white matter lesions or one gadolinium-enhancing lesion; three or more periventricular lesions; one juxtacortical lesion; one infratentorial lesion. These criteria may be applied to identify pediatric cases, but have not been clinically validated in this population.[647]

The worldwide prevalence of pediatric MS is unknown. Data from individual countries or MS centers reported prevalence rates of MS in childhood ranging from 3.1 to 4.4 percent of all MS cases.[648-650] A Canadian study estimated the incidence of initial pediatric demyelinating events (including MS, neuromyelitis optica, acute disseminated encephalomyelitis, complete transverse myelitis, and recurrent optic neuritis) as 0.9 per 100,000 individuals.[651]

The natural history of MS is extremely variable, with a waxing and waning pattern that may gradually worsen over time.[645] Four broad categories are recognized: relapsing remitting MS (RRMS), which accounts for about 85 percent of cases; secondary progressive MS (SPMS), which represents a progression of RRMS with accumulating irreversible neurological deficit and disability; primary progressive MS (PPMS), which is characterized by progressive disease from onset, and accounts for 10 to 15 percent of MS cases; and, progressive relapsing MS (PRMS), defined as progressive disease from onset with superimposed relapses.

Malignant MS is a poorly defined subset of MS that comprises a heterogeneous group of demyelinating disorders that is applied only to cases that succumb within 5 years of onset, accounting for less than 5 percent of all MS subjects.[652]

The therapeutic approach to MS has evolved over the past two decades. Four first-line disease modifying therapies have received U.S. Food and Drug Administration approval for use in adults with RRMS: glatiramer acetate, intramuscular and subcutaneous interferon-β1a, and subcutaneous interferon-β1b.[647] Evidence supporting their use in children is very limited.

Most treatment decisions in children with MS are based in part on results achieved in adults. Corticosteroids are used to treat acute, symptomatic relapses, but are associated with serious adverse effects in children.[645] Second-line agents in children have included cyclophosphamide, mitoxantrone, mycophenolate mofetil, daclizumab, rituximab or natalizumab, primarily described in retrospective case series and reports with limited follow-up.[647]

There is no consensus on how to treat malignant MS. Approaches have included plasmapheresis, aggressive immunosuppression with mitoxantrone, cladribine, and cyclophosphamide, with no documented effect in this setting. Given the extremely poor prognosis of malignant MS, and the lack of effective treatment, autologous HSCT has been used to treat a small number of pediatric malignant MS cases. Accordingly, this systematic review will present only results from HSCT reports compared to usual care and the disease course.

Evidence Summary

The overall grade of strength of evidence for drug-free clinical remission and the use of HSCT for the treatment of severe, refractory malignant multiple sclerosis is shown in Table 127.

Malignant MS is very rare in children, with three reports comprising the sole identified source of published evidence on the use of autologous HSCT in this setting. There are no proven therapies for malignant MS, which has a dismal prognosis. In this context, that five of five patients (100 percent) entered a state of clinical remission, with no relapses at followup, signals that autologous HSCT following chemotherapy-induced immune suppression may be associated with these results.

Table 127. Overall grade of strength of evidence for drug-free clinical remission and the use of HSCT for the treatment of severe, refractory malignant multiple sclerosis

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with severe, refractory malignant multiple sclerosis (MS) what is the comparative effectiveness and harms of autologous HSCT and drug therapies? All patients in these studies had severe, refractory disease, with very poor prognosis, so the comparator is usual care and natural history. Outcomes of interest include extended, drug-free clinical remission, TRM, and other long-term benefits and harms.	There are three case series or case reports with a total of 5 pediatric patients.	The risk of bias is high.	The consistency of the evidence on long-term benefits and harms is unknown. The evidence is consistent in showing an extended drug-free interval and clinical remission can be achieved with autologous HSCT.	Drug-free clinical remission of severe, refractory MS in the short-term is considered a health outcome. There is direct evidence that an extended drug-free clinical remission can be achieved with autologous HSCT. The evidence comparing usual care is indirect.	The precision of the evidence for long-term benefits and harms is unknown. The evidence that an extended drug-free clinical remission can be achieved with autologous HSCT is precise. The precision of the evidence comparing usual care is unknown.	Not applicable due to lack of obvious effect size for adverse events including TRM. Strong strength of association for achieving an extended period of drug-free clinical remission following HSCT (5 of 5, 100%), ranging from 14 to 66 months.	The overall body of evidence is insufficient to draw conclusions on long-term benefits or harms with single autologous HSCT for the treatment of severe, refractory MS in children. Although the overall body of evidence is insufficient to come to conclusions about the relative balance of benefits (e.g., increased overall survival) or harms (treatment-related mortality, secondary malignancies), moderate strength evidence suggests that an extended drug-free clinical remission can be achieved with single autologous HSCT for the treatment of severe, refractory MS in children.

Results

A total of three reports were included in this review. Table 128 shows the criteria that were used to select studies for this section.

Table 128. Study selection criteria: MS

Study Design	Population	Intervention	Comparator	Outcomes	Followup	Setting
Any study design	Pediatric patients (0-21 yrs) with malignant MS	Autologous HSCT	None applicable	Survival, drug-free remission post-HSCT, HSCT-related adverse events	All durations of followup	In-patient

Table 129 shows the study and patient characteristics of three reports (total N=5) on the use of autologous HSCT in pediatric patients.[653-655] They ranged in age from 9 to 18 years, with two females and three males.

In the first report, peripheral blood stem cells were mobilized using cyclophosphamide and G-CSF.[653] One patient underwent conditioning using a BEAM regimen (BCNU, etoposide, cytosine-arabinoside, melphalan), the other (a young male) was conditioned using cyclophosphamide. Total body irradiation was not used in either case. ATG and methylprednisolone were administered 1 and 2 days after stem-cell infusion. In the second report, peripheral blood stem cells were mobilized using cyclophosphamide and G-CSF, and the patient was conditioned with busulfan and ATG.[654] In the third report, peripheral blood stem cells were mobilized using cyclophosphamide and G-CSF, and conditioned using a BEAM regimen plus cyclophosphamide plus ATG.[655]

Table 129. Multiple sclerosis study characteristics and population

Study	Design	Age Range (yrs)	Mean Age (yrs)	Sex F (%)	Disease Stage	HSCT (N)	Comparator (N)	Treatment Period
Fagius, 2009[653]	Case series	9, 16	NA	1 female, 1 male	Refractory malignant MS of short duration	2	NA	Since 2004
Kimiskidis, 2008[654]	Case report	18	NA	male	Refractory malignant MS of short duration	1	NA	2001
Mancardi, 2005[655]	Case reports	16, 18	NA	1 female, 1 male	Refractory malignant MS of short duration	2	NA	NR

In the Fagius study, both patients experienced stabilization of their disease course.[653] One was alive at 35 months followup, with expanded disability status scale (EDSS) score reduced from 4.0 at HSCT to 0 at last followup. The second patient in the Fagius study was alive at 28 months, with EDSS score reduced from 8.0 at HSCT to 1.0 at followup. Adverse effects of autologous HSCT were not reported individually, but were as expected with the conditioning regimen, comprising fever, mucositis, and alopecia.

Kimiskidis and colleagues reported their patient showed rapid neurological improvement that was sustained and gradually increased following HSCT.[654] His EDSS score dropped from 5.0 at HSCT to 1.5 at 66 months' followup. The patient experienced no relapses since HSCT, with no immunomodulatory therapies, and at publication had graduated from college.

Mancardi and colleagues reported results for two pediatric cases.[655] The first patient was alive at 29 months' followup, with EDSS score reduced from 7.5 to 4.0, the ability to walk 500 meters unaided, independent in activities of daily living, and no relapses. HSCT-related adverse effects were not reported. The second patient was alive at 14 months' followup, with dramatically improved neurological condition and EDSS score reduced from 9.0 to 4.5; information was not provided about the patient's mobility or capability to perform activities of daily living. This patient experienced fever for two weeks post-HSCT, but no pathogen was identified.

In total, five pediatric patients with malignant MS have been reported alive following intense immune suppression and autologous HSCT. All had durable remission of severe, disabling disease and life-threatening disease for 14 to 66 months followup, improved EDSS scores, and improvement in neurological function. Where reported, mobility improved, along with the ability to perform activities of daily living. No patient relapsed in the followup periods reported.

Ongoing Research

According to ClinicalTrials.gov, there are no active clinical studies involving HSCT recruiting patients with any type of multiple sclerosis.

Conclusion

The overall body of evidence is insufficient to draw conclusions on long-term benefits or harms with single autologous HSCT for the treatment of severe, refractory MS in children.

Moderate strength evidence suggests that an extended drug-free clinical remission can be achieved with single autologous HSCT for the treatment of severe, refractory MS in children.

Crohn's Disease

Background and Setting

Crohn's disease is an idiopathic, chronic inflammatory disease of the gastrointestinal tract that primarily affects the small intestine and colon.

There is wide discrepancy in the prevalence and incidence estimates of Crohn's disease in North America.[656] Prevalence has been estimated between about 44 to nearly 200 per 100,000 persons, perhaps representing the effect of environmental or genetic factors in its development. Similarly, incidence estimates vary considerably, from about 3.1 to about 5 cases per 100,000 person-years; the incidence in children is estimated at about 5 per 100,000. With about 300 million people in the United States, approximately 9,000 to 44,000 cases are diagnosed with Crohn's disease annually.

The natural history of Crohn's disease is characterized by recurring flares with periods of inactive disease and remission.[657] The waxing and waning nature dictates that patients require medication for a large period of their life, primarily to maintain remission but also to control flares. About 50 percent of cases will remain in a state of remission or mild intermittent disease, but about 5 percent will have severe, drug-refractory disease.[656] Surgery is required in up to 80 percent of cases at some point.[657]

While Crohn's disease-related mortality is relatively low, the range and severity of symptoms varies from mild to disabling. The most common symptoms of Crohn's disease are abdominal pain, often in the lower right area, and diarrhea. Rectal bleeding, weight loss, arthritis, skin problems, and fever may also occur. Bleeding may be serious and persistent, leading to anemia. Children with Crohn's disease may suffer delayed development and stunted growth. The most common complication is blockage of the intestine. Nutritional complications are common in Crohn's disease, with deficiencies of proteins, calories, and vitamins. These deficiencies may be caused by inadequate dietary intake, intestinal loss of protein, or poor absorption, also referred to as malabsorption. Other complications associated with Crohn's disease include arthritis, skin problems, inflammation in the eyes or mouth, kidney stones, gallstones, or other diseases of the liver and biliary system. Some of these problems resolve during treatment for disease in the digestive system, but some must be treated separately.

Current therapy for Crohn's disease consists of corticosteroids, immunomodulators and biological therapy blocking TNF-alpha (e.g., infliximab).[657] Corticosteroids efficiently suppress inflammation, but have not been shown definitively to alter the natural course of Crohn's disease. Immunomodulators and biologicals such as azathioprine, 6-mercaptopurine, methotrexate, etanercept, and infliximab can induce and maintain remission, but their overall effect on the long-term course of Crohn's disease and the ultimate need for surgery are not definitively established.[657] Their postoperative role also is not defined. In general, the optimal timing of therapies relative to disease course is not clear.

Autologous HSCT has been used to treat a small number of pediatric Crohn's disease cases, all of which have been severe, progressive, disabling, and refractory to nearly all drug therapies. Accordingly, this systematic review will present only results from HSCT reports, with the comparison considered usual care and the disease course.

Evidence Summary

The overall grade of strength of evidence for drug-free clinical remission and the use of HSCT for the treatment of severe, refractory Crohn's Disease is shown in Table 130.

The evidence signals that autologous HSCT following chemotherapy-induced immune suppression may be associated with prolonged resolution of severe, refractory, disabling Crohn's disease into a drug-free, much-improved state, 3 to 6 months post-HSCT.

Table 130. Overall grade of strength of evidence for drug-free clinical remission and the use of HSCT for the treatment of severe, refractory Crohn's disease

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/Conclusion
For pediatric patients with severe, refractory, disabling Crohn's disease (CD), what is the comparative effectiveness and harms of autologous HSCT and drug therapies? All patients in these studies had severe, refractory, disabling disease, with very poor prognosis, so the comparator is usual care and natural history. Outcomes of interest include extended, drug-free clinical remission, TRM, and other long-term benefits and harms.	There is one case series that reports a total of 4 pediatric patients and one long-term follow-up study that reports 3 new pediatric patients.	The risk of bias is high.	The consistency of the evidence on TRM and long-term benefits and harms is unknown. The evidence is consistent in showing an extended drug-free interval and clinical remission can be achieved with autologous HSCT.	Drug-free clinical remission of severe, refractory, disabling CD in the short-term is considered a health outcome. There is direct evidence that an extended drug-free clinical remission can be achieved with autologous HSCT. The evidence comparing usual care is indirect.	The precision of the evidence for long-term benefits and harms is unknown. The evidence that an extended drug-free clinical remission can be achieved with autologous HSCT is precise. The precision of the evidence comparing usual care is unknown.	Not applicable due to lack of obvious effect size for adverse events including TRM. Strong strength of association for achieving an extended period of drug-free clinical remission following HSCT (7 of 7, 100%), ranging from 7 to 60 months.	The overall body of evidence is insufficient to draw conclusions on long-term benefits and harms with single autologous HSCT in children with severe, refractory, disabling CD. Although the overall body of evidence is insufficient to come to conclusions about the relative balance of benefits (e.g., increased overall survival) or harms (treatment-related mortality, secondary malignancies), moderate strength evidence suggests that an extended clinical remission, free from immune suppressant therapy following taper and discontinuation of corticosteroids 3-6 months post-HSCT, can be achieved with single autologous HSCT in children with severe, refractory, disabling CD.

Results

Two reports were included in this review. Table 131 shows the criteria that were used to select studies for this section.

Table 131. Crohn's disease study selection criteria

Study Design	Population	Intervention	Comparator	Outcomes	Followup	Setting
Any study design	Pediatric patients (0-21 yrs) with severe, refractory Crohn's Disease	Autologous HSCT	None applicable	Survival, drug-free remission post-HSCT, HSCT-related adverse events	All durations of followup	In-patient

One pilot study[658] and one long-term follow-up study[659] (Table 132) reported results on the use of autologous HSCT utilizing a conditioning regimen of high-dose cyclophosphamide plus equine or rabbit ATG and T-cell depleted CD-34+ enriched peripheral blood stem cells mobilized with cyclophosphamide and G-CSF. Mesna, methylprednisolone, and G-CSF were started in conjunction with the conditioning regimen.

Patients were 5 males, ages 15-21 years, and 2 females, ages 18 and 21 years. Pretransplant CDAI scores averaged 288 ± 37 (range: 101-337), with mean Karnofsky performance score (KPS) of 48 ± 10 (range: 40-60). All were highly symptomatic, completely disabled, with a clinical history and histologic evidence of Crohn's disease, and had failed treatment with corticosteroids, mesalamine, metronidazole, azathioprine, 6-mercaptopurine, and infliximab. Failure was defined as a Crohn's Disease Activity Index (CDAI) of 250-400 despite those therapies. All immunosuppressive and disease-modifying agents were discontinued at stem-cell mobilization, except systemic corticosteroids, which were tapered over 2 to 6 months. The key outcome was clinical remission, defined as CDAI≤150, and freedom from immune suppressant therapy following taper and discontinuation of corticosteroids post-HSCT. Adverse effects of autologous HSCT were also reported.

Table 132. Crohn's disease study characteristics and population

Study	Design	Age Range (yrs)	Mean Age (yrs)	Sex F (%)	Disease Stage	HSCT (N)	Comparator (N)	Treatment Period
Oyama, 2005[658]	Phase I	15-21	17 ± 3	25	Severe, disabling refractory to all standard treatments	4	NA	NR
Burt, 2010[659]	Phase I/II	16-21	18	33	Severe, disabling, refractory to all standard treatments	3	NA	NR

In the Oyama pilot study, all patients were alive at mean followup of 24 ± 15 months (range: 7-36 months).[658] They had a rapid and dramatic post-HSCT improvement, discontinued all immunosuppressive therapies, regained normal appetite and oral intake, with cessation of diarrhea and abdominal pain. The mean CDAI score improved by 77 percent, declining from 288 ± 37 (range: 250-337), to 66 ± 13 (range 51-78). The mean Karnofsky Performance Status

improved by 92 percent, from 48 ± 10 (range: 40-60) to 92 ± 10 (range: 80-100). Adverse HSCT-related events were not individually documented, but the procedure was reported as well tolerated. One patient (not identified) developed Mallory-Weiss syndrome that responded to intravenous fluids. One patient (unidentified) relapsed at 15 months after achieving remission at 6 months. Among the total patient population (pediatric cases not reported separately), after a median follow-up of 18 months (range 7-37 months) 11 of 12 remained in drug-free clinical remission.

In the second report,[659] all 3 patients not previously reported in the Oyama paper[658] were alive at 60 months follow-up, in an immune suppressant drug-free state but still with active Crohn's disease. All had undergone colectomy with or without ileostomy at 18 to 44 months following HSCT.

Ongoing Research

According to ClinicalTrials.gov, two Phase I clinical trials in the U.S. are recruiting pediatric patients with severe Crohn's disease (CDAI>250) for autologous HSCT (NCT00692939, NCT00278577).

Conclusion

The overall body of evidence is insufficient to draw conclusions on long-term benefits and harms with single autologous HSCT in children with severe, refractory, disabling CD.

Moderate strength evidence suggests that an extended clinical remission, free from immune suppressant therapy following taper and discontinuation of corticosteroids 3-6 months post-HSCT, can be achieved with single autologous HSCT in children with severe, refractory, disabling CD.

Miscellaneous Nonhematologic Autoimmune Diseases

Background and Setting

Myasthenia Gravis

Myasthenia gravis is an autoimmune disease characterized by failure of neuromuscular transmission secondary to destruction of acetylcholine receptors at the neuromuscular junction synapse by anti-acetylcholine antibodies.[660] The estimated incidence of Myasthenia gravis is about 1 per 30,000.[661] It typically presents in adulthood, but has been diagnosed in children as young as one year of age. Myasthenia gravis affects women more than men (67 percent of cases), with a peak onset in the 20s. Spontaneous remissions occur in about 25 percent of patients, but rarely last more than two years and do not typically recur.

Myasthenia gravis is controlled in most cases by the use of acetylcholinesterase inhibitors, but more severe, progressive disease is treated with immunomodulating approaches, including IVIG, corticosteroids, azathioprine, thymectomy, and plasmapheresis.[661] High-dose cyclophosphamide has been used to treat severe MG, with good initial response in 90 percent of cases, although 80 percent have recurrence and require continual immunosuppression by 5 years following treatment.[662] High-dose chemotherapy with allogeneic HSCT has been reported in one case of severe, refractory disease.

Calcinosis Cutis

Calcinosis cutis is a term used to describe a group of disorders in which calcium deposits form in the skin, first described by Virchow in 1855. It occurs in four major types according to etiology: dystrophic, metastatic, iatrogenic, and idiopathic. It may be associated with autoimmune diseases such as dermatomyositis, systemic lupus, systemic sclerosis, and others.[663, 664] The incidence and prevalence of calcinosis cutis in the U.S. is unknown.

Damage caused by calcium deposits may be localized or systemic. Lesions may become painful, limit mobility of an adjacent joint, or compress adjacent neural structures. Ulceration and secondary infection may occur. Vascular calcification may cause ischemia and necrosis of the affected organ. Medical therapy is limited and of unproven benefit. Intralesional corticosteroids, probenecid, colchicine, magnesium or aluminum antacids, sodium etidronate and diphosphonates, myoinositol hexaphosphonate, warfarin, diltiazem, sodium thiosulfate may be effective. Pediatric use of most of these agents is unapproved.

High-dose immunoablation with allogeneic HSCT has been reported in one pediatric patient with diffuse, severe refractory calcinosis cutis.

Overlap Syndrome

An overlap syndrome is an autoimmune disease of connective tissue in which the patient presents with symptoms of two or more diseases. As many as 25 percent of all patients with connective tissue disease show signs of an overlap syndrome. Examples of overlap syndromes include mixed connective tissue disease and scleromyositis, but the exact diagnosis depends from which diseases the patient shows symptoms. In overlap syndromes, features of systemic lupus, systemic sclerosis, polymyositis, dermatomyositis, rheumatoid arthritis and Sjögren's syndrome are found often.[665]

The prevalence of mixed connective tissue disease is not known precisely, falling somewhere between that of systemic sclerosis and polymyositis and systemic lupus. It is found more often in females than males (8:1 ratio), and occurs in children. Morbidity is greater in children than adults, with higher prevalence of myocarditis, glomerulonephritis, thrombocytopenia, seizures, and aseptic meningitis.[665]

Mixed connective tissue disease is viewed as incurable, with variable prognosis. The presentation ranges from mild self-limited disease, to major organ involvement that requires aggressive treatment. No controlled clinical trials have been performed to evaluate therapy in mixed connective tissue disease. Treatment strategies generally involve conventional therapies that are used for other autoimmune diseases such as systemic lupus, systemic sclerosis, and polymyositis. Given the heterogeneous clinical course of mixed connective tissue disease, therapy is individualized according to specific organ involvement and the severity of underlying disease activity. Agents include corticosteroids, antimalarials, methotrexate, cytotoxics (most often cyclophosphamide), and vasodilators, with varying degrees of success.[666]

Nonmyeloablative allogeneic HSCT has been reported in one severe, refractory pediatric case.

Evidence Summary

The overall grade of strength of evidence for drug-free clinical remission and the use of HSCT for the treatment of severe, refractory myasthenia gravis, overlap syndrome, or diffuse calcinosis cutis is shown in Table 133.

One case report each showed prolonged resolution of myasthenia gravis or overlap syndrome into a drug-free, much-improved state following chemotherapy-induced immunosuppression

with allogeneic HSCT. Similarly, immunosuppression and autologous HSCT was followed by complete resolution of disabling diffuse calcinosis cutis in one patient.

Table 133. Overall grade of strength of evidence for drug-free clinical remission and the use of HSCT for the treatment of severe, refractory myasthenia gravis, overlap syndrome, or diffuse calcinosis cutis

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/ Conclusion
For pediatric patients with severe, refractory myasthenia gravis (MG), overlap syndrome (OS), and cutaneous cutis (CC), what are the comparative effectiveness and harms of HSCT and drug therapies? Patients in these reports had severe, refractory, disease, with very poor prognosis, so the comparator is usual care and natural history. Outcomes of interest include long-term drug-free clinical remission, TRM, and other long-term benefits and harms.	There are three case reports on a total of 3 pediatric patients.	The risk of bias is high.	The consistency of evidence cannot be determined for the use of allogeneic HSCT to treat MG or OS, and autologous HSCT to treat CC. The consistency of the evidence for TRM and other long-term benefits and harms of HSCT cannot be determined.	Drug-free clinical remission of severe, refractory autoimmune disease in the short-term is considered a health outcome. There is direct evidence that an extended drug-free clinical remission can be achieved with allogeneic HSCT in MG or OS. There is direct evidence that an extended drug-free clinical remission for at least 2 years can be achieved with autologous HSCT in CC. The evidence comparing usual care is indirect.	The precision of the evidence for HSCT in MG, OS, and CC cannot be determined. The precision of the evidence for TRM and other long-term benefits and harms cannot be determined.	Not applicable due to lack of obvious effect size.	The overall body of evidence is insufficient to draw conclusions on benefits and harms with allogeneic HSCT to treat severe, refractory MG or OS, and autologous HSCT for the treatment of severe, refractory CC is insufficient to draw conclusions. The overall body of evidence is insufficient to demonstrate that an extended drug-free remission can be achieved with allogeneic HSCT to treat severe, refractory MG or OS, and autologous HSCT for the treatment of severe, refractory CC.

Results

A total of three reports for these miscellaneous diseases were included in this review. Table 134 shows the criteria that were used to select studies for this section.

Table 134. Study selection criteria: MG, OS, CC

Study Design	Population	Intervention	Comparator	Outcomes	Followup	Setting
Any study design	Pediatric patients (0-21 yrs) with severe, refractory myasthenia gravis, overlap syndrome, and cutaneous cutis	Autologous or allogeneic HSCT	None applicable	Survival, drug-free remission post-HSCT, HSCT-related adverse events	All durations of followup	In-patient

As shown in Table 135, three case reports are available, one each on the use of allogeneic HSCT to treat myasthenia gravis[667] or overlap syndrome,[668] and one on autologous HSCT to treat calcinosis cutis.[669]

The myasthenia gravis case report outlined the outcome of reduced-intensity, matched-sibling, peripheral blood allogeneic HSCT using busulfan, fludarabine, and alemtuzumab.[667] The patient was severely affected 17-year-old male who had failed prior treatment with pyridostigmine, IVIG, corticosteroids, thymectomy, azathioprine, mycophenolate mofetil, plasmapheresis, rituximab, and high-dose cyclophosphamide.

The patient with overlap syndrome was a 15-year-old female with pulmonary vasculitis, severe Cushing's syndrome, stunted growth, profound adrenal steroid dependency, and iatrogenic liver toxicity secondary to failed treatment with methotrexate and cyclophosphamide.[668] She underwent reduced-intensity allogeneic HSCT using fludarabine, cyclophosphamide, and total body irradiation, followed by infusion of HLA-matched bone marrow stem cells.

The third case report involved a 16-year-old female who had diffuse, severely disabling calcinosis cutis with arthritis, myalgia, anemia, recurrent pulmonary hemorrhage, CNS abnormalities, and painful skin ulcers.[669] Her condition did not adequately respond to corticosteroids, cyclophosphamide, azathioprine, methotrexate, hydroxychloroquine, and thalidomide. She developed pulmonary hypertension and ischemic digital necrosis, at which time she was referred for high-dose immunosuppression and autologous HSCT. Peripheral blood stem cells were mobilized using cyclophosphamide and G-CSF, and reinfused following a conditioning regimen comprising BCNU, etoposide, cytarabine, and melphalan.

Table 135. Miscellaneous nonhematologic autoimmune disease study characteristics and population

Study	Design	Age Range (yrs)	Mean Age (yrs)	Sex F (%)	Disease Stage	HSCT (N)	Comparator (N)	Treatment Period
Strober, 2009[667]	Case report	17	NA	M	Intractable myasthenia gravis, previously treated with pyridostigmine, IVIG, corticosteroids, thymectomy, azathioprine, mycophenolate mofetil, rituximab, and cyclophosphamide	Matched sibling allogeneic	NA	NR
Elhasid, 2004[669]	Case report	16	NA	F	Severe, disabling refractory diffuse calcinosis, previously treated with corticosteroids, cyclophosphamide, azathioprine, methotrexate, hydroxychloroquine, and thalidomide	Autologous	NA	NR
Jones, 2004[668]	Case report	15	NA	F	Severe, refractory overlap syndrome and pulmonary small vasculitis, previously treated with corticosteroids, methotrexate, cyclophosphamide, IVIG, NSAIDs, aspirin	Related donor allogeneic	NA	2002

The patient with myasthenia gravis achieved T- and B-cell immune reconstitution within 7 months post-HSCT, and during the next 12 months was weaned off pyridostigmine, developed normal muscle strength and lost 60 pounds of weight.[667] He experienced mucositis that required total parenteral nutrition and patient-controlled analgesia for 11 days, 1 episode of gram-positive bacteremia that resolved with vancomycin, and CMV reactivation that resolved with ganciclovir. His oropharyngeal muscles and speech normalized, although he still had ophthalmoplegia. At 40 months post-HSCT, despite the presence of elevated acetylcholine receptor antibody levels, he was free of all myasthenia gravis treatments, was able to play basketball, and was reported as completely independent.

The patient with overlap syndrome achieved greater than 90 percent donor chimerism at 12 months post-HSCT.[668] She was weaned off methylprednisolone, IVIG, and asthma medications over the next year, her cushingoid features resolved, she grew approximately 7 inches over 3 years' followup and became a full-time student in a regular classroom. She had no evidence of clinical graft-versus-host disease or systemic infection over 36 months' followup, but continued to have occasional periods of fatigue and mild Gottron-like rash, which was reported to decrease in frequency at followup.

The patient with calcinosis cutis engrafted promptly, with no significant HSCT-related complications reported.[669] She regained mobility and ability to perform unaided activities of daily living, such as sitting, standing, and walking. At 6 weeks post-HSCT, the subcutaneous calcinosis nodules began to liquefy and calcium salts extruded through her skin. Deep calcinosis plaques disappeared, all skin ulcers healed completely, and her pulmonary blood pressure normalized. At 24 months' followup, the patient was free from clinical and laboratory evidence of disease activity.

Ongoing Research

According to ClinicalTrials.gov, one Phase I study is recruiting patients with severe, refractory myasthenia gravis for autologous HSCT (NCT00424489). A Phase I study is recruiting patients with severe, refractory systemic vasculitis and overlap syndrome for autologous HSCT (NCT00278512). No studies are recruiting for HSCT in patients with calcinosis cutis.

Conclusion

The overall body of evidence is insufficient to draw conclusions on benefits and harms with allogeneic HSCT to treat severe, refractory MG or OS, and autologous HSCT for the treatment of severe, refractory CC is insufficient to draw conclusions.

The overall body of evidence is insufficient to demonstrate that an extended drug-free remission can be achieved with allogeneic HSCT to treat severe, refractory MG or OS, and autologous HSCT for the treatment of severe, refractory CC.

Hematologic Autoimmune Diseases

Background and Setting

Evans Syndrome

Evans syndrome is an uncommon autoimmune disease characterized by simultaneous or sequential development of autoimmune thrombocytopenia and autoimmune hemolytic anemia, with some patients also being neutropenic.[670-672] While the etiology is unknown, evidence suggests this disease is secondary to a more generalized immune dysregulation, with several clinical and laboratory features in common with systemic lupus and autoimmune lymphoproliferative syndrome.[671, 673]

The exact frequency of Evans syndrome is unknown. Familial occurrence is rare. It has a chronic, relapsing course, with substantial morbidity and mortality. In a 1997 survey of North American pediatric hematologists, the median reported age at diagnosis was about 8 years (range: 0.2–27 years).[674] This late presentation age may indicate the disease was undiagnosed until the second presentation of cytopenia, which was usually months to years after the first presentation. Evans syndrome in adults has been anecdotally reported. No randomized trials have been conducted in patients with Evans syndrome, and the evidence for treatment is based on case reports, case series, and retrospective studies.[675] Corticosteroids, IVIG, danazol, cyclosporine, azathioprine, cyclophosphamide, vincristine, rituximab, alemtuzumab, and splenectomy have been used, but response to therapy varies even within the same individual.

Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia occurs when an individual develops anti-self antibodies that destroy red blood cells. The incidence of autoimmune hemolytic anemia has been reported in the range of 1 per 50,000 to 75,000, rising with age, mostly as secondary rather than idiopathic disease.[676] In children, the onset of autoimmune hemolytic anemia is more likely to be sudden and severe compared to that in adults. It has a relatively good prognosis in most cases, with good response to corticosteroids, and often not requiring splenectomy. It can develop into a refractory state that does not respond well to steroids, IVIG, azathioprine, cyclophosphamide, plasmapheresis, or splenectomy.

Autoimmune Thrombocytopenia

Chronic autoimmune thrombocytopenia is a disorder of diminished platelet count, secondary to the development of anti-self antibodies directed against platelet surface glycoproteins, resulting in splenic platelet destruction.[677] Acute idiopathic thrombocytopenia purpura has an annual incidence in the U.S. of about 1.6 per 10,000, but it is estimated that chronic idiopathic thrombocytopenia purpura develops in 7 to 28 percent of children who have acute disease. Chronic, refractory autoimmune thrombocytopenia has been reported to have a mortality rate of 4 to 16 percent, largely attributed to bleeding or infection [678]. It may respond to corticosteroids and IVIG, but can become refractory and nonresponsive to immunosuppressants that include cyclophosphamide, azathioprine, vinblastine, mycophenolate mofetil, and rituximab.

Given the poor response among a proportion of patients with severe Evans syndrome, autoimmune hemolytic anemia, and autoimmune thrombocytopenia to immunosuppressant therapies, with attendant serious adverse effects, HSCT has been investigated in a small number of children with severe, refractory Evans syndrome, autoimmune hemolytic anemia, and autoimmune thrombocytopenia.

Evidence Summary

The overall grade of strength of evidence for drug-free clinical remission and the use of HSCT for the treatment of severe, refractory Evans syndrome, autoimmune hemolytic anemia, or autoimmune thrombocytopenia is shown in Table 136.

One case report each showed resolution of Evans syndrome or autoimmune hemolytic anemia into a drug-free, much-improved state following chemotherapy-induced immune suppression with allogeneic HSCT. Similarly, one case report showed resolution of severe, refractory autoimmune hemolytic anemia following autologous HSCT. The single case report of autologous HSCT for autoimmune thrombocytopenia showed no response to the procedure.

Table 136. Overall grade of strength of evidence for drug-free clinical remission and the use of HSCT for the treatment of severe, refractory Evans syndrome, autoimmune hemolytic anemia, or autoimmune thrombocytopenia

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Overall Grade/ Conclusion
For pediatric patients with severe, refractory Evans syndrome (ES), autoimmune hemolytic anemia (AIHA), or autoimmune thrombocytopenia (AITP), what are the comparative effectiveness and harms of HSCT and drug therapies? Outcomes of interest include long-term drug-free clinical remission, TRM, and other long-term benefits and harms.	There are six case reports and two case series, for a total of 18 pediatric patients, who underwent HSCT for severe, refractory ES (n=8), AIHA (n=9), and AITP (n=1).	The risk of bias is high for all diseases evaluated.	The consistency of evidence cannot be determined for the use of allogeneic HSCT to treat severe, refractory ES or AIHA, or autologous HSCT to treat severe, refractory AIHA or AITP.	Drug-free clinical remission of severe, refractory autoimmune disease in the short-term is considered a health outcome. There is direct evidence that an extended drug-free clinical remission can be achieved with allogeneic HSCT for severe, refractory ES or AIHA and autologous HSCT for severe, refractory AIHA.	The precision of the evidence for allogeneic or autologous HSCT in severe, refractory ES, AIHA, or AITP cannot be determined. The precision of evidence on TRM and other long-term benefits and harms of HSCT cannot be determined.	Not applicable due to lack of obvious effect size.	The overall body of evidence is insufficient to draw conclusions about the comparative benefits or harms of single autologous or allogeneic HSCT compared to conventional therapy or disease natural history pediatric patients with severe, refractory ES, AIHA, or AITP. The overall body of evidence is insufficient to conclude that an extended drug-free clinical remission can be achieved with allogeneic HSCT for severe, refractory ES or AIHA and autologous HSCT for severe, refractory AIHA.

Results

A total of seven publications comprising eight studies (six case reports and two case series) on autoimmune hematologic conditions were included in this review. Table 137 shows the criteria that were used to select studies for this section.

Table 137. Study selection criteria: Refractory Evans syndrome, autoimmune hemolytic anemia, or autoimmune thrombocytopenia

Study Design	Population	Intervention	Comparator	Outcomes	Followup	Setting
Any study design	Pediatric patients (0-21 yrs) with severe, refractory Evans syndrome, autoimmune hemolytic anemia, or autoimmune thrombocytopenia	Allogeneic or autologous HSCT	None applicable	Survival, drug-free remission post-HSCT, HSCT-related adverse events	All durations of followup	In-patient

Evans Syndrome

Four studies (three case reports and one case series) described results of allogeneic HSCT in eight patients with severe, refractory Evans syndrome (Table 138).

The case series described 5 cases of Evans syndrome reported to the European Group for Blood and Marrow Transplantation (EBMT) registry between 1984 and 2007[679]. After receiving unspecified standard therapy, patients (100% male, age range 2-21) were referred for allogeneic HSCT (3 bone marrow, 1 peripheral blood, and 1 cord blood) with various combination conditioning regimens including cyclophosphamide, fludarabine, busulfan, thiotepa, ATG, TBI and received immunosuppressive cyclosporine A with either methotrexate or mycophenolate mofetil therapy for GVHD. Three patients were alive at 36, 85 and 113 months following allogeneic HSCT; one was dead from disease at 59 months and one was dead from interstitial pneumonitis at 6 months following allogeneic HSCT.[679] All five patients were reported to have aGVHD (grade 1 n=1, grade 2 n=1, grade 3 n=1, NR n=2) and cGVHD (extensive: n=1, limited: n=1, NR: n=3), but no other HSCT-related adverse events were reported.

In the Connor et al. report, the female subject presented at age 6 months with Evans syndrome.[680] Over the next several years, she was treated with corticosteroids, IVIG, cyclosporine A, mycophenolate mofetil, rituximab alone and with other drugs, and underwent a splenectomy, without experiencing durable remission. Her condition worsened, she developed pulmonary hypertension with dilated right ventricle and tricuspid regurgitation. She was referred for an unrelated, single-antigen mismatched allogeneic HSCT, using a conditioning regimen of alemtuzumab, fludarabine, and melphalan, with cyclosporine A and mycophenolate mofetil as graft-versus-host disease prophylaxis. The patient developed full donor chimerism, was weaned off all immunosuppressants, developed normalized pulmonary pressures, and exhibited normal right ventricular size and function at 10 months following allogeneic HSCT.[680] No HSCT-related adverse events were reported.

A second case report describes the results achieved with an unrelated cord blood HSCT in a 7-year old boy with severe, refractory Evans syndrome who failed a previous double autologous HSCT.[681] His disease was poorly responsive to previous therapy, including corticosteroids, IVIG, cyclosporine A, mycophenolate mofetil, vincristine, vinblastine, cyclophosphamide, rituximab, and danazol. He became pancytopenic, with disfiguring hypercorticism and polyneuropathy, and underwent double high-dose chemotherapy with autologous HSCT, with

temporary improvement. After suffering a massive intracranial bleed, he received a 7/10 HLA-matched female cord blood HSCT, with a conditioning regimen comprising busulfan, ATG, thiotepa and etoposide. The patient developed graft-versus-host disease with grade II skin, liver, and mucosa involvement that resolved after a short course of prednisone and cyclosporine A.[681] At 1.5 years' followup, he was reported with 100 percent donor chimerism, normal blood counts, in good clinical condition, free of graft-versus-host disease and the need for immunosuppressant drugs.

The third case involved a nearly 5-year-old boy who presented with Evans syndrome at age 5 months.[682] His disease responded poorly to courses of therapy with corticosteroids, IVIG, 6-mercaptopurine, danazol, cyclosporine, azathioprine, vincristine, and anti-D, with increasingly worse mucosal bleeding and intracranial hemorrhage. He was referred for a matched-sibling cord blood allogeneic HSCT, with a myeloablative conditioning regimen consisting of total body irradiation, followed by cyclophosphamide, and cyclosporine-A graft-versus-host disease prophylaxis. The patient engrafted with adequate absolute neutrophil count by day 16 post-HSCT.[682] However, he developed graft-versus-host disease with severe pulmonary insufficiency that resolved promptly following high-dose corticosteroid treatment. He ultimately experienced fulminant hepatic failure of unknown origin 286 days after transplant, and died on day 289.

Table 138. Evans syndrome, autoimmune hemolytic anemia, and autoimmune thrombocytopenia study characteristics and population

Study	Design	Age Range (yrs)	Mean Age (yrs)	Sex F (%)	Disease Stage	HSCT (N)	Comparator (N)	Treatment Period
Connor, 2008[680]	Case report	7	NA	100	Severe, refractory ES	1	NA	NR
Urban, 2006[681]	Case report	6	NA	0	Severe, refractory ES	1	NA	2003
Raetz, 1997[682]	Case report	5	NA	0	Severe, refractory ES	1	NA	NR
Daikeler, 2009[679]	Case series	2-21	11	0	Refractory ES	5	NA	unselected (1984-2007)
Paillard, 2000[683]	Case report	8	NA	0	Severe, refractory AIHA	1	NA	1998
De Stefano, 1999[684]	Case report	12	NA	0	Severe, refractory AIHA	1	NA	NR
Daikeler, 2009[679]	Case series	2-14	7	29%	Refractory AIHA	7	NA	unselected (1984-2007)
Huhn, 2003[685]	Case report	17	NA	0	Severe, refractory AITP	1	NA	NR

Autoimmune Hemolytic Anemia

One case series and two case reports describe results on the use of HSCT to treat severe, refractory autoimmune hemolytic anemia (Table 138). The first report involves a boy, 8 years of age, who had severe AIHA that was refractory to prednisone, IVIG, cyclophosphamide, plasmapheresis, and splenectomy.[683] As a consequence of life-threatening anemia, he underwent initial high-dose immunosuppressive chemotherapy with cyclophosphamide plus ATG followed by infusion of peripheral blood stem cells that had been mobilized using G-CSF. Because his

disease did not respond to the initial HSCT procedure, he was treated again with a high-dose BEAM regimen and infusion of autologous stem cells. The patient was considered to be in hematological remission at 35 days following autologous HSCT, with no infectious complications.[683] Although he relapsed at 7 months; this resolved with a course of corticosteroids and he was reported in complete hematological remission at 20 months' followup.

The second autoimmune hemolytic anemia case was that of a 12-year-old male whose disease had failed to respond to prednisone, azathioprine, cyclosporine A, cyclophosphamide, and splenectomy.[684] As his condition worsened, he underwent high-dose immunosuppression using thoraco-abdominal irradiation, cyclophosphamide, and CAMPATH-1G followed by infusion of autologous peripheral blood stem cells mobilized using cyclophosphamide. He relapsed 7 weeks after HSCT, and underwent allogeneic HSCT with HLA-compatible unrelated donor bone-marrow stem cells following conditioning using busulfan, thiotepa, and fludarabine. Graft-versus-host disease prophylaxis comprised cyclosporine A, methotrexate, and ALG. The patient experienced an uncomplicated post-HSCT course, donor cell engraftment, restoration of normal immune system function, beneficial effects on body growth and skeletal deformities, with normal hemoglobin levels at 18 months after allogeneic HSCT without the need for immunosuppressant therapy.[684]

The case series reported on 7 cases of AIHA reported to the European Group for Blood and Marrow Transplantation (EBMT) registry between 1984 and 2007.[679] After receiving unspecified standard therapy, patients (100% male, age range 2-21) were referred for allogeneic HSCT with various combination conditioning regimens including cyclophosphamide, fludarabine, busulfan, thiotepa, ATG, TBI and received immunosuppressive cyclosporine A with either methotrexate or mycophenolate mofetil therapy for GVHD. Of the 7 patients treated, 4 were alive at 3.9, 86, 112, 124 months, respectively. Three patients died during the study, one from hepatic VOD at 0.7 months of followup, one from infectious complications at followup of 1.4 months, and one died from disease progression at 5.2 months followup.[679]

Autoimmune Thrombocytopenia

One pediatric case of autoimmune thrombocytopenia was reported in a nonrandomized Phase I/II study that included patients who had severe autoimmune thrombocytopenia that had not responded to prednisone, IVIG, azathioprine, danazol, plasmapheresis, interferon, or splenectomy.[685] This 17-year-old male underwent high-dose immunosuppression using cyclophosphamide followed by infusion of peripheral blood stem cells that were mobilized by G-CSF treatment (Table 138). The patient did not respond to autologous HSCT.[685]

Ongoing Research

According to ClinicalTrials.gov, no clinical trials of HSCT are recruiting patients with severe, refractory Evans syndrome, autoimmune hemolytic anemia, or autoimmune thrombocytopenia.

Conclusion

The overall body of evidence is insufficient to draw conclusions about the comparative benefits or harms of single autologous or allogeneic HSCT compared to conventional therapy or disease natural history pediatric patients with severe, refractory ES, AIHA, or AITP.

The overall body of evidence is insufficient to conclude that an extended drug-free clinical remission can be achieved with allogeneic HSCT for severe, refractory ES or AIHA and autologous HSCT for severe, refractory AIHA.

Summary and Discussion

This systematic review of HSCT in the pediatric population addresses indications for which there is uncertainty or evolving evidence, often comprising uncontrolled single arm studies and case reports, although for some solid tumors there were substantial numbers of patients reported. Randomized controlled trials were rare for any of the indications included in this systematic review. HSCT is usually reserved for patients or for subgroups of patients who have diseases with very poor prognosis, and often refractory to best available treatment.

The strength of the body of evidence for each indication was assessed according to the principles described in the AHRQ Methods Guide, Grading the Strength of a Body of Evidence When Comparing Medical Interventions, produced by AHRQ. The four required domains—risk of bias, consistency, directness, and precision—were considered for all indications. For most diseases there were no head-to-head comparative studies; in those situations, directness was based on the outcome (e.g., overall survival or other clinically important health outcomes) rather than on the comparison. An optional domain, strength of association (magnitude of effect), was used in this process where a large effect was particularly evident, a prime example again being Wolman's disease where even very small case examples of survival or cure suggest effectiveness of HSCT. Therefore, while risk of bias is presumed to be very high in a body of evidence comprising small numbers of case reports and series, reducing the strength of evidence, the large magnitude of effect—even if only based on case reports and case series—increases our confidence that the intervention can be effective, thereby permitting assignment of strength greater than "insufficient." This does not, however, imply the intervention will succeed in all cases, but that the effects observed can be attributed to it despite absence of controlled data.

For inherited metabolic diseases, controlled trials with sufficient followup are needed to evaluate the long-term balance of benefit and harms associated with HSCT. Some of these diseases have a homogenous and dismal natural history. For example, the implications of transplantation for a rapidly progressing lysosomal storage disorder like Wolman's disease are clear; this is a choice between certain death and potential survival, albeit with associated risk of adverse effects associated with transplant. By contrast, type I autoimmune juvenile diabetes can be managed long-term satisfactorily, at relatively low risk, in a large proportion of children with intensive insulin therapy (IIT) and lifestyle modifications. The risk-benefit ratio for HSCT compared to IIT must take into account contextual factors including potential long-term benefit (cure) and harms, particularly those secondary to cytotoxic chemotherapy. The decision to apply a high-risk procedure such as HSCT to this population is not clear-cut. For most conditions addressed in this systematic review, evidence is insufficient to draw conclusions as to the relative risk-benefit ratio of HSCT versus other management approaches.

For the diseases systematically reviewed here, the strength of evidence for specific outcomes (see below) was high in 2 instances, moderate or low in 19, and was insufficient for the majority (n = 39) of indications and outcomes addressed. The SOA domain provided justification for increasing overall GRADE evidence strength ratings for several diseases, despite absence of a robust body of literature. SOA was not deemed applicable for settings where evidence was inconsistent.

Malignant Solid Tumors (Key Questions 1 and 2)

Evidence suggesting benefit of HSCT compared with conventional therapy:
- Low strength evidence on overall survival suggests a benefit with single HSCT compared to conventional therapy for *high-risk recurrent or progressive anaplastic astrocytoma*.

Evidence suggesting harm of HSCT compared with conventional therapy:
- Low strength evidence on overall survival suggests harm due to higher treatment-related mortality with single HSCT compared to conventional chemotherapy for *nonanaplastic mixed or unspecified ependymoma*.

Evidence suggesting no benefit of HSCT compared with conventional therapy:
- Moderate strength evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for *metastatic rhabdomyosarcoma*.
- Low strength evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for extraocular retinoblastoma with CNS involvement, high-risk Ewing's sarcoma family of tumors, and high-risk relapsed Wilm's tumor.

Insufficient evidence:
- The body of evidence on overall survival with tandem HSCT compared to single HSCT is insufficient to draw conclusions for *high-risk Ewing's sarcoma family of tumors*, *neuroblastoma*, *central nervous system embryonal tumors*, and *pediatric germ cell tumors*.
- The body of evidence on overall survival with single HSCT compared to conventional therapy is insufficient to draw conclusions for *central nervous system embryonal tumors*, *high-risk rhabdomyosarcoma of mixed stages*, *congenital alveolar rhabdomyosarcoma*, *cranial parameningeal rhabdomyosarcoma with metastasis*, *allogeneic transplantation for metastatic rhabdomyosarcoma*, *extraocular retinoblastoma with no CNS involvement*, *trilateral retinoblastoma*, and six types of glial tumor (*newly diagnosed anaplastic astrocytoma*, *newly diagnosed glioblastoma multiforme*, *anaplastic ependymoma*, *choroid plexus carcinoma*, *recurrent/progressive glioblastoma multiforme*, and *nonanaplastic, mixed or unspecified ependymoma*).

Nonmalignant Diseases: Inherited Metabolic Diseases (Key Questions 3 and 4)

The inherited metabolic diseases were split into three categories for this review. Rapidly progressive disease was defined as progression to death within 10 years; the outcome of interest is overall survival. Slowly progressive disease was defined as progression to death of 10 years or greater; the outcomes of interest are neurocognitive and neurodevelopmental outcomes. For diseases that have both rapidly and slowly progressive forms of disease, outcomes of interest are overall survival and neurocognitive and neurodevelopmental outcomes respectively.

Rapidly Progressive Diseases

Evidence suggesting benefit of HSCT compared with conventional therapy:
- High strength evidence on overall survival suggests a benefit with single HSCT compared to conventional management for *Wolman's disease*.

Evidence suggesting no benefit of HSCT compared with conventional therapy:
- Low strength evidence on overall survival suggests no benefit with single HSCT compared to symptom management or disease natural history for *Niemann-Pick Type A*.

Insufficient evidence:
- The body of evidence on overall survival with single HSCT compared to symptom management is insufficient to draw conclusions for *mucolipidosis II* (I-cell disease), *Gaucher disease Type II*, *cystinosis* and *infantile free sialic acid disease*.

Slowly Progressive Diseases

Evidence suggesting benefit of HSCT compared with conventional therapy:
- Low strength evidence on neurodevelopmental outcomes suggests a benefit with single HSCT compared to enzyme replacement therapy for *attenuated and severe forms of MPS II* (Hunter's disease).
- Low strength evidence on neurocognitive outcomes suggests a benefit with single HSCT compared to enzyme replacement therapy for *attenuated form of MPS II* (Hunter's disease).

Evidence suggesting no benefit of HSCT compared with conventional therapy:
- Low strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared to enzyme replacement therapy for *Gaucher Type III*.
- Low strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared to enzyme replacement therapy for the *severe form of MPS II* (Hunter's disease).
- Low strength evidence on neurocognitive or neurodevelopmental outcomes suggests no benefit with single HSCT compared to symptom management, substrate reduction therapy or disease natural history for *MPS III* (Sanfilippo).

Insufficient evidence:
- The body of evidence on neurocognitive or neurodevelopmental outcomes with single HSCT compared to symptom management and/or disease natural history is insufficient to draw conclusions for *Niemann-Pick type C*, *MPS IV* (Morquio syndrome), *aspartylglucosaminuria*, *Fabry's disease*, *β-mannosidosis*, *mucolipidosis III*, *mucolipidosis IV*, *glycogen storage disease type II* (Pompe disease), *Salla disease*, and *adrenomyeloneuropathy*.

Diseases With Both Rapidly and Slowly Progressive Forms

Evidence suggesting benefit of HSCT compared with conventional therapy:
- High strength evidence on number of subcutaneous nodules and number of joints with limited range of motion suggests a benefit with single HSCT compared to symptom management or disease natural history for *Farber's disease Type 2/3*.

Evidence suggesting no benefit of HSCT compared iwth conventional therapy:
- Low strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared to symptom management or disease natural history for *infantile ceroid lipofuscinosis*.

Insufficient evidence:
- The body of evidence on overall survival and/or neurocognitive and neurodevelopmental outcomes with single HSCT compared to symptom management and or disease natural

history is insufficient to draw conclusions for *galactosialidosis* (type unspecified), *Sandhoff disease* (type unspecified), *Farber's disease Type I, infantile GM₁ gangliosidosis, juvenile GM₁ gangliosidosis, infantile Tay-Sachs, juvenile Tay-Sachs*, and *juvenile ceroid lipofuscinosis*.

Autoimmune Diseases (Key Questions 5 and 6)

The main consideration in this systematic review was the comparative balance of long-term benefits and harms of HSCT. With the exception of newly diagnosed type I juvenile diabetes, children in the studies reviewed herein had severe, typically disabling disease, refractory to a wide variety of standard therapies. Thus, the disease natural history in those settings assumed the role of comparator.

Insufficient evidence:

- The overall body of evidence is insufficient to draw conclusions about the comparative benefits (e.g., increased overall survival) or harms (treatment-related mortality, secondary malignancies) of single autologous or allogeneic HSCT versus conventional therapy or disease natural history in patients with *newly diagnosed type 1 diabetes mellitus*, or those with severe, refractory, poor prognosis autoimmune diseases, including: *systemic lupus erythematosus, juvenile idiopathic arthritis, systemic sclerosis, malignant multiple sclerosis, Crohn's disease, myasthenia gravis, overlap syndrome, diffuse cutaneous cutis, Evans syndrome, autoimmune hemolytic anemia*, and *autoimmune cytopenia*.
- Although the overall body of evidence is insufficient to come to conclusions about the relative balance of benefits (e.g., increased overall survival) or harms (treatment-related mortality, secondary malignancies), moderate strength evidence suggests that extended periods of drug-free clinical remission can be achieved in some cases with single autologous HSCT for patients with *newly diagnosed type I juvenile diabetes*, and severe, refractory *juvenile idiopathic arthritis, systemic lupus erythematosus, systemic sclerosis*, and *Crohn's disease*.

This systematic review addresses a broad range of diseases, for the majority of which HSCT is considered only in patients who have diseases with very poor prognosis, refractory to best available treatment. It is only in such settings that the rigors and risks associated with HSCT would likely be considered. These risks include treatment related mortality, iatrogenic infections secondary to neutropenia, potential for secondary malignancy and over the long term cognitive and developmental delays. Families and their physicians face not only the challenges of severe disease, but when these diseases are uncommon or rare, challenges to the accumulation of knowledge about effective therapy are substantial. The present systematic review offered the opportunity to rigorously assess the evidence for HSCT in pediatric disease; simultaneously, it revealed gaps in the evidence, suggesting opportunities to address these.

Cancer research has numerous well-defined conventions for reporting outcomes, but these were not used consistently in the literature. For example, overall survival may be reported as time from diagnosis for newly diagnosed disease or time from recurrence for relapsed disease. When reporting overall survival, papers were often unclear which time point was used in their calculation; some even reported overall survival from time of transplant. Moreover, some papers did not report overall survival at all, but reported only measures related to disease progression. Similarly there was lack of consistency in reporting adverse events. For example, even such an important harm as treatment related mortality was not always reported. Without an explicit statement of the occurrence of treatment-related mortality, it is impossible to ascertain if there

was no mortality or a failure to report the mortality that occurred. Inconsistencies also occurred in the reporting of toxicities, although there are well-defined conventions for grading the severity of toxicity.

There were few randomized controlled trials for any of the indications included in the systematic review. While this might be expected with uncommon and rare diseases, some solid tumors reviewed herein had substantial numbers of patients. For example, some 600 patients underwent tandem HSCT for neuroblastoma. In high-risk Ewing's sarcoma and high-risk rhabdomyosarcoma, more than 250 patients underwent HSCT for each disease. The widespread reporting of aggregated data is another obstacle to evaluating the outcomes of HSCT. For example, it is common to report studies of HSCT that include patients with a variety of diseases without reporting disease specific outcomes. Within a single study, patients with disparate prognosis may be aggregated without reporting stratified results.

The inherited metabolic diseases illustrate how rare the disease, and thus the evidence, can be. Among those included in the systematic review, evidence typically consisted of no more than six cases. Yet some diseases have a homogeneous and dismal natural history. In particular, among diseases we classified as rapidly progressing, or refractory to standard therapies, spontaneous remission is highly unlikely or impossible. Therefore, we attributed the reported results to HSCT. For example, the implications of transplantation for a rapidly progressing lysosomal storage disorder like Wolman's syndrome are clear; this is a choice between certain death and potential survival, albeit with associated risk of adverse effects associated with transplant.

Most autoimmune diseases in children are rare, and particularly in the cases included in this report, represent a daunting therapeutic challenge. With the exception of newly diagnosed type I juvenile diabetes, patients with autoimmune diseases reviewed here had severe, disabling illness that had not responded to or had relapsed following a large number of standard therapies. HSCT was essentially a last resort for these children and adolescents. In a large proportion of subjects in those settings, HSCT was followed by a period of sustained remission of severe symptoms and therefore respite from immune suppressive therapy. While the durability of clinical remission, and the balance of long-term risks and benefits remains unknown, the obvious strength of association permits the conclusion that HSCT was likely causative.

By contrast, type I autoimmune juvenile diabetes can be satisfactorily managed over the long term, at relatively low risk, in a large proportion of children with intensive insulin therapy (IIT) and lifestyle modifications. The risk-benefit ratio for HSCT compared to IIT must balance the potential for long-term benefit (cure) and harms, particularly those associated with cytotoxic chemotherapy agents used in preparation for HSCT. While evidence suggests a sustained period of insulin independence and adequate metabolic control may be achieved with HSCT, the decision to apply this high-risk procedure to this population is not clear-cut. To date, no trials of HSCT in newly diagnosed type 1 diabetes have been conducted or registered in the U.S.

Future Research

The available literature to assess the comparative effectiveness of HSCT to conventional therapy in pediatric patients largely comprised small case series and case reports. The challenges of conducting research in rare diseases or rare disease settings need to be acknowledged. Many of these diseases are very rare, so the pace of patient accrual may be slow; this may be accompanied by changes in practices, both for induction chemotherapy and stem cell transplantation itself and other aspects of management and treatment. Also, patients are likely to

be clinically diverse in terms of disease site, tumor histology or stage, prior and co-interventions, and other factors. Specific recommendations for future research follow.

1. For diseases with adequate patient populations, promote multicenter randomized trials to increase the scientific rigor in which HSCT can be evaluated.

2. Use established registries to standardize the collection of demographic data, treatments, and to facilitate the evaluation of comparative harms and benefits of treatments.

3. Recognizing that observational studies, including case series, and case reports will continue to be attractive to investigators, recommendations to improve the usefulness and generalizability of such studies are:

    - Conduct prospective studies with contemporaneous treatments.
    - Patients in both single arm and comparative studies would be comparable in terms of key variables, such as disease, anatomic site, disease stage, and prior treatment.
    - Consistent reporting of survival outcomes, with a clear definition of the survival time i.e., time from diagnosis, time from transplant or time from recurrence.
    - Consistent harms reporting is essential in facilitating the comparative evaluation two treatments. Complete reporting of treatment related mortality, secondary malignancy, serious infections, and veno-occlusive disease would be standard.
    - Make studies comparative when possible.
    - Multivariable regression analyses can be helpful in controlling for potential confounders, when sufficient sample sizes can be obtained, and would adhere to good modeling practices.[686-692]
    - Guidance for study quality in observational studies has been addressed by Deeks et al.[693]

4. For solid tumors, future studies would focus on single diseases, and collect detailed information on prognostic factors that may allow for more refined stratification of high-risk categories which may highlight those likely to benefit from HSCT and allowing for less uncertainty in the interpretation of results. Followup would be sufficient to assess the impact of HSCT on the development of secondary malignancies and long term impact on neurocognitive development and fertility.

5. For pediatric patients with slowly progressive forms of inherited metabolic diseases, controlled trials with sufficient followup are needed to evaluate the long-term balance of benefit and harms. Trials would use standardized measure of neurocognitive and neurodevelopmental outcomes.

6. For pediatric patients with autoimmune diseases, controlled trials with sufficient followup are needed to evaluate the long-term balance of benefit and harms.

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Acronyms and Abbreviations

aGVHD	acute graft vs. host disease
AHRQ	Agency for Healthcare Research and Quality
AIHA	autoimmune hemolytic anemia
ALCL	anaplastic large cell lymphoma
ALL	acute lymphoblastic leukemia
Allo	allogeneic
AML	acute myelogenous leukemia
ASBMT	American Society for Blood and Marrow Transplantation
AT/ RT	atypical teratoid/rhabdoid tumor
ATG	antithymocyte globulin
Auto	autologous
BAALC	brain and acute leukemia, cytoplasmic
BL	Burkitt-like
BMF	bone-marrow failure
BMT	bone-marrow transplant
CAMT	congenital amegakaryocytic thrombocytopenia
CC	calcinosis cutis
C-CSF	granulocyte colony-stimulating factor
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDC	Centers for Disease Control and Prevention
cGVHD	chronic graft vs. host disease
CI	confidence interval
CIBMTR	Center for International Bone Marrow Transplant Research
CML	chronic myelogenous leukemia
CNS	central nervous system
COCALD	childhood onset of cerebral adrenoleukodystrophy
COG	Children's Oncology Group
CR	complete remission
Cy	cyclophosphamide
DAI	disease activity index
DBA	Diamond Blackfan anemia
DFS	disease-free survival
DFS	disease-free survival
DLBCL	diffuse large B-cell lymphoma
DM	diabetes mellitus
DQ	developmental quotient
DOD	dead of disease
DOT	dead of treatment
EBMT	European Group for Blood and Marrow Transplantation
EDSS	expanded disability status scale
EFS	event-free survival
EPC	Evidence-based Practice Center

ERT	enzyme-replacement therapy
ES	Evans syndrome
ESFT	Ewing sarcoma family of tumors
F	female
FA	Fanconi anemia
FFS	failure-free survival
Flu	fludarabine
GCT	germ-cell tumor
GFR	glomerular filtration rate
GI	gastrointestinal
GVHD	graft versus host disease
GVM	graft versus malignancy
Hb	hemoglobin
HbF	fetal hemoglobin
HDC	high-dose chemotherapy
HL	Hodgkin's lymphoma
HLA	human leukocyte antigen
HR	hazard ratio
HSCT	hematopoietic stem-cell transplant
HU	hydroxyurea
ICGG	International Collaborative Gaucher Group
IIT	intensive insulin therapy
IPI	international prognostic index
IQ	intelligence quotient
IVIG	intravenous immune globulin
JIA	juvenile idiopathic arthritis
JCML	juvenile chronic myelogenous leukemia
JMML	juvenile myelomonocytic leukemia
JRA	juvenile rheumatoid arthritis
KQ	Key Question(s)
L&H	lymphocytic and histiocytic
LBL	lymphoblastic lymphoma
LCL	large-cell lymphoma
LDH	lactate dehydrogenase
LFS	leukemia-free survival
LL	lymphoblastic lymphoma
M	male
MA	meta analysis
MALT	mucosa-associated lymphoid tissue
MDS	myelodysplastic syndrome
MG	myasthenia gravis
MLD	metachromatic leukodystrophy
Mo(s).	month(s)
MPS	mucopolysaccharidosis
MRD	matched related donor
MRD	minimal residual disease

MRI	magnetic resonance imaging
MSC	mesenchymal stem cells
MS	multiple sclerosis
MSD	matched sibling donor
MUD	matched unrelated donor
N, n	number
NA	not applicable
NB	neuroblastoma
NCCN	National Comprehensive Cancer Network
NHL	non-Hodgkin's lymphoma
NHLBI	National Heart, Lung, and Blood Institute
NK	natural killer
NOS	not otherwise specified
NR	not reported
OS	osteosarcoma
OS	overall survival
OS	overlap syndrome
PBSC	peripheral blood stem cells
PBSCT	peripheral blood stem-cell transplant
PDQ®	Physician Data Query
PFS	progression-free survival
Ph+/-	Philadelphia chromosome positive/negative
PICOTS	patients, interventions, comparator, outcomes, timing, setting
PNET	primitive neuroectodermal tumor
PPMS	primary progressive multiple sclerosis
PR	partial remission
PRMS	progressive relapsing multiple sclerosis
Pt(s)	patient(s)
PTCL	peripheral T-cell lymphoma
QOL	quality of life
RA	refractory anemia
RAEB	refractory anemia with excess blasts
RCT	randomized, controlled trial
RMS	rhabdomyosarcoma
RR	relative risk
RRMS	relapsing, remitting multiple sclerosis
RuSH	Registry and Surveillance System in Hemoglobinopathies
sAML	secondary acute myelogenous leukemia
SCD	sickle-cell disease
SCID	severe combined immunodeficiency
SCIG	subcutaneous immune globulin
SCN	severe congenital neutropenia
SCT	stem-cell transplant
SDS	Schwachman Diamond syndrome
SE	standard error
SLE	systemic lupus erythematosus

SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SPMS	secondary progressive multiple sclerosis
SS	systemic sclerosis
SSc	systemic sclerosis
TBI	total body irradiation
TEC	Technology Evaluation Center
TEP	Technical Expert Panel
TFS	thalassemia-free survival
TKI	tyrosine kinase inhibitor
TNF	tumor necrosis factor
TRM	treatment-related mortality
Tx	treatment/therapy
UCB	umbilical cord blood
URD	unrelated donor
VEGF	vascular endothelial growth factor
VLCFA	very long chain fatty acids
VOD	veno-occlusive disease
WBC	white blood cell
WT	Wilms tumor
Yr(s)	year(s)

Appendix A. Search Strategies

Last search date: August 17, 2011

Search Strategy: PubMed/MEDLINE®

All Child: 0-18 years=3709

#107 Search #104 AND #106

#106 Search "Humans"[Mesh]

#104 Search #102 AND #103

#103 Search #55 OR #88 OR #90 OR #101

#102 Search #45 OR #47

#101 Search "Fabry Disease" OR "Fabry's disease" OR "Farber Lipogranulomatosis" OR "Fabry Disease" OR "Fabry's disease" OR "Farber Lipogranulomatosis" OR Gangliosidos* OR "Sandhoff Disease" OR "sandhoff's disease" OR "Gaucher Disease" OR "gaucher's disease" OR "Niemann-Pick Disease*" OR "Tay-Sachs Disease" OR Aspartylglucosaminuria OR "beta-Mannosidosis" OR Mucolipidos* OR "Wolman Disease" OR "Ceroid Lipofuscinos*" OR "Ceroid-Lipofuscinos*" OR galactosialidosis OR Cystinosis OR "Sialic Acid Storage Disease" OR "salla disease" OR "peroxisomal storage disorder*" OR adrenomyeloneuropath* OR "immune cytopenia*"

#90 Search "Ewing's Sarcoma" OR "Wilms Tumor" OR Rhabdomyosarcoma* OR Retinoblastoma* OR Medulloblastoma* OR PNET OR "Primitive Neuroectodermal Tumor*" OR Astrocytoma* OR Mucopolysaccharidos* OR Sphingolipidos* OR "Lysosomal Storage Disease*" OR "Glycogen Storage Disease*" OR "Niemann-Pick Disease*" OR Adrenoleukodystrophy OR "Juvenile Rheumatoid Arthritis" OR "Systemic Lupus Erythematosus" OR SLE OR Scleroderma OR "Crohn Disease" OR "Crohn's disease" OR "Autoimmune Disease*"

#88 Search ((((((((("Mucopolysaccharidoses"[Mesh] OR "Sphingolipidoses"[Mesh]) OR "Lysosomal Storage Diseases"[Mesh]) OR "Glycogen Storage Disease"[Mesh]) OR "Niemann-Pick Diseases"[Mesh]) OR "Adrenoleukodystrophy"[Mesh]) OR "Arthritis, Juvenile Rheumatoid"[Mesh]) OR "Lupus Erythematosus, Systemic"[Mesh]) OR "Scleroderma, Systemic"[Mesh]) OR "Crohn Disease"[Mesh]) OR "Autoimmune Diseases"[Mesh]

#55 Search ((((("Sarcoma, Ewing's"[Mesh] OR "Wilms Tumor"[Mesh]) OR "Rhabdomyosarcoma"[Mesh]) OR "Retinoblastoma"[Mesh]) OR "Medulloblastoma"[Mesh]) OR "Neuroectodermal Tumors, Primitive"[Mesh]) OR "Astrocytoma"[Mesh]

#47 Search "stem cell*" OR "bone marrow"

#45 Search "Bone Marrow Transplantation"[Mesh] OR ("Hematopoietic Stem Cell Transplantation"[Mesh] OR "Peripheral Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Stem Cell Transplantation"[Mesh])

Additional searches were performed using

"stem cell*" OR "bone marrow"
Search "Bone Marrow Transplantation"[Mesh] OR ("Hematopoietic Stem Cell Transplantation"[Mesh] OR "Peripheral Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Stem Cell Transplantation"[Mesh]) OR "stem cell*" OR "bone marrow"

AND

"Precursor Cell Lymphoblastic Leukemia-Lymphoma"[Mesh] OR "Leukemia, Myeloid, Acute"[Mesh] OR "acute lymphoblastic leukemia" OR acute myeloid leukemia"

"Lymphoma, Non-Hodgkin"[Mesh] OR "non-Hodgkin* lymphoma*"

"Hodgkin Disease"[Mesh] OR "hodgkin lymphoma"

"Leukemia, Myelomonocytic, Juvenile"[Mesh] OR "juvenile myelomonocytic leukemia"

"Leukemia, Myelogenous, Chronic, BCR-ABL Positive"[Mesh] OR "chronic myelogenous leukemia"

"Myelodysplastic-Myeloproliferative Diseases"[Mesh] OR "myelodysplastic disease*"

"Neuroblastoma"[Mesh] OR neuroblastoma*

"Leukodystrophy, Globoid Cell"[Mesh] OR "globoid leukodystrophy"

"Leukodystrophy, Metachromatic"[Mesh] OR "metachromatic leukodystrophy"

"Fucosidosis"[Mesh] OR fucosidosis

"alpha-Mannosidosis"[Mesh] OR "alpha-mannosidosis" OR "alpha-mannosidoses"

"Peroxisomal Disorders"[Mesh] OR "peroxisomal storage disorder*" OR adrenoleukodystroph*

"Osteopetrosis"[Mesh] OR osteopetrosis

"bone marrow failure" OR "Fanconi Anemia"[Mesh] OR "Fanconi* anemia" OR "Dyskeratosis Congenita"[Mesh] OR "dyskeratosis congenita" OR "Shwachman-Diamond" OR "Anemia, Diamond-Blackfan"[Mesh] OR "Diamond-Blackfan" OR "Diamond Blackfan"

"Ependymoma"[Mesh] OR ependymoma*

"Glioma"[Mesh] OR glioma*

"Choroid Plexus Neoplasms"[Mesh] OR ("choroid plexus" AND (tumor OR tumour OR tumors OR tumours OR neoplasm*))

medulloepithelioma* OR (supratentorial AND (PNET OR "primitive neuroectodermal")) OR pineoblastoma* OR "cerebral neuroblastoma*" OR ganglioneuroblastoma* OR

ependymoblastoma* OR "atypical teratoid/rhabdoid tumor*" OR "Pinealoma"[Mesh] OR ("Rhabdoid Tumor"[Mesh] AND atypical AND teratoid*) OR "Astrocytoma"[Mesh] OR "Oligodendroglioma"[Mesh] OR astrocytoma* OR oligodendroglioma* OR "glioblastoma multiforme"

"Diabetes Mellitus, Type 1"[Mesh] OR ("type 1" AND (diabetes OR diabetic OR DM)) OR "juvenile diabetes"

"Neoplasms, Germ Cell and Embryonal"[Mesh] AND germ) OR "germ cell tumor*"

Searches were also performed in EMBASE and the Cochrane Central Register of Controlled Trials for the above disease entities.

Additional searches were performed for the disease entities above and NOT the stem cell transplantation set to obtain literature on the therapeutic measures to be used as comparisons.

Diabetes

#15 Search (#10 AND #13) NOT #5 Limits: Humans, Clinical Trial, Editorial, Practice Guideline, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Guideline, English, All Infant: birth-23 months, All Child: 0-18 years, Publication Date from 1995/10/01 to 2010/07/12

#14 Search (#10 AND #13) NOT #5

#13 Search "Immunosuppression"[Mesh] OR immunomodulation OR immunosuppressant OR immunosuppressive OR "immune modulation" OR "immune suppression"

#10 Search "Diabetes Mellitus, Type 1"[Mesh] OR ("type 1" AND (diabetes OR diabetic OR DM)) OR "juvenile diabetes"

#5 Search "Bone Marrow Transplantation"[Mesh] OR ("Stem Cell Transplantation"[Mesh] OR "Peripheral Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Hematopoietic Stem Cell Transplantation"[Mesh]) OR "bone marrow transplant*" OR "stem cell support" OR "stem cell transplant*"

Other Autoimmune Diseases

#23 Search (#20 AND #13) NOT #5 AND (severe OR refractory OR "poor prognosis") Limits: Humans, Clinical Trial, Editorial, Practice Guideline, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Guideline, English, All Infant: birth-23 months, All Child: 0-18 years, Publication Date from 1995/10/01 to 2010/07/12

#22 Search (#20 AND #13) NOT #5 Limits: Humans, Clinical Trial, Editorial, Practice Guideline, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Guideline, English, All Infant: birth-23 months, All Child: 0-18 years, Publication Date from 1995/10/01 to 2010/07/12

#21 Search (#20 AND #13) NOT #5

#20 Search (("Arthritis, Juvenile Rheumatoid"[Mesh] OR "Lupus Erythematosus, Systemic"[Mesh]) OR "Scleroderma, Systemic"[Mesh]) OR "Crohn Disease"[Mesh]

#13 Search "Immunosuppression"[Mesh] OR immunomodulation OR immunosuppressant OR immunosuppressive OR "immune modulation" OR "immune suppression"

#5 Search "Bone Marrow Transplantation"[Mesh] OR ("Stem Cell Transplantation"[Mesh] OR "Peripheral Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Hematopoietic Stem Cell Transplantation"[Mesh]) OR "bone marrow transplant*" OR "stem cell support" OR "stem cell transplant*"

Ewing's Sarcoma

#42 Search #40 NOT #5 Limits: Humans, Clinical Trial, Editorial, Practice Guideline, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Guideline, English, All Infant: birth-23 months, All Child: 0-18 years, Publication Date from 1995/10/01 to 2010/07/12

#41 Search #40 NOT #5

#40 Search (#27 AND #39) AND #32

#39 Search (("Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh])) OR "secondary "[Subheading] OR recurrent OR recurrence OR (stage AND IV) OR secondary OR metastatic OR metastas*

#32 Search "therapeutic use "[Subheading] OR "therapy "[Subheading] OR therapy OR treatment OR therapeutic*

#27 Search "Sarcoma, Ewing's"[Mesh] OR (Ewing* AND sarcoma)

#5 Search "Bone Marrow Transplantation"[Mesh] OR ("Stem Cell Transplantation"[Mesh] OR "Peripheral Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Hematopoietic Stem Cell Transplantation"[Mesh]) OR "bone marrow transplant*" OR "stem cell support" OR "stem cell transplant*"

Wilms Tumor

#52 Search #50 NOT #5 Limits: Humans, Clinical Trial, Editorial, Practice Guideline, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Guideline, English, All Infant: birth-23 months, All Child: 0-18 years, Publication Date from 1995/10/01 to 2010/07/12

#51 Search #50 NOT #5

#50 Search (#48 AND #49) AND #32

#49 Search (("Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh])) OR "secondary "[Subheading] OR recurrent OR recurrence OR (stage AND IV) OR secondary OR metastatic OR metastas* OR "unfavorable histology" OR relapse OR relapsed

#48 Search "Wilms Tumor"[Mesh] OR (wilm* AND (tumor OR tumors OR tumour*))

#32 Search "therapeutic use "[Subheading] OR "therapy "[Subheading] OR therapy OR treatment OR therapeutic*

#5 Search "Bone Marrow Transplantation"[Mesh] OR ("Stem Cell Transplantation"[Mesh] OR "Peripheral Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Hematopoietic Stem Cell Transplantation"[Mesh]) OR "bone marrow transplant*" OR "stem cell support" OR "stem cell transplant*"

Rhabdomyosarcoma

#60 Search #58 NOT #5 Limits: Humans, Clinical Trial, Editorial, Practice Guideline, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Guideline, English, All Infant: birth-23 months, All Child: 0-18 years, Publication Date from 1995/10/01 to 2010/07/12

#59 Search #58 NOT #5

#58 Search (#56 AND #57) AND #32

#57 Search (("Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh])) OR "secondary "[Subheading] OR relapse OR relapsed OR refractory OR "high-risk" OR extraocular OR recurrent OR recurrence

#56 Search "Rhabdomyosarcoma"[Mesh] OR rhabdomyosarcoma*

#32 Search "therapeutic use "[Subheading] OR "therapy "[Subheading] OR therapy OR treatment OR therapeutic*

#5 Search "Bone Marrow Transplantation"[Mesh] OR ("Stem Cell Transplantation"[Mesh] OR "Peripheral Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Hematopoietic Stem Cell Transplantation"[Mesh]) OR "bone marrow transplant*" OR "stem cell support" OR "stem cell transplant*"

Retinoblastoma

#67 Search #65 NOT #5 Limits: Humans, Clinical Trial, Editorial, Practice Guideline, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Guideline, English, All Infant: birth-23 months, All Child: 0-18 years, Publication Date from 1995/10/01 to 2010/07/12

#66 Search #65 NOT #5

#65 Search (#64 AND #57) AND #32

#64 Search "Retinoblastoma"[Mesh] OR retinoblastoma*

#57 Search (("Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh])) OR "secondary "[Subheading] OR relapse OR relapsed OR refractory OR "high-risk" OR extraocular OR recurrent OR recurrence

#32 Search "therapeutic use "[Subheading] OR "therapy "[Subheading] OR therapy OR treatment OR therapeutic*

#5 Search "Bone Marrow Transplantation"[Mesh] OR ("Stem Cell Transplantation"[Mesh] OR "Peripheral Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Hematopoietic Stem Cell Transplantation"[Mesh]) OR "bone marrow transplant*" OR "stem cell support" OR "stem cell transplant*"

Germ Cell Tumors

#74 Search #72 NOT #5 Limits: Humans, Clinical Trial, Editorial, Practice Guideline, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Guideline, English, All Infant: birth-23 months, All Child: 0-18 years, Publication Date from 1995/10/01 to 2010/07/12

#73 Search #72 NOT #5

#72 Search (#70 AND #49) AND #32

#70 Search ("Neoplasms, Germ Cell and Embryonal"[Mesh] AND germ) OR "germ cell tumor*"

#49 Search (("Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh])) OR "secondary "[Subheading] OR recurrent OR recurrence OR (stage AND IV) OR secondary OR metastatic OR metastas* OR "unfavorable histology" OR relapse OR relapsed

#32 Search "therapeutic use "[Subheading] OR "therapy "[Subheading] OR therapy OR treatment OR therapeutic*

#5 Search "Bone Marrow Transplantation"[Mesh] OR ("Stem Cell Transplantation"[Mesh] OR

"Peripheral Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Hematopoietic Stem Cell Transplantation"[Mesh]) OR "bone marrow transplant*" OR "stem cell support" OR "stem cell transplant*"

CNS Embryonal Tumors

#121 Search #120 NOT #117 Limits: Humans, Clinical Trial, Editorial, Practice Guideline, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Guideline, English, All Infant: birth-23 months, All Child: 0-18 years, Publication Date from 1995/10/01 to 2010/07/12

#120 Search (#110 AND #49) AND #32 Limits: Humans, Clinical Trial, Editorial, Practice Guideline, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Guideline, English, All Infant: birth-23 months, All Child: 0-18 years, Publication Date from 1995/10/01 to 2010/07/12

#117 Search "Bone Marrow Transplantation"[Mesh] OR ("Stem Cell Transplantation"[Mesh] OR "Peripheral Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Hematopoietic Stem Cell Transplantation"[Mesh]) OR "bone marrow transplant*" OR "stem cell support" OR "stem cell transplant*"

#110 Search medulloblastoma* OR medulloepithelioma* OR (supratentorial AND (PNET OR "primitive neuroectodermal")) OR pineoblastoma* OR "cerebral neuroblastoma*" OR ganglioneuroblastoma* OR ependymoblastoma* OR "atypical teratoid/rhabdoid tumor*"

#49 Search (("Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh])) OR "secondary "[Subheading] OR recurrent OR recurrence OR (stage AND IV) OR secondary OR metastatic OR metastas* OR "unfavorable histology" OR relapse OR relapsed

#32 Search "therapeutic use "[Subheading] OR "therapy "[Subheading] OR therapy OR treatment OR therapeutic*

CNS Glial Tumors

#131 Search #129 NOT #117 Limits: Humans, Clinical Trial, Editorial, Practice Guideline, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Guideline, English, All Infant: birth-23 months, All Child: 0-18 years, Publication Date from 1995/10/01 to 2010/07/12

#129 Search (#126 AND #128) AND #32

#128 Search ("Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh]) OR relapse OR relapsed OR recurrent OR recurrence OR "high-risk"

#126 Search "Astrocytoma"[Mesh] OR "Oligodendroglioma"[Mesh] OR astrocytoma* OR oligodendroglioma* OR "glioblastoma multiforme"

#32 Search "therapeutic use "[Subheading] OR "therapy "[Subheading] OR therapy OR treatment OR therapeutic*

#117 Search "Bone Marrow Transplantation"[Mesh] OR ("Stem Cell Transplantation"[Mesh] OR "Peripheral Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Hematopoietic Stem Cell Transplantation"[Mesh]) OR "bone marrow transplant*" OR "stem cell support" OR "stem cell transplant*"

Appendix B. Excluded Studies

Retrieval Code (field 12)
DNG   do not retrieve full copy
GET   retrieve full copy
UNC   uncertain; needs check by second reviewer

Two Arms of Study Code (field 12)
NAR   narrative review portion
SYS   systematic review portion

Selection Decision Code
(after reviewing retrieved article, enter into field 12)
INC   include
EXC   exclude (with codes for exclusion reasons)

Full Review Codes (field 42)
I. Key Question Codes
NRQ   not relevant question (note if ANM, NDE, NRD, NRI, NRO)
Q1   comparative benefits HSCT vs Ctx in solid tumors
Q2   comparative harms HSCT vs Ctx in solid tumors
Q3   comparative benefits HSCT vs other Tx in IMD
Q4   comparative harms HSCT vs other Tx in IMD
Q5   comparative benefits HSCT vs other Tx in autoimmune diseases
Q6   comparative harms HSCT vs other Tx in autoimmune diseases
Q#?   unclear if relevant to any key question

II. Study Design Codes
ADB   administrative database
ANM   animal study
CEA   cost/cost-effectiveness analysis
CCS   case-control study
COH   cohort study
COM   commentary
CR   case report (n$\leq$5)
CS   case series
D?   design unclear/possibly relevant
DAC   diagnostic accuracy study
DUP   duplicated patient population
EDT   editorial
FLA   foreign language article
GUI   guideline
INV   in vitro
LTR   letter
MA   meta-analysis
NAB   no abstract
NPC   not relevant comparator
NPD   no primary data
NRD   not relevant disease
NR   not relevant disease b/c part of narrative review
NRE   not relevant design
NRI   not relevant intervention
NRO   not relevant outcome (or no follow-up)
NRP   not relevant population
NRS   not relevant study
PI   phase I trial
PII   phase II trial
PRG   prognostic study
PRO   prospective single-arm study

QEX   quasi-experimental study (nonrandomized comparative)
RAD   radiology study
RCT   randomized controlled trial
REG   registry
RET   retrospective study
REV   review article
SR   systematic review
STG   disease staging study
XSL   cross-sectional study

III. Sample Size Code (single-arm only)
FEW   n < 10
N10 $10 \leq n < 25$
N25 $25 \leq n < 50$
N50 $50 \leq n < 100$
N100 $n \geq 100$
N?   n unclear

IV. Basic Disease Codes
AID   Autoimmune disease
ALD   adrenoleukodystrophy
ALL   acute lymphoblastic leukemia
AMA   alpha-mannosidosis
AML   acute myelogenous leukemia
AMN   adrenomyeloneuropathy
ASP   aspartylglucosaminuria
AST   astrocytoma
BMA   beta-mannosidosis
BMF   bone marrow failure
CLF   ceroid lipofuscinosis
CLL   chronic lymphocytic leukemia
CML   chronic myelogenous leukemia
CNS   CNS tumors, NOS
CRN   Crohn's
CYS   cystinosis
DME   Diabetes mellitus type 1
DNS   disease not specified
ESF   Ewing/Ewing sarcoma family of tumors
ENV   Evan's syndrome
FAB   Fabry disease
FAR   Farber disease
FUC   Fucosidosis
GAL   galactosialidosis
GAUI   Gaucher I
GAUII Gaucher II
GAUIII Gaucher III
GCT   germ cell tumor
GLD   globoid leukodystrophy
GM1 GM_1 gangliosidosis
GSDII glycogen storage disease II
HGB   hemoglobinopathy
HL   Hodgkin lymphoma
IBD   inflammatory bowel disease
ICP   immune cytopenia
IMD   inherited metabolic disease
JML   juvenile myelomonocytic leukemia
JRA   juvenile rheumatoid arthritis
MDS   myelodysplasia
MED   medulloblastoma

MLII mucolipidosis II
MLIII mucolipidosis III
MLIV mucolipidosis IV
MLD metachromatic leukodystrophy
MPSI Hurler syndrome
MPSII Hunter syndrome
MPSIII Sanfilippo syndrome
MPSIV Morquio syndrome
MPSVI Maroteaux-Lamy syndrome
MPSVII Sly syndrome
NBL neuroblastoma
NHL non-Hodgkin lymphoma
NPA Niemann-Pick A
NPB Niemann-Pick B
NPC Niemann-Pick C
OSC osteosarcoma
OST osteopetrosis
PID primary immune deficiency
PNET primitive neuroectodermal tumor
RBA retinoblastoma
RMS rhabdomyosarcoma
SAL Salla disease
SAN Sandhoff disease
SAS sialic acid storage disease
SCL scleroderma/SS
SLE systemic lupus erythematosus
STG stage of disease
STS soft tissue sarcoma
TAY Tay-Sachs disease
WIL Wilms tumor
WOL Wolman disease

IV. Disease code modifiers
HR high risk
LR low risk
MET metastatic
NEW newly diagnosed
PRD progressive disease
REC recurrent disease
REF refractory
REL relapsed
REM remission
SEV severe
STG stage of disease

V. Disease Code Characteristics
GRW growth
HRD hearing defects
HSM hepatosplenomegaly
IQ intelligence quotient
JNT joint
MR mental retardation
NCD neurocognitive development
NMD neuromuscular development
ORT orthopedic/skeletal
SOH state of health
SPE speech
SZS seizures

V. Intervention Codes
AUT autologous HSCT
ALO allogeneic HSCT
BSC best supportive care

CHM chemotherapy
CRT chemoradiotherapy
ERT enzyme replacement therapy
HSCT hematopoietic stem cell transplantation
IMM immune suppression
INS insulin therapy
PAL palliative
PRI primary treatment (previously untreated)
SEQ sequential high-dose chemotherapy with single autologous HSCT
SUR surgery only
T? treatment unclear
TAN tandem autologous HSCT
TBI total body irradiation
UMB umbilical cord blood HSCT

VI. Outcome Codes
CNR continuous remission
CRM complete remission
CVS cardiovascular AE
DFR drug free remission
DFS disease-free survival
DSS (cancer) disease-specific survival
EFS event free survival
ENG engraftment
ESO esophagus AEs
FU? follow-up uncertain
GVH graft versus host disease
INF infection
HEM hematologic toxicities
HEP hepatic AEs
HRT heart AEs
LC local control
LNG lung AEs
LRC locoregional control
MFS (distant) metastasis-free survival
MIR minor response
MUC mucositis
NV nausea/vomiting
OAE other AE
OS overall survival
OTE other time-to-event outcome
OTO otologic/auditory AEs
O? outcome unclear
PFS progression-free survival
PR partial remission
PRD progressive disease
QOL quality of life
RFS recurrence free survival
REN renal toxicities
RET retinopathy
RSP tumor response
SEL serum enzyme levels
SKN skin AEs
STD stable disease
TAE toxicity/adverse events (not specified)
TRM treatment-related mortality
TTR time-to-recurrence
VPR very good partial response

Excluded Studies: Original Review

[No Author]. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. J Pediatr 1994 125(2):177-88.
Rec#: 75370
Reprint: exc nrp

[No Author]. Adverse events and their association with treatment regimens in the diabetes control and complications trial. Diabetes Care 1995 18(11):1415-27.
Rec#: 62830
Reprint: exc nrp

[No Author]. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol 1998 116(7):874-86.
Rec#: 62640
Reprint: exc nrp

[No Author]. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. The Diabetes Control and Complications Trial Research Group. Ann Intern Med 1998 128(7):517-23.
Rec#: 62660
Reprint: exc nrp

[No Author]. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. N Engl J Med 2000 342(6):381-9.
Rec#: 62520
Reprint: exc nrp

Abbott, I. R., S. J. Gaskill, T. C. Hayes, and B. J. Menick. 28-Month-Old girl with delayed ambulation and speech. Pediatr Neurosurg 2000 33(3):162-6.
Rec#: 76430
Reprint: exc nro

Abd El-Aal, H. Role of radio-iodinated meta-iodo benzyl guanidine in assessment of children with neuroblastoma at NEMROCK. J Egypt Natl Canc Inst 2006 18(4):375-81.
Rec#: 2370
Reprint: exc nrp

Abdel-Haq, N., S. Savasan, M. Davis, B. I. Asmar, T. Painter, and H. Salimnia. Asaia lannaensis bloodstream infection in a child with cancer and bone marrow transplantation. 2009.
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Appendix C. Systematic Review Data Abstraction

Appendix Table C1. Design, participant selection and enrollment: Ewing's tumors

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Bernstein, USA/Canada 2006	6290	malig nh	esft	mets at dx	110		phase 2 study	110	0	
Bhatia, USA, 2007	43210	malgi nh	esft	metastatic dz	60	1992-1994	Children's Oncology Group therapeutic protocol	60		protocol also included less intense CT regimens for other subgroups-not abstracted
Burdach, Germany and Austria, 2000	14310	malig nh	esft	relapse (early, late or multiple) or primary multifocal disease	28	1986-1994	cs	28	0	
Burdach, Germany, 2003	10030	malig nh	esft	primary multifocal or early relapse	32	1986-1994 (single HSCT) 1995-2000 (tandem HSCT)	Comparative study using historical controls	32	0	study included 54 patients who underwent single or tandem HSCT and survival reported as <=17 yrs of age or >17
Burke, USA 2007	4060	malig nh	esft	"high risk" defined as pelvic primary (n=5) and/or mets (n=4)	7	1992-2003	consecutive pts with es	7	0	One pt age 23 not abstracted
Costa, USA, 2008	1710	malig nh	esft	NR	1	2000-2007	CR	1	0	
Drabko, Poland 2005	6680	malig nh	esft	"high risk"- 1st line therapy with mets or relapse	21	1996-2002	cs from two centers	21	0	

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Fazekas, Austria, 2008	2720	m nh	esft	CR1	1		CR	1	0	
Hara , Japan 1998	17950	malig nh	esft	advanced dz or CT-resistant or relapse relapse n=1	3	1993-1997	cs	3	0	
Harimaya, Japan, 2003	9850	malig nh	esft	primary dx, high-risk (spinal column)	2		cs	2	0	
Hawkins, USA 2000	15360	malig nh	esft	grp 1: CR2 n=8 PR2 n=1 grp 2: CR1 n=2 CR2 n=2 CR3 n=1 PD n=2	grp 1 n=9 grp 2 n=7	1993-1997	cs	16	0	2 different conditioning regimens used grp 1 and grp 2
Kasper, Germany, 2006	2570	malig nh	esft	upfront therapy, 3 with mets transplanted in CR n=4 and PR n=1	5	1998-2004	cs	5	0	other patients >21 yrs not abstracted
Kogawa, Japan, 2004	8410	malig nh	esft	primary dx	1		cr	1	0	
Koscielniak Germany 2005	7860	m nh	esft	relapsed after tandem auto-auto HSCT	1	1998	CR	1	0	
Kushner, USA, 1995	21430	malig nh	esft	newly dx'd poor risk b/c of tumor volume >100 cm3 or mets to bone or BM	24		Prospective CS	24	0	
Kushner, USA, 2001	14240	malig nh	esft	newly diagnosed with mets to bone or BM - if achieve VGPR or CR, eligible for HSCT	10	1990-1998	cs	10	0	only abstracted pts <21 for HSCT and the 5 pts <21 who did not proceed to HSCT

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Laws, Germany, 2003	9450	malig nh	esft	relapsed	2	1988-1998	cr	2	0	study included a total of 18 patients, but age was only reported for 2 pts
Lucas, USA 2008	2450	malig nh	esft	relapsed with mets	1		CR	1	0	
Lucidarme, France, 1998	17610	malig nh	esft	refractory dz 1st PR n=1 2nd PR n=1 PD n=1	3	1987-1995	phase 2 study	3	0	
Meyers, USA, 2001	13670	malig NH	ESFT	newly diagnosed metastatic to bone and/or BM	32	Feb 1996-Nov 1998	CS	32	9 patients did not proceed to HSCT b/c 4 had progressive dz, 2 secondary to toxicity and 3 who died from toxicity during high-dose phase of the therapy.	
Milano, Italy, 2006	43290	malig nh	esft		36	1990-2005				
Navid, US and Canada, 2006	5930	malig nh	esft	mets or tumor >8cm	11	1996-2000	prospective phase II trial	9	2	

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Numata, Japan, 2002	12130	malig nh	esft	primary dx	1	May 1996	CR	1	0	
Oberlin, France, 2008	46850	malig nh	esft	newly dxd with mets		1991-1999	cs			study transplanted 75 patients; survival data reported as <15 yrs of age and >=15; only abstracted <15 yr data
Ozkaynak, USA 1998	18540	malig nh	esft	2nd CR n=4 2nd VGPR n=5 1st CR n=5 1st VGPR n=1 (5 pts transplanted in 1st CR or VGPR were high-risk- 4 with mets at dx bone and/or BM and one had large pelvic primary)	15	1992-1995	cs	15	0	
Pession, Italy, 1999	16120	malig nh	esft	CR 2 n=2 PR n=1	3	1992-1994	cs	3	0	
Prete, Italy 1998	17210	malig nh	esft	"high risk" (large pelvic mass and/or metastatic dz)	17	1993-1997	cs	17	0	

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Sari, Turkey, 2010	42790	malig nh	esft	mets at dx	36	1992-2005	CS	36	0	study included pts with nonmet dz- did not abstract b/c only survival report for high risk pts was by mets vs nonmets
Tanaka, Japan, 2002	11770	malig NH	ESFT	PD n=1 CR1 n=5	6	"HSCT since 1986"	CS	6		one patient 35 y/o not abstracted
van Winkle, USA, 2005	43550	malig nh	esft	recurrent/refractory	22	1992-1996	CS	22	0	
Yaniv, Israel, 2004	9100	malign nh	esft	"high risk" mets at dx, poor response to CT defined as <90% necrosis at definitive surgery, primary tumor not resecAppendix Table 1, relapsed	11			11	0	
Burdach, Germany and Austria, 2010	2077	ET multiple primary bone mets	ESFT	high-risk ET with multiple primary bone mets	group A n = 8 (<=17 yrs) group B n =13 (<=17yrs) (Total N = 37)	group A: 1995 - 2000 group B: 1992 - 1996	CS	21	0	

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Diaz, Spain, 2010	2135	NH- solid tumor	ESFT	high-risk localized tumor (tumor volume >200mL, inoperable tumor, or poor histological response to neoadjuvant CT) and those with mets at diagnosis	47	1995-2009	retrospective CS	47	0	
Ilari, Italy, 2010	2230	NH solid tumor	ESFT	Poor prognosis ESFT (metastasis or axis location, or tumor >200 mL or necrosis <95%)	26	1998-2007	consecutive patients, retrospective review	24- 2 patients rapidly progressed during induction and did not proceed to HSCT		
Ladenstein, Austria, France, UK, Switzerland, Netherlands, Germany, Sweden, 2010	2270	primary disseminated multifocal Ewings	ewings sarcoma	Primary treatment	n=99 < 14 years of age (entire study included 281 patients median age 16.2 years (range 0.4-49 years)- survival data divided <=14 years of age and >14	1999-2005	Prospective CS	99	0	

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Kwon, Korea, 2010	2268	NH solid tumor	Ewings sarcoma		1	2005-2007	retrospective chart review	1	0	

Appendix Table C2. Participant characteristics:Treatment, Ewing's tumors

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Burdach, Germany and Austria, 2000	14310	28		at tx 15 yrs (8-21)		50,50		primary site for relapsed: long bone n=9 pelvis n=1 scapula n=1 chest wall/rib n=1 primary site for multifocal disease: various	entire study incl 36 pts; only abstracted <21 yrs old
Burdach, Germany, 2003	10030	32			<= 17 yrs				
Burke, USA 2007	4060	7		14 yrs (.5-17)		71, 29	mets in 4 (lung n=2, bone BM and liver n=1, bone and lung n=1)	primary tumor site pelvis n=5 scapula n=1 chest wall n=1	
Costa, USA, 2008	1710	1	15 yrs at first HSCT			NR	NR	es	
Drabko, Poland 2005	6680	21		at tx 15 yrs (6-21)		52,48	at HSCT: CR1 n=10 CR2 n=1 PD n=1 PR n=9	pelvis n=3 long bone n=9 vertebra n=1 sternum or clavicle n=3 scapula n=1 rib n=1 skull n=1 NR n=2	
Fazekas, Austria, 2008	2720	1	13 yrs at diagnosis			100,0	stage IV	pelvis	
Hara , Japan 1998	17950	3		5 yrs (2-12)			relapsed n=1 stage 3 n=1 stage 4 n=1	PNET n=2 ES n=1	
Harimaya, Japan, 2003	9850	2	12yrs and 14yrs			50,50	localized to spinal column		

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Hawkins, USA 2000	15360	16		at HSCT 14.6 yrs (6-21)				grp 1 2/9 with mets; primary tumor site long bone n=5, axial n=3, kidney n=1 grp 2: 4/7 mets; primary tumor site long bone n=2 axial n=5	
Kasper, Germany, 2006	2570	5		at HSCT 19 (17-21)				mets: lung n=2 bone n=1	
Kogawa, Japan, 2004	8410	1	7 yrs			0,100		primary cervical spine, epidural, extra-osseous	
Koscielniak Germany 2005	7860	1	15 YEARS AT TANDEM TX 15 yrs + 8 mos at relapse/allo			0,100	initial stage - disseminated dz with BM mets		
Kushner, USA, 2001	14240	5		16.5 y (8-21 yrs)		70,30	mets to bone or BM	primary site of tumor pelvis n=4 long bone n=3 chest wall n=1 paraspinal n=1 perineum n=1	
Laws, Germany, 2003	9450	2			at HSCT 14 yrs and 19 yrs	0,100	relapsed	primary tumor femur n=2	
Lucas, USA 2008	2450	1	4 YRS			0,100	stage IV	iliac crest with mets to BM, multiple vertebrae, ribs, bilateral lung	
Lucidarme, France, 1998	17610	3		8.5 yrs (2-17) at 1st tx		68, 32	mets at HSCT n=3		age is median for all 22 patients in this mixed study

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Meyers, USA, 2001	13670	32		13 yrs (1-22)		62,38	metastatic to bone or BM	primary site: pelvis n=12 chest wall n=5 femur n=3 multiple sites n=6 other n=6	
Navid, US and Canada, 2006	5930	9		14.9 yrs (11.7-17.4 yrs)		67, 33	nomets n=3 mets n=6)5 underwent HSCT	HSCT pubis n=1 kidney n=1 chest wall n=1 femur n=1 rib n=1 no HSCT ilium n=1 thorax n=1 leg n=1 rib n=1	
Numata, Japan, 2002	12130	1	20 years at HSCT			0,100		ES- inguinal area	
Oberlin, France, 2008	46850			12.3 yrs (2 m0s-25 yrs))		59,41			
Ozkaynak, USA 1998	18540			15 (5-21)		53,47			
Pession, Italy, 1999	16120	3		6 yrs (3-12)		33,66			
Prete, Italy 1998	17210			8 (5-14)		65,35	metastatic dz at dx n=14 localized dz at dx n=3 BM involvement n=3		
Tanaka, Japan, 2002	11770	6		at dx 17.5 yrs (8-19)		66,33	"hi risk" incl large tumor size, pelvic location,lung mets, pleural cavity involvement	sternum with pleural cavity disssem n=1, ilium n=2 (one with sacral invasion), spinal cord n=1, chest wall with lung involvement n=1 and humerus n=1	

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Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Yaniv, Israel, 2004	9100	11		13 yrs (0.3-19)		64,36		scapula n=1 cranium n=1 ilium n=3 femur n=2 abdomen n=1 radius n=1 sacrum n=2	
Ladenstein, Austria, France, UK, Switzerland, Netherlands, Germany, Sweden, 2010	2270	99 (<= 14 years old)	Not reported separately for <= 14 years	Not reported separately for <= 14 years	Not reported separately for <= 14 years	Not reported separately for <= 14 years	disseminated multifocal	Ewing's sarcoma Primary not reported separately for <= 14 years but for entire study population of 281 patients, extremity 31%, chest/spine/head and neck 24%, abd/pelvis 45% and sites of mets BM plus lung 10%, bone plus lung 45%, bone plus BM plus lungs	36%, other plus lungs 10%
Ilari, Italy, 2010	2230	24		103 months (range 12-192 months)		42,58	localized n=16 metastatic n=8	primary tumor extremity n=7 axial n=17 Sites of mets lung n=5, BM n=3, bone n=3, other n=2	
Diaz, Spain, 2010	2135	47		13 years (4-21 yrs)		68, 32	localized/regional at diagnosis 57% with metastases at diagnosis 43%	primary site of tumor distal extremity 23%, proximal extremity 13%, pelvis 30%, chest 19%, spine/paravertebral 15%	
Kwon, Korea, 2010	2268	1	8 years			100,0	stage 4		

Appendix Table C3. Participant characteristics: Comparator, Ewing's tumors

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Bernstein, USA/Canada 2006	6290	110		14.6 yrs (3.0-27.3)	white 74% Afr Amer 6% Hispanic 15% other 5%	61,39		primary site extremity 36% pelvis 29% spine 5% chest wall 16% other 14% mets site isolated lung 35% lung + other 15% isolated bone 13% isolated BM 7% other 30%	12% of patients between 20-31 yrs old
Bhatia,USA, 2007	43210	60		total cohort (which included pts that rec'd lesser intensity regimens than the n=60) age at dx: 12 yrs (0-30)		56,44			
Kushner, USA, 1995	21430	non-metastatic dz n=17 metastatic dz n=7		nonmet 15 yrs (1.5-21) mets 17 yrs (9-21)		non met 76,24 met 86,14		nonmets (ESFT and PNET): primary tumor site chest wall n=4 long bone n=7 paraspinal n=1 pelvis n=3 thigh n=1 retroperitoneal n=1 mets: primary tumor site long bone n=3 pelvis n=3 perineum n=1 sites of mets lung only n=3 mult sites incl bone or BM n=4	

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Milano, Italy, 2006	43290	36		115 mos (20-214)			"high risk"- tumor vol >200 ml or site with poor px (pelvis, chest wall or vertebra) or pulmonary or BM mets at dx First diagnosis pts with mets n=16 (44%)	pelvis n=9 (5 bone and 4 soft tissue) femur n=2 scapula n=2 hip n=2 clavicle n=1 vertebra n=4 humerus n=3 tibia n=3 abdomen n=2 rib n=1 fibula n=2 chest wall n=4 pretibial soft tissue 1 foot soft tissue 1 radius 1 mets lung n=9 BM mets n=7	
Sari, Turkey, 2010	42790	36	all pts <18 yrs old for pts with mets 89% <15 and 11% >=15			39,61		primary tumor chest wall n=4 vertebra n=3 pelvis n=10 extremity n= 19	
Van Winkle, USA, 2005	43550	22		14.1 yrs (2.8-22.5 yrs) age of all pts in the study which included other tumor types besides ESFT		57,43	recurrent/refractory 1 pt with extraosseus ESFT	sites of recurrence lung 28% extremity 28% pelvis 10% H/N 10% other 24%	

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Burdach, Germany and Austria, 2010	2077	8	14	15 yrs	NR	37, 63	high-risk ES (>3 involved bones) LN mets (n=2) and lung disease (n=6)	sternum n=1, VC n=7, pelvis n=7, lung n=4, LN n=1, MB nonspecified n=1, rib n=1, humerus n=4, cranium n=3, scapula n=1, femur=3, fibula=1, tibia=1, talus=1, clavicle n=1	

Appendix Table C4. Treatment characteristics: Ewing's tumors

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Bernstein, USA/Canada 2006	6290	110							CT +/- complete surgical resection +/- full-dose RT or lower dose RT to microscopic residual dz.Up to 3 metastatic sites excl BM with RT	CT: I, E, vincr, doxorub, CPM)	
Bhatia,USA, 2007	43210	60							high-intensity CT	doxorubicin, CPM and ifos	
Burdach, Germany and Austria, 2000	14310	28	for auto [n=21] BM n=2 PB n=17 BM+ PB n=2 for allo [n=7] all BM	auto n=21 allo n=7		MEL, Eto, Carbo, TBI n=10 MEL, E, TBI n=15 MEL, E, carbo n=1 MEL, TBI n=1 E, TBI n=1					

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Burdach, Germany, 2003	10030	<+17 yrs single HSCT n=18 tandem n=14		single auto or tandem auto auto	all pts recd local RT to met sites	single TBI,MEL,E +/- carboplatin tandem MEL, E times 2					
Burke, USA 2007	4060	7	pb	single auto n=1 tandem auto n=6	complete surgical resection n=6 no surgery n=1 RT n=2 (one to primary tumor and one to an orbital met)	1st: Eto, Carboplatin, CPM 2nd: MEL, CPM n=4; Thio, CPM n=1; MEL and TBI n=1		rec'd for fever, nutrition and hematologic indications prn (n=7)			All pts achv'd CR after first HSCT; only 6 went on to 2nd HSCT b/c one pt progressed with local and metastatic dz 30 days after 1st HSCT
Costa, USA, 2008	1710	1	NR	auto	vincristine, CY, doxorubicin, ifos, VP-16						

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Drabko, Poland 2005	6680	21	pb	auto		BUS, MEL n=12 MEL, VP-16, TBI n=1 MEL, VP16, CBCA n=6 Treo, Mel n=2					
Fazekas, Austria, 2008	2720	1		auto	hemipelvectomy	BUS, MEL					
Hara , Japan 1998	17950	3	bm or pb or both	auto	no preHSCT surgery or RT	double-conditioning regimen thio and MEL		TPN, Abx			
Harimaya, Japan, 2003	9850	2	pb	auto	surgery n=2 (one partially resected; one en bloc) RT n=1 (pt partially resected)	carboplat and E n=1 carboplat, E, ifos n=1			partial surgical resection, multiagent CT, RT	VAIA	
Hawkins, USA 2000	15360	16	pb n=15 bm n=1	auto n=14 syngeneic n=1 allo n=1 (HLA-matched sibling)		grp 1: BUS, MEL, Thio followed by HSCT then total marrow myeloablative RT followed by a second HSCT grp 2: BUS, MEL, Thio		prophylactic Abx if low granulocyte count			

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Kasper, Germany, 2006	2570	5	pb	auto		MEL and E n=2 BUS and MEL n=3					
Kogawa, Japan, 2004	8410	1	pb	auto	surgery and RT	NR					
Koscielniak Germany 2005	7860	1	mismatched related	allo	tandem auto-auto local RT	BUS, Thio, Flu, CPM					
Kushner, USA, 1995	21430	2		auto	surgery GTR n=1 no surg n=1	MEL, TBI			non met dz CT, surg, RT	CT CPM, doxo, VIN, ifos, E nonmets: GTR n=14 inoperable n=2 amputation n=1 RT n=7 met dz: GTR n=3 no surg n=4 RT 71 % (n=5)	
Kushner, USA, 2001	14240	5	bm and pb n=3 bm n=2	auto	RT n=4	TBI, MEL or thio, carboplatin			induction CT and in one pt RT		

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Laws, Germany, 2003	9450	2		auto	resection of primary tumor with wide margins n=2 RT to mets n=2	TBI, MEL, E n=1 NR n=1					
Lucas, USA 2008	2450	1		allo, matched mother	chemotherapy leading to resolution of disease at primary tumor site, BM, and lungs and stable disease in the vertebrae and ribs for 6 months	BUS, MEL thymoglobulin	cyclosporin and methotrexate				
Lucidarme, France, 1998	17610	3	bm or pb	auto x 1 (n=1) auto x 2 (n=2)	surgery for primary tumor n=1 (pt with PD) and RT after HSCT after	thio RT n=1		TPN Abx			

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Meyers, USA, 2001	13670	23	pb	auto	local RT of primary tumor and mets sites	TBI, MEL, Eto		filgrastim	repeated cycles of CT		9 patients were not transplanted b/c did not achieve good response in primary tumor and all mets sites
Milano, Italy, 2006	43290	36							CT n =16 conservative surgery after CT n=14 RT n=3	ICE/CAV n=18 ICE n=2 CECAT n=16	
Navid, US and Canada, 2006	5930	9		auto	surgery n=6 RT n=7	CPM and E n=3 CPM, Topotecan n=2			4 patients did not undergo HSCT b/c did not achieve PR or CR with induction CT.		
Numata, Japan, 2002	12130	1	pb	auto	conventional CT and regional RT	carboplatin, e, ifo					
Oberlin, France, 2008	46850										

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Ozkaynak, USA 1998	18540	15	bm n=7 bm and pb n=8	auto		MEL, Carbopl, E +/- CPM					
Pession, Italy, 1999	16120	3	bm	auto	one patient RT to primary tumor	BUS, E, thio					
Prete, Italy 1998	17210	17	pb	auto		BUS, E, Thio (n=16) L-PAM (n=1)					
Sari, Turkey, 2010	42790	36							CT only 8% CT and RT 55% CT and surgery 6% CT,RT and surg 22%	CT EVAIA vincr, ifos, mesna, E, adriamy, actino-D	
Tanaka, Japan, 2002	11770	6	PB	auto	surgery n=2 RT n=2 both surg and RT n=2						
van Winkle, USA, 2005	43550	22							CT	ICE	
Yaniv, Israel, 2004	9100	11	pb and bm	auto		MEL, E , carbopl or BUS and MEL					

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Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Ladenstein, Austria, France, UK, Switzerland, Netherlands, Germany, Sweden, 2010	2270	n=99	autologous	myeloablative	resection of primary and metastatic tumor sites	induction VIDE x 6 cycles and one cycle of VAI high dose CT oral busulfan and melphalan					
Ilari, Italy, 2010	2230	24	auto	myeloablative	local therapy (surgery with or without RT)- surgery could have been at diagnosis (n=2) or after 4 courses CT (n=13) or after HSCT (n=5); in inoperable pts, RT was after HSCT	etoposide, thiotepa and CY					
Diaz, Spain, 2010	2135	47		auto	64% local radiation	high-dose busulfan and melphalan					

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Kwon, Korea, 2010	2268	1	auto	sequential high-dose (2 consequent courses of RIC followed by a high-dose with auto HSCT)	4 cycles of chemotherapy No surgical resection of primary tumor	RIC: etoposide, cyclophosphamide, carboplatin high-dose: carboplatin , etoposide, melphalan with or without TBI					
Burdach, Germany and Austria, 2010	2077	21	auto n = 8 (one pt received auto followed by allo b/c of progression after initial auto SCR)	myeloablative chemotherapy EVAIA and/or VAIA	TB-MRI assessment surgery and/or irradiation	VAIA and E/VAIA high-dose melphalan x 2 and etoposide allo: BU and CY or			induction chemo VAIA and E/VAIA		

Appendix Table C5. Outcome assessment: Treatment, Ewing's tumors

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes
Burdach, Germany and Austria, 2000	14310	28	EFS
Burdach, Germany, 2003	10030	<=17 yrs	EFS
Burke, USA 2007	4060	7	DFS OS
Costa, USA, 2008	1710	1	OS
Drabko, Poland 2005	6680	21	DFS OS
Fazekas, Austria, 2008	2720	1	DFS
Hara , Japan 1998	17950	3	DFS OS
Harimaya, Japan, 2003	9850	2	OS
Hawkins, USA 2000	15360	16	EFS
Kasper, Germany, 2006	2570	5	OS
Kogawa, Japan, 2004	8410	1	OS DFS
Koscielniak Germany 2005	7860	1	PFS
Kushner, USA, 1995	21430	2	PFS
Kushner, USA, 2001	14240		EFS
Laws, Germany, 2003	9450	2	DFS
Lucas, USA 2008	2450	1	OS
Lucidarme, France, 1998	17610	3	OS
Meyers, USA, 2001	13670	32 and 23	EFS
Navid, US and Canada, 2006	5930	9	EFS OS
Numata, Japan, 2002	12130	1	DFS OS
Oberlin, France, 2008	46850	<15 yrs	EFS OS
Ozkaynak, USA 1998	18540	15	EFS OS (NR)
Pession, Italy, 1999	16120	3	OS DFS
Prete, Italy 1998	17210	17	EFS OS
Sari, Turkey, 2010	42790		
Tanaka, Japan, 2002	11770	6	DFS OS
Yaniv, Israel, 2004	9100		
Ladenstein, Austria, France, UK, Switzerland, Netherlands, Germany, Sweden, 2010	2270	99	OS
Diaz, Spain, 2010	2135	47	PFS
Kwon, Korea, 2010	2268	1	OS

Appendix Table C6. Outcome assessment: Comparator, Ewing's tumors

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes
Bernstein, USA/Canada 2006	6290	110	EFS	OS
Bhatia,USA, 2007	43210			
Kushner, USA, 1995	21430	24	PFS	
Milano, Italy, 2006	43290	36	EFS OS	
Sari, Turkey, 2010	42790	36	EFS OS	
van Winkle, USA, 2005	43550	22	OS	
Burdach, Germany and Austria, 2010	2077	8	OS	

Appendix Table C7. Time to event outcomes: Treatment, Ewing's tumors

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	2 yr	5 yr
Costa, USA, 2008	1710	1	73 + months			
Drabko, Poland 2005	6680	21		24 mos (13-59 mos)	HSCT in CR .68 not in CR <.10	
Fazekas, Austria, 2008	2720	1				
Hara , Japan 1998	17950	3	DOD 3 mos A with D 25+ mos A NED 59+			
Harimaya, Japan, 2003	9850	2	A without D 67+ months DOD from recurrent tumor at 28 mos			
Kasper, Germany, 2006	2570	5	A NED 93+ mos A NED 70+ A NED 59+ A NED 46+ DOD 30 months			
Kogawa, Japan, 2004	8410	1	60 months +			
Koscielniak Germany 2005	7860	1				
Lucas, USA 2008	2450	1	9 months + with disease			
Lucidarme, France, 1998	17610	3	1 tx DOD 2 mos (n=1) of PD 2 txs DOD 7 mos after 2nd tx (?) 2 txs A NED 28+ mos after first tx			
Meyers, USA, 2001	13670					
Navid, US and Canada, 2006	5930	HSCT DOD n=2 at 27 and 28 mos A NED n=3 at median 67 mos (57-73)				
Numata, Japan, 2002	12130	1	50+ months			
Oberlin, France, 2008	46850	<15 yrs				49%
Ozkaynak, USA 1998	18540	15				
Pession, Italy, 1999	16120	3	DOD 7 months ANED 58+ A w D 53+			
Prete, Italy 1998	17210	17		15 (1-40 mos)	70%	

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Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	2 yr	5 yr
Tanaka, Japan, 2002	11770		n=1 DOD 19 mos n=5 A NED median 57 mos (42-90 mos)			
Ilari, Italy, 2010	2230	24	7 year OS			64% (95%CI 38-81) (7 year OS)
Kwon, Korea, 2010	2268	1	DOD 11 months			
Ladenstein, Austria, France, UK, Switzerland, Netherlands, Germany, Sweden	2270	99	OS			mean .46 SD 0.05 (3 year OS)

Appendix Table C7. Time to event outcomes: Treatment, Ewing's tumors Continued

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_2	Med (mos)_2	2 yr_2	3 yr_2	5 yr_2	Outcome_3	Med (mos)_3
Burdach, Germany, 2003	10030		EFS in <=17 yrs old	32% +/- 11% with single 40% +/- 13% with tandem					
.Burke, USA 2007	4060		tandem group NED n=4 after mean f/u of 6.25 yrs (3-10 yrs) DOD n=2 at 0.3 and 3.2 yrs					group single tx DOD at .5 yrs	
Costa, USA, 2008	1710	1							
Drabko, Poland 2005	6680	21	DFS		in CR .63 and not in CR 0				

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_2	Med (mos)_2	2 yr_2	3 yr_2	5 yr_2	Outcome_3	Med (mos)_3
Fazekas, Austria, 2008	2720	1	DFS	relapsed 4 mos after HSCT (non-pulm); died after palliative CT					
Hawkins, USA 2000	15360		EFS (n=16)			36%		EFS	grp 1 A NED: 66.7 % median 42 mos (27-66) PD 33.3% median 12 mos (6.3-17) grp 2: PD/DOD 28.6 % median 6.7 mos (0.1-26) NED/DOC n=2 (one at 9.6 months and one 31 mos after a 2nd HSCT (allo after auto) for MDS that the pt had prior to the auto tx
Kasper, Germany, 2006	2570	5							
Kogawa, Japan, 2004	8410	1	DFS	60+ months					
Koscielniak Germany 2005	7860	1	PFS	after allo 3.5 yrs					PFS after tandem 8 mos
Laws, Germany, 2003	9450		DFS	30 mos and 6 mos					
Lucas, USA 2008	2450	1							
Lucidarme, France, 1998	17610	3							
Meyers, USA, 2001	13670		EFS		20%				

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_2	Med (mos)_2	2 yr_2	3 yr_2	5 yr_2	Outcome_3	Med (mos)_3
Navid, US and Canada, 2006	5930	HSCT DOD n=2 at 27 and 28 mos A NED n=3 at median 67 mos (57-73)	no HSCT DOD n=2 @ 10 and 16 months A NED n=2 @ 73 and 80 months						
Numata, Japan, 2002	12130	1	DFS	50 + months					
Oberlin, France, 2008	46850	<15 yrs	EFS				46%		
Ozkaynak, USA 1998	18540	15	EFS			51% (for pts in 1st remission 66% +/- 19%; for 2nd remission 37%)			
Pession, Italy, 1999	16120	3		DOD 7 months ANED 58+ A w D 53+					
Prete, Italy 1998	17210	17	EFS		63%				
Tanaka, Japan, 2002	11770		DFS	n=4 median 48.5 mos (31-74) n=1 NED at 79 mos					
Diaz, Spain, 2010	2135	47	PFS 56% +/- 4% with a median followup of 92 months for survivors (range 6-168 months)	by localized vs mets at dx PFS for pts with local dz:78% +/- 8% and for mets 27% +/- 10%					

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_2	Med (mos)_2	2 yr_2	3 yr_2	5 yr_2	Outcome_3	Med (mos)_3
Ilari, Italy, 2010	2230	24	7 year EFS 61% (95%CI 36-79)						
Ladenstein, Austria, France, UK, Switzerland, Netherlands, Germany, Sweden	2270	99	3 year EFS			mean 0.40 SD 0.05			

Appendix Table C8. Time to event outcomes: Comparator, Ewing's tumors

Study (Investigator, country, year)	Record Number	Group (N)	1 yr	2 yr	3 yr	5 yr	Outcome_2	1 yr_2	2 yr_2	3 yr_2	5 yr_2	Comment
Bernstein, USA/Canada 2006	6290	110	77% +/- 4%	46% +/- 5			EFS	65% +/- 5	24% +/- 4%			No statistical difference was seen in EFS or OS between pts with isolated lung mets and or those with other or more than isolated mets
Milano, Italy, 2006	43290	36			with ICE/CAV CT 67%+/-12% with other CT 22%		EFS			with ICE/CAV 74% with other CT 27%		
Sari, Turkey, 2010	42790					27%	EFS				18%	
van Winkle, USA, 2005	43550	22	43 % (SE 11)	33% (SE 10)								

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Appendix Table C9. Adverse events: Treatment, Ewing's tumors

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	% Engraftment Failure	% TRM	Severity or Grade Secondary Malignancies	F/U (mos) SM	% SM	Comments SM
Burdach, Germany and Austria, 2000	14310	28								
Burdach, Germany, 2003	10030	reported engr, TRM, infec compl, sec malig, and major organ tox, but not by age of < or > 17 yrs								
Burke, USA 2007	4060	7	sepsis n=1		0	0				
Costa, USA, 2008	1710	1			0	0	AML at 53 months post HSCT			
Drabko, Poland 2005	6680	21				5% (n=1 day 35 from multiorgan failure secondary to infection)				
Hara , Japan 1998	17950	3				0 NR				
Harimaya, Japan, 2003	9850	2			0	0				
Kasper, Germany, 2006	2570	5			0	0				
Koscielniak Germany 2005	7860				0	0				
Kushner, USA, 2001	14240	1 HSCT pt died at 17 mos after HSCT with NED but pulmonary failure								
Lucas, USA 2008	2450	1			0	0				
Lucidarme, France, 1998	17610	3				0 (NR)				

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	% Engraftment Failure	% TRM	Severity or Grade Secondary Malignancies	F/U (mos) SM	% SM	Comments SM
Meyers, USA, 2001	13670		sepsis leading to death	4% n=1 patient from HSCT group (incl in TRM)		of HSCT group n=23 n=3 13%				
Navid, US and Canada, 2006	5930	9			0	0				
Numata, Japan, 2002	12130				0	0	CML chronic phase	50 months after HSCT		
Ozkaynak, USA 1998	18540	15			0 (one patient not assessable secondary to early toxic death)	n=2 ATN day 0 and septic shock day 8				
Pession, Italy, 1999	16120	3				0 NR				
Prete, Italy 1998	17210	17				0				
Tanaka, Japan, 2002	11770			0		0	CML		14%	not clear if the 35 y/o pt or one of the 6 abstracted pts
Diaz, Spain, 2010	2135	47	septic shock	n = 1						
Ilari, Italy, 2010	2230	24	sepsis	n = 4		0				

Appendix Table C9. Adverse events: Treatment, Ewing's tumors Continued

Study (Investigator, country, year)	Record Number	% Hepatic veno-occlusive disease (Hepatic Sinusoidal Obstruction)	Comments hVOD	Severity or Grade Serious Hemorrhagic Event	% SHE
Drabko, Poland 2005	6680	10%	moderate to severe		
Meyers, USA, 2001	13670			HSCT pt died from hemorrhagic pericarditis (included in TRM)	4%
Ladenstein, Austria, France, UK, Switzerland, Netherlands, Germany, Sweden	2270	n = 5	grade 3		
Diaz, Spain, 2010	2135				6%

Appendix Table C10. Adverse events: Comparator, Ewing's tumors

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	Severity or Grade Secondary Malignancies	F/U (mos) SM	% SM
Bernstein, USA/Canada 2006	6290		death	5 of 110 (4.5%)	MDS	at 20 mos after dx	1/110 1%
Bhatia, USA, 2007	43210						cumulative incidence of t-MDS/AML of 11% at 5 yrs from dx
Kushner, USA, 1995	21430	24			leukemia dead at 10.5 mos after HSCT in CR from ESFT		4
Meyers, USA, 2001	13670	9 nonHSCT		11% sepsis during induction CT			
Sari, Turkey, 2010	42790	36					0%

Appendix Table C11. Design, participant selection and enrollment: Wilm's tumor

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Kremens, Germany, 2002	11240	malignant NH	Wilms	1st remission n=4 1st relapse n=19	23	Apr 1992-Dec 1998	Case series	23	0	
Saarinen-Pihkala, Finland, 1998	17940	Malig NH	Wilms	1st CR	3		CS	3	0	
Spreafico, Italy, 2008	2380	malig NH	Wilms and one case of CCSK	relapsed, high risk (3 relapsed in prior RT field)	20	Jan 2001-June 2006	CS consecutive cases	20		20 patients enrolled; 5 did not receive tx (3 due to disease progression and 2 at discretion of M.D.).
Campbell, USA, 2004	8570	malig NH	Wilms	relapsed	13	1991-2001	CS	13	0	
Tucci, Brazil, 2007	3910	malig NH	Wilms	resistant, relapsed	1		CR	1	0	
Hempel, Germany, 1998	18100	malig NH	Wilms	relapse s/p 2nd lung metastasectomy	1		CR	1	0	
Termuhlen, USA, 2006	4890	malig NH	Wilms	CR1 n=1 CR2 n=1	2		CS	2	0	
Kullendorff, Sweden, 1997	19290	malig NH	Wilms	2nd relapse	4	1987-1992	CS	4	0	includes one patient with CCSK
Maurer, Austria, 1997	18670	malign NH	Wilms	relapsed during 1st line CT	1		CR	1	0	

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Pein, France, 1998	17570	malig NH	Wilms	recurrent, high risk 2nd CR n=16 3rd CR n=3 5th CR n=1 2nd PR n=4 3rd CR n=5	28	Oct 1988-Oct 1994	CS	28	1 4 mos after HSCT	
Valera, Brazil, 2004	8620	malig NH	Wilms	relapsed, 2nd CR	3		CS	3	0	
Goldman, USA, 2001	13330	malign NH	Wilms	relapsed (6 mos after dx)	1	1994-1998	CR	1	0	
Dagher, USA, 1998	17840	malign NH	Wilms	multiply recurrent	1		CR	1	0	
Hempel, Germany, 1996	20550	malig NH	Wilms	progressive disease, 1st, 2nd or subsequent relapse, metastatic dz	7	April 1992-May 1995	CS	7		1 pt was misdxd and had RMS and is not included in the analysis
Fazekas, Austria, 2008	2720	malig NH	Wilms	relapsed	1		CR	1	0	
Park, Korea, 2006	5450	malign NH	Wilms	recurrent	3	1994-2004	CS	3	0	
Abu-Ghosh 2002 USA	45610		Wilms		11	1992-1999 37 N Amer centers and 2 S Amer centers	CS	11	0	
Malogolowkin USA 2008	44950	malign NH	Wilms	relapsed, high risk	60	1995-2002	CS	60	0	
Lucas, USA, 2010	2295	NH solid tumor	Wilms	chemotx resistant/refractory wilms	1		CR			
Brown, USA, 2010	2075	NH solid tumor	Wilms	3rd CR	1		CR	n=1	0	

Appendix Table C12. Participant characteristics: Treatment, Wilm's tumor

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Campbell, USA, 2004	8570	13		at dx 4.8 years (1-15 years)		31%,69	initial I n=2 II n=1 III n=5 IV n=5	FH n=12 UH n=1	
Dagher, USA, 1998	17840	1		7 years at HSCT		100 F	recurrent	right-sided tumor bed	pt had a left-sided wilms tumor, FH, stage II at age 9 mos and underwent L nephrectomy and CT. At age 6, developed a right kidney wilms tumor for which she underwent R nephrectomy, CT and RT. At 7 yrs of age she had a right-sided recurrence and HSCT
Fazekas, Austria, 2008	2720	1	5 yrs at tx			100 M	"intermediate risk" not further defined		

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Goldman, USA, 2001	13330	1		2 yrs at HSCT		100% M	III	relapse in lungs and abdomen	
Hempel, Germany, 1996	20550	7		at tx 7.3 yrs (3.8-14.7 yrs)		86,14		UH n=1 FH n=6	
Hempel, Germany, 1998	18100	1	11 months			100,0	initial stage 2	"medium" malignancy	
Kremens, Germany, 2002	11240	23		at dx 74 months	11-210 months	52,48	I n=4 II n=4 III n=3 IV n=13 (note does not total 23)	n=14 Intermediate risk n=5 high-risk n=1 completely necrotic	
Kullendorff, Sweden, 1997	19290	4		at dx median 67 months (43-119 mos)		33,66	I n=2 III n=2	FH n=3 UH n=1 site or relapse lung n=2 and bone n=2	
Maurer, Austria, 1997	18670	1	at dx 8 yrs			100 F	IV with lung mets	UH	
Park, Korea, 2006	5450	3		2 yrs (2-3 yrs)		66,33	initial stage: II (n=3)	UH n=2 FH n=1 site of relapse lung n=2, abdomen n=1	
Pein, France, 1998	17570	29		6 yrs (2-16 years)		41,59	at dx: I n=4 II LN + n=5 II LN- n=7 III n=5 IV n=6 V n=2	UH n=6 (3 anaplastic, 3 CCS) FH n=23	
Saarinen-Pihkala, Finland, 1998	17940	3		at dx 46 months (6-60)		66%, 33%	V (n=3) mets to lung n=1	FH n=2 "rhabdomyomatous" n=1	
Spreafico, Italy, 2008	2380	15		at dx 4.1 years (1.1-11.2)		30,70	Initial stage I n=1 II n=2 III n=8 IV n=8	UH n=1 CCSK n=1	

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Termuhlen, USA, 2006	4890	2		40.5 mos (21-60 mos)		100 F	V n=2	FH n=2	
Tucci, Brazil, 2007	3910	1							
Valera, Brazil, 2004	8620	3		at dx 7 yrs (3-9 yrs)		66,33	II n=1 III n =1 IV n=1	FH n=1 not reported n=2	
Brown, USA, 2010	2075	1	at initial diagnosis 4 yrs at 3rd CR (HSCT) 17 yrs old				male 100%	at initial diagnosis stage 1 at 3rd CR (prior to HSCT) pulmonary and mediastinal involvement only		
Lucas, USA, 2010	2295	1	at diagnosis 12 months age at HSCT 24 months				male 100%	Wilms- left kidney plus right lung nodules	favorable histology	

Appendix Table C13. Participant characteristics: Comparator, Wilm's tumor

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Abu-Ghosh 2002 USA	45610	11		at dx 39 months (13-192 mos)		relapsed/recurrent, high-risk stage at initial dx: I 18% II 9% III 36% IV 27% V 9%	FH 82%, UH 18% site of relapse lung 36%, pleura 9%, kidney 18%, kidney and lung 18% and liver 9%	
Malogolowkin USA 2008	44950	60	at dx 0-23 mos n=4 24-47 mos n=21 48+ n=35		47,53	initial stage II n=1 III n=39 IV n=20	FH n=56 focal anapl n=3 diffuse anapl n=1 site of relapse lung only n=33 operative bed +/- lung +/- other n=7 liver +/- other n=6 abd or pelvis +/- lung n=6 lung and other n=6 other n=2	
Park, Korea, 2006	5450	7 (2 lost to f/u)		2 yrs (1-11yrs)	71,29	initial stage: I n=1 II n=3 III n=1 IV n=2 relapsed, high risk	FH n=7 relapse lung n=3, abd n=2, lung and abd n=1, abd, lung and bone marrow n=1	Although 13 pts in this study did not undergo HSCT, only 9 were high risk relapse, 2 were lost to f/u so only 7 abstracted.
Tucci, Brazil, 2007	3910	10		2 years		relapsed		Recurred in a mean time of 13.4 +/- 10 months (range 2-36). One of 10 of the relapsed pts had favorable px factors.

Appendix Table C14. Treatment characteristics: Wilm's tumor

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Abu-Ghosh 2002 USA	45610	11							ICE	
Campbell, USA, 2004	8570	13	PB	auto	nephrectomy n=13 reinduction CT n=12	T/CPM n=6 T/CPM/C n=2 T/E n=1 C/CPM/Mel n=4				
Dagher, USA, 1998	17840	1	PB	auto	bilateral nephrectomy, CT and RT	E/C/CPM				
Fazekas, Austria, 2008	2720	1		auto						
Goldman, USA, 2001	13330	1	PB	auto	nephrectomy Flank RT	VP-16/T/cytoxan				
Hempel, Germany, 1996	20550	7	PB	auto		MEC				
Hempel, Germany, 1998	18100	1	BM	auto	Nephrectomy lung metastasectomy x 2 RT to lung	C/M/E				
Kremens, Germany, 2002	11240	23	PB	autologous		MEC n=19 M x2 n=1 E, thio and cyc n=1 mel and ifos n=2	hydration, TPN, prophylactic Abx, irradiated blood products			6 patients received RT after HSCT (2 lung consolidation; 4 to palliate recurrence after HSCT
Kullendorff, Sweden, 1997	19290	4	BM n=2 PB and BM n=2	auto		mel/VP-16/C				

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Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Malogolowkin USA 2008	44950	60						prior nephrectomy, Radiation, CT	CPM, E, C	
Maurer, Austria, 1997	18670	1	PB and BM	sequential double auto	nephrectomy RT to lung mets and surgical removal of lung mets	1st: modified MEC 2nd: EC				
Meyers, USA, 2001	13670	23	PB	auto	local control RT to primary tumor and mets	TBI MEL E	filgrastim			
Park, Korea, 2006	5450	3	PB	auto	nephrectomy; prior first-line CT RT after relapse n=1	MEC	TPN	CT RT if stage III or IV or UH (n=3)	In the early group (treated 1983-1993) doxorubicin was added in cases where patient had initially received 2 drugs. In the late group (treated 1983-1993) pts received combinations of CPM/E and C/E.	Groups of pts were divided into two groups (early and late) according to date of relapse.
Pein, France, 1998	17570	29	BM n=28 PB n=1	auto		MEC	"standard"			
Saarinen-Pihkala, Finland, 1998	17940	3	BM	auto	bilateral nephron-sparing nephrectomy	MEL				

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Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Spreafico, Italy, 2008	2380	14	PB	auto	nephrectomy n=14	MEC n=7 M/T n=2 E/T/CPM n=2 HD-ICE n=1 HD-ICE, M/CPM n=1 MC n=1 E/T/CPM		CT	ICE	M=melphalan T=thiotepa CPM=cyclophosphamide E=etoposide C=carboplatin
Termuhlen, USA, 2006	4890	2	PB n=1 PB and BM n=1	auto	nephron-sparing nephrectomy n=2 RT to 1 kidney n=1	Mel/T/vincristine	dopamine, anti HTN Rx, hydration			
Tucci, Brazil, 2007	3910	1	PB	auto	nephrectomy; lung lesions resected; RT to lung and liver	E,Mel,C		multiagent salvage CT, abdominal RT (n=6), and lung RT (n=3)	cisplatin, C, CPM, E, ifo	
Valera, Brazil, 2004	8620	3	BM	auto	nephrectomy	C/E/M C/E/pulm RT C/E/Ifos				
Brown, USA, 2010	2075	1		auto	nephrectomy chemotherapy at diagnosis at 1st relapse, lung RT and chemo	carboplatin, etoposide, melphalan				

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Lucas, USA, 2010	2295	1	allogeneic (unrelated matched cord blood)		left nephrectomy, chemotherapy	busulfan, melphalan, thymoglobulin				

Appendix Table C15. Outcome assessment: Treatment, Wilm's tumor

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration
Campbell, USA, 2004	8570	13	EFS, OS		median 30 mos (7-120)
Dagher, USA, 1998	17840	1	OS	DFS	
Fazekas, Austria, 2008	2720	1	OS		
Goldman, USA, 2001	13330	1	OS		
Hempel, Germany, 1996	20550	7	DFS, OS		
Hempel, Germany, 1998	18100	1	DFS		
Kremens, Germany, 2002	11240	23	OS, EFS		58 mos (37-116)
Kullendorff, Sweden, 1997	19290	4	OS		
Maurer, Austria, 1997	18670	1	OS		
Park, Korea, 2006	5450	3	OS, EFS		
Pein, France, 1998	17570	28	DFS, OS		37 mos (7-96 mos)
Saarinen-Pihkala, Finland, 1998	17940	3	DFS		
Spreafico, Italy, 2008	2380	14	DFS, OS		
Termuhlen, USA, 2006	4890	2	OS		
Tucci, Brazil, 2007	3910	1	DFS, OS		
Valera, Brazil, 2004	8620	3	DFS		
Brown, USA, 2010	2075	1	DFS		15 mos
Lucas, USA, 2010	2295	1	EFS		2.5 years

Appendix Table C16. Outcome assessment: Comparator, Wilm's tumor

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	F/U Frequency/Duration
Abu-Ghosh 2002 USA	45610	11	PFS OS	median f/u 4.3 yrs
Malogolowkin USA 2008	44950	60	EFS OS	
Park, Korea, 2006	5450	7	EFS OS	
Tucci, Brazil, 2007	3910	10	DFS OS	

Appendix Table C17. Time to event outcomes: Treatment, Wilm's tumor

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	3 yr	4 yr	HR (95%) CI	Outcome_2	Med (mos)_2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	HR (95% CI)_2	Outcome_3
Campbell, USA, 2004	8570	13				73%	.40-6.86	EFS					60%	.40-6.88	
Dagher, USA, 1998	17840	1	1.8 years					DFS	.5 years						
Fazekas, Austria, 2008	2720	1	A NED at 12 mos												
Goldman, USA, 2001	13330	1	A NED at 16+ mos												
Hempel, Germany, 1996	20550	7	n=6 A NED at median 2.1 yrs (0.5-3.7 yrs) n=1 DOD 19 mos					DFS	n=1 8 mos n=6 A NED at median 2.1 yrs (0.5-3.7 yrs)						
Hempel, Germany, 1998	18100	1	DFS A NED at 32 mos post HSCT												

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	3 yr	4 yr	HR (95%) CI	Outcome_2	Med (mos)_2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	HR (95% CI)_2	Outcome_3
Kremens, Germany, 2002	11240	23	60.9% (+/- 10.2%)					EFS 48.2% (+/- 13.6)							OS and EFS in subgroup that received MEC consolidation (n=19) OS 63.2% (+/- 11.0%) EFS 54.1% (+/- 14.9%)
Kullendorff, Sweden, 1997	19290	4	2 A & W at 17 and 28 mos 2 DOD 33 and 7 mos after HSCT												
Malogolowkin USA 2008	44950	60				42.3		EFS					48		
Maurer, Austria, 1997	18670	1	A & W at 4 years in CR2 yrs												
Meyers, USA, 2001	13670	23						EFS		~40%	24%				

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	3 yr	4 yr	HR (95%) CI	Outcome_2	Med (mos)_2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	HR (95% CI)_2	Outcome_3
Park, Korea, 2006	5450	3	median 53+ months (31+-76+)					EFS	median 53 months (31-76 mos)						
Pein, France, 1998	17570	28			60% +/- 18%			DFS				50% +/- 17			
Saarinen-Pihkala, Finland, 1998	17940	3	DFS	median 51 months (40-53 months)											
Spreafico, Italy, 2008	2380	20	median f/u 25 months (14-79)		55% +/- 13%			DFS	25 mos (14-79)			56% +/- 12%			
Termuhlen, USA, 2006	4890	2	A NED 7 year after HSCT n=1 DOD 6 y 2 m after HSCT n=1		100%	100%									

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	3 yr	4 yr	HR (95%) CI	Outcome_2	Med (mos)_2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	HR (95% CI)_2	Outcome_3
Tucci, Brazil, 2007	3910	1	A WED 84 mos from relapse					DFS A WED 84 mos from relapse							
Valera, Brazil, 2004	8620	3						A & W at 12 mos and 48 mos one patient relapsed after HSCT then underwent CT and is in 3rd CR for 22 mos							

Appendix Table C18. Time to event outcomes: Comparator, Wilm's tumor

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	1 yr	2 yr	3 yr	4 yr	5 yr	Outcome_2	Med (mos)_2	3 yr_2	5 yr_2
Abu-Ghosh 2002 USA	45610	11		~73%	63.6 +/- 14.5%	63.6 +/- 14.5%	63.6 +/- 14.5%	63.6 +/- 14.5%	PFS		63.6 +/- 14.5%	
Malogolowkin USA 2008	44950											
Park, Korea, 2006	5450	7	DOD n=5 median 15 mos (2-30 mos) A NED n=1 20+ mos A with D n=1 130+ mos						EFS	median 8 months (2-20 mos)		
Tucci, Brazil, 2007	3910	10				83.3%		42.8%	DFS		66.6%	42.8%

Appendix Table C19. Adverse events: Treatment, Wilm's tumor

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	% Engraftment Failure	% TRM	Comment TRM	Severity or Grade Serious Hemorrhagic Event	% SHE
Campbell, USA, 2004	8570	13			0%	0%			
Dagher, USA, 1998	17840	1				0			
Fazekas, Austria, 2008	2720	1				0			
Goldman, USA, 2001	13330	1				0			
Hempel, Germany, 1996	20550	7				0			
Hempel, Germany, 1998	18100	1			0%	0%			
Kremens, Germany, 2002	11240	23				0%			
Kullendorff, Sweden, 1997	19290	4				0			
Maurer, Austria, 1997	18670	1 long term renal tubular dysfunction				0			
Meyers, USA, 2001	13670	23	sepsis (died)	4%		13%	one for unreported reasons	hemorrhagic pericarditis after RT (died)	4

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	% Engraftment Failure	% TRM	Comment TRM	Severity or Grade Serious Hemorrhagic Event	% SHE
Park, Korea, 2006	5450	3				0			
Pein, France, 1998	17570	29				0			
Saarinen-Pihkala, Finland, 1998	17940	3			0%	0%			
Spreafico, Italy, 2008	2380		died of sepsis 4 months after tx in CR n=1	7%					
Termuhlen, USA, 2006	4890	2			0	0			
Tucci, Brazil, 2007	3910				0%	0%			
Valera, Brazil, 2004	8620	3				0			

Appendix Table C20. Adverse events: Comparator, Wilm's tumor

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	Comment	TRM	% TRM	Severity or Grade Secondary Malignancy
Abu-Ghosh 2002 USA	45610		septic shock	27	reversible	TRM	0	
Malogolowkin USA 2008	44950	60	one patient died of infl B virus and aspergillus infec during maintenance chemo	2%		TRM		MDS n=1 2%

Appendix Table C21. Design, participant selection and enrollment: Rhabdomyosarcoma

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Bisogno, Italy, 2009	75340	Malignant solid tumor	Rhabdomyosarcoma	Metastatic RMS	HSCT (70)	1999-2006	prospective single arm	70	0	
Breneman, USA, 2003	75360	Malignant Solid Tumor	Rhabdomyosarcoma	Metastatic RMS	Comparator (127)	1991-1997	Case series	127		
Carli, Italy, 1999	16010	Malignant Solid Tumor	Rhabdomyosarcoma	Metastatic RMS	HSCT (52) Comparator (44)	1989-	single arm study	96		52 transplanted and 44 failed to meet transplant requirements and served as comparators.
Doelken, Germany, 2005	6570	Malignant Solid Tumor	Rhabdomyosarcoma	Relapsed	HSCT (2)		Case reports	2	0	
Donker, Netherlands, 2009	1420	Malignant Solid tumor	Alveolar Rhabdomyosarcoma	Stage IV RMS	HSCT (1)		case study	1	0	Allo transplant
Grundy, UK, 2001	14200	Malignant solid Tumor	Rhabdomyosarcoma congenital	Congenital RMS	HSCT (1)		case report	1		This report also details three other children who died by 3 months of age. The paper also details all other known cases (7). In these cases all patients died
Hara, Japan, 1998	17950	malignant Solid tumor	rhabdomyosarcoma	Stage III or IV or relapsed RMS	HSCT (7)	1993-1997	Case series	7	0	abstracted from a study of multiple solid tumors

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Koscielniak, Germany, 1997	19800	Malignant Solid Tumor	Rhabdomyo sarcoma	Metastatic and recurrent	HSCT (36)	1986-1994	retrospective case series	36	0	This paper contains both Allo and Auto transplants. The data are reported together as they cannot be separated.
Kuroiwa, Japan, 2009	390	Malignant Solid Tumor	Rhabdomyo sarcoma	RMS with Beckwith-Weide-mann	HSCT (1)		case report	1	0	
Kwan, Hong Kong, 1996	20800	Malignant Solid Tumor	Rhabdomyo sarcoma	Metastatic RMS	HSCT (1)		Case Report	1	0	
Lucidarme, France, 1998	17610	Malignant Solid Tumor	Rhabdomyo sarcoma	Refractory or relapsed RMS	HSCT (8)	1987-1995	single arm phase II	HSCT (8)	0	
Matsubara, Japan, 2003	10810	Malignant Solid Tumor	Rhabdomyo sarcoma	High-risk RMS	HSCT (22)	1990-1999	Case series	22	0	There is one patient who is 22 years old. He is included in these results. His survival is similar when compared to a 16 and a 20 year old with a similar site of relapse and status at transplant

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
McDowell, UK, 2010	75350	Malignant Solid Tumor	Rhabdomyosarcoma	Metastatic RMS	HSCT (101) Comparator (45)	1998-2005	Two single arms	HSCT (101) Comparator (45)		This is not a comparative study but two single arms within the same study
Misawa, Japan, 2003	11040	Malignant Solid Tumor	Alveolar RMS	Refractory RMS	HSCT (1)	1997	Case Study	1	0	Allogeneic transplant
Moritake, Japan, 1998	18280	Malignant Solid Tumor	Rhabdomyosarcoma	relapsed	HSCT (1)	1994	Case report	1	0	
Navid, USA, 2006	5930	Malignant Solid tumor	Rhabdomyosarcoma	Metastatic RMS	HSCT (8)	1996-2000	case series	8	1 LFU at 78 months post transplant 2 people were removed from the protocol (one due to fungal infection, one due to delayed hem. recovery) 1 patient was non-compliant	only two were transplanted as they achieved CR, one other achieved CR but was the LFU

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Oue, Japan, 2003	10950	Malignant solid Tumor	Rhabdomyo sarcoma	Metastatic RMS	HSCT (1)	1991-2001	case series	1	one patient died prior to surgery due to progressive disease	
Pappo, USA, 1999	48020	Malignant Solid Tumor	Rhabdomyo sarcoma	relapsed RMS	Comparator (605)	1984-1997	retrospective analysis of three single arm studies	605	0	
Pappo, USA, 2001	47860	Malignant Solid Tumor	Rhabdomyo sarcoma	Metastatic RMS	Comparator (48)	1994-1996	Case series	48		
Raney, USA, 2008	2440	Malignant Solid Tumor	Rhabdomyo sarcoma	Metastatic RMS	Comparator (91)	1978-1997	case series	91		
Sandler, USA, 2001	12810	Malignant Solid Tumor	Rhabdomyo sarcoma	Metastatic RMS	Comparator (152)	1988-1991	Case series	152		
Sato, Japan, 1998	48070	Malignant Solid Tumor	Rhabdomyo sarcoma	Stage III or IV RMS	HSCT (5)	1993-1998	case series	HSCT (5)	HSCT (5)	only abstracted treatment arm as comparator treatment was not specified for two historical controls
Scully, USA, 2000	14580	Malignant Solid Tumor	Rhabdomyo sarcoma	Recurrent RMS	HSCT (1)		Case report	1	0	
Shaw, Israel, 1996	20050	Malignant solid Tumor	Rhabdomyo sarcoma	Stage IV RMS	HSCT (9)		prospective case series	9	0	this was a study with mixed solid tumors

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Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Van Winkle, USA, 2005	43550	Malignant Solid tumor	Rhabdomyo sarcoma	Recurrent/r efractory RMS	Compara tor(27)	1992-1996	Case series	27	0	these patients were enrolled in three treatment protocols but will be reported together
Walterhouse, USA, 1999	17240	Malignant Solid Tumor	Rhabdomyo sarcoma	Metastatic RMS	HSCT (8)	1992-1994	case series	8	0	
Williams, Canada, 2004	9010	Malignant Solid Tumor	Rhabdomyo sarcoma	Metastatic	13 (compar ator) 4 (HSCT)	1989-1999	retrosp ective review	13 (compa rator) 4 (HSCT)	0	

Appendix Table C22. Participant characteristics: Treatment, rhabdomyosarcoma

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Bisogno, Italy, 2009	75340	HSCT (70)			<1 year (1) <10 years (38) >=10 (32)		47% Male 53% Female	metastatic most common primary sites include head and neck, limbs and abdomen/pelvis	63% Alveolar RMS 36% Embryonal 1% not otherwise spec	
Carli, Italy, 1999	16010	HSCT (52)		31 pts. < 10 21 Pts. > 10				metastatic	Alveolar (44%) Embryonal/NOS (56%) Primary site Extremity, parameningeal, other (75%), Genitourinary tract and Head and Neck (25%)	
Doelken, Germany, 2005	6570	HSCT (2)	Pt 1-11.5 Pt 2-13				2 males	Pt 1-Stage IV with mets to lung, pancreas and marrow Pt2-initial stage T1b N0M0, metastatic disease at transplant	Both Alvelolar RMS with various metastatic sites at transplant	
Donker, Netherlands, 2009	1420	HSCT (1)	8 years			White	Female	Stage IV RMS	extensive local, abdominal and thoracic lymph node metastases, no BM invasion.	

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Grundy, UK, 2001	14200	HSCT (1)	diagnosed at birth				Male		congenital alveolar RMS/right thigh and multiple skin nodules	
Hara, Japan, 1998	17950	HSCT (7)	6.8 at diagnosis	3	1-18 years			stage III (2), stage IV (3), relapsed (2)	43% Alveolar 57% Embryonal	
Koscielniak, Germany, 1997	19800	HSCT (36)		6 at diagnosis	(<1-22)				RMS alveolar (61%) RMS embryonal (36%) Undifferentiated (3%)	Patient population contains at least one patient over the age of 21. 27 patients had metastatic disease and 9 had relapsed disease.
Kuroiwa, Japan, 2009	390	HSCT (1)		<1 at transplant					Alveolar RMS/primary skin lesions	
Kwan, Hong Kong, 1996	20800	HSCT (1)	14 years				Female	Stage IV/ Group IV	Alveolar RMS/primary site left thenar region/metastatic to the breast	

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Lucidarme, France, 1998	17610				2-17 for whole study			5/8 had metastatic disease at transplant		
Matsubara, Japan, 2003	10810	HSCT (22)		8.5 at transplant	2-22 years		14 males (64%) 8 Females (36%)	group III (14) or IV at transplant (8)	Alveolar 7 (32%) and Embryonal 15 (68%) varied primary sites parameningeal was the most common (7)	
Matsubara, Japan, 2005	7580	HSCT (5)	17.6 months at diagnosis	16 months at diagnosis	3-41		20% Male, 80% Female		distant metastasis	
McDowell, UK, 2010	75350	HSCT (101)	HR' 10.6' SR' 4.28	HR' 1.7-17.5' SR' 0.52-9.93			HR' 56% Male SR' 60% Male	Metastatic	21% Embryonal, 64% Alveolar, 8% unspecified, 6% unknown primary sites include 28% Orbit,	
Misawa, Japan, 2003	11040	HSCT (1)	17 at presentation				Female	Stage I, Clinical Group III undifferentiated RMS	Alveolar RMS	
Moritake, Japan, 1998	18280	HSCT (1)	10 at diagnosis				male	metastatic to BM	Unspecified subtype/ primary nasal tumor	
Navid, USA, 2006	5930	HSCT (8)	15.5	13.1	(1.6-18.7)		38% Male 62% Female	metastatic/	Alveolar RMS/various primary sites	

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Oue, Japan, 2003	10950	HSCT (1)	4.6 years				female	metastatic	primary site Lt. buttock metastatic to the Lt. femur	
Sato, Japan, 1998	48070	HSCT (5)	5.34 at diagnosis	7	.7-10 years		60% Male 40% female	Stage III RMS	60% Embryonal, 40% undifferentiated retroperitoneum (2), parameningeal (1), Femur (1), Orbit (1)	
Scully, USA, 2000	14580	HSCT (1)	~ 5 at transplant				Female	local recurrence	Local recurrence of embryonal RMS/upper arm primary site	
Shaw, Israel, 1996	20050	HSCT (9)	8.5 years		4-15			Stage IV various primary sites		
Taguchi, Japan, 2005	7430	HSCT (1)	4				M	metastatic	maxilla and mandible	
Walterhouse, USA, 1999	17240	HSCT (8)	14	12.5	3-17 years		63% Female 37% Male	Stage IV/group 4 RMS various primary sites	63% Alveolar, 25% Embryonal, 12% unknown various metastatic sites	
Williams, Canada, 2004	9010	HSCT (4)			TX. < 10 ' Comp 7<10' 6>10		TX' 75% Female 25% Male' Comp' 54% Male' 47% Female	Stage IV mets to lung	Embryonal RMS/ primary head and neck, parameningeal, bladder/prostate	

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Appendix Table C23. Participant characteristics: Comparator, rhabdomyosarcoma

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Breneman, USA, 2003	75360	Comparator (127)		7	0-19		56% male 44% Female	Stage IV/Category IV	36% embryonal, 46% alveolar, 3% undiff most common primary sites extremity (28%), parameningeal (20%) and Trunk (20%) Lung was the most common metastatic site, followed by bone marrow, and lymph nodes	
Carli, Italy, 1999	16010	Comparator (44)			3 Pts. <1, 27 Pts. <10, 14 Pts >=10				Alveolar (30%) Embryonal/NOS (70%) Primary site Extremity, parameningeal , other (80%), Genitourinary tract and Head and Neck (20%)	
McDowell, UK, 2010	75350	Comparator (45)		4.28	0.52-9.93		60% Male 40% Female	No bone or bone marrow mets parameningeal (22%) and pelvis (31%) most common primary sites	57% Embryonal 33% alveolar 9% unspecified or unknown 71% had mets to the lung	This is the standard risk group in this two arm risk stratified study.

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Com ment
Pappo, USA, 1999	48020	Comparat or (605)	8 years at diagnos is		0-20	73% White	57 % Male 43% Female	stage I 17%, stage II 8%, Stage III 36%, Stage IV 36%, unknown 3% 9% clinical group I, 9% clinical group II, 45% clinical group III, 37% clinical group IV	botryoid (3%), embryonal (53%), alveolar or undiffer (45%) most common primary tumor sites extremities (26%) Parameningeal (19%) and retroperitoneum (13%)	
Pappo, USA, 2001	47860	Comparat or (48)		10 at diagnos s	0-19	70% White, 15% Black, 15% Other	52% Male, 48% Female	Metastatic	29% Embryonal, 48% alveolar, 4% Undifferentiated, 19% Unspecified Primary sites 43% retroperitoneum/peri neum/trunk, 23% extremities, 15% GU/bladder/prostate, 19% other	
Sandler, USA, 2001	12810	Comparat or (152)		8.5	(0-19)		58% Male, 42% Female	metastatic	48% Embryonal, 37% alveolar, 15% Other primary sites include 31% extremity, 18% HN (including orbit and parameningeal), 18% retroperitoneum, 34% other	
Van Winkle, USA, 2005	43550	Comparat or(27)	11.3		2.1-20.5		48% Female 52% Male	at recurrence 4% stage I, 0 stage II, 11% stage III, 63% Stage IV, 22% Unknown	37% alveolar 41% Embryonal 11% Undifferentiated 11% unknown	

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Williams, Canada, 2004	9010	Comparator (13)			7 patients <10 6 patients >10		54% Male 47% Female	Stage IV mets to all sites	9 patients Alveolar, 3 embryonal,1 mixed-primary site Trunk(6), bladder/prostate (2), extremity (4) Genitourinary (1)	

Appendix Table C24. Treatment characteristics: Rhabdomyosarcoma

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Condition-ing Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Bisogno, Italy, 2009	75340	HSCT (70)	PBSC	Auto	surgery + chemo including ifosfamide, vincristine, actinomycin, CY, carboplatin, vincristine, etoposide	thiotepa, melphalan, CY					those with at least a partial response moved onto HD with stem cell support. Patients received three rounds of HDC and stem cell infusion.
Breneman, USA, 2003	75360	Comparator (127)							Chemo +/- RT	melphalan-vincristine + vincristine, dactinomycin and CY (VAC) or VAC + ifosfamide + etoposide	
Carli, Italy, 1999	16010	HSCT (52) Comparator (44)	PBSC or BM	Auto	epirubicin, carboplatin, vincristin, actinomycin, ifosfamide, etoposide	Melphalan				epirubicin, carboplatin, vincristin, actinomycin, ifosfamide, etoposide	

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Condition-ing Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Doelken, Germany, 2005	6570	HSCT (2)	Pt1- PBSC from HLA-identical sibling Pt 2 PBSC from HLA-identical fraternal twin	Pt1- Allogeneic Pt 2- Auto then Allo	pt1-CWS-96 Arm B protocol including ifosfamide, vincristine, carboplatin, epirubicin and actinomycin D, etoposide and RT Pt2- CWS-91 protocol chemo+ RT, relapsed +2 years, Auto transplant after HD w/ thiotepa and CY, resection and RT lung mets	Pt1- TBI, etoposide, CY Pt2- immunosuppression with treosulfane and fludarabine W/O HD chemo (for Allo)	Pt 1- cyclosporin A and MTX and prednisolone and CellCept after AGVHD developed				
Donker, Netherlands, 2009	1420	HSCT (1)	Bone Marrow	Allogeneic	SIOP MMT-98 protocol; including vincristine, dactinomycin, ifosfamide, carboplatin, epirubicin, etoposide and CY.	etoposide, CY and TBI	CsA was given				

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Condition-ing Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Grundy, UK, 2001	14200	HSCT (1)			chemo including vincristine, actinomycin D, CY, doxorubicin, etoposide + amputation of the right leg	melphalan					transplant was followed by more chemo
Hara, Japan, 1998	17950	HSCT (7)	PBSC or BM	Auto	Chemo containing cisplatin, CY, vincristine. Ifosfamide, dactinomycin, etoposide, carboplatin and pirarubicin were administered in some patients +/- surgery and LRT	Thiotepa, melphalan and busulfan		laminar air flow, total parenteral nutrition and antibiotics, G-CSF			6 patients were transplanted in CR one was not in CR

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Condition-ing Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Koscielniak, Germany, 1997	19800	HSCT (36)	BM -26 patients PBSC- 5 patients Allogeneic - 5 patients	Auto-31 Allo-5	CWS-81, CWS-86, CWS-91, (23 patients), MMT stage IV (12) CWS relapse (1), treatment included vincristine, dactinomycin, CY, doxorubicin, ifosfamide, VP16, carboplatin, epiadriamycin	melphalan, VP16, carboplatin +/- RT		14 received G-CSF or GM-CSF support			
Kuroiwa, Japan, 2009	390	HSCT (1)		Auto	Chemo including vincristine, actinomycin D, CY	ifosfamide-cisplatin-etoposide					
Kwan, Hong Kong, 1996	20800	HSCT (1)	PBSC	Auto	adriamycin and CY + Surgery and post-operative radiation	Vincristine, ifosfamide, actinomycin D HDC with carboplatin, etoposide, melphalan					transplanted in CR

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Condition-ing Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Lucidarme, France, 1998	17610	HSCT (8)	PBSC or BM	Auto	chemo including CY or ifosfamide +/- surgery +/- RT	Thiotepa		laminar air-flow, right atrial catheters, parenteral nutrition, broad spectrum anti-biotics, blood products			

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Condition-ing Regi men	Immunosu ppressive therapy for GVHD prophylaxi s	Supporti ve Care	Comparati ve Treatment	Comparative Treatment Dose/Regimen	Comment
Matsubara, Japan, 2003	10810	HSCT (22)	PBSC and BM	Auto	treatment varied and included VAC (vincristine, dactinomycin and CY) VAC-THP (pirarubicin + VAC), VCA(vincristine, dactinomycin, CY, doxorubicin, VAI (vincristine, dactinomycin, ifosfamide) +/- cisplatin, etoposide or methotrexate and +/- surgery & RT	includ ed Hi-MEC (etop oside, carbo platin, melph alan), Hi-MEC + piraru bicin, etopo side + melph alan + ifosfa mide, etopo side + thiote pa, Melph alan alone		intraveno us hyperali mentatio n or blood products as needed. G-CSF was used in 14 patients transplan ted after 1993			

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Condition-ing Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
McDowell, UK, 2010	75350	HSCT (101) Comparator (45)	Auto	PBSC	doxorubicin or carboplatin	sequential high dose therapy containing cyclophosphamide, etoposide, carboplatin			chemo and surgery +/- radiotherapy followed by maintenance therapy 9 courses of VAC	ifosfamide, vincristine, actinomycin D, carboplatin, etoposide, and epirubicin (induction) after local therapy patients received 9 courses of VAC (maintenance therapy)	sequential HD therapy was given at 14 day intervals regardless of blood count. Four does were given
Misawa, Japan, 2003	11040	HSCT (1)	PBSC	Allogeneic from HLA-identical sibling	vincristine, CY, pirarubicin alternating with etoposide, ifosfamide, and cisplatin	pirarubicin, etoposide, carboplatin, melphalan	Cyclosporine and methylprednisolone				
Moritake, Japan, 1998	18280	HSCT (1)	BM	Allogeneic	VCR, actinomycin D, CY, pirarubicin and ifosfamide + RT	etoposide, carboplatin, pirarubicin, melphalan	methotrexate				

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Condition-ing Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Oue, Japan, 2003	10950	HSCT (1)		Auto-Auto	chemo + RT	Ifosfamide and melphalan (first) Busulfan and thiotepa (second)		G-CSF, blood products			this is a tandem transplant
Pappo, USA, 1999	48020	Comparator (605)							chemo +/- RT	vincristine-Actinomycin (14%), vincristine-Actinomycin-CY or similar (37%), vincristine, doxorubicin, actinomycin, CY +/- other agents (25%), window + other (24%)	
Pappo, USA, 2001	47860	Comparator (48)							Chemo +/- RT	Topotecan + VAC alternating with vincristine, topotecan, CY or topotecan + VAC	
Raney, USA, 2008	2440	comparator (91)							chemo +/- RT	vincristin, actinomycin D, CY +/-doxorubicin, cisplatin, dacarbazine, etoposide and/or ifosfamide	
Sandler, USA, 2001	12810	Comparator (152)							Chemo +/- RT	ifosfamide, doxorubicin and VAC	

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Condition-ing Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Sato, Japan, 1998	48070	HSCT (5)	PBSC	Auto	Chemo +/- surgery and or RT	Hi-MEC +/- pyrarubicin		Hydroxyzine and hydrocortisone and G-CSF			
Scully, USA, 2000	14580	HSCT (1)	PBSC	Auto	prior chemo for initial disease, chemo for recurrence included ifosfamide carboplatin, etoposide	HDC with CY and carboplatin					tumor was excised after SC rescue and radiation was delivered
Shaw, Israel, 1996	20050	HSCT (9)	PBSC and BM	Auto	Chemo +/- surgery and or radiation therapy chemo included vincristine, adriamycin, CY etoposide, ifosfamide	carboplatin, melphalan,		parenteral nutrition, antibiotics and anti-fungal therapy was provided based on the pt status. G-CSF or GM-CSF was used in some patients			
Taguchi, Japan, 2005	7430	HSCT (1)			carboplatin and etoposide						
Van Winkle, USA, 2005	43550	Comparator(27)							chemo	Ifosfamide and etoposide	

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Condition-ing Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Walterhouse, USA, 1999	17240	HSCT (8)	PBSC	Auto	Chemo and radiation +/- surgical resection chemo regimens included vincristine, dactinomycin, CY, melphalan, etoposide, ifosfamide and doxorubicin	thiotepa, CY, carboplatin		G-CSF, fluconazole prophylaxis, broad spectrum abx for fever, parenteral nutrition and blood product support			patients achieving a complete response were offered HDC with stem cell rescue
Williams, Canada, 2004	9010	HSCT (4) Comparator (13)		Auto	ifosfamide and etoposide alternating vincristine, CY, doxorubicin and/or actinomycin +/- radiation and surgical resection	etoposide, CY with or without melphalan			Chemo +/- radiation and surgical resection	ifosfamide and etoposide alternating vincristine, CY, doxorubicin and/or actinomycin	13 patients received radiation with curative intent of these 4 received HDC with Stem cell support

Appendix Table C25. Outcome assessment: Treatment, rhabdomyosarcoma

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Comment
Bisogno, Italy, 2009	75340	HSCT (70)	Survival	Toxicity		Children less that 10 had significantly better outcomes than older children 54.3%. Under multivariate modeling RR of 2.59 (1.3-5.1) for children over 10 for the role of age as a prognostic factor for survival
Carli, Italy, 1999	16010	HSCT (52)	Overall Survival	Event Free		who was transplanted ended up being center based not response based
Doelken, Germany, 2005	6570	HSCT (1)	Pt 1- died of progressive disease 146 days post transplant due to disease progression Pt 2- recurred three years after Auto transplant, five years after Auto transplant he received an Allo he died 379 days post Allo transplant due to disease progression.			Transplants were not perfomed on patients in complete remission
Donker, Netherlands, 2009	1420	HSCT (1)	Survival		Patient was followed and has survived 4 years post-transplant	Patient had severe ifosfamide tubulopathy that evolved into chronic renal insufficiency but is stable with conservative therapy. Transplant was completed on a patient in complete remission.
Dunkel, USA, 2000	14610	HSCT (4)	Survival	No major harms reported	100% of patients were alive at a median FU of 57 months (46-80)	
Grundy, UK, 2001	14200	HSCT (1)	Survival		Patient recurred and died at 2 years 3 months of age.	
Hara, Japan, 1998	17950	HSCT (7)	Survival	Harms	4 alive NED median 26.5 months (15-32) 3 DOD median 6 months (3-6) 1 TRM 1 month	

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Comment
Koscielniak, Germany, 1997	19800	HSCT (36)	Survival	estimated Event Free Survival at 2 years after HDC 36 +/- 7% 2 years after diagnosis 55 +/- 8%' Harms	9 alive NED median FU of 57 (32-108) months after diagnosis, 27 (20-100) months after HDC. 1 alive in 2nd CR after additional local treatment	
Kuroiwa, Japan, 2009	390	and ifosfamide-cisplatin-etoposide	Survival		Patient is alive with controlled disease at age 3 years 11 months, 46 months after diagnosis	Patient survived transplant and recurred with metastatic disease after transplant was treated with Chemo
Kwan, Hong Kong, 1996	20800	HSCT (1)	survival		Alive NED 3 months post transplant	
Lucidarme, France, 1998	17610	HSCT (8)	Survival	Harms	One patient was in complete remission at 33 months post-transplant 7 were DOD median 7 months (2-38) post transplant	two patients were transplanted in partial remission and 6 had progressive disease at the time of transplant.
Matsubara, Japan, 2005	7580	HSCT (5)	Survival	harms	60% alive at a median of 107 months FU 40% died at a median of 26 months FU	the two patients who died developed CNS involvement the three others remained non CNS
McDowell, UK, 2010	75350	HSCT (101)	Survival	Harms	16.56 (0.76-101.39)	8 SAE were reported but not further described.
Misawa, Japan, 2003	11040	HSCT (1)	Survival- Patient died of progressive disease 165 days after transplant			Patient was NOT in CR when the transplant was completed
Moritake, Japan, 1998	18280	HSCT (1)	Survival ~21 months after transplant the patient dies due to progressive disease			Patient received donor leukocyte infusion 12 months after transplant as salvage

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Comment
Navid, USA, 2006	5930	HSCT (8), 2 transplanted 6 were not	Survival	harms	2 alive NED median 79 months (65-92) post enrollment 1 LFU at 78 months 3 DOD 12 months (9-16) post enrollment 2 Toxic Death median 6.5 (5-8) months post enrollment	Only two patients were transplanted as they reached CR and stayed on study. One who achieved CR was LFU. In a Cox model for all those who were transplanted (more than just RMS) there was no evidence that transplantation had an effect on survival
Oue, Japan, 2003	10950	HSCT (1)	Survival	Harms	patient was alive 19 months after disease onset	harms were for non RMS patients as this was a mixed tumor study
Sato, Japan, 1998	48070	HSCT (5)	Event Free Survival		alive without evidence of disease (EFS) of 23.4 months post-transplant	Transplanted in Complete remission
Scully, USA, 2000	14580	HSCT(1)	Survival	Harms	Alive with secondary malignancy approximately 3 years after transplant for RMS	
Shaw, Israel, 1996	20050	HSCT (9)	Survival	Harms	44% DOD median 286 days follow-up 44% NED median 745 days FU 11% AWD 350 days FU	
Taguchi, Japan, 2005	7430	HSCT (1)	Survival	NR	19 months	Dead at 19 months after transplant Non CNS group
Walterhouse, USA, 1999	17240	HSCT (8)	Survival	Harms	38% DOD at median of 15 months after diagnosis (not transplanted) 75% of those transplanted are DOD median 12 months post transplant or 20 months post diagnosis 25% alive NED at 53 months post trans patient who declined transplant DOD 30 m from diag	Five patients achieved a complete response and were eligible for transplant, one refused

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Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Comment
Williams, Canada, 2004	9010	HSCT (4)	Survival	Event Free Survival		patients with embryonal histology, metastasis confined to the lung, and < 10 had 100% survival at 3 years compared to 0% for the remaining patients

Appendix Table C26. Outcome assessment: Comparator, rhabdomyosarcoma

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Comment
Breneman, USA, 2003	75360	Comparator (127)	Survival			
Carli, Italy, 1999	16010	Comparator	Overall Survival	Event Free survival		
Grundy, UK, 2001	14200					
McDowell, UK, 2010	75350	Comparator (45)	Survival	Harms	30.16 months (0.69-105.40)	
Pappo, USA, 1999	48020	Comparator (605)	survival		five year survival botroid 64% (40-88), embryonal 26% (21-31), alveolar/undiff 5% (2-8)	histologic subtype at initial diagnosis associated with survival after recurrence, but survival not affected by site of recurrence.
Pappo, USA, 2001	47860		Survival	Harms		number of metastatic sites influenced survival 1 or 2 vs. +2
Sandler, USA, 2001	12810	Comparator (152)	Survival	Harms		Patients who are < 10 or with embryonal RMS, or a GU primary site, or no nodal disease at presentation and patients lacking bone or bone marrow involvement at presentation fared significantly better.
Van Winkle, USA, 2005	43550	Comparator (27)	Survival	Harms		Male gender (p=.015), Embryonal histology at recurrence (p=.005), and CR (p=.014) were associated in univariate analysis with improved survival
Williams, Canada, 2004	9010	Comparator (13)	Survival	Event Free Survival		

Appendix Table C27. Time to event outcomes: Treatment, rhabdomyosarcoma

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	p	HR (95%) CI
Bisogno, Italy, 2009	75340	HSCT (70)	42.3% (30.5-53.6) 3 year survival								
Carli, Italy, 1999	16010	HSCT (52)	3 year 40.0(25.5-54.7)		~86%	~46%	40.0(25.5-54.7)	~40%	~40%	0.2 for three year versus comparator	
Matsubara, Japan, 2003	10810	HSCT (22)	45% at 5 years								
McDowell, UK, 2010	75350	HSCT (101)					23.70%		17.93%	<0.001	2.46 (1.51-4.03)
Williams, Canada, 2004	9010	All 17 together	35% (13-58) FFS 29.4% (18-40)	3 yrs							

Appendix Table C27. Time to event outcomes: Treatment, rhabdomyosarcoma Continued

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	5 yr_2	p_2	HR (95% CI)_2
Bisogno, Italy, 2009	75340	HSCT (70)	Progression free survival at 3 years 35.3 (24.3-46.5)							
Carli, Italy, 1999	16010	HSCT (52)	EFS 29.7 (15.6-43.8)	~46%	~30%	29.7 (15.6-43.8)	~20%	~20%	0.3 for 3 years versus comparator	
Matsubara, Japan, 2003	10810	HSCT (22)	DFS					36%		
McDowell, UK, 2010	75350	HSCT (101)	Event Free Survival			16.53%		14.88%	<0.001	2.68 (1.64-4.37)
Williams, Canada, 2004	9010	All 17 together	Overall Survival HSCT (4) only			100%				

Appendix Table C27. Time to event outcomes: Treatment, rhabdomyosarcoma Continued

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_3	3 yr_3	5 yr_3	p_3	Comment
Matsubara, Japan, 2003	10810	HSCT (22)	OS (CR) vs. OS (PR) OS Embryonal vs. OS Alveolar OS >8 years vs. OS <8 years		70% vs. 0% 75% vs. 0% 18% vs. 75%	no difference reported 0.015 no difference reported	
McDowell, UK, 2010	75350	HSCT (101)					This study also reported survival differences by induction treatment, however this is beyond the scope of the review.
Williams, Canada, 2004	9010	All 17 together	Failure Free Survival	75% (33-107)			

Appendix Table C28. Time to event outcomes: Comparator, rhabdomyosarcoma

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
Breneman, USA, 2003	75360	comparator (127)			~85%	~50%	39% (30-48)	~25%	~25%
Carli, Italy, 1999	16010	Comparator (44)	27.7 (13.3-42.1) 3 year		~66%	~35%	27.7 (13.3-42.1)	~26%	~26%
McDowell, UK, 2010	75350	Comparator (45)					62.14%		47.68%
Pappo, USA, 1999	48020	Comparator (605)	17% (14-21)	4.7 years (.8-12.6)					
Pappo, USA, 2001	47860	Comparator (48)				46% (31-60)			
Sandler, USA, 2001	12810	Comparator (152)			~75%	~43%	~40%	~34%	~37.5%
Van Winkle, USA, 2005	43550	Comparator(27)			56 (10)	26 (8)			
Williams, Canada, 2004	9010	Comparator (13)	15% (-4-35)	3 year					

Appendix Table C28. Time to event outcomes: Comparator, rhabdomyosarcoma Continued

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	5 yr_2	Comment
Breneman, USA, 2003	75360	comparator (127)	FFS	~69%	~33%	25% (17-33)	~20%	~20%	FFS influenced by distant metastasis in lymph nodes. OS influenced by number of metastatic sites
Carli, Italy, 1999	16010	Comparator (44)	EFS	~53%	~30%	19.2 (6.8-31.6)	~20%	~20%	
McDowell, UK, 2010	75350	Comparator (45)	Event free survival			54.92%		51.00%	
Pappo, USA, 1999	48020	Comparator (605)							
Pappo, USA, 2001	47860	Comparator (48)	failure Free	~57%	24% (13-36)	~21%	~21%		
Sandler, USA, 2001	12810	Comparator (152)	FFS	~63%	~36%	~28%	~28%	~27%	
Van Winkle, USA, 2005	43550	Comparator(27)							
Williams, Canada, 2004	9010	Comparator (13)	Failure Free survival			15% (-4-35)			

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Appendix Table C29. Adverse events: Treatment, rhabdomyosarcoma

Study (Investigator, country, year)	Record Number	Group (N)	% Infection	Comment	Group (N) TRM	Severity or Grade TRM	F/U (mos) TRM	% TRM	Comment TRM	% Secondary Malignancy	Comments SM
Bisogno, Italy, 2009	75340		12.7					4.3			
Carli, Italy, 1999	16010				HSCT (52)			1.9% TRM (1/52)	Sepsis related death		
Hara, Japan, 1998	17950		14% (1/7)	sepsis			1 month	14% (1/7)	on additional non RMS patient experienced TRM so in all 2/28 (7.1%)		
Koscielniak, Germany, 1997	19800		2.8			one patient dies due to sepsis					
McDowell, UK, 2010	75350							5.0	It is unclear from the authors' description if any of these are within the first 100 days.		
Navid, USA, 2006	5930	HSCT (8)						25% (2/8)	two patients experienced TRM (radiation pneumonitis and disseminated alveolar infection)		

Study (Investigator, country, year)	Record Number	Group (N)	% Infection	Comment	Group (N) TRM	Severity or Grade TRM	F/U (mos) TRM	% TRM	Comment TRM	% Secondary Malignancy	Comments SM
Oue, Japan, 2003	10950							8.3	Patients from a mixed tumor study. Neither of these patients had RMS		
Scully, USA, 2000	14580	HSCT (1)								one patient	developed precursor T-lymphoblastic lymphoma and early myeloid dysplastic syndrome
Shaw, Israel, 1996	20050							6.6	Patients from a mixed tumor study. Neither patient had RMS		
Walterhouse, USA, 1999	17240			Sepsis in 4 fungal infection in 1							

Appendix Table C30. Adverse events: Comparator, rhabdomyosarcoma

Study (Investigator, country, year)	Record Number	Group (N)	% Infection	Comment	Group (N) TRM	% TRM	Comment TRM
Carli, Italy, 1999	16010				Comparator (44)	2.3% TRM (1/44)	due to anthracycline related cardiotoxicity
McDowell, UK, 2010	75350	Comparator (45)	2% (1/45)			4.4% (2/45)	
Pappo, USA, 2001	47860	Comparator (48)	8.3% Bacteremia (4/48)	at various doses of Topotecan		4.2% (2/48)	died of tracheobronchitis and interstitial pneumonitis. One other patient died on treatment of adult respiratory distress but the authors said this could not with certainty be related to Topotecan.
Sandler, USA, 2001	12810		30.9% Grade IV, and 5.2%) Grade V	28.3% (43/152) Grade IV infection, and 4.6%(7/152) Grade V infection 2.6% (4/152) catheter infection Grade IV, .7 % (1/152) catheter infection Grade V		5.9% (9/152)	seven infection related and two (thrombocytopenia and hemorrhage and one to pulmonary toxicity) It is unclear if these are all within the first 100 days
Van Winkle, USA, 2005	43550					0.6	TRM from infection among 336 courses of ICE

Appendix Table C31. Design, participant selection and enrollment: Retinoblastoma

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)
Antoneli, Brazil, 2003	48830	malignant solid tumor	retinoblastoma	extraocular	Comparator (83)	1987-1991 period 1 1992-2000 period 2	case series	83	8 LFU (9.6%)
Chang, Taiwan, 2006	48660	malignant solid tumor	Retinoblastoma	Extraocular	Comparator(15)	1982-2004	retrospective analysis of medical records	15	0
Chantada, Argentina, 1999	16020	Malignant solid tumor	retinoblastoma	Extraocular	Comparator (10)	1995-1998	Case Series	10	0
Cozza, Italy, 2009	70	malignant solid tumor	retinoblastoma	metastatic retinoblastoma	HSCT (3) Comparator (3)	1988-2007	retrospective review	6	0
Dai, Canada, 2008	1410	malignant solid tumor	retinoblastoma	Trilateral retinoblastoma	HSCT (1)		Case report	1	1
Dunkel, USA, 2000	14610	malignant solid tumor	retinoblastoma	metastatic	HSCT (4)	1993-1996	Case series	4	0
Dunkel, USA, 2010	71500	malignant solid tumor	trilateral retinoblastoma	trilateral retinoblastoma	HSCT (13)	1997-2005	Case Series	13	0
Gunduz, Turkey, 2006	5310	malignant solid tumor	retinoblastoma	metastatic retinoblastoma	Comparator (18)	1999-2005	retrospective case series	18	0
Hertzberg et al, Germany, 2001	13810	Malignant Solid Tumors	Retinoblastoma	Metastatic	HSCT (1)	NR	Case Report	1	0

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)
Jubran, USA, 2004	9480	malignant solid tumor	retinoblastoma	metastatic	HSCT (4) Comparator (3) untreated (3)	1991-1999	retrospective review	10	0
Kremens, Germany, 2003	10860	malignant solid tumor	retinoblastoma	metastatic	HSCT (5)	1992-2001	Case series	5	0
Matsubara, Japan, 2005	7580	malignant solid tumor	retinoblastoma	metastatic retinoblastoma without CNS involvement	HSCT (5)	1986-2000	Case Series	5	0
Moshfeghi et al, USA, 2002	12230	malignant solid tumor	Retinoblastoma	Metastatic	HSCT (1)	NR	Case Report	1	0
Namouni, France, 1997	18090	Malignant Solid Tumor	Retinoblastoma	Metastatic or relapse or invasion of the cut end of optic nerve	HSCT (34)	1989-1994	Case Series	25, received HSCT' 9 progressed/died before treatment	
Rodriguez-Galindo, USA, 2003	10420	malignant solid tumor	retinoblastoma	metastatic	HSCT (4)		case series	4	0
Schvartzman, Argentina, 1996	49250	malignant solid tumor	retinoblastoma	extraocular	Comparator (41) Stage II(29) Stage III (6) Stage Iv (6)	1987-1993	prospective single arm non-randomized	41	0
Taguchi, Japan, 2005	7430	malignant solid tumor	retinoblastoma	Metastatic	HSCT (1)		Case Report	1	0

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)
Dunkel, USA, 2010	2149	retinoblastoma	retinoblastoma	non-CNS metastasis	15	1993-2006	case series	15	0
Dunkel, USA, 2010	2148	retinoblastoma	retinoblastoma	CNS metastasis	8	2000 - 2006	case series	8	0
Dimaras, Canada, 2009	2137	Metastatic Retinoblastoma	retinoblastoma	Metastatic	1	2001	case report	1	0

Appendix Table C32. Participant characteristics: Treatment, retinoblastoma

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)
Cozza, Italy, 2009	70	HSCT (3)		440months (diagnosis of metastasis whole group n=6)	18-110 months (n=6)		50% male, 50% female (n=6)		CSF, Pineal, orbit, bone and bone marrow
Dai, Canada, 2008	1410	HSCT (1)	12 months				Female	trilateral retinoblastoma	with CSF involvement
Dunkel, USA, 2000	14610	HSCT (4)	30.5 months at diagnosis	30.5 months at diagnosis	17-44		50% Male, 50 % Female		distant metastasis (BM, Orbit, liver, bone) no CNS involvement
Hertzberg et al, Germany, 2001	13810	HSCT (1)	7				F	metastatic retinoblastoma	lymph nodes, bones and bone marrow
Jubran, USA, 2004	9480	HSCT (4)	12.3 month at diagnosis	11.5 months at diagnosis	2-24				distant no CNS involvement
Kremens, Germany, 2003	10860	HSCT (5)	51.8 months (treatment)	34 months	20-110				bone marrow, extraocular tumor
Matsubara, Japan, 2005	7580	HSCT (5)	17.6 months at diagnosis	16 months at diagnosis	3-41		20% Male, 80% Female		distant metastasis
Moshfeghi et al, USA, 2002	12230	HSCT (1)	5			White	F	metastatic	bone marrow, right humerus, both supraorbital bones, and both tibias, ovary

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)
Namouni, France, 1997	18090	HSCT (25)		34 months	(9-125) months		76% Male 14% Female	extraocular retinoblastoma	cut end of optic nerve (5) disruption of ocular globe(1) isolated orbital relapse (7) bone or bone marrow (8) CNS/spinal axis (4)
Rodriguez-Galindo, USA, 2003	10420	HSCT (4)	28.5 age at diagnosis	30.5	17-36	75% white 25% Hispanic	75% Male 25% female		distant metastases no CNS involvement
Taguchi, Japan, 2005	7430	HSCT (1)	4				male	metastatic	maxilla and mandible
Dimaras, Canada, 2009	2137	1	4 months at diagnosis				male	CSF mets	CSF
Dunkel, USA, 2010	2148	8	22 months	24.5 months	4-38 months			4b	CNS
Dunkel, USA, 2010	2149	15	25 months	26 months	1-44 months			metastatic retinoblastoma	orbit, bone, bone marrow, liver

Appendix Table C33. Participant characteristics: Comparator, retinoblastoma

Study (Investigator, country, year)	Re-cord Num ber	Grou p (N)	Age (mean)	Age (med-)	Age (Rng)	Race (%)	Gen-der M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Antoneli, Brazil, 2003	4883 0	Com parat or (83)	32.9 months		2-145	62.7 % Whit e	53% Male	extraocular retinoblastoma	69 class I/III CCG classification 14 Class IV/V	Class IV CNS involvement
Chang, Taiwan, 2006	4866 0			26.3 at diagno sis	1.7-89 mont hs			all stages of extraocular retinoblastoma were reported together	most common sites Orbit (7) and CNS (7)	
Chantada, Argentina, 1999	1602 0	Com parat or (10)		2 years	1-7		40% M, 60% F	extraocular	Various sites including 3 patients with bone marrow involvement at diagnosis (30%)	
Cozza, Italy, 2009	70	Com parat or (3)		41.5 at diagno sis	3-110 at diagn osis		50% male' 50% femal e		CSF (3)	
Gunduz, Turkey, 2006	5310	Com parat or (18)		45 months at diagno sis	13-86				distant and CNS (5) CNS (9) distant only (4)	
Jubran, USA, 2004	9480	Com parat or (6)	31.3 months at diagnos is	17.5 months	1-96				distant no CNS	two patients were not treated for their extraocular disease, one received no treatment at all
Schvartzman, Argentina, 1996	4925 0	Com parat or (41)						Extraocular retinoblastoma	Orbital (29) intracranial (6) these patients had CNS mets hematogenous metastasis (6) three of these patients also had CNS mets	

Appendix Table C34. Treatment characteristics: Retinoblastoma

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen
Antoneli, Brazil, 2003	48830	Comparator (83)						Chemo +/- radiation	Cisplatin, teniposide, vincristine, doxorubicin, cyclophosphamide (period 1) Cisplatin and teniposide with alternating ifosfamide and etoposide (period 2)
Chang, Taiwan, 2006	48660	Comparator (15)						Chemo +/- radiation	cyclophosphamide, vincristine, adriamycin, intrathecal methotrexate +/- radiation
Chantada, Argentina, 1999	16020	Comparator (10)					GCSF, platelet and RBC transfusions	Idarubicin	10mg/m2/d
Cozza, Italy, 2009	70	HSCT (3) comparator (3)	PBSC	auto	ifosfamide, carboplatin, etoposide, vincristine, doxorubicin cyclophosphamide (some combination of these)	etoposide, thiotepa, cyclophosphamide +/- radiation		ifosfamide, carboplatin, etoposide, vincristine, doxorubicin cyclophosphamide, thiotepa with methotrexate (some combination of these)	

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen
Dai, Canada, 2008	1410	HSCT (1)	PBSC	Auto	cyclosporine-modulated vincristine, etoposide, carboplatin with intraventricular topotecan/cytarabine	carboplatin, etoposide cyclophosphamide			
Dunkel, USA, 2000	14610	HSCT (4)	BM (3) PBSC (1)	Auto	vincristine, doxorubicin, cyclophosphamide, cisplatin, etoposide, carboplatin (some combination)	thiotepa and carboplatin + radiation			
Dunkel, USA, 2010	71500	HSCT (13)	PBSC (6) Marrow (1) PBSC and Marrow (1) Unknown (1)	Auto	vincristine, cisplatin, cyclophosphamide and etoposide (11) carboplatin, etoposide, cyclophosphamide, doxorubicin (1)' single agent cyclophosphamide (1)	thiotepa based (6) cyclophosphamide and melphalan (2) both (one tandem)			
Gunduz, Turkey, 2006	5310	Comparator (18)					GCSF was given to those on treatment B	Treatment A cyclophosphamide, doxorubicin, vincristine, carboplatin, etoposide with intrathecal chemo +/- radiation(4) Treatment B- ifosfamide, carboplatin, etoposide +/- radiation (14)	

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen
Hertzberg et al, Germany, 2001	13810	HSCT (1)	PBSC	Auto	vincristine, cyclophosphamide, etoposide, and carboplatin	HDC Thiotepa by etoposide and carboplatin	Platelet and Red Blood cell transfusion		
Jubran, USA, 2004	9480	HSCT (4) Comparator (6)	BM	Auto	Chemo +/- radiation one patient received no treatment	cyclophosphamide, etoposide and thiotepa		three received no treatment for extraocular disease one radiation alone, one chemo alone, one chemo+ radiation	cyclophosphamide, etoposide, vincristine, carboplatin, thiotepa
Kremens, Germany, 2003	10860	HSCT (5)	PBSC	Auto	cisplatin, etoposide, vindesine vincristine, DTIC, ifosfamide, doxorubicin or cyclophosphamide, etoposide, carboplatin, vincristine	thiotepa, etoposide, carboplatin (4) +/- radiation BCNU, cyclophosphamide, and etoposide (1)	barrier nursing, oral decontamination, oral antifungal, pneumocystis carinii prophylaxis, parenteral nutritional support		
Matsubara, Japan, 2005	7580	HSCT (5)	PBSC (1) BM (4)	Auto	vincristine, cyclophosphamide, doxorubicin, cisplatin, etoposide, carboplatin (some combination) +/- radiation	melphalan with some combination of cisplatin, cyclophosphamide, etoposide, carboplatin, thiotepa +/- radiation	GCSF		
Moshfeghi et al, USA, 2002	12230	HSCT (1)		Auto	six courses of chemotherapy, local orbital radiation				

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen
Namouni, France, 1997	18090	HSCT (25)	Marrow	Auto	etoposide, carboplatin, cyclophosphamide, vincristine, doxorubicin, 8 patients had irradiation	Carboplatin, Etoposide, cyclophosphamide +/- radiation	parenteral antibiotics, antifungal therapy, platelet and RBC transfusions		
Rodriguez-Galindo, USA, 2003	10420	HSCT (4)	BM	Auto	carboplatin, etoposide, cyclophosphamide, doxorubicin and carboplatin or cisplatin + radiation	carboplatin and etoposide or cyclophosphamide with busulfan and melphalan or etoposide or topotecan	antifungal therapy		
Schvartzman, Argentina, 1996	49250	Comparator (41)						Chemo +/- radiotherapy	Cyclophosphamide, Doxorubicin, Vincristine Stage III and IV also received cisplatin and etoposide
Taguchi, Japan, 2005	7430	HSCT (1)			carboplatin and etoposide				
Dimaras, Canada, 2009	2137	1	cord blood	autologous	systemic chemotherapy and intraventricular chemo	carboplatin, etoposide, cyclophosphamide			
Dunkel, USA, 2010	2148	8		autologous	surgery, chemotherapy	carboplatin, etoposide, cyclophosphamide, cisplatin, thiotepa			
Dunkel, USA, 2010	2149	15	bone marrow, peripheral blood, both	autologous	enuculation with or without chemo	carboplatin, thiotepa, topotecan, etoposide			

Appendix Table C35. Outcome assessment: Treatment, retinoblastoma

Study (Investigator, country, year)	Re-cord Num-ber	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Comment
Cozza, Italy, 2009	70	HSCT (3)	Survival	NR	66% alive at median FU of 61.5 months 33% dead at 16 months	
Dai, Canada, 2008	1410	HSCT (1)	Survival	NR	death at 32 months follow-up	she had CNS involvement
Dunkel, USA, 2000	14610	HSCT (4)	Survival	No major harms reported	100% of patients were alive at a median FU of 57 months (46-80)	
Hertzberg et al, Germany, 2001	13810	1	Survival	Harms	Alive 4 years+ post transplant	
Jubran, USA, 2004	9480	HSCT (4)	Survival	No major harms reported	100% dead at median of 25 months FU	
Kremens, Germany, 2003	10860	HSCT (5)	Survival	No major harms reported	100% alive median 57 months (8-107)	
Matsubara, Japan, 2005	7580	HSCT (5)	Survival	harms	60% alive at a median of 107 months FU 40% died at a median of 26 months FU	the two patients who died developed CNS involvement the three others remained non CNS
Moshfeghi et al, USA, 2002	12230	1	Survival	NR	16 months	dead at 16 months
Namouni, France, 1997	18090	cut end of optic nerve/ocular globe (6) Isolated orbital (7) Various metastasis (8) CNS/spinal axis (4)	Overall Survival	Harms	Cut end/globe-83% (NED) at median 33 (8-55) 20% (DOD) 9 months Isolated orbital-86% (NED) at median 51.5 (25-74), 14% (PD) 5 bone or bone marrow-63% (NED) at median 37 (11-70), 37% (DOD) 13(10-20) CNS-75% (DOD) at median 10 (7-26), 25% (NED) 63	all numbers are months the 37% DOD with bone mets developed CNS after transplant
Rodriguez-Galindo, USA, 2003	10420	HSCT (4)	Survival	Harms	50% alive at median FU of 6.5 years (6-7) 50% dead at median FU of 66 months (44-88)	2 who are deceased developed CNS involvement
Taguchi, Japan, 2005	7430	HSCT (1)	Survival	NR	19 months	Dead at 19 months after transplant Non CNS group
Dimaras,	2137	HSCT (1)	Survival	Harms	8.3 years post transplant	

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Comment
Canada, 2009						
Dunkel, USA, 2010	2148	HSCT (8)	Survival	Event free survival, harms		
Dunkel, USA, 2010	2149	HSCT (15)	survival	harms, retinoblastoma free		13 of the 15 actually received transplant

Appendix Table C36. Outcome assessment: Comparator, retinoblastoma

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	Independent Response Assessor	F/U Frequency/Duration	Comment
Antoneli, Brazil, 2003	48830	Comparator (83)	Survival	Harms			
Chang, Taiwan, 2006	48660	Comparator (15)	Survival	No major harms reported			
Chantada, Argentina, 1999	16020	Comparator (10)	Survival	Harms (no majors reported)	toxicity was evaluated using the modified Children's cancer group criteria.	60% (NED) 16 months (4-30) 20% (DOD) 7.5 months (5-10) 10% (dead of parental abuse) 8 months 10% DOD with CNS involvement at 3 months	in document 1 DOD at 3 mon CNS, NON-CNS 75% NED, 25% DOD. The one patient dead of parental abuse was not included.
Cozza, Italy, 2009	70	Comparator (3)	Survival	NR		100% dead at median of 8 months FU	
Gunduz, Turkey, 2006	5310	Comparator (18)	Survival	No majors reported		100% of patients with CNS involvement were dead at mean 24 months fu(4-62), this is 9 with CNS only and 5 with CNS and distant metastasis. 100% with distant metastasis only were alive at a median FU of 28.5 months (9-62)	
Jubran, USA, 2004	9480	Comparator (6)	Survival	No major harms reported		100% of those treated (3) were dead at median 7 month FU 100% of those not treated(3) were dead at median 2 months FU	4 patients had CNS involvement (3 were untreated)
Schvartzman, Argentina, 1996	49250	Comparator (41)	Survival	No major Harms reported		50 months	

Appendix Table C37. Time to event outcomes: Treatment, retinoblastoma

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr
Namouni, France, 1997	18090	HSCT (25)	~70%	22 months	~97%	~70%	~70%	~70%	~70%
Dunkel, USA, 2010	2149	HSCT (15)	67%	108 months					67%

Appendix Table C37. Time to event outcomes: Treatment, retinoblastoma Continued

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	5 yr_2	Outcome_3	Med (mos)_3	1 yr_3	2 yr_3	3 yr_3	4 yr_3	5 yr_3	Comment
Namouni, France, 1997	18090	HSCT (25)	Intention to treat overall survival n=34	~88%	~60%	~57%	~52%	~52%	Event Free intention to treat n=34	37 months	~88%	~62%	~57%	~53%	~53%	8 of 9 excluded died due to CNS involvement
Dunkel, USA, 2010	2149	HSCT (15)	retinoblastoma free					67%	progression free	10 years					59%	

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Appendix Table C38. Time to event outcomes: Comparator, retinoblastoma

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	1 yr	2 yr	3 yr	4 yr	Comment
Antoneli, Brazil, 2003	48830	Comparator period 1(43) Comparator period 2(40)	Period 1 Class I/III 65.3% Class IV-V 0% Period 2 Class I/III 75.5% class IV/V 20%						no differences in survival between treatment periods was found
Chang, Taiwan, 2006	48660	Comparator (15)	39.2 +/- 14.7 at 5 years						
Schvartzman, Argentina, 1996	49250	Comparator (41)	Stage II 85% (75-97) 29 pts Stage III 0 (CNS) 6 pts Stage IV 50% (11-89) 6 pts	39 months (12-84) of surviving patients	Stage II 85% stage III and IV ~50%	Stage II 85% stage III and IV ~25%	Stage II 85% stage III and IV ~25%	Stage II 85% stage III and IV ~25%	

Appendix Table C39. Adverse events: Treatment, retinoblastoma

Study (Investigator, country, year)	Record Number	Group (N)	Infectious	Severity or Grade	%	Comment	TRM	% TRM	Comment TRM
Dunkel, USA, 2010	71500	HSCT (13)	Infectious				TRM	7.7% (1/13)	Death due to septicemia and multi-organ failure during induction chemo
Rodriguez-Galindo, USA, 2003	10420	HSCT (4)	Infectious	candida albican sepsis	25% (1/4)	successfully treated with antifungals	TRM		
Dunkel, USA, 2010	2149	HSCT (15)					TRM	12.5 % (1/15)	

Appendix Table C40. Adverse events: Comparator, retinoblastoma

Study (Investigator, country, year)	Record Number	Group (N)	TRM	% TRM	Secondary Malignancies	% SM	Comments SM
Antoneli, Brazil, 2003	48830	Comparator (83)	TRM	4.2	Secondary Malignancies	3.6 % (3/83)	two osteogenic sarcoma and one nonlymphocytic leukemia

Appendix Table C41. Design, participant selection and enrollment: Neuroblastoma

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Berthold, Germany, 2005	6760	Malignant Non-Hematopoietic	Neuroblastoma	Consolidate high-risk	295	1997-2002	RCT	212	83	
George, USA, 2006	5440	Malignant Non-Hematopoietic	Neuroblastoma	Consolidate high-risk	97	1994-2002	case series	82	8	6 (of 97) pts developed progressive disease during induction; 2 did not receive HSCT because of parental wishes; 82 (of 89) patients underwent tandem HSCT
Hobbie, USA, 2008	1690	Malignant Non-Hematopoietic	Neuroblastoma	Consolidate high-risk	35	1997-2001	case series	13	22	Lost to F/U: 18 pts died of progressive disease; 4 pts alive with no disease with no follow-up at centre This study is a sub-group analysis (from Georg, 2006, #5440) of late effects

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Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Eval-uated	n, Withdrawn (Lost to F/U)	Comment
Kim, South Korea, 2007	2870	Malignant Non-Hematopoietic	Neuroblastoma	Consolidate high-risk	36	1996-2004	retrospective analysis	36	0	
Ladenstein, EGBMT, 2008	1610	Malignant Non-Hematopoietic	Neuroblastoma	Consolidate high-risk Relapse Not specified	3571	1978-2006	case series	3421 (3350 for outcomes)	(221 for outcomes given autologous single and tandem HSCT)	80%, consolidate high-risk; 10%, relapse; 10%, specified
Matthay, US, 2009; 1999	6210	Malignant Non-Hematopoietic	Neuroblastoma	Consolidate high-risk	560	1991-1996	RCT	539	21	
Pritchard, United Kingdom, 2005	8030	Malignant Non-Hematopoietic	Neuroblastoma	Consolidate high-risk	90	1982-1985	RCT	65	35	
Sung, South Korea, 2007	3950	Malignant Non-Hematopoietic	Neuroblastoma	Consolidate high-risk	52	1997-2005	case series	52		
Sung, Korea, 2010	2433	Malignant Non-Hematopoietic	Neuroblastoma	Consolidate high-risk	161	2000-2005	retrospective analysis	141	20	

Appendix Table C42. Participant characteristics: Treatment, neuroblastoma

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)
George, USA, 2006	5440	97		35 mos, at diagnosis	6 mos-18 yrs, at diagnosis		IV, 90%; III, 10%	Abdomen, 37; Adrenal, 54; Cervical/paraspinal, 7; Unknown, 2
Hobbie, USA, 2008	1690	13		22 mos	13 mos-72 mos	M, 85%; F, 15%	IV	
Kim, South Korea, 2007	2870	36		3-yr, at diagnosis	7 mos-121 mos	M, 69%; F, 31%	III, 6%; IV, 94%	Abdomen, 89%; Other, 11%
Ladenstein, EGBMT, 2008	1610	3350		47 months	4-744 months	59% M, 41% F	IV, 89% (n=1,681)	
Sung, South Korea, 2007	3950	52		36 mos, at diagnosis	13 mos-129 mos		IV, 100%; MYCN-amplified, 56%; multi-organ (>=3) metastasis, 38%	Shimada classification: favorable, 27; unfavorable, 71; undetermined, 2 Site: Abdomen, 81; Other, 19
Sung, Korea, 2010	2433	71		36	13-144	M, 46%	IV	

Appendix Table C43. Participant characteristics: Comparator, neuroblastoma

Study (Investigator, country, year)	Record Number	Group (N)	Age (Range)	Disease Stage/category	Disease Histology/Site (%)
Berthold, Germany, 2005	6760	149	(< 1 year, 8%; > 1 year, 92%)	I, 1%; II, 1%; III, 5%; IVS, 3%; IV, 90%	
Matthay, US, 2009; 1999	6210	189	(< 1 yr, 3%; 1-2 yr, 23%; > 2 yr, 74%, at diagnosis)	III, 11%; IV, 89%	Favorable, 3%; Unfavorable, 63%; Unknown, 33%
Pritchard, United Kingdom, 2005	8030	32	(6-12 mos, 9%; 13-24 mos, 25%; > 24 mos, 66%, at diagnosis)	III, 19%; IV, 81%	Abdominal, 88%; Other, 12%

Appendix Table C44. Treatment characteristics: Neuroblastoma

Study (Investigator, country, year)	Dis-ease	Re-cord Num-ber	Gro-up (N)	Stem Cell Source	Type of HSCT	Prior Treat-ment	Condi-tioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Suppo-rtive Care	Compara-tive Treatment	Comparative Treatment Dose/Regi-men	Com-ment
Berthold, Germany, 2005	Neuro blasto ma	6760	149	PBSC	single auto	3 cycles of chemo (cisplati n and etoposi de); vindesin e; 3 cycles of vincristi ne and dacarba zine; ifosfami de; doxorub icin; radiothe rapy; surgery	melphala n; etoposide ; carboplati n; (dose and drug adjustme nts in 6 patients)	chimeric monoclonal antibody; retinoic acid after Nov 2002	drugs given to control pain and allergic reactio ns during immun othera py	maintenan ce chemothe rapy	oral cyclophosph amide	
George, USA, 2006	Neuro blasto ma	5440	82	PBSC	tande m auto auto	5 cycles of chemo (multi-agents); surgery after 4th or 5th cycle; radiothe rapy	high-dose chemo (etoposid e, cyclophos phamide, carboplati n, melphala n); total body irradiation	13-cis-retinoic acid				

Study (Investigator, country, year)	Dis-ease	Re-cord Num-ber	Gro up (N)	Stem Cell Source	Type of HSCT	Prior Treat-ment	Condi-tioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Suppo rtive Care	Compara-tive Treatment	Comparative Treatment Dose/Regi-men	Com-ment
Hobbie, USA, 2008	Neuro blasto ma	1690	13	PBSC	tande m auto auto	5 cycles of chemo; surgery after 4th or 5th cycle; radiothe rapy	high-dose chemo (etoposid e, cyclophos phamide, carboplati n, melphala n) and total body irradiation	13-cis-retinoic acid				
Kim, South Korea, 2007	Neuro blasto ma	2870	36	PBSC	tande m auto auto, 25%; single auto, 75%	4-5 cycles of chemo (cisplati n, VP-16, doxorub icin, cycloph osphamide); surgery; radiothe rapy and chemo	MEC (melphala n, etoposide , carboplati n), 65% (N=46 procedur es); no total body irradiation	interleukin-2; 13-cis-retinoic acid				single-auto group consiste d of CD34+ non-selected arm (n=13, 36%) and CD4+ selected arm (n=14, 39%)

Study (Investigator, country, year)	Disease	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Ladenstein, EGBMT, 2008	Neuroblastoma	1610	3350	BM, 41%; 3%, BM+PBSC; PBSC, 56% (n=3295)	tandem auto auto, 14%; single auto, 86%	not specified 1-4 cycles of chemo (various agents); surgery; radiotherapy; total body irradiation (33%)	busulfan; melphalan; cyclophosphamide; thiotepa; total body irradiation (14%, n=2,333) 1-4 cycles of chemo (various agents); melphalan (81%); total body irradiation (34%)					auto-transplant group
Matthay, US, 2009; 1999	Neuroblastoma	6210	189	BM	single auto	5 cycles of chemo (cisplatin; doxorubicin; etoposide; cyclophosphamide); radiotherapy; surgery	carboplatin; etoposide; melphalan; total body irradiation	retinoic acid (n=50)	growth factors	conventional therapy	3 cycles of cisplatin; etoposide; doxorubicin; ifosfamide; mesna	

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Study (Investigator, country, year)	Dis-ease	Re-cord Num-ber	Gro up (N)	Stem Cell Source	Type of HSCT	Prior Treat-ment	Condi-tioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Suppo rtive Care	Compara-tive Treatment	Comparative Treatment Dose/Regi-men	Com-ment
Pritchard, United Kingdom, 2005	Neuro blasto ma	8030	32	BM	single auto	vincristi ne; cycloph ospham ide; cisplatin ; teniposi de; surgery (no radiothe rapy)	melphala n		nutritio nal supple ments	no further therapy		

Study (Investigator, country, year)	Dis-ease	Re-cord Num-ber	Gro up (N)	Stem Cell Source	Type of HSCT	Prior Treat-ment	Condi-tioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Suppo rtive Care	Compara-tive Treatment	Comparative Treatment Dose/Regi-men	Com-ment
Sung, South Korea, 2007	Neuro blasto ma	3950	52	PBSC	tande m auto auto, 88%; single auto, 12%	1997-2003: 5-7 cycles of chemot herapy; surgery; radiothe rapy (if tumor remaine d post-surgery); 1-3 cycles of chemot herapy if no tumor or 3-5 cycles of chemo if tumor evident 2004-2005: 6 cycles of chemo; surgery; 3-4 cycles of chemo	1997-2003: high-dose chemo 2004-2005: chemo and total body irradiation	13-cis-retinoic acid and interleukin-2				

Study (Investigator, country, year)	Disease	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Sung, Korea, 2010	Neuroblastoma	2433	71	PBC	Tandem	Induction and consolidation; total body irradiation	see Table 1 in article		13-cis-retinoic acid; interleukin-2; local radiotherapy	Single	single PBC	

Appendix Table C45. Outcome assessment: Treatment, neuroblastoma

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Comment
George, USA, 2006	5440	82	OS; PFS	secondary malignancies	5.6-yr (15.1 mos-9.9-yr)	
Hobbie, USA, 2008	1690	13	Endocrine; Sensory; Musculoskeletal; Pulmonary; GI; Dental; Renal; Cardiovascular; Secondary malignancies		9-yr since diagnosis	
Kim, South Korea, 2007	2870	9 (tandem auto auto)	OS; DFS		27 mos (1-93) from transplant; 42 mos (11-103) from diagnosis	
Ladenstein, EGBMT, 2008	1610	455	OS; EFS		5-yr	tandem auto auto
Sung, South Korea, 2007	3950	50	OS; EFS	SM; TRM; Other	53 mos (19 mos-117 mos)	
Sung, Korea, 2010	2433	71	EFS	TRM; Secondary malignancies	5 years	

Appendix Table C46. Outcome assessment: Comparator, neuroblastoma

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes
Bernstein, USA/Canada 2006	6290	110	EFS	OS
Kushner, USA, 1995	21430	24	PFS	
Milano, Italy, 2006	43290	36	EFS OS	
Sari, Turkey, 2010	42790	36	EFS OS	
van Winkle, USA, 2005	43550	22	OS	

Appendix Table C47. Time to event outcomes: Treatment, neuroblastoma

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	3 yr	4 yr	5 yr	Test	p	Outcome_2	3 yr_2	5 yr_2	Test_2	p_2
George, USA, 2006	5440	82	time of 1st transplant to death	74 (62-82)		64 (52-74); 7-yr, 54 (38-67)	Kaplan-Meier		PFS, time from date of 1st transplant to progression or relapse of primary tumor or death	61 (50-71)	54 (42-64); 7-yr, 52 (40-63)	Kaplan-Meier	
Kim, South Korea, 2007	2870	9	OS	66.7 (19.3)			Kaplan-Meier	NS compared to CD34+ selected single-auto arm	DFS	50 (20.4)		Kaplan-Meier	p = 0.50 (NS) compared to CD34+ selected single-auto arm
Ladenstein, EGBMT, 2008	1610	455	OS			33 (3)		0.10	EFS		27 (2)		0.19
Sung, South Korea, 2007	3950	52	OS			64.3 (14.3)	Kaplan-Meier (log-rank)		EFS		62.1 (13.7)	Kaplan-Meier	
Sung, Korea, 2010	2433	71							EFS		51.2% (12.4%)	intention-to-treat	0.03

Appendix Table C48. Time to event outcomes: Comparator, neuroblastoma

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	3 yr	5 yr	Test	p	HR (95%) CI	Outcome_2	3 yr_2	5 yr_2	Test_2	p_2	HR (95% CI)_2
Berthold, Germany, 2005	6760	149	death from any cause or until last exam if patient survived	62 (54-70)		Kaplan-Meier (log-rank)	0.09	1.329 (0.958-1.843)	EFS; time until disease progression or relapse, a 2nd neoplastic disease, or death from any cause or until last exam	47 (38-55)		Kaplan-Meier (log-rank)	0.02	1.404 (1.048-1.881)
Kim, South Korea, 2007	2870	14	OS	55.1% (+/-13.9)		Kaplan-Meier			DFS	40.6% (+/-14.7)		Kaplan-Meier		
Ladenstein, EGBMT, 2008	1610	2895	OS		38 (1)				EFS		33 (1)			
Matthay, US, 2009; 1999	6210	189	definition not mentioned		39 (4%)	log-rank	0.39 (compared to controls)		EFS		30 (4)	log-rank	0.04 (compared to controls)	
Pritchard, United Kingdom, 2005	8030	32	time to death from any cause		47 (30-64)	log rank	0.1		EFS		38 (21-54)	log-rank	0.08	

Appendix Table C49. Time to event outcomes: Regression modeling, neuroblastoma

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Study (Investi-gator, country, year)	Record Num-ber	Design/Outcome/ Model	Candidate predictors/Methods for Identifying Candidates	Univariate Results, Variable (p value)	Selected Predictors/Methods for Selecting predictors Multivar	Proportional Hazards Assumption Assessed?/Interactions Considered	Multivariate Model Results, Variable (p Value)	Discrimination/Validation Methods/Results
Ladenstein, EGBMT, 2008	1610	Cox proportional hazards	OS: age at transplant (< 2 yr vs. > 2-yr)				Hazards Ratio (95% CI, p-value): 1.6 (1.4-1.9; < 0.0001)	significantly better OS rates in patients less than 2 years of age at diagnosis
Sung, South Korea, 2007	3950	Cox proportional hazards	EFS	EFS (< 0.05)	application of TBI, application of local radiotherapy, longer interval (>= 12 weeks) between 1st and 2nd transplant.	Yes	Hazards Ratio (95% CI, p-value): EFS, 9.66, 7.17, 5.73; 1.31-71.26, 1.69-30.38, 1.32-24.88; 0.026, 0.007, 0.020	EFS, application of TBI and local radiotherapy, and longer interval between transplants being favorable predictors.

Appendix Table C50. Adverse events: Treatment, neuroblastoma

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	% Engraftment Failure	% TRM	Severity or Grade Secondary Malignancies	F/U (mos) SM	% SM	Comments SM
Burdach, Germany and Austria, 2000	14310	28								
Burdach, Germany, 2003	10030	reported engr, TRM, infec compl, sec malig, and major organ tox, but not by age of < or > 17 yrs								
Burke, USA 2007	4060	7	sepsis n=1		0	0				
Costa, USA, 2008	1710	1			0	0	AML at 53 months post HSCT			
Drabko, Poland 2005	6680	21				5% (n=1 day 35 from multiorgan failure secondary to infection)				
Hara , Japan 1998	17950	3				0 NR				
Harimaya, Japan, 2003	9850	2			0	0				
Kasper, Germany, 2006	2570	5			0	0				

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Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	% Engraftment Failure	% TRM	Severity or Grade Secondary Malignancies	F/U (mos) SM	% SM	Comments SM
Koscielniak Germany 2005	7860				0	0				
Kushner, USA, 2001	14240	1 HSCT pt died at 17 mos after HSCT with NED but pulmonary failure								
Lucas, USA 2008	2450	1			0	0				
Lucidarme, France, 1998	17610	3				0 (NR)				
Meyers, USA, 2001	13670		sepsis leading to death	4% n=1 patient from HSCT group (incl in TRM)		of HSCT group n=23 n=3 13%				
Navid, US and Canada, 2006	5930	9			0	0				
Numata, Japan, 2002	12130				0	0	CML chronic phase	50 months after HSCT		

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Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	% Engraftment Failure	% TRM	Severity or Grade Secondary Malignancies	F/U (mos) SM	% SM	Comments SM
Ozkaynak, USA 1998	18540	15			0 (one patient not assessable secondary to early toxic death)	n=2 ATN day 0 and septic shock day 8				
Pession, Italy, 1999	16120	3				0 NR				
Prete, Italy 1998	17210	17				0				
Tanaka, Japan, 2002	11770			0		0	CML		14%	not clear if the 35 y/o pt or one of the 6 abstracted pts
Sung, Korea, 2010	2433	71				3% (5 years F/U)		5 years	0	Thyroid cancer in patient receiving only the first HSCT

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Appendix Table C50. Adverse events: Treatment, neuroblastoma Continued

Study (Investigator, country, year)	Record Number	% Hepatic veno-occlusive disease (Hepatic Sinusoidal Obstruction)	Comments hVOD	Severity or Grade SHE	% SHE
Drabko, Poland 2005	6680	10%	moderate to severe		
Meyers, USA, 2001	13670			HSCT pt died from hemorrhagic pericarditis (included in TRM)	4%

Appendix Table C51. Adverse events: Comparator, neuroblastoma

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	Severity or Grade Secondary Malignancies	F/U (mos) SM	% SM
Bernstein, USA/Canada 2006	6290		death	5 of 110 (4.5%)	MDS	at 20 mos after dx	1/110 1%
Bhatia,USA, 2007	43210						cumulative incidence of t-MDS/AML of 11% at 5 yrs from dx
Kushner, USA, 1995	21430	24			leukemia dead at 10.5 mos after HSCT in CR from ESFT		4
Meyers, USA, 2001	13670	9 nonHSCT		11% sepsis during induction CT			
Sari, Turkey, 2010	42790	36					0%

Appendix Table C52. Design, participant selection and enrollment: Germ cell tumor

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Agarwal, USA, 2009	72940	Malignant Non-Hematopoietic	Germ cell tumor	Relapsed	37	1995-2005	case series	37	0	
Lazarus, USA, 2007	72950	Malignant Non-Hematopoietic	Germ cell tumor	Relapsed	32	1989-2001	retrospective analysis of CIBMTR data	32	0	20 tandem; 12 single; based on data from the CIBMTR on childhood cohort
De Giorgi, UK, 2005	77240	Malignant non-hematopoietic	Germ cell tumors	Relapsed	18	1987-2003	cohort	18		
Einhorn, USA, 2007	77230	Malignant non-hematopoietic	Germ cell tumors	Relapsed	17	1996-2004	Case series	17	0	Pediatric data from author; N=184

Appendix Table C53. Participant characteristics: Treatment, germ cell tumor

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)
Lazarus, USA, 2007	72950	20		20	17-20		Testes (100)	NS (67); SM (0); CC (0); EB (33); Other (0)
Einhorn, USA, 2007	77230	17		20	17-21		NS (81); SM (19)	Testes

Appendix Table C54. Participant characteristics: Comparator, germ cell tumor

Study (Investigator, country, year)	Record Number	Group (N)	Age (median)	Age (Range)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Agarwal, USA, 2009	72940	37	28	9-59	M (92)	Testes (65); Chest/Neck/RP (27); CNS (8)	NS (84); SM (16)	4 (11%) pediatric patients (0-19 yrs)
Lazarus, USA, 2007	72950	12	19	15-20		Testes (90); Extragonadal (10)	NS (53); SM (21); CC (16); EB (5); Other (5)	
De Giorgi, UK, 2005	77240	18	6.5	1-18	M (56)	CNS (39); Sacr (39); Retro (17); Med (6)	NG (94); GM (6)	

Appendix Table C55. Treatment characteristics: Germ cell tumor

Study (Investigator, country, year)	Record Number	Grp (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Condition-ing Regimen	Immunosuppress ive therapy for GVHD prophylaxis	Compara-tive Treatment	Comparative Treatment Dose/Regimen
Agarwal, USA, 2009	72940	37	PBSC	single auto	4 cycles of cisplatin-based chemotherapy (n=29); additional chemotherapy (n=8)	etoposide; carboplatin	(G-CSF)		
Lazarus, USA, 2007	72950	32	BM, 14%; PBC, 74%; BM+PBSC, 12%	Tandem auto auto vs. single auto	(n=100) BEP, 66%; EP, 14%; PVB, 5%; VAB, 0%; Other, 5%; no chemotherapy, 10% - (n=102) surgery, 89% (n=102) 1-5 cycles of chemotherapy, 32%; 6-10 cycles, 56%; >= 11 cycles, 7%; no chemotherapy, 1%	3 drugs, 53%; 2 drugs, 45%; 1 drug, 2%		single auto: BM, 30%; PBSC, 61%; BM+PBSC, 9%	Prior treatment: (n=196) BEP, 60%; EP, 15%; PVB, 9%; VAB, 1%; Other, 7%; no chemotherapy, 8% - surgery, 87% (n=197) 1-5 cycles of chemotherapy, 23%; 6-10 cycles, 62%; >= 11 cycles, 12%; no chemotherapy, 1%
De Giorgi, UK, 2005	77240	18	PB; BM	single HSCT	standard-dose chemotherapy	CarboPEC; CE; TE; CarboPETM; Other			
Einhorn, USA, 2007	77230	17	PB	tandem HSCT	standard-dose chemotherapy	2 cycles of carboplatin plus etoposide			

Appendix Table C56. Outcome assessment: Treatment, germ cell tumor

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	Independent Response Assessor	F/U Frequency/Duration
Lazarus, USA, 2007	72950	20	OS; EFS	TRM; other	No	1-yr; 3-yr; 5-yr
Einhorn, USA, 2007	77230	17	OS; DFS			4 years

Appendix Table C57. Outcome assessment: Comparator, germ cell tumor

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	Independent Response Assessor	F/U Frequency/Duration
Agarwal, USA, 2009	72940	4	EFS; OS	TRM; 2nd malignancies; other effects		3-yr
Lazarus, USA, 2007	72950	12	OS; PFS	TRM; other effects	No	1-yr; 3-yr; 5-yr
De Giorgi, UK, 2005	77240	18	OS; EFS	TRM; other		1-3-5 yr

Appendix Table C58, Time to event outcomes: Treatment, germ cell tumor

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	1 yr	2 yr	3 yr	4 yr	5 yr	Outcome_2	3 yr_2	5 yr_2
Lazarus, USA, 2007	72950	20	OS	67 (34-86)		42 (15-67)		36 (10-59)	EFS	49 (27-72)	
Einhorn, USA, 2007	77230	17	OS	76.5 (59-99.5)		63 (43-92)		63 (43-92)	EFS		52 (11)

Appendix Table C59. Time to event outcomes: Comparator, germ cell tumor

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	1 yr	3 yr	5 yr	Outcome_2	1 yr_2	3 yr_2	5 yr_2	Test_2
Agarwal, USA, 2009	72940	4 (0-19 yrs)	OS		50 (7-93)		EFS		50 (7-93)		log-rank
Lazarus, USA, 2007	72950	12	interval between transplant and death from any cause	65 (40-82)	49 (24-68)	49 (24-68)	PFS, survival without recurrence or cancer progression, as measured by exam, radiographs, and/or an increase in serum cancer markers (n=195)	60 (36-78)	49 (26-69)	49 (26-69)	
De Giorgi, UK, 2005	77240	18	OS	67 (45-88)	56 (33-78.5)	49 (25-72)	DFS	50 (26-74.5)	50 (26-74.5)	50 (26-74.5)	

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Appendix Table C60. Adverse events: Treatment, germ cell tumor

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	% Engraftment Failure	% TRM
Burdach, Germany and Austria, 2000	14310	28				
Burdach, Germany, 2003	10030	reported engr, TRM, infec compl, sec malig, and major organ tox, but not by age of < or > 17 yrs				
Burke, USA 2007	4060	7	sepsis n=1		0	0
Costa, USA, 2008	1710	1			0	0
Drabko, Poland 2005	6680	21				5% (n=1 day 35 from multiorgan failure secondary to infection)
Hara , Japan 1998	17950	3				0 NR
Harimaya, Japan, 2003	9850	2			0	0
Kasper, Germany, 2006	2570	5			0	0
Koscielniak Germany 2005	7860				0	0
Kushner, USA, 2001	14240	1 HSCT pt died at 17 mos after HSCT with NED but pulmonary failure				
Lucas, USA 2008	2450	1			0	0
Lucidarme, France, 1998	17610	3				0 (NR)
Meyers, USA, 2001	13670		sepsis leading to death	4% n=1 patient from HSCT group (incl in TRM)		of HSCT group n=23 n=3 13%
Navid, US and Canada, 2006	5930	9			0	0
Numata, Japan, 2002	12130				0	0
Ozkaynak, USA 1998	18540	15			0 (one patient not assessable secondary to early toxic death)	n=2 ATN day 0 and septic shock day 8
Pession, Italy, 1999	16120	3				0 NR
Prete, Italy 1998	17210	17				0
Tanaka, Japan, 2002	11770			0		0

Appendix Table C60. Adverse events: Treatment, germ cell tumor Continued

Study (Investigator, country, year)	Record Number	Severity or Grade SM	F/U (mos) SM	% SM	Comments SM	Group (N)_7	% Hepatic veno-occlusive disease (Hepatic Sinusoidal Obstruction)	Comments hVOD	Severity or Grade SHE	% SHE
Costa, USA, 2008	1710	AML at 53 months post HSCT								
Drabko, Poland 2005	6680						10%	moderate to severe		
Meyers, USA, 2001	13670								HSCT pt died from hemorrhagic pericarditis (included in TRM)	4%
Numata, Japan, 2002	12130	CML chronic phase	50 months after HSCT							
Tanaka, Japan, 2002	11770	CML		14%	not clear if the 35 y/o pt or one of the 6 abstracted pts	1 of 7				

Appendix Table C61. Adverse events: Comparator, germ cell tumor

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	Severity or Grade Secondary Malignancy	F/U (mos) SM	% SM
Bernstein, USA/Canada 2006	6290		death	5 of 110 (4.5%)	MDS	at 20 mos after dx	1/110 1%
Bhatia,USA, 2007	43210						cumulative incidence of t-MDS/AML of 11% at 5 yrs from dx
Kushner, USA, 1995	21430	24			leukemia dead at 10.5 mos after HSCT in CR from ESFT		4
Meyers, USA, 2001	13670	9 nonHSCT		11% sepsis during induction CT			
Milano, Italy, 2006	43290						
Sari, Turkey, 2010	42790	36					0%
van winkle, USA, 2005	43550						

Appendix Table C62. Design, participant selection and enrollment: Embryonal tumors

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evalu-ated	n, Withdrawn (Lost to F/U)
Chi, USA, 2004	7900	Malignant non-hematopoietic	CNS Embryonal Tumors	Initial therapy	21	1997-2003	Case series	21	0
Dhall, USA/Australia/Argentina, 2008	52130	Malignant non-hematopoietic	CNS Embryonal Tumors	Initial therapy	21	1991-2002	Case series	21	0
Fangusaro, USA, 2008	3420	Malignant non-hematopoietic	CNS Embryonal Tumors	Initial therapy	43	1991-2002	Case series	43	0
Gardner, USA/Australia, 2008	71930	Malignant non-hematopoietic	CNS Embryonal Tumors	Initial therapy	13	1992-2002	Case series	13	0
Geyer, USA, 2005	73920	Malignant non-hematopoietic	CNS Embryonal Tumors	Initial therapy	299	1993-1997	RCT	284	15
Gidwani, USA, 2008	71940	Malignant non-hematopoietic	CNS Embryonal Tumors	Initial therapy	1		Case report	1	0
Packer, USA, 2006	77250	Malignant non-hematopoietic	CNS Embryonal Tumors	Initial therapy	421	1996-2000	RCT	379	42
Perez-Martinez, Spain, 2005	70470	Malignant non-hematopoietic	CNS Embryonal Tumors	Initial therapy	13	1995-2002	Case series	13	0
Sung, Korea, 2007	4770	Malignant non-hematopoietic	CNS Embryonal Tumors	Initial therapy	14 (11 tandem; 3 single)	1999-2005	Case series	14	
Taylor, UK, 2005	52760	Malignant non-hematopoietic	CNS Embryonal Tumors	Initial therapy	68	1992-2000	Case series	68	0

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)
Aihara, Japan, 2010	2008	Malignant non-hematopoietic	CNS Embryonal Tumors (MB)	Initial therapy	3		Case report	3	0
Badopadhayay, Australia, 2011	92	Malignant non-hematopoietic	CNS Embryonal Tumors	Initial therapy	33	1999-2005	Case series	18	15

Appendix Table C63. Participant characteristics: Treatment, embryonal tumors

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)
Chi, USA, 2004	7900	21		38 months	7-119	76% M	M1 (19); M2 (9.5); M3 (71)	MB
Dhall, USA/Australia/Argentina, 2008	52130	21		21 months	5-35 months	50% M	M0	MB
Fangusaro, USA, 2008	3420	43		37 months	0-120 months	51% M	M0 (82); M1-M3 (18)	PNET
Gardner, USA/Australia, 2008	71930	13		35 months	4-52 months	54% M	M0 (77); M1 (8); M3 (15)	AT/RT
Gidwani, USA, 2008	71940	1	(4 months)			100% M	M0	AT/RT
Perez-Martinez, Spain, 2005	70470	13		3 months	1-14 months	61.5% M	M1-M4 (NR)	MB (69); PNET (31)
Sung, Korea, 2007	4770	14		51.5 months	17-198 months	50% M	M0 (64); M1 (7); M3 (29)	MB (79); PNET (21)
Aihara, Japan, 2010	2008	3		12 years	7-13 yrs	100% M	M3	Medulloblastoma (MB)
Badopadhayay, Australia, 2011	92	33		20.5 months	3-37 months	61% M	Grade 3-4	MB (27%); AT/RT (18%); PNET (3%)

Appendix Table C64. Participant characteristics: Comparator, embryonal tumors

Study (Investigator, country, year)	Record Number	Group (N)	Age (median)	Age (Range)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)
Geyer, USA, 2005	73920	284		0-36 months	57% M	M0 (75); M1+ (25)	MB (32); PNET (16); AT/RT (10); Other (41)
Packer, USA, 2006	77250	379		36-252 months	59% M	M0	MB
Taylor, UK, 2005	52760	68	94 months	34-197 months	29% M	M2 (19); M3 (81)	MB

Appendix Table C65. Treatment characteristics: Embryonal tumors

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Supportive Care
Chi, USA, 2004	7900	21	PB	single	surgery; chemotherapy	carboplatin; thiotepa; etoposide	IV antibiotics; antifungal agents
Dhall, USA/Australia/Argentina, 2008	52130	21	BM; PB	single	surgery; chemotherapy	carboplatin; thiotepa; etoposide	
Fangusaro, USA, 2008	3420	43	BM; PB	single	surgery; chemotherapy	carboplatin; thiotepa; etoposide	radiotherapy for greater/= 6 years of age (37%)
Gardner, USA/Australia, 2008	71930	13		single	surgery; chemotherapy	carboplatin; thiotepa; etoposide	31% radiation
Gidwani, USA, 2008	71940	1	PB	tandem	surgery; chemotherapy	carboplatin-thiotepa-etoposide; busulfan-melphalan-thiotepa	
Perez-Martinez, Spain, 2005	70470	13	PB	single	surgery; chemotherapy; radiation	busulfan-melphalan; busulfan-thiotepa	clonazepam; antibiotics; nutritional support
Sung, Korea, 2007	4770	14	PB (92%); BM (8%)	Tandem (79%); Single (21%)	surgery, radiotherapy and/or chemotherapy	cyclophosphamide; melphalan; carboplatin-thiotepa-etoposide for 2nd transplant	43% post-radiotherapy prior to HSCT
Aihara, Japan, 2010	2008	3	PBC	Tandem	surgery; radiotherapy and chemotherapy	ICE	
Badopadhayay, Australia, 2011	92	33	BM/PBC	Single	Induction chemotherapy with stem-cell support	Carboplatin; melphalan	care for febrile neutropenia

Appendix Table C66. Outcome assessment: Treatment, embryonal tumors

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration
Chi, USA, 2004	7900	21	OS; EFS	TRM	40-48 months
Dhall, USA/Australia/Argentina, 2008	52130	21	OS; EFS	QOL; TRM	
Fangusaro, USA, 2008	3420	43	OS; EFS	TRM; SM; Other	5 years
Gardner, USA/Australia, 2008	71930	13	OS; EFS	TRM; Other	54 months
Gidwani, USA, 2008	71940	1	OS; DFS	SM; Other	2 years
Perez-Martinez, Spain, 2005	70470	13	EFS	TRM; SM; Other	34 months (5-93)
Sung, Korea, 2007	4770	14	OS; EFS	TRM; SM; Other	up to 5 years
Aihara, Japan, 2010	2008	3	EFS (complete remission)		40-41 months
Badopadhayay, Australia, 2011	92	33	OS		5 years

Appendix Table C67. Outcome assessment: Comparator, embryonal tumors

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration
Geyer, USA, 2005	73920	284	OS; EFS	TRM; SM; Other	6.6 years
Packer, USA, 2006	77250	379	OS; EFS	TRM; SM; Other	5 years
Taylor, UK, 2005	52760	68	OS; EFS	TRM; Other	7.2 years

Appendix Table C68. Time to event outcomes: Treatment, embryonal tumors

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	2 yr	3 yr	4 yr	5 yr	Outcome_2	2 yr_2	3 yr_2	5 yr_2
Chi, USA, 2004	7900	21	OS		60 (36-84)			EFS		49 (27-72)	
Dhall, USA/Australia/Argentina, 2008	52130	21	OS				70 (10)	EFS			52 (11)
Fangusaro, USA, 2008	3420	43	OS			49 (33-62)		EFS			39 (24-53)
Gardner, USA/Australia, 2008	71930	13	OS	23 (11)				EFS		23 (11)	
Gidwani, USA, 2008	71940	1	OS	Alive				DFS	Disease-free		
Perez-Martinez, Spain, 2005	70470	13	OS					EFS	57 (15)		
Sung, Korea, 2007	4770	11	OS	82 (59-100)			82 (59-100)	EFS	73 (46-99)	73 (46-99)	58 (25-91)
Aihara, Japan, 2010	2008	3						EFS (complete remission)		67% (2/3 patients)	
Badopadhayay, Australia, 2011	92	18		50% MB; 20% AT/RT; 0% PNET			50% MB				

Appendix Table C69. Time to event outcomes: Comparator, embryonal tumors

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_1	2 yr	3 yr	5 yr	Outcome_2	2 yr_2	3 yr_2	5 yr_2
Geyer, USA, 2005	73920	284	OS			43 (3)	EFS			27 (3)
Packer, USA, 2006	77250	379	OS			86 (9)	EFS			81 (2)
Sung, Korea, 2007	4770	3	OS	67 (13-100)			EFS	67 (13-100)		
Taylor, UK, 2005	52760	68	OS		50 (38-62)	44 (32-56)	EFS		40 (28-51)	35 (23-46)

Appendix Table C70. Quality of life: Embryonal tumors

Study (Investigator, country, year)	Record Number	Group (N)	Scale	Domain	F/U	Group	n	mn+/-sd
Dhall, USA/Australia/Argentina, 2008	52130	21	Parent Form of the Child Health Questionnaire	mean intellectual function and QOL	70 months; 124 months	single	4	within average range

Appendix Table C71. Adverse events: Treatment, embryonal tumors

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	% Engraftment Failure	% TRM	Severity or Grade SM	F/U (mos) SM	% SM	Comments SM
Burdach, Germany and Austria, 2000	14310	28								
Burdach, Germany, 2003	10030	reported engr, TRM, infec compl, sec malig, and major organ tox, but not by age of < or > 17 yrs								
Burke, USA 2007	4060	7	sepsis n=1		0	0				
Costa, USA, 2008	1710	1			0	0	AML at 53 months post HSCT			
Drabko, Poland 2005	6680	21				5% (n=1 day 35 from multiorgan failure secondary to infection)				
Hara , Japan 1998	17950	3				0 NR				
Harimaya, Japan, 2003	9850	2			0	0				
Kasper, Germany, 2006	2570	5			0	0				
Koscielniak Germany 2005	7860				0	0				
Kushner, USA, 2001	14240	1 HSCT pt died at 17 mos after HSCT with NED but pulmonary failure								
Lucas, USA 2008	2450	1			0	0				
Lucidarme, France, 1998	17610	3				0 (NR)				

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Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	% Engraftment Failure	% TRM	Severity or Grade SM	F/U (mos) SM	% SM	Comments SM
Meyers, USA, 2001	13670		sepsis leading to death	4% n=1 patient from HSCT group (incl in TRM)		of HSCT group n=23 n=3 13%				
Navid, US and Canada, 2006	5930	9			0	0				
Numata, Japan, 2002	12130				0	0	CML chronic phase	50 months after HSCT		
Ozkaynak, USA 1998	18540	15			0 (one patient not assessable secondary to early toxic death)	n=2 ATN day 0 and septic shock day 8				
Pession, Italy, 1999	16120	3				0 NR				
Prete, Italy 1998	17210	17				0				
Tanaka, Japan, 2002	11770			0		0	CML		14%	not clear if the 35 y/o pt or one of the 6 abstracted pts

Appendix Table C71. Adverse events: Treatment, embryonal tumors Continued

Study (Investigator, country, year)	Record Number	% Hepatic veno-occlusive disease (Hepatic Sinusoidal Obstruction)	Comments hVOD	Severity or Grade Serious Hemorrhagic Event	% SHE
Drabko, Poland 2005	6680	10%	moderate to severe		
Meyers, USA, 2001	13670			HSCT pt died from hemorrhagic pericarditis (included in TRM)	4%

Appendix Table C72. Adverse events: Comparator, embryonal tumors

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	Severity or Grade Secondary Malignancies	F/U (mos) SM	% SM
Bernstein, USA/Canada 2006	6290		death	5 of 110 (4.5%)	MDS	at 20 mos after dx	1/110 1%
Bhatia,USA, 2007	43210						cumulative incidence of t-MDS/AML of 11% at 5 yrs from dx
Kushner, USA, 1995	21430	24			leukemia dead at 10.5 mos after HSCT in CR from ESFT		4
Meyers, USA, 2001	13670	9 nonHSCT		11% sepsis during induction CT			
Milano, Italy, 2006	43290						
Sari, Turkey, 2010	42790	36					0%
van winkle, USA, 2005	43550						

Appendix Table C73. Design, participant selection and enrollment: Glial tumors

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Ayan, Turkey, 1995	74690	Malignant Non-hematopoietic	Glial	Newly diagnosed, high-risk	Anaplastic ependymoma 4	January 1990 - May 1991	Case series	4	1 patient lost to follow up at 9 months, had no response to treatment	
Berger, France, 1998	75380	Malignant non-hematopoietic	glial	Newly Diagnosed	HSCT Choroid plexus tumor (2) Conventional Therapy Choroid plexus tumor (20)	1984-1995	Case series	22	0	
Bertolone, United States, 2003	10380	Malignant Non-Hematopoietic	Glial	Patients with no previous CHM or RT who had been histopathologically confirmed to have a high-grade astrocytoma after surgical resection	18	April 1985 - May 1990	Randomized trial with non randomized infant component	18	0	4 patients were excluded due to consensus pathology diagnosis, 1 juvenile pilocytic astrocytoma 2 low-grade astrocytoma and 1 medulloblastoma
Bouffet, France, 1997	78760	Malignant Non-Hematopoietic	Glial	Recurrent	5	NR	Case Series	5	0	13 children with high grade glioma were enrolled in this study. 8 were newly diagnosed and exclude while 5 were recurrent after induction chemotherapy

Study (Investiga-tor, country, year)	Re-cord Number	Indication	Dis-ease	Therapeutic Setting	Group (N)	Partici-pant Selection (Treat-ment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Bouffet, France, 2000	78770	Malignant Non-hematopoietic	Glial	Newly diagnosed pontine glioma	36	March 1990-?	Case series	24	12	
Busca, Italy, 1997	73190	Malignant Non-hematopoietic	Glial	Malignant recurrent or progressive CNS tumor	Ependymoma 2, Anaplastic Astrocytoma 1, Glioblastoma Multiforme 2, Oligodendroglioma 1	May 1991 - August 1996	Case series	6	0	Preliminary results of the present study indicate that children with both recurrent and newly diagnosed brain tumors may benefit from high-dose chemotherapy
Conter, France, 2009	73540	Malignant Non-hematopoietic	Glial	Varied	Ependymoma 24	November 1996 - December 2002	Retrospective case series	24	0	
Doireau, France, 1998	55990	Malignant Non-Hematopoietic	Glial	Recurrent or unresectable tumors	8	May 1992 - January 1998	Case series	8	1 dead of disease	
Dunkel, United States, 1998	78780	Malignant Non-Hematopoietic	Glial	Recurrent	10	NR	Case Series	10	0	16 patients were enrolled in this study, 6 were excluded based on newly diagnosed pontine tumors with no previous therapy

Study (Investigator, country, year)	Record Number	Indication	Dis-ease	Therapeutic Setting	Group (N)	Participant Selection (Treat-ment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Finlay, United States	1300	Malignant Non-Hematopoietic	Glial	Recurrent Malignant Astrocytoma	27	NR	Quasi-Experimental Study w/ prospective cohort compared to CCG-945 controls	27, 56 control	0	
Grill, France, 1996	73240	Malignant Non-Hematopoietic	Glial	Recurrent	Ependymoma 16	1988 - 1994	Case Series	16	0	authors suggest the high-dose busulfan-thiotepa combination had little if any activity in refractory or relapsed ependymoma of children. New therapeutic approaches must be evaluated
Grill, France, 2001	74360	Malignant non-hematopoietic	Glial	Newly Diagnosed, high grade ependymoma	73	June 1990 - December 1998	Case Series	73	0	
Grovas, United States, 1999	16600	Malignant Non-hematopoietic	Glial	Newly Diagnosed High-Risk	11	1993-1995	Case series	11	0	
Grundy, United Kingdom, 2007	73750	Malignant non-hematopoietic	Glial	Newly Diagnosed, 9 pts metastatic	Ependymoma 89	1992 - 2003	case-series	89	0	

Study (Investiga-tor, country, year)	Re-cord Numb er	Indication	Dis-ease	Therapeutic Setting	Group (N)	Partici-pant Selection (Treat-ment Period)	Design	n, Evaluate d	n, Withdrawn (Lost to F/U)	Comment
Grundy, United States, 2010	51800	Malignant Non-Hematopoie tic	Glial	No prior adjuvant drug or radiotherapy	45	March 1993 - July 2003	Case series	41	4	
Gururangan, United States, 1998	18000	Malignant non-hematopoiet ic	Glial	recurrent	N=7, 1 ependymoma, 4 glioblastoma multiforme, 1 anaplastic astrocytoma, 1 CPC	1989-1996	Cohort	n=7	0	
Horn, Untied States, 1999	74470	Malignant non-hematopoiet ic	Glial	Varied	Ependymoma 83	1987-1991	Retrospectiv e case series	83	0	11 center retrospective
Hurwitz, United States, 2001	53330	Malignant Non-Hematopoie tic	Glial	Recurrent or Progressive brain tumors	45	June 1993 - March 1998	Case Series	45	0	75 enrolled 45 eligible based on histology
Jaing, Taiwan, 2004	74030	Malignant Non-hematopoiet ic	Glial	Newly diagnosed high and low grade ependymomas	Ependymoma 46			43	3 excluded due to one death in immediate postoperati ve period and 2 spinal cord tumors. 2 patients were also lost to follow up	

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Jakacki, United States, 1999	15920	Malignant non-hematopoietic	glial	High-dose chemotherapy	11	April 1997 - June 1998	Case series	11	0	Study enrollment stopped early due to concerns about radio-potentiating effects of chemotherapy given concurrently with radiation 1 pt excluded due to age above 21 years
Kobrinsky, United States, 1999	53560	Malignant Non-Hematopoietic	Glial	Recurrent or unresponsive	42	December 1988 - February 1992	Case Series	42	0	99 patients enrolled, 42 eligible based on histology glioma
Korones, United States, 2006	52670	Malignant Non-Hematopoietic	Glial	Recurrent	9	June 2002 - October 2003	Retrospective case series	9	0	2 patients excluded due to being above age 21
Kuhl, Germany, 1998	17700	Malignant Non-hematopoietic	Glial	Untreated, newly diagnosed ependymoma	21	1987 - 1991	Phase II trial	10	11	
Macdonald, United States, 2005	55000	Malignant Non-Hematopoietic	Glial	Newly Diagnosed High-Grade	102	1993-1998	Randomized Trial	76	11 pts did not complete HDCT due to toxicities	26 patients excluded after central neuroradiographic review or pathological review
Mahoney, United States, 1996	73250	Malignant Non-hematopoietic	Glial	Recurrent or Progressive	7	December 1990 - September 1993	case series	7	0	7 of 19 patients included based on tumor diagnosis

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Study (Investiga-tor, country, year)	Re-cord Numb er	Indication	Dis-ease	Therapeutic Setting	Group (N)	Partici-pant Selection (Treat-ment Period)	Design	n, Evaluate d	n, Withdrawn (Lost to F/U)	Comment
Mason, United States, 1998	73180	Malignant Non-hematopoiet ic	Glial	Recurrent	Ependymoma 15	Decembe r 1986 - Novembe r 1993	PII trial	15	0	Given the dismal performance of this regimen in controlling recurrent intracranial ependymoma in children we cannot recommend this approach of invasive chemotherapy with this regimen as an effective strategy for recurrent disease.
Massimino, Italy, 2005	55220	Malignant Non-Hematopoie tic	Glial	Consolidate high-risk	21	August 1996-March 2003	Case series	21	0	*Was in comparator search
Merchant, United States, 2002	74280	Malignant non-hematopoiet ic	Glial	Varied	Ependymoma 64	June 1997 -	PII trial	64	0	
Ozkaynak, United States, 2004	7850	Malignant Non-Hematopoie tic	Glial	Relapsed/Progress ive : Tandem Treatment	6	1995-2002	Case Series	6	0	Tandem Treatment, not on initial indications for abstraction

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Robertson, United States, 1998	74630	Malignant non-hematopoietic	Glial	High-risk	ependymoma 20, anaplastic ependymoma 12	May 1986 - June 1992	RCT	32	0	High degree of discordance between local institutional diagnoses and centralized review (31% concordance)
Shih, United States, 2008	2530	Malignant Non-Hematopoietic	Glial	Recurrent	5	1989-2004	Retrospective case series	5	0	Of 27 initial patients 5 met inclusion criteria for this abstraction (19)
Sio, Italy, 2006	6950	Malignant Non-Hematopoietic	Glial	Relapsed	14	April 1998 - April 2004	Case series (off-label compassionate use)	14		52 total patients, 38 excluded based on histology or age > 21
Thorarinsdottir, United States, 2007	73050	Malignant Non-hematopoietic	Glial	Malignant CNS	6	1998 - 2005	Case series	6	0	6 of 15 patients included based on tumor type
Wrede, Germany, 2009	75590	Malignant Non-hematopoietic	Glial	Newly Diagnosed	34 CPC	2000-2008	Case series	29 CPC	5	
Yule, United Kingdom, 1997	18960	Malignant Non-hematopoietic	Glial	High-Risk and Recurrent Tandem (?)	5	1993-1995	Case Series	5	0	8 patients excluded based on tumor histology
Zacharoulis, United States, 2007	73020	Malignant Non-hematopoietic	Glial	No previous treatment, confirmed ependymoma	29	1991-1997 (Head Start 1), 1997 - 2002 (Head Start 2)	Cohort study	29	0	

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Gilheeney, United States, 2010	2187	Malignant Solid Tumor	High Grade Glioma	Metastatic or Recurrent Glioma	Anaplastic Astrocytoma (1); Oligoastrocytoma (1); Glioblastoma multiforme (2)	1999-2002	Case Series	4	0	

Appendix Table C74. Participant characteristics: Treatment, glial tumors

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Berger, France, 1998	75380	Choroid Plexus Carcinoma (2)			24 and 33 months			0, 2 (0, 100)	One patient had spinal metastases at diagnosis	Both CPC located supratentorially (100)	
Bouffet, France, 1997	78760	5	7	6	3-14		nr	3,2 (60, 40)	All high-grade	1 parieto-occipital, 3 brain stem, 1 thalamus	
Bouffet, France, 2000	78770	24		7 years	3-17 years		NR	15, 21	Diffuse pontine tumor	At least 2/3rd of pts tumor had to be in the pons	these patient characteristics were reported for the whole patient population and not those evaluated by HDC
Busca, Italy, 1997	73190	Ependymoma 2, Anaplastic Astrocytoma 1, Glioblastoma Multiforme 2, Oligodendroglioma 1		11 years for total group of 11 patients,	3-16 years for total group of 11 patients			5, 6 (46, 54%) for total group		Ependymoma 2, Anaplastic Astrocytoma 1, Glioblastoma Multiforme 2, Oligodendroglioma 1	
Dunkel, United States, 1998	78780	10	7.89	7.9	3.5-14.9		nr	7, 3 (70, 30)	10 High-grade glial malignancies	Pons	
Finlay, United States	1300	27	NR	8.5	.2-20.0	NR	NR	15,12 (55,45%)	NR	Glioblastoma Multiform 17 (63%) Aplastic Astrocytoma 10 (37%)	

Study (Investigator, country, year)	Re-cord Num-ber	Group (N)	Age (mean)	Age (median)	Age (Range)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Grill, France, 1996	73240	Ependymoma 16		3 years	.5 to 15 years			8, 8 (50, 50)	2 patients had tumor cells in CSF. 3 WHO low-grade tumors, 13 WHO high-grade tumors	6 Supratentorial, 10 Infratentorial	
Grovas, United States, 1999	16600	11		12years	5-18years		ne	7,4 (63)		11 Glioblastoma multiform (100)	one patient's GBM arose from pilocytic xanthoastrocytoma
Gururangan, United States, 1998	18000	N=7, 1 cpc, 1 ependymoma, 4 glioblastoma multiforme, 1 anaplastic astrocytoma			Ependymoma 18mo, Anaplastic Astrocytoma 23mo, Glioblastoma multiforme .24, 3.6, 10.8, and 57.6mo		no	Ependymoma 0,1 (0, 100), anaplastic astrocytoma 0, 1 (0,100), Glioblastoma multiforme 2,2 (50, 50)	All patients recurrent	1 ependymoma, 4 glioblastoma multiforme, 1 anaplastic astrocytoma	
Jakacki, United States, 1999	15920	11	7.2 years	7.2 years	3.1-12.6 years		NR	4, 7 (36, 64)	High grade glial tumor or a diffuse pontine tumor	3 GBM (27), 2 AA (18), 6 Pons (55)	
Mahoney, United States, 1996	73250	Anaplastic Astrocytoma 2, Ependymoma 3, Glioblastoma multiforme 1, Brainstem glioma 1		Anaplastic Astrocytoma 12, Ependymoma 5, Glioblastoma multiforme 15.5, Brainstem Glioma 5	AA (8-16), EP (3-7.5), GBM 15.5, BSG 5			AA 2,0 (100, 0) EP 1,2 (33, 67), GBM 1,0 (100, 0), BSG 0,1 (0, 100)		Anaplastic Astrocytoma 2 (29), Ependymoma 3 (43), Glioblastoma multiforme 1 (14), Brainstem glioma 1 (14)	

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Study (Investigator, country, year)	Re-cord Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Mason, United States, 1998	73180	Ependymoma 15	45 months	22 months	5 months - 12 years			8, 7 (53, 47)	9 low-grade ependymoma (60%), 6 anaplastic (40%)	13 posterior fossa (87%), 2 supratentorial (13%)	
Massimino, Italy, 2005	55220	21	NR	10	3.5-19	NR	NR	7, 14 (33, 67%)	NR, All High-Grade	GBM 10 (48), Anaplastic AST 9 (42), Anaplastic oligodendroglioma 2 (10) spine 2 (10), Posterior fossa 2 (10), Supratentorial 17 (80)	
Ozkaynak, United States, 2004	7850	6	11.5	11	4.5-18		nr	3,3 (50, 50)	Progressive 3 (50), Recurrent 3 (50)	AA 2 (33), GBM 1 (17), BSG 2 (33), Ependymoma 1 (17)	
Shih, United States, 2008	2530	5	7.8 yrs	7.4 yrs	.4-16.6 yrs		NR	nr	NR	1 EPD, 2 AA, 2 GBM	
Thorarinsdottir, United States, 2007	73050	Oligodendrogliomas 1, Ganglioma 1, Anaplastic glioma 3, Ependymoma 1		Oligodendrogliomas 27 months, Ganglioma 25 months, Anaplastic glioma 18 months, Ependymoma 6 months	Oligodendrogliomas 27 months, Ganglioma 25 months, Anaplastic glioma (9-29) months, Ependymoma 6 months			Oligodendrogliomas 1 male, Ganglioma 1 male, Anaplastic glioma 2 male, 1 female (67, 33), Ependymoma 1 female	All WHO grade III	Oligodendrogliomas right frontal, Ganglioma temporal, Anaplastic glioma 1 c-spine 1 brainstem and one parietal, Ependymoma IV ventricle	

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Yule, United Kingdom, 1997	18960	5		11.5	10.25	5-14	NR	nr		1 anaplastic ependymoma (25%), 1 recurrent GBM (25), 1 GBM (25), 1 suprasellar gbm (25)	
Zacharoulis, US, 2007	73020	Ependymoma 29	2.3 years	2.1 years	.7-8.9 years		NR	18, 11 (62, 38)	M0 24 (83), M1 1 (3), M2 0, M3 4 (14)	Posterior fossa 22 (76), supratentorial 7 (24)	
Gilheeney, United States, 2010	2187	Anaplastic Astrocytoma (1); Oligoastrocytoma (1); Glioblastoma multiforme (2)	AA 7.4 years; OA 8.9 years; GBM 11.6	AA 7.4 years; OA 8.9 years; GBM 11.6	AA 7.4 years; OA 8.9 years; GBM 4.4-18.8 years						

Appendix Table C75. Participant characteristics: Comparator, glial tumors

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Ayan, Turkey, 1995	74690	Anaplastic ependymoma 4		12.5 years	5-15 years			3, 1 (75, 25%)	Anaplastic 4 (100%)	frontal lobe 1 (25), temporoparietal-occipital lobe 1 (25%), Multiple parenchymal meningial lesions 1 (25%), Temporoparietal lobe 1 (25%). CSF cytology positive in one patient (25%)	
Berger, France, 1998	75380	Choroid plexus carcinoma (22)		31 mo	4-111 mo			9, 11 (35, 55)	3 patients had metastases at diagnosis (2 spinal/bifocal, 1 bifocal) 4 patients had no metastases and 13 patients had unknown metastases	12 supratentorial (60), 8 infratentorial (40)	
Bertolone, United States, 2003	10380	18		4	<1 year - 16 years		NR	11, 8 (58, 42)		11 Anaplastic Astrocytoma (61), 3 Ependymoma (17), 2 Glioblastoma multiforme (11), 1 Anaplastic mixed glioma (6), 1 anaplastic ganglioglioma (6)	

Study (Investi- gator, country, year)	Record Num- ber	Group (N)	Age (mean)	Age (median)	Age (Range)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Conter, France, 2009	73540	Ependymoma 24		8.6 years	5-17 years			16, 8 (67, 33)	Grade 2 13 (57), Grade 3 10 (43)	Supratentorial 4 (17), Infratentorial 20 (83)	
Doireau, France, 1998	55990	8	4.6	3.8	3 mo - 4.5			nr	Six patients had low-grade tumors while two had grade III tumors. All tumors were progressive and three had metastases before chemotherapy.	5 astrocytoma (63), 3 oligoastrocytoma (37)	Ages at diagnosis
Finlay, United States	1300	56	nr	11.1	.1-19.3	nr	nr	29,27 (52,48%)	NR	Glioblastoma Multiform 27 (48%) Aplastic Astrocytoma 29 (52%)	
Grill, France, 2001	74360	Ependymoma 73		27 months	5-62 months			40, 33 (55, 45)	73 Ependymoma 100%	56 (82%) of patients had a high grade tumor, 12 (18%) had a low-grade tumor	5 patients were not assigned a histological grade
Grundy, United Kingdom, 2007	73750	Metastatic ependymoma 9, non-metastatic ependymoma 80		1.93, 1.36	(.05-3.16), (.24-2.25)			54 (67.5 % male), 4 (44 % male)	Non-metastatic 80 (90), Metastatic 9 (10)	Infratentorial 69 (86), Supratentorial 11 (14) Infratentorial 7 (78), Supratentorial 2 (22) WHO II 54 (68), WHO III 26 (32) WHO II 5 (56), WHOIII (44)	

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Grundy, United States, 2010	51800	41		High Grade Glioma 1.8 years, Brain Stem Glioma 2.52 years	High Grade Glioma .33-3.09 years, Brain Stem Glioma .68-3.01 years				18, 8 (69)	HGG: Anaplastic Astrocytoma 7, Astroblastoma 1, Anaplastic oliodendroglioma 2, Glioblastoma 5, unknown 3 Diffuse pontine glioma: diffuse astrocytoma 1, glioblastoma 1, unclassified 1, inoperable 4	High Grade Glioma 19 (73), Brain Stem Tumor 7 (27) HGG metastatic in posterior fossa 2 (11), metastatic in supratentorial 17 (89) Brain Stem Glioma metastatic in Brainstem 7 (100), 15 cpc	
Horn, United States, 1999	74470	Ependymoma 83		51.5 mo	8mo - 20 years				50, 33 (60, 40)	M0 61 (85), M1-M3 11 (15)	WHO II grade 2 51 (61), WHO II grade 3 31 (37) Infratentorial 64 (77), Supratentorial 19 (23)	Age ≤ 3 29 *=(35), Age >3 54 (65)
Hurwitz, United States, 2001	53330	45		7.7	4mos-19yr		NR		56, 44%	Recurrent or progressive disease	Astrocytoma 4 (9), Malignant Glioma 13 (29), Brain Stem Glioma 15(33), Ependymoma 13 (29)	Age and Gender reported for entire 75 enrolled pts, not available by histology
Jaing, Taiwan, 2004	74030	Ependymoma 43		6.6 years	8 months to 18 years				25, 18 (58, 42)	Grade II 20 (47), Grade III [anaplastic] (53)	Supratentorial 15 (35), Infratentorial (65)	
Kobrinsky, United States, 1999	53560	42	NR	NR	NR	NR	White 63, Black 12, Hispanic 19, Asian 3, Other/Mixed 3	Male 54, Female 45		NR	High grade astrocytoma 20 (48), Brain stem glioma 22 (52)	Race and sex statistics reported for the sum total 99 patients

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Korones, United States, 2006	52670	9	12.2	9	5-21		NR	7,2 (77,23%)		5 Glioblastoma, 2 anaplastic astrocytoma 2 brainstem glioma	
Kuhl, Germany, 1998	17700	21			3-16				19 anaplastic (90), 14 infratentorial (67). 29% of patients had microscopic tumor cells in CSF	21 ependymoma (100%)	
Macdonald, United States, 2005	55000	76		11.95yrs	3-20yrs		69.7% white, 14.5% Hispanics, 10.5% Blacks, and 5.3% other	36, 40 (47. 53%)	All patients had histologic verification of high-grade astrocytoma	GMB/GV 40 (53), AA 30 (39), Other 6 (8)supratentorial tumor 86.8%, five patients had metastatic disease	4 patients not evaluable because imaging reports demonstrating residual disease were not available before chemotherapy
Merchant, United States, 2002	74280	Ependymoma 64		3 years	1.1 - 22.9 years			32, 32 (50, 50%)	45 differentiated ependymoma (70), 19 anaplastic ependymoma (30)		
Robertson, United States, 1998	74630	32		7	2-17.3		Caucasian 22 (69), African American 3 (9), Hispanic 4 (13), Other 3 (9)	17, 15 (53, 47)	Anaplastic 12 (38)	posterior fossa 21 (66), supratentorial 11 (34)	

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Sio, Italy, 2006	6950	14	9.6	8.4	4.2-19.6		nr	9, 5 (64, 36)		Ependymoma 2 (14), Anaplastic Astrocytoma 3 (21), Brain Stem Glioma 8 (57), Glioblastoma Multiforme 1 (7)	
Wrede, Germany, 2009	75590	34 CPC		2.3 years	.3-17.1 years			17, 17 (50, 50%)	Metastatic 7 (21%)	Lateral Ventricle 30 (88%), Fourth ventricle 4 (12%)	

Appendix Table C76. Treatment characteristics: Glial tumors

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Ayan, Turkey, 1995	74690	Anaplastic Ependymoma 4							"8 in 1" chemotherapy	methylprednisolone, vincristine, lomustine, procarbazine, hydroxyurea, cisplatin, cytosine arabinoside, cyclophosphamide in a targeted 8 courses or until disease progression	

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Berger, France, 1998	75380	HSCT CPC (2) Conventional therapy CPC (20)	Peripheral blood	Autologous	Surgical resection	1 HSCT patient received: carboplatin, procarbazine, etoposide, cisplatin, vincristine, cyclophosphamide. 1 patient received etoposide, ifosfamide and carboplatin			Conventional chemotherapy was given to 17 of 20 remaining patients. 2 of the patients who did not receive chemotherapy had radiotherapy, and two had no treatment other than partial surgical resection. Chemotherapy regimen varied by patient.	10 patients had: carboplatin, procarbazine, etoposide, cisplatin, vincristine, cyclophosphamide. 3 patients had etoposide, carboplatin. 1 patient had carboplatin and ifosfamide; 1 patient received monthly lomustine	

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Bertolone, United States, 2003	10380	18			Surgical Excision				Standard Chemotherapy Regimen (A) vs. Experimental 8-in-1 Chemotherapy Regimen (B)	(A) 10 week induction with 8 weekly injections of vincristine, 48 week maintenance with 8 cycles of vincristine, CCNU, and prednisone. (B) 10 week induction of two cycles of 8-in-1 chemotherapy followed by 5400 GY radiotherapy	8-in-1 chemotherapy consisted of (Vincristine, CCNU, procarbazine, hydroxyurea, cisplatin, cytarabine, dacarbazine, and methylprednisone)

Study (Investigator, country, year)	Record Num-ber	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylax-is	Supportive Care	Compar-ative Treatment	Compar-ative Treatment Dose/Reg-imen	Comment
Bouffet, France, 1997	78760	5	Bone Marrow	Single Autologous	2 VM-BCNU-PCZ with radiotherapy, 2 VM-CDDP-FU-DTIC-CPM-PCZ one with radiotherapy, and 1 VM-BCNU-PCZ						
Bouffet, France, 2000	78770	24	Bone Marrow	Autologous	NR, Newly Diagnosed	RT initiated as soon as possible after post-op recovery in surgery or after radiologic diagnosis. 50-50Gy given over 6 weeks at a rate of 8-9 Gy per week in 5 daily fracs. HDC initiated 40-60 days after RT. HDC consisted of busulfan 150mg/m^2/d on -8,-7,	-6, and -5. And Thiotepa 300 mg/m^2/d -4, -3, and -2. clonazepam .1 mg/kg/day Day -8 to -1. ABM reinfused 48 hours after chemo.				Only 24 of 35 children proceeded to HDC. One child died during RT, 8 other children experienced early disease progression preventing consolidation, two families declined further treatment.

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Busca, Italy, 1997	73190	Ependymoma 2, Anaplastic Astrocytoma 1, Glioblastoma Multiforme 2, Oligodendroglioma 1	ABMT	Autologous	All pts had maximal surgical resection. 3 pts (50%) had 1st line RT, 1 pt. had 1st line chemotherapy (17%). 3 pts had secondary total resection after relapse (50%), 3 pts had secondary chemotherapy and 1 pt had radiotherapy (17%).	Two regimen: A, BCNU 2x/d for 3 days and etoposide 1x/d for 3 days (n=5). B, Thiotepa and etoposide 1x/d for 3 days (n=6)		HEPA filtered room, low microbial diet, IV acyclovir, oral nonabsorbable antibiotics, and cotrimoxazole. Broad-spectrum antibiotics were administered to febrile patients. Blood component therapy to keep elevated platelet count			

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Conter, France, 2009	73540	Ependymoma 24							Surgical resection followed by radiotherapy	In a complete resection, patients were given 60 Gy HFRT in two daily frac of 1 Gy (photon energy was >8 MeV. For partial removal, second look surgery discussed before RT. If not complete resection a 6 Gy boost was given to the initial 60Gy	No patients received chemotherapy

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Doireau, France, 1998	55990	8			ventriculo-peritoneal shunt in 1 pt, 2 pts had biopsy alone, and partial excision in 6 patients				chemotherapy	16 month/seven cycle of carboplatin (15 mg/kg), procarbazine (4 mg/kg), etoposide (5 mg/kg), cisplatin (1mg/kg) vincristine (.05 mg/kg), and cyclophosphamide (50 mg/kg)	
Dunkel, United States, 1998	78780	10	Bone Marrow	Single Auto	10 radiotherapy, 5 with chemotherapy, 1 with beta-interferon	6 Thiotepa Etoposide, 2 BCNU Thiotepa Etoposide, 2 Carboplatin Thiotepa Etoposide					
Finlay, United States	1300	27	Bone marrow	Autologous	NR	ThioTEPA 900 mg/m^2 w/ etoposide 750 or 1,500 mg/m^2 over 3 days (n=11), 600 mg/m^2 over 3 days preceded by carmustine (n=5), or carboplatin 1,500 mg/m^2 over 3 days (n=11) w/ AEUC of 7 mg/ml/min day	NR	NR	Chemotherapy Only		

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Grill, France, 1996	73240	Ependymoma 16	Bone Marrow Stem Cells in 15 pts and PBSC in 1 pt.	Autologous	NR. 8 patients received HDCT + autologous SCT as first treatment of relapse, 8 patients received ASCT as second or further relapse treatment	Busulfan, Thiotepa,		Isolated laminar air flow rooms with atrial catheters. Parenteral nutrition and broad spectrum antibiotics when needed.			

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Grill, France, 2001	74360	73							Resection and Chemotherapy followed by irradiation in the event of progression or relapse	Maximal surgical resection followed by three courses of two different drugs (carboplatin and procarbazine, etoposide and mannitol, and vincristine cyclophosphamide and uromitexan). Irradiation for relapse was 50 Gy 1.8 Gy/frac 5x week	

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Grovas, United States, 1999	16600	11	2 PBSC (18), 9 ABMT (82)	single autologous	NR, newly diagnosed	carmustine, thiotepa, and etoposide. Carmustine at dose of 100 mg/m^2 for six doses, Thiotepa 300 mg/M^2/d * 3 , Etoposide 250 mg/m^2/d *3		Corticosteroids for control of tumor mass effect and cerebral edema. Pts not given corticosteroids had dexamethasone 5 mg/m^2/d *3. 6 Pts given G-CSF on reinfusion (55). All pts received RT on approximately day +42. 30 fracs 180 cGy 5200 cGy w/ 540 boost			1 patient died before radiotherapy
Grundy, United Kingdom, 2007	73750	Ependymoma 89							Chemotherapy w or w/o RT	4 courses alternating myelosuppressive and non-myelosuppressive carboplatin, vincristine, methotrexate, cyclophosphamide and mesna, cisplatin. RT after progression	

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Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Grundy, United States, 2010	51800	41			Surgical Resection: HGG 14 (74), Brain Stem Glioma 0 (0)				Chemotherapy with or without radiotherapy	Four courses with 7 cycles: course 1 vincristine (1.5mg/^2) and carboplatin (550 mg/m^2), course 2 Vincristine (1.5mg/m^2) Methotrexate (8000mg/m^2) and Folinic Acid 15 mg, course 3 Vincristine (1.5 mg/m^2) Cyclophosphamide (1500mg/m^2) and Mesna (1800 mg	Course 4 Cisplatin continuous infusion for 4 hours (40 mg/m^2 x 2 days), children 10 kg and under were dosed to weight rather than surface area. Six patients completed Chemotherapy

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Gururangan, United States, 1998	18000	N=7,1 cpc, 1 ependymoma, 4 glioblastoma multiforme, 1 anaplastic astrocytoma	Bone marrow	Autologous	Surgery and chemotherapy in all pts except the astrocytoma patient who had biopsy online	Four patients had carboplatin, thiotepa, and etoposide, one patient had thiotepa and etoposide only, and one patient had carboplatin, thiotepa and carmustine		Varied by treatment protocol. Patients received antifungal and antibiotics if febrile and neutropenic. Maintenance of platelet counts. GCSF use varied by protocol.			
Horn, Untied States, 1999	74470	Ependymoma 83							Patients in this multicenter retrospective study were classified as having either surgery alone 6 (7), chemotherapy alone 17 (20), radiation alone 31 (37), or radiation and chemotherapy 29 (35).	Chemotherapy type was broken into: None 37 (45), Nitrosourea based 13 (16), Alkylating agent based 21 (25), Nitrosourea and alkylating 9 (11), other types 3 (4) No RT 23 (28), Local 36 (41), Local and cranial 5 (6), and craniospinal 21 (25)	

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Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Hurwitz, United States, 2001	53330	45							Chemotherapy	Dexamethasone .25 mg/kg 14 and 7 hours before other drug administration, paclitaxel 1mg/kg 350mg/m^2 over 24 hours every 3 weeks, and diphenhydramine 1mg/kg	

Study (Investigator, country, year)	Record Num-ber	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylax-is	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Reg-imen	Comment
Jaing, Taiwan, 2004	74030	Ependymoma 43							Surgical excision followed by 30 Gy irradiation w/ 20-25 Gy boost to the primary tumor area [spinal mets irradiated with a total dose of 30-45 Gy]. 9 pts did not receive RT due to >3 years old. 13 pts received chemotherapy	Chemotherapy protocols varied between patients [5 protocols, either platinum or nitrosourea or other combinations exclusive of nitrosourea or platinum]	

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Jakacki, United States, 1999	15920	11	PBSC	Autologous given in four doses concurrent with chemotherapy and radiotherapy	NR, newly diagnosed	CCNU 130mg/m^2, vincristine 1.5mg/m^2 on day 0 and procarbazine 150 mg/m^/d on 1-7.PBSC infusion was infused 36-72 hrs after procarbazine. RT began 48-72 hrs after PBSC 180cGY (5040-5940 cGy).2nd, 3rd, and 4th chemotherapy regimens started 4 wks after prev		Pts who developed a procarbazine related rash received diphenhydramine prior to subsequent doses			1 pt with spinal cord glioblastoma had 3600 cGy craniospinal radiation therapy with boost to tumor area, all other pts had involved field RT.4 pts w/ non-brainstem large volume tumors had <4 PBSC and Chemotherapy, due to progression recruitment was stopped

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Kobrinsky, United States, 1999	53560	High grade astrocytoma 20, brain stem glioma 22			Previously treated with chemotherapy and/or radiation therapy				Etoposide or etoposide/ mannitol	150mg/M^2 Iv over 3h for 5 days	
Korones, United States, 2006	52670	9			3 RT alone, 2 RT and Chemo, 4 BMT and other therapy				Chemotherapy	Temozolomide and VP-16	

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Kuhl, Germany, 1998	17700	21							Chemotherapy: procarbazine, ifosfamide, mesna, vp-16, methotrexate, CF-rescue, cisplatin, cytarabine followed by radiotherapy of 35.2 gy in 22 frac and maintenance chemotherapy in some patients (% unknown for EPD)		

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylax-is	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Reg-imen	Comment
Macdonald, United States, 2005	55000	76			Induction, four 3 week cycles in three different regiments: A) carboplatin, VP-16 B) ifosfamide, mesna VP-16 C) Cyclophosphamide, mesna, VP-16.			Corticosteroids used at clinician recommendation; recommended for raised intracranial pressure and adrenal insufficiency restriction	Chemotherapy with Radiotherapy	Interim therapy: one 12-week course Vincristine at 1.5 mg/m^2 (2 mg max) for 8 weeks w/ 6-week RT followed by 4-week rest. Maintenance cycle of eight 4-week cycles 6 weeks after RT consisting of oral CCNU 100mg/m^2 * 1 day and vincristine 1.5 mg/m^2	(Dose information not entered due to char limit - available in paper)

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Mahoney, United States, 1996	73250	7	Bone Marrow	Autologous	Radiation and Chemotherapy	CTX 4 days, Melphalan 3 days following marrow infusion patients were given escalating CTX dose with mesna support		Amino Acid withholding during melphalan treatment. Irradiated CMV for hematocrit level maintenance, Fluconazole, Acyclovir in pts. With positive HSV			
Mason, United States, 1998	73180	Ependymoma 15	ABMR	Autologous	Maximal surgical resection in all pts. 13 pts had radiotherapy (87%), 14 of the pts had prior chemotherapy (93%).	5 patients received thiotepa/etoposide (33), 10 received thioTEPA/etoposide/ carboplatin (67)		platelet counts maintained above 50,000, hemoglobin maintained above 8.0g/dL, febrile neutropenic patients treated with broad-spectrum antibiotics and antifungal agents. Pts received trimethoprim-sulfamethoxazole prophylaxis from day 30			

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Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Massimino, Italy, 2005	55220	21	PBC	Single Auto, in 4 pts two cycles due to residual tumor response after first course	Surgical Excision	CDDP plus VP-16 week 1 and 4; VCR plus CTX and hd-MTX week 7 and 10, hd-Thiotepa and G-CSFT week 13					

Study (Investigator, country, year)	Record Num-ber	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylax-is	Supportive Care	Compar-ative Treatment	Compar-ative Treatment Dose/Reg-imen	Comment
Merchant, United States, 2002	74280	Ependymoma 64							Radiotherapy with three dimensional treatment planning	Conventional fractionation of 1.8 Gy/d to 59.4 Gy. 4 young children with Ependymoma received 54.0 Gy. Dose limiting to upper cervical spinal cord was 54 Gy, optic chiasm 55.8 Gy, optic nerves 50.4 Gy, and optic globe 50.4 Gy	

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Ozkaynak, United States, 2004	7850	6	PBSC	Tandem Autologous	2 Surgery XRT (5400 cGY) and Chemotherapy (CTX, CDDP, VP-16, VCR, CCNU), 3 XRT alone (dose NA), 1 surgery and chemo (CCG-9921)	Cyclophosphamide 4-6 g/m^2 with G-CSF 10 ug/kg/d, Thiotepa 240 mg/m^2/d * 3, carboplatin 400 mg/m^2/d * 3,		Rifampin, trimethoprim/sulfamethoxazole, gentamicin, amphotericin-B, fluconazole, acyclovir.			4 of these pts. GBM, Ependymoma, 1 BSG, and 1 AA had only 1 PBSC. 2 were due to parental decision and 2 were due to tumor progression after first course transplant

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Robertson, United States, 1998	74630	Ependymoma 32							Maximal surgical resection, randomized assignment to one of two treatment arms.	Regimen A: Craniospinal radiotherapy w/ 8 weekly doses of IV vincristine concurrent with radiotherapy. Pts then received 8 6-week courses of vincristine, ccnu, and prednisone. Regimen B: 8-in-1 regimen, followed by RT, and then maintenance 8-in-1	8-in-1 regimen consisted of methylprednisone, vincristine, lomustine [ccnu] or carmustine [bcnu], procarbazine, hydroxyurea, cisplatin, cytarabine, and cyclophosphamide

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Shih, United States, 2008	2530	5	Bone Marrow	Single Autologous	1 chemotherapy for EPD, 1 chemotherapy + local RT for AA, 1 craniospinal irradiation for AA, 1 Chemotherapy + craniospinal irradiation for GBM, and 1 craniospinal irradiation for GBM	1 Busulfan and Thiotepa for EPD, 2 Thiotepa and cyclophosphamide for AA, 1 carboplatin and etoposide for GBM, and 1 Thiotepa and cyclophosphamide for GBM					

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Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Sio, Italy, 2006	6950	14			Surgery 3 (21%), Chemotherapy 6 (43%), Radiotherapy 12 (86%), Bone Marrow Transplant 2 (14%), 1 patient had no prior treatment			Authors not explicit; antibiotics, blood products were administered when required and steroid therapy was limited to treatment of raised intracranial pressure or cerebral edema in brain tumor pts.	Chemotherapy	Temozolomide single oral dose for 5 consecutive days (214 mg/m^2/day in patients with no prior CSI and 180 mg/m^2/day in CSI or BMT) Courses were repeated every 21-28 days. TMZ reduced by 25% in patients with grade 4 toxicity.	
Thorarinsdottir, United States, 2007	73050	6	PBSC	Autologous	Newly Diagnosed	3 cycles induction cisplatin, cyclophosphamide, etoposide, vincristine. 3 cycles consolidation carboplatin, thiotepa					

Study (Investigator, country, year)	Record Num-ber	Group (N)	Stem Cell Sour ce	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Compar-ative Treatment	Compar-ative Treatment Dose/Reg-imen	Comment
Wrede, Germany, 2009	75590	34 CPC			Newly Diagnosed, surgical resection				6 cycles chemotherapy 31 (91%), radiotherapy in children over 3 years of age		3 patients did not receive chemotherapy (9%)
Yule, United Kingdom, 1997	18960	5	BMP	Tandem Autologous	Surgery 2 (50), RT 1 (25), No Chemotherapy	2 dose CTX accompanied by mesna at 160%. Starting dose CTX was 2.5m/m^2/d and escalated at .5m/m^2/d to 2 g/m^2. stem		oral dexamethasone before CTX 10 mg/m^2/d, prophylactic acyclovir 1,500 mg/m^2/d) and ciprofloxacin (10 mg/kg/d), and oral nystatin.			
Zacharoulis, United States, 2007	73020	Ependymoma 29	PBSC	Autologous	Newly diagnosed	Maximal surgical resection followed by induction (vincristine, etoposide, cyclophosphamide w/ mesna, methotrexate) and consolidation (carboplatin, thiotepa, etoposide) chemotherapy with radiotherapy when indicated by tumor response, age, and location		platelet counters were maintained above 10,00/mm with transfusion as necessary. Febrile neutropenic pts were given broad spectrum IV antibiotics. Pts received PCP pneumonia prophylaxis			

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Gilheeney, United States, 2010	2187	Anaplastic Astrocytoma (1); Oligoastrocytoma (1); Glioblastoma multiforme (2)		Autologous	AA: resection and radiotherapy; OA: sub-total resection; GBM: 1 patient gross total resection, 1 patient resection radiotherapy and chemotherapy	Thiotepa 300mg/m^2 day -8, -7, -6; topotecan 2 mg/m^2 day -8, -7, -6, -5, -4; carboplatin ~500 mg day -5, -4, -3		Granulocyte colony-stimulating factor			

Appendix Table C77. Outcome assessment: Treatment, glial tumors

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration
Berger, France, 1998	75380	HSCT CPC (2)	Survival, tumor response	toxicity	21 and 25 mo
Bouffet, France, 1997	78760	5	Survival		
Bouffet, France, 2000	78770	24	Survival, EFS	Toxicity	26 months
Busca, Italy, 1997	73190	Ependymoma 2, Anaplastic Astrocytoma 1, Glioblastoma Multiforme 2, Oligodendroglioma 1	OS, PFS, Tumor response	toxicity	
Dunkel, United States, 1998	78780	10	Survival		
Finlay, United States	1300	27	EFS, OS	toxicity	14 months
Grill, France, 1996	73240	Ependymoma 16	Tumor response, outcome, toxicity		1.7 - 66 months
Grovas, United States, 1999	16600	11	Tumor response, toxicity, survival		Study entry, +21, +42, +100 days and then every 2 months until 1 year after ASCR
Gururangan, United States, 1998	18000	N=6, 1 ependymoma, 4 glioblastoma multiforme, 1 anaplastic astrocytoma	Progression, survival	toxicity, but not given by tumor type	NR
Jakacki, United States, 1999	15920	12	OS, PFS, Tumor response	toxicity	5-19months
Mahoney, United States, 1996	73250	7	Toxicity, Tumor Response, PFS, OS		2.6 years
Mason, United States, 1998	73180	Ependymoma 15	Survival, Progression,	Toxicity	

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration
Massimino, Italy, 2005	55220	21	OS, PFS	TAE	Median FU 57mo (13-84)
Ozkaynak, United States, 2004	7850	6	Disease Outcome	Toxicity	
Shih, United States, 2008	2530	5	Time to Progression, OS, Final Status		73-3727 days
Thorarinsdottir, United States, 2007	73050	6	Tumor Response, PFS, OS, Toxicity		median 22 months (8-82 mo)
Yule, United Kingdom, 1997	18960	4	Tumor Response, Outcome, OS	Toxicity	median 27 months (12-34)
Zacharoulis, United States, 2007	73020	29	EFS, OS	toxicity	.6-12+ years FU range
Gilheeney, United States, 2010	2187	Anaplastic Astrocytoma (1); Oligoastrocytoma (1); Glioblastoma multiforme (2)	Survival	Harms	.1-7.7 years

Appendix Table C78. Outcome assessment: Comparator, glial tumors

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration
Ayan, Turkey, 1995	74690	Anaplastic Ependymoma 4	Tumor Response, Progression, Survival	Toxicity	9-35 mo
Berger, France, 1998	75380	Conventional therapy CPC (20)	OS, tumor response	toxicity	1-72 mo
Bertolone, United States, 2003	10380	18	Survival	Toxicity	5 year
Conter, France, 2009	73540	OS, EFS			87.5 mo (66-90, 95% CI)
Doireau, France, 1998	55990	8	OS	Tumor response	5.5 years
Finlay, United States, 2008	1300	56	EFS, OS	toxicity	nr
Grill, France, 2001	74360	Ependymoma 73	PFS, OS		4.7 years median FU (5 mo - 8 years)
Grundy, United Kingdom, 2007	73750	Ependymoma 89	OS, PFS,	toxicity	median 6 years (1.5-11.3 years) [for pts alive at last FU]
Grundy, United States, 2010	51800	26	OS, PFS		median FU .89 years, (.19-8.04 years)
Horn, Untied States, 1999	74470	Ependymoma 83	EFS, OS		75.5 mo (9 - 121 mo)
Hurwitz, United States, 2001	53330	45	TTP, progressive disease and early death, tumor response	toxicity	
Jaing, Taiwan, 2004	74030	Ependymoma 43	OS, PFS	toxicity	5 year
Kobrinsky, United States, 1999	53560	42	OS		4 yr

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration
Korones, United States, 2006	52670	9	PFS, tumor response	toxicity	16 months
Kuhl, Germany, 1998	17700	10	PFS, OS, Tumor Response, Toxicity		7 years
Macdonald, United States, 2005	55000	76	OS, EFS, Tumor Response	Toxicity	Physical and Neurological examination every 3 weeks during induction and interim therapy. Then, at 1 year intervals from entry or at time of progressive disease or relapse.
Merchant, United States, 2002	74280	Ependymoma 64	OS, PFS		17 months (3-44 months)
Robertson, United States, 1998	74630	Ependymoma 32	PFS, OS,		6.5 years
Sio, Italy, 2006	6950	14	PFS, OS, status at final follow up	Toxicity	Range 1-41 months based on survival
Wrede, Germany, 2009	75590	CPC	OS, EFS		0-8.2 yrs (2.2 yrs median)

Appendix Table C79. Time to event outcomes: Treatment, glial tumors OS

Study (Investigator, country, year)	Record Num-ber	Group (N)	OS	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%) CI
Berger, France, 1998	75380	CPC (2)	21 and 25 mo									
Bouffet, France, 1997	78760	5	Total, (1) Parieto-occipital, (3) Brain stem, (1) Thalamus	3, .4, 4, 3								
Bouffet, France, 2000	78770	24	Group OS	10±3.6	~25	~4	0	0	0			
Busca, Italy, 1997	73190	Ependymoma 2, Anaplastic Astrocytoma 1, Glioblastoma Multiforme 2, Oligodendroglioma 1	Two patients died. One AA at 15 months and 1 oligodendroglioma at 10 months. All other patients alive with no progression or evidence of disease									
Dunkel, United States, 1998	78780	10	range .1-18 months	4								
Finlay, United States	1300	ABMR transplanted(N=27), AA (N=10) and GBM (N=17)	AA and GBM @ 4 months 22±7% months AA @ 4 months 40±14% months GBM @ 4 months 12±6%					AA: 40±14% GBM: 12±6%		Chemo vs. ABMR unstratified and stratified (Cox)	.018, stratified by histology .010	1.9 (1.1-3.1)

Study (Investigator, country, year)	Record Number	Group (N)	OS	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%) CI
Grill, France, 1996	73240	Ependymoma 16	5 patients alive at last followup. 1 patient was in second complete response, 1 patient had relapse in the spinal cord, 1 pt had stable residual mass, 1 pt was alive with hemispheric disseminated disease, and 1 patient was alive without evidence of disease	20 months (1.7-45 mo)								
Gururangan, United States, 1998	18000	N=7, 1 ependymoma, 4 glioblastoma multiforme, 1 anaplastic astrocytoma	2 glioblastoma patients died of disease. One toxic death at .03 months and one dead of disease at 17 mo. Two other patients are alive with no evidence of disease at 40+ and 98+ mo. Ependymoma patient DOD at 25 mo. AA pt alive/NED at 98+, 1 CPC DOD 5mo									
Jakacki, United States, 1999	15920	12	Total (12), GBM (4), AA (2), Pons (6) with 1 Pons patient alive	8.5 (5-19), 15 (6-19), 8 (7-9) ,8 (5-14)								

Study (Investigator, country, year)	Record Num-ber	Group (N)	OS	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%) CI
Mahoney, United States, 1996	73250	Anaplastic Astrocytoma 2, Ependymoma 3, Glioblastoma multiforme 1, Brainstem glioma 1	AA 1 month and 4 months, EPD 7 months 9 months and 25+ months, GBM 7 months, BSG 2 months									
Mason, United States, 1998	73180	Ependymoma 15		4.5 months	33±11%	20±9%						
Massimino, Italy, 2005	55220	21	Total, GBM, other glioma	37, ~12, >60	~74, ~60, ~73	~50, ~40, ~73	~50, ~30, ~73	~44, ~30, ~73	~37, 0, ~73	log-rank	=.008 (GBM vs. other glioma)	
Ozkaynak, United States, 2004	7850	6	3 patients had stable disease at a median follow up of 62 months. 3 patients were dead of disease at a median follow up of 4 months.									
Shih, United States, 2008	2530	5	Total, EPD (1), AA (2), GBM (2)	3.9, 2.4, 7.1, 63								
Thorarinsdottir, United States, 2007	73050	Oligodendrogliomas 1, Ganglioma 1, Anaplastic glioma 3, Ependymoma 1	ODG 8 mo, GG 59 mo, AG 10 22 and 33.5 mo, EPD 37 mo	ODG 8 mo, GG 59 mo, AG 22 mo, EPD 37 mo								

Study (Investigator, country, year)	Record Number	Group (N)	OS	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%) CI
Yule, United Kingdom, 1997	18960	4	1 GBM patient survived with stable disease at a follow up of 12 months, a recurrent gbm patient died of disease at 6 months follow up, 1 anaplastic ependymoma patient died of disease at 15 months, and 1 suprasellar gbm pt died of toxicity, 1 CPC DOD 11mo									
Zacharoulis, United States, 2007	73020	Ependymoma 29		~48		69%		38	38±10% (Kaplan Meier curve vies 24%?)	Univariate Cox Proportional Hazards likelihood ratio	EFS Unstratified: Age P=.04, Extent of resection p=.49, Site P=.65. OS: Age p=.20, Extent of resection p=.53, Site P=.70	
Gilheeney, United States, 2010	2187	Anaplastic Astrocytoma (1); Oligoastrocytoma (1); Glioblastoma multiforme (2)	AA: 1 pt alive w/ residual disease at 7.7 years; OA: 1 pt dead of toxicity at 1 mo; GBM: 2 pts DOD at .5-8 years									

Appendix Table C79. Time to event outcomes: Treatment, glial tumors OS Continued

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_2	Med (mos)_2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	5 yr_2	Test_2	p_2
Berger, France, 1998	75380	CPC (2)									
Bouffet, France, 1997	78760	5									
Bouffet, France, 2000	78770	24	PFS	~7	~4	~4	0	0	0		
Busca, Italy, 1997	73190	Ependymoma 2, Anaplastic Astrocytoma 1, Glioblastoma Multiforme 2, Oligodendroglioma 1	PFS Ependymoma 2, Anaplastic Astrocytoma 1, Glioblastoma Multiforme 2, Oligodendroglioma 1	Two patients disease progressed . One AA at 11 months and 1 oligodendroglioma at 4 months. All other patients alive with no progression or evidence of disease							
Dunkel, United States, 1998	78780	10									
Finlay, United States	1300	ABMR transplanted(N=27), AA (N=10) and GBM (N=17)	EFS: Total ABMR (27)					22±7%		Unstratified comparison EFS ABMR vs CHM (Cox)	.014
Grill, France, 1996	73240	Ependymoma 16	For those who had stable disease after HDCT (4), PFS lasted 5-8 mo with a median of 7 months								

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_2	Med (mos)_2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	5 yr_2	Test_2	p_2
Gururangan, United States, 1998	18000	N=7, 1 ependymoma, 4 glioblastoma multiforme, 1 anaplastic astrocytoma	PFS	Two patients progressed one GBM at 8 mo and 1 ependymoma at 16 mo. 1 patient died of toxicity before progression							
Jakacki, United States, 1999	15920	12	PFS: Total (12), GBM (4), AA (2), Pons (6) with 1 Pons patient	4.75 (2-12+), 4 (2-7), 4.75 (4.5-5), 7 (3-12+)							
Mahoney, United States, 1996	73250	Anaplastic Astrocytoma 2, Ependymoma 3, Glioblastoma multiforme 1, Brainstem glioma 1	PFS Anaplastic Astrocytoma 2, Ependymoma 3, Glioblastoma multiforme 1, Brainstem glioma 1	PFS evaluated in 3 of 7 patients. GBM 4 mo, BSG 1 mo, EPD 12 mo							
Mason, United States, 1998	73180	Ependymoma 15	PFS	4 months	~22	0					
Massimino, Italy, 2005	55220	21	PFS: Total, GBM, other glioma	~18, ~10, ~12	~55, ~40, ~73	~46, ~20, ~73	~46, ~20, ~73	~46, ~20, ~73	~40, 0, ~73	log-rank	=.04 PFS other gliomas vs PFS glioblastoma
Ozkaynak, United States, 2004	7850	6									
Shih, United States, 2008	2530	5	Time to Progression: Total, EPD (1), AA (2), GBM (2)	2.54, .95, 1.4, 5, 2.5							

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_2	Med (mos)_2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	5 yr_2	Test_2	p_2
Thorarinsdottir, United States, 2007	73050	Oligodendrogliomas 1, Ganglioma 1, Anaplastic glioma 3, Ependymoma 1	PFS	ODG 8 mo, GG 59 mo, AG 3 17 and 33.5 mo, EPD 37 mo	ODG 8 mo, GG 59 mo, AG 17 mo, EPD 37 mo						
Yule, United Kingdom, 1997	18960	4									
Zacharoulis, United States, 2007	73020	Ependymoma 29	EFS	~22		35%		14%	12±6 %		

Appendix Table C79. Time to event outcomes: Treatment, glial tumors OS Continued

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_3	Med (mos)_3	2 yr_3	4 yr_3	5 yr_3	Comment
Berger, France, 1998	75380	CPC (2)						
Bouffet, France, 1997	78760	5						
Bouffet, France, 2000	78770	24						
Busca, Italy, 1997	73190	Ependymoma 2, Anaplastic Astrocytoma 1, Glioblastoma Multiforme 2, Oligodendroglioma 1						
Dunkel, United States, 1998	78780	10						
Finlay, United States	1300	ABMR transplanted(N=27), AA (N=10) and GBM (N=17)						
Grill, France, 1996	73240	Ependymoma 16						
Gururangan, United States, 1998	18000	N=7, 1 ependymoma, 4 glioblastoma multiforme, 1 anaplastic astrocytoma						
Jakacki, United States, 1999	15920	12						1 GBM patient was given an alternative treatment of HDC for progression and was not included in OS, but remains alive 18 months after initial treatment
Mahoney, United States, 1996	73250	Anaplastic Astrocytoma 2, Ependymoma 3, Glioblastoma multiforme 1, Brainstem glioma 1						
Mason, United States, 1998	73180	Ependymoma 15						One patient is alive 25+ months post ABMR
Massimino, Italy, 2005	55220	21						
Ozkaynak, United States, 2004	7850	6						
Shih, United States, 2008	2530	5						All Patients Were Dead of Disease as final status
Thorarinsdottir, United States, 2007	73050	Oligodendrogliomas 1, Ganglioma 1, Anaplastic glioma 3, Ependymoma 1						
Yule, United Kingdom, 1997	18960	4						

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_3	Med (mos)_3	2 yr_3	4 yr_3	5 yr_3	Comment
Zacharoulis, United States, 2007	73020	Ependymoma 29	Post-progression survival Ependymoma 22	~28	46%	9%	9%	14 pts (48%) Dead of Disease, 3 Dead of Toxicity (10.3), 2 are alive with progressive disease (7%), 4 are alive with stable disease (14%), 6 have no evidence of disease at last followup (21)

Appendix Table C80. Time to event outcomes: Comparator, glial tumors OS

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%) CI
Ayan, Turkey, 1995	74690	Anaplastic Ependymoma 4		33 mo (16-35 mo) [1 pt not included due to loss to fu at 9 months. Pt was non-responsive to therapy)								
Berger, France, 1998	75380	CPC total (20), CPC partial resection (12), CPC gross total surgical resection (8)	1 patient in the partial resection group (9%) was alive and well at 55mo follow up. 7 patients in the gross total resection group were alive and well at a median 25 mo (3-72mo) follow up	Total median OS was 10 mo (1-41mo). Partial resection OS had a median of 11 mo (3-41 mo). Gross total resection OS was 5 mo in 1 patient.							Kaplan Meier survival curves for gross total resection vs. partial resection were significantly different at p=.009	
Bertolone, United States, 2003	10380	18	GBM and AA only non-infants, Infants	~48, ~22	~83, ~52	~64, ~25	~57, ~25	36+-13%, 25+-15%	36+-13%, 25+-15%			
Conter, France, 2009	73540	Ependymoma 24	8 patients died all of neoplastic disease				79.2%		74.8%			
Doireau, France, 1998	55990	8	87.5% at median 4.8 years F/U									

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%) CI
Finlay, United States, 2008	1300	56	@ 4 months	~.7 months AA ~ .6 months GBM ~ 6 months Bulky ~.7 months Non-Bulky ~1.2 months	HSCT, Comparator |AA: ~41%, ~26%, GBM: ~43%, ~22%		HSCT, Comparator |AA: 40+-14%,7+-4% GBM: 12+-6%, 0		HSCT, Comparator |AA: 40+-14%,~4 GBM: 12+-6%, 0	Wilcoxon	.018 overall, by histology .010	1.9 (1.1-3.1)

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%) CI
Grill, France, 2001	74360	Ependymoma 73, Supratentorial 13, Posterior Fossa 60, Low grade 8, High grade 60, Complete resection 44, incomplete resection 29, no residuum, radiographic residuum		~5.2 years for total population	Ependymoma 88%,	Ependymoma 79 (68-87%)	Ependymoma 53%	Ependymoma 73%, Supratentorial 100, Posterior Fossa 50 (37-64), Low grade 58 (26-85%), High grade 61 (47-73), Complete resection 69 (53-82), incomplete resection 46 (28-65), no residuum 74 (59-86), radiographic residuum 35	Ependymoma 24%	two-tailed log rank test	RR difference multivar/univar between Age p=.86/.61, Location p=.0004/.013, Grade .97/.89, Surgery p=.92/.22, Imaging p=.0009/.008	
Grundy, United Kingdom, 2007	73750	Non-metastatic ependymoma 80, metastatic ependymoma 9				90, 78		59, 33				

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%) CI
Grundy, United States, 2010	51800	41	HGG, Brain Stem Tumor, CPC		57.9 (33.2-76.3 CI), 14.3 (.7-46.5), 50.3 (23.1-72.4)		40.5 (18.7-61.5), 0, 21.5 (5.2-45.0)		34.7 (14.6-56.0), 0, 21.5 (5.2-45.0)			
Horn, Untied States, 1999	74470	Ependymoma 83							57.2±5%			
Hurwitz, United States, 2001	53330	45										
Jaing, Taiwan, 2004	74030	WHO II 20, WHO III 23, Male 25, Female 23, <3 25, >3 34, Supratentorial 15, Infratentorial 28, GTR 18, STR 19, biopsy 6, RT involved field 31, without RT 12, CHM 13, without CHM 30	WHO II 74%, WHO III 35, Male 49, Female 62, <3 42, >3 57, Supratentorial 57, Infratentorial 52, GTR 82, STR 37, biopsy 33, RT involved field 58, without RT 48, CHM 54, without CHM 54						Ependymoma total 53.9	Fischer's exact chi-square test	5 year OS: Histology p=.005, Gender p=.425, Age p=.036, Location p=.917, Surgical resection <.001, Leptospinal dissemination .388, Radiotherapy .150, Chemotherapy .279	
Kobrinsky, United States, 1999	53560	42	Brain Stem Glioma, High Grade Astrocytoma	~5, ~5	9+-5%, 28+-10%,	0, ~9%	0, ~9%					

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Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%) CI
Korones, United States, 2006	52670	5 (2 BSG, 2 AST, 1 Glioblastoma)	OS: 1 AA pt DOD at 4 mos, 1 AWD at 10+ mo, 1 glioblastoma pt DF at 15+ mo, 2 BSG pts DOG at 9 and 4 mo									
Kuhl, Germany, 1998	17700	10	Anaplastic Ependymoma (11)						62 ± 11,			
Macdonald, United States, 2005	55000	76	Total (76), Regiment A (23), Regimen B (27), Regimen C (26), Anaplastic Astrocytoma (30), Glioblastoma Multiforme (40), Other (6)	~13, ~18, ~19, ~12, ~12, ~14, ~46	~51, ~55, ~55, ~37, ~46, ~45, ~62	~30, ~33, ~39, ~19, ~28, ~28, ~62	~28, ~27, ~39, ~16, ~22, ~22, ~62	~25, ~20, ~39, ~16, ~25, ~24, ~40	24±5, 18±8, 39±10, 16±7, 25±8, 22±7, 40±22	Log-rank?	P=.23, P=.47	
Merchant, United States, 2002	74280	Ependymoma 64										
Robertson, United States, 1998	74630	Ependymoma 32			97%		75%		53%			

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Study (Investigator, country, year)	Record Number	Group (N)	Outcome	Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%) CI
Sio, Italy, 2006	6950	14	OS: Brainstem Glioma	Total 5.5 (n=8), Ependymoma 4.5(n=2), Anaplastic Astrocytoma 5 (n=3), Brainstem Glioma 6 (n=2) 6 Alive with Disease at median 11.5 mos, Brainstem Glioma 11 (n=5), GBM 12 mos (n=1)								
Wrede, Germany, 2009	75590	CPC 34	OS: CPC (N=29)		~82		~70		36	Cox, CPC vs CPP/ APP	P.003	26.4

Appendix Table C81. Time to event outcomes: Comparator, glial tumors PFS

Study (Investigator, country, year)	Record Number	Group (N)	Outcome _2	Med (mos)_ 2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	5 yr_2	Test_2	p_2	HR (95% CI)_2	Comment
Ayan, Turkey, 1995	74690	Anaplastic Ependymoma 4	PFS, Anaplastic Ependymoma 4	27 mo (only 1 pt evaluated. Other patients had only partial response or no response to treatment)									
Berger, France, 1998	75380	CPC total (20), CPC partial resection (12), CPC gross total surgical resection (8)											

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_2	Med (mos)_2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	5 yr_2	Test_2	p_2	HR (95% CI)_2	Comment
Bertolone, United States, 2003	10380	18											The infants category includes 1 case excluded by this review of medulloblastoma that could not be abstracted separately
Conter, France, 2009	73540	Ependymoma 24	PFS	median time to first relapse was 22 months (4-46 months)			62.5%		54.2%				
Doireau, France, 1998	55990	8	Event free survival: 50% at 4 years										1 patient died at 32 months
Finlay, United States, 2008	1300	56	EFS CHM unstratified		HSCT, Comparator |AA: ~30, ~10 GBM: 22+-7%, 0%		HSCT, Comparator |AA: ~22+-7, 0 GBM: 22+-7, 0%		HSCT, Comparator |AA: ~22+-7, 0 GBM: 22+-7, 0%				

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Study (Investigator, country, year)	Record Number	Group (N)	Outcome_2	Med (mos)_2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	5 yr_2	Test_2	p_2	HR (95% CI)_2	Comment
Grill, France, 2001	74360	Ependymoma 73, Supratentorial 13, Posterior Fossa 60, Low grade 8, High grade 60, Complete resection 44, incomplete resection 29, no residuum, radiographic residuum	PFS Ependymoma 73	Ependymoma total ~ 1.8 years	Ependymoma 56%	Ependymoma 29%	Ependymoma 23 %	Ependymoma 12%	Ependymoma 12%				At time of analysis 31 patients had died of progressive disease from 3 months to 5.8 years (Median 29 months). Age was analyzed in univariate analysis but no difference between strata > 2 years and below 2 years was observed

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_2	Med (mos)_2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	5 yr_2	Test_2	p_2	HR (95% CI)_2	Comment
Grundy, United Kingdom, 2007	73750	Non-metastatic ependymoma 80, metastatic ependymoma 9	EFS: Non-metastatic ependymoma 80, metastatic ependymoma 9	~34, ~18		64, 33		43, 0		Cox-proportional hazards model	Metastatic OS vs non-metastatic p<.0001	4.1 (2.0-8.7 95% CI)	
Grundy, United States, 2010	51800	41	Event Free Survival HGG, Brain Stem Tumor		52.6 (28.7-71.9),0.0		24.1 (7.8-45.1)		18.1 (4.6-38.6)				7 pts alive at last follow up
Horn, Untied States, 1999	74470	Ependymoma 83	PFS						42.2±5.5%				

Study (Investigator, country, year)	Record Number	Group (N)	Outcome _2	Med (mos)_ 2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	5 yr_2	Test_2	p_2	HR (95% CI)_2	Comment
Hurwitz, United States, 2001	53330	45	Time to progression	Astrocytoma 21.2 (1.2-49.3), Malignant glioma 1.4 (.4-7.2), Brain Stem Glioma 1.4 (.5-37.8), Ependymoma 2.1 (.0-30.3)									No astrocytoma patients had progressive disease or early death, 10 malignant glioma (77%) had progressive disease and early death, 9 brainstem glioma (60%), 7 ependymoma (53)

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_2	Med (mos)_2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	5 yr_2	Test_2	p_2	HR (95% CI)_2	Comment
Jaing, Taiwan, 2004	74030	WHO II 20, WHO III 23, Male 25, Female 23, <3 25, >3 34, Supratentorial 15, Infratentorial 28, GTR 18, STR 19, biopsy 6, RT involved field 31, without RT 12, CHM 13, without CHM 30	PFS WHO II 68%, WHO III 27, Male 42, Female 52, <3 22, >3 51,Supratentorial 42, Infratentorial 52, GTR 72, STR 31, biopsy 18, RT involved field 52, without RT 31, CHM 35, without CHM 52						Ependymoma total 45.9	Fischer's exact chi-square test	5 year PFS: Histology p=.002 Gender p=.775, Age p=.005, Location p=.957, Surg resection <.001, Leptospinal dissemination .663, Radiotherapy .029, Chemotherapy .820		
Kobrinsky, United States, 1999	53560	42											

Study (Investigator, country, year)	Record Number	Group (N)	Outcome _2	Med (mos)_ 2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	5 yr_2	Test_2	p_2	HR (95% CI)_2	Comment
Korones, United States, 2006	52670	5 (2 BSG, 2 AST, 1 Glioblastoma)	PFS: 1 BSG pt progressed at 4 mo, 1 GBM progression free at 15+ mo, anaplastic astrocytoma progression free at 10+ mo										
Kuhl, Germany, 1998	17700	10	PFS Anaplastic Ependymoma (11), pts with residual tumor (11), pts with no residual tumor (10)	10 months					52 ± 11, 36±15, 70±14		non-significant statistical difference		

Study (Investigator, country, year)	Record Number	Group (N)	Outcome _2	Med (mos)_ 2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	5 yr_2	Test_2	p_2	HR (95% CI)_2	Comment
Macdonald, United States, 2005	55000	76	Event-free Survival: Total, A (23), B (27), C (26), AA (30), GBM (40), Other (6)	~5, ~9, ~3, ~3, ~3, ~3, ~11	~23, ~27, ~10, ~20, ~26, ~15, ~40	~10, ~14, ~8, ~8, ~10, ~8, ~21	~10, ~14, ~4, ~8, ~10, ~8, ~21	~8, ~14, ~4, ~8, ~7, ~8, ~21	8±3, 14±7, 4±4, 8±6, 7±5, 8±4, 21±18	Log-rank?	P=.07, P=.28		Of the 76 patients 56 (74%) died; 52 deaths were disease related, 1 was due to infection , 2 to hemorrhage, and 1 to AML development. All analysis ITT EFS defined as minimum time from entry to disease progression, relapse a second mal. Neoplasm/death
Merchant, United States, 2002	74280	Ependymoma 64	PFS			88±6%	71%						6 ependymoma patients suffered recurrent or progressive disease.

Study (Investigator, country, year)	Record Number	Group (N)	Outcome_2	Med (mos)_2	1 yr_2	2 yr_2	3 yr_2	4 yr TRM	5 yr_2	Test_2	p_2	HR (95% CI)_2	Comment
Robertson, United States, 1998	74630	Ependymoma 32	PFS		88%		56%		38%		No significant difference between the two chemotherapy groups, p>.2		
Sio, Italy, 2006	6950	14	Progression Free Survival: Total, Ependymoma, Anaplastic Astrocytoma, Brainstem glioma, Glioblastoma multiforme	3 (n=14), Ependymoma 11 (n=2), Anaplastic Astrocytoma 3 (n=3), Brain Stem Glioma 1 (n=8), Glioblastoma multiforme 11 (n=1)									
Wrede, Germany, 2009	75590	CPC 34	EFS CPC N=29		~56		~56		~36	Cox, CPC vs. CPP/APP	p<.0001	HR=15.2	

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Appendix Table C82. Neurological outcomes : Glial tumors

Study (Investigator, country, year)	Record Number	Group (N) (NNO)	Comments (NNO)	Group (N) (NDP)	Comments (NDP)	Group (N) (OOI)	Comments (OOI)
Conter, France, 2009	73540		Two patients were placed in a special school, and two were ≥ 2 years behind at school	Ependymoma 16 (living patients)	Mild retardation 2 (13), Severe retardation 2 (13)	Ependymoma 16 (living patients)	Diplopia 5 (32), mild decrease of visual acuity 1 (6), Severe decrease of visual acuity 1 (6)
Grundy, United States, 2010	51800	21 children alive at last follow up (all histologies, 7 of whom were high-grade gliomas; authors do not give histology in toxicity discussion)	5 children required special needs education				
Thorarinsdottir, United States, 2007	73050			Oligodendrogliomas 1, Ganglioma 1, Anaplastic glioma 3, Ependymoma 1	ODG pt had decreased neurologic responsiveness/ blindness, GG pt had ADD, 1 AG patient had L hemiparesis, 1 AG pt had Ataxia, 1 EPD pt had hypotonia/multiple neuropathies GR 2-4 hearing loss/poor speech		

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Appendix Table C83. Adverse events: Treatment, glial tumors

Study (Investi-gator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	Comment	Group (N) TRM	Severity or Grade TRM	F/U (mos) TRM	% TRM	Comment TRM
Bouffet, France, 2000	78770	24	1 Aspergillus fumigatus , 1 cytomegalovirus	4, 4		24	1 VOD, 1 toxic exfoliative dermatitis with acute renal failure, 1 aspergillus fumigatus pneumonia		4, 4, 4	
Finlay, United States	1300					HSCT (27)	5 toxic deaths	median 17 days	19%	Single death in thiotepa/etoposide (9%), 2 with carmustine (40%), and 2 with carboplatin (9%)regimens
Grill, France, 1996	73240	Ependymoma 16	six documented infectious episodes (2 septicemia, 3 pneumonia, 1 viral encephalitis)	38%		Ependymoma 16	1 death at day 50 following ABMT, 1 pt experienced coma w/ seizures during multiorgan failure leading to death		13%	
Gururangan, United States, 1998	18000					N=4 glioblastoma multiforme	1 patient died of treatment related toxicity at .03 months.		25%	
Jakacki, United States, 1999	15920	12	Two patients had interstitial pneumonia which resolved with treatment	17						

Study (Investi-gator, country, year)	Record Number	Group (N)	Severity or Grade Infection	%	Comment	Group (N) TRM	Severity or Grade TRM	F/U (mos) TRM	% TRM	Comment TRM
Mahoney, United States, 1996	73250					Ependymoma 3	Death at 32 days after BMT due to pulmonary hemorrhage in pt with multiple relapsed ependymoma	1 mo	33%	
Mason, United States, 1998	73180					Ependymoma 15	Toxic mortality		5 pts (33%)	Authors state toxic mortality rate was unexpected and unacceptable
Thorarinsdottir, United States, 2007	73050	Oligodendrogliomas 1, Ganglioma 1, Anaplastic glioma 3, Ependymoma 1	# G+ bacterium: Oligodendrogliomas 2, Ganglioma 3, Anaplastic glioma 0, 1, 2, Ependymoma 4	ODG 100, GG 100, AG 67, EPD 100						
Zacharoulis, United States, 2007	73020	Ependymoma 29	3 cases of sepsis leading to toxic morality.	10.3 %	No toxic deaths since 1998					
Gilheeney, United States, 2010	2187	Oligoastrocytoma (1)				Oligoastrocytoma (1)		1 mo	100 % (n=1)	

Appendix Table C83. Adverse events: Treatment, glial tumors Continued

Study (Investigator, country, year)	Record Number	Group (N)	Group (N) Hepatic veno-occlusive disease (Hepatic Sinusoidal Obstruction)	Severity or Grade hVOD	% hVOD	Comments hVOD	Serious Hemorrhagic Event	Group (N)_12	Severity or Grade SHE	% SHE
Bouffet, France, 2000	78770	24	24	4 mild-severe, 1 fatal	17, 4	Pt died due to multiorgan failure	Serious Hemorrhagic Event			
Grill, France, 1996	73240	Ependymoma 16	Ependymoma 16		3 grade 2 VOD (19%)		Serious Hemorrhagic Event	Ependymoma 16	2 pts had severe epistaxis requiring platelet transfusion	13%

Appendix Table C84. Adverse events: Comparator, glial tumors

Study (Investi-gator, country, year)	Record Number	Group (N)	Infectious	Severity or Grade	%	Comment	Group (N) TRM	TRM	Severity or Grade TRM	F/U (mos) TRM	% TRM	Serious Hemorrhagic Event	Group (N)_12	Severity or Grade SHE	% SHE	Comments SHE
Grundy, United Kingdom, 2007	73750		Infectious				Ependymoma 89	TRM	1 postoperative death		1%	Serious Hemorrhagic Event				
Macdonald, United States, 2005	55000	Total (76), A (23), B (27), C (26)	Infectious	3 or 4	6 (8), 2 (9), 3 (11), 1 (4)	1 patient died due to infection (group not given)		TRM				Serious Hemorrhagic Event	Total (76)	Death	2 (3)	Group not given for deaths
Robertson, United States, 1998	74630		Infectious				Ependymoma 32	TRM	1 toxic treatment related death	1 death at 14 months	3%	Serious Hemorrhagic Event				

Appendix Table C85. Design, participant selection and enrollment: Inherited metabolic diseases

Study (Investi-gator, country, year)	Record Number	Indica tion	Disease	Therapeutic Setting	Grou p (N)	Participant Selection (Treatment Period)	Design	n, Evaluat ed	n, Withdrawn (Lost to F/U)	Comment
Arvio M, Finland, 2001	14180	Inherit ed Metab olic Disea ses	aspartylglucos aminuria		7 HSCT , 12 non-HSCT	transplant: 1991-1997follow-up: 1-7.6 yrs	case series	5 HSCT, 12 non-HSCT		2 HSCT with longer follow-up entered under Malm #8490
Autti T, Finland, 1999	15540	Inherit ed Metab olic Disea ses	aspartylglucos aminuria		2 HSCT , 6 non-HSCT , 7 non-disea sed	follow-up: 4-7 yrs	quasi-experim ental	15	0	
Banjar H, Saudi Arabia, 1998	17920	Inherit ed Metab olic Disea se	Gaucher Type 3		7	follow-up: 2.5-3.5 yrs	case series	3	0	This study combined two disease types, Gaucher Type 1 and Gaucher Type 3. Three of the pts had Gaucher Type 3.
Chan LL, Malaysia, 2002	11330	Inherit ed Metab olic Disea se	Gaucher Type 3		1	treatment: Jun 1996 - May 1998follow-up: 1.8 yrs on treatment, 2.7 yrs after treatment stopped	case report	1	0	
Chen R, Taiwan, 2007	4490	Inherit ed Metab olic Disea se	Gaucher Type 3		1	transplant: Jul 2004follow-up: 1.5 yrs	case report	1	0	

Study (Investi-gator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Coppa GV, Italy, 1999	16350	Inherited Metabolic Disease	MPS II, Hunter disease		1	transplantation: 1995follow-up: 4 yrs	case report	1	0	
Ehlert K, Germany, 2006	4690	Inherited Metabolic Disease	Farber disease		3	follow-up: 0.7-1.3 yrs	case series	3	0	
El-Beshlawy A, Egypt, 2006	5750	Inherited Metabolic Disease	Gaucher Type 3		22	follow-up: 5-26 mos	case series	11	0	This study combined Gaucher Type 1 and Gaucher Type 3 pts, and 11 were Gaucher Type 3.
Erikson A, Sweden, 1995	21630	Inherited Metabolic Disease	Gaucher Type 3		8	follow-up: 2.0-2.4 yrs	case series	3	0	This study included 5 adult pts and 3 pediatric pts.
Goker-Alpan O, US, 2008	1790	Inherited Metabolic Diseases	Gaucher Type 3		32		2 HSCT followed by ERT; 30 ERT only	2	0	
Grewel S, US, 2003	9750	Inherited Metabolic Disease	Mucolipidosis II (I-cell disease)		1	follow-up: 5 yrs	case report	1	0	

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Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Guffon N, France, 2009	680	Inherited Metabolic Disease	MPS II, Hunter disease		8	transplantations: 1990-2000 follow-up: 5-14 yrs	case series	8	0	
Hsu YS, Taiwan, 1999	16540	Inherited Metabolic Diseases	Niemann-Pick Type C		1	follow-up: 0.8 yrs	case report	1	0	
Imaizumi M, Japan, 1994	23220A	Inherited Metabolic Diseases	MPS II, Hunter disease		4	follow-up: 2 yrs	case series	1	0	this study combined diseases, only one was Hunter disease
Imaizumi M, Japan, 1994	23220B	Inherited Metabolic Disease	Mucolipidosis II (I-cell disease)		4	transplant: 1986follow-up: 5.6 yrs	case series	1	0	this case series combined diseases, only 1 in case series had mucolipidosis II
Jacobs JFM, Netherlands, 2005	6740	Inherited Metabolic Disease	Tay-Sachs disease		1	follow-up: 2 yrs	case report	1	0	
Laitinen A, Finland, 1997	19620	Inherited Metabolic Disease	aspartylglucosaminuria		1	follow-up: 4 mos	case report	1	0	

Study (Investi-gator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Lange MC, Brazil, 2006	5690	Inherited Metabolic Disease	MPS III, Sanfilippo syndrome		8	transplant: 1988-2000 (total study pop)follow-up: 3.3-14.2 yrs (total study pop)	case series	1	0	only 1 of 8 pts in study population with Sanfilippo syndrome (MPS III)
Li P, US, 1996	20260	Inherited Metabolic Disease	MPS II, Hunter disease		1	follow-up: 5 yrs	case report	1	0	
Lonnquist T, Finland, 2001	12960	Inherited Metabolic Disease	ceroid lipofuscinosis		3	transplant: Jun 1996 - Oct 1998follow-up: 2-4 yrs	case series	3	0	
Maegawa GHB, Canada, 2009	56590A	Inherited Metabolic Disease	Sandhoff's disease		5	follow-up: 2 yrs	single arm	3	0	This study combined diseases and 3 are Sandhoff's disease.
Maegawa GHB, Canada, 2009	56590B	Inherited Metabolic Disease	Tay-Sachs disease		5	follow-up: 2 yrs	single arm	2	0	This study combined diseases and 2 pts had Tay-Sachs disease.
Malm G, Sweden, 2004	8490	Inherited Metabolic Diseases	aspartylglucosaminuria		2	transplant: 1996follow-up: 5 yrs	case series	2	0	

Study (Investi-gator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
McKinnis EJR, US, 1996	20560	Inherited Metabolic Disease	MPS II, Hunter disease		1	transplant: 1988follow-up: 5.6 yrs	case report	1	0	
Morel CF, Canada, 2007	3010	Inherited Metabolic Diseases	Niemann-Pick Type A		1	follow-up: 2.7 yrs	case report	1	0	
Muenzer J, US, 2006	57160	Inherited Metabolic Disease	MPS II, Hunter disease		96	follow-up: 1 yr	RCT	96	0	Age range of study participants: 5-31 yrs and cannot separate the adult data from the pediatric data.
Muenzer J, US, 2007	57070	Inherited Metabolic Diseases	MPS II, Hunter disease		12	follow-up: 1 yr	RCT for 6 mos, followed by open-label extension for another 6 mos	12	0	
Mullen CA, US, 2000	15300	Inherited Metabolic Disease	MPS II, Hunter disease		1	follow-up: 2.2 yrs	case report	1	0	

Study (Investi-gator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Paciorkowski AR, US, 2008	2980	Inherited Metabolic Disease	Niemann-Pick Type C		1	follow-up: 1 yr	case report	1	0	
Page KM, US, 2008	1280A	Inherited Metabolic Disease	Tay-Sachs disease		19	transplant: Sep 1998 - Apr 2007	case series	1	0	this is one case within a case series which included other diseases
Page KM, US, 2008	1280B	Inherited Metabolic Disease	MPS II, Hunter disease		19	transplantations: Sep 1998 - Apr 2007	case series	2	0	This study combined several diseases, only 2 pts had MPS II.
Patterson MC, US, 2007	56970	Inherited Metabolic Disease	Niemann-Pick Type C		41	enrollment: Mar 2002 - Apr 2004 follow-up: 1 yr	randomized controlled trial	12	1	This study included adults. Results presented by grps of <12 (n=12) and >=12 (n=29). Most results were presented for the >=12 grp, but some results were available for the <12 grp.
Patterson MC, US, 2010	56500	Inherited Metabolic Disease	Niemann-Pick Type C		10	treatment: Aug 2003- Jan 2008 follow-up: 1 yr RCT, 1 yr extension study	open label extension study	9	1 withdrew due to adverse event of Crohn disease	12 entered RCT, 10 entered 1 yr extension

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Pineda M, Spain, 2009	56560	Inherited Metabolic Disease	Niemann-Pick Type C		66	observational period: 2003 - Jul 2008	retrospective observational	66	0	
Ringden O, Sweden, 1995	22020	Inherited Metabolic Diseases	Gaucher Type 3		6	follow-up: 5-11 yrs	case series	6	0	
Ringden O, Sweden, 2006	5940A	Inherited Metabolic Disease	MPS III, Sanfilippo syndrome		71	follow-up: 0.4-14.0 yrs	case series	2	0	This is a study of HSCT in 71 pts with inborn errors of metabolism; 2 pts have MPS III.
Ringden O, Sweden, 2006	5940B	Inherited Metabolic Disease	Sandhoff's disease		71	follow-up: 0.4-14.0 yrs	case series	1	0	This is a study of HSCT in 71 pts with inborn errors of metabolism; 1 pt has Sandhoff's disease.
Schiffman R, Netherlands, 2008	56750	Inherited Metabolic Disease	Gaucher Type 3	substrate reduction therapy combined with ERT	30	follow-up: 2 yrs	phase II open-label clinical trial	30	0	Year 1: 21 received substrate reduction therapy, 9 received no treatment Year 2: all received substrate reduction therapy

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Study (Investi-gator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Schiffmann R, Netherlands, 1997	58150	Inherited Metabolic Disease	Gaucher Type 3		5	follow-up: up to 5 yrs	case series	5	0	
Seto T, Japan, 2001	13460A	Inherited Metabolic Disease	MPS II, Hunter disease		23	follow-up: up to 7.0 yrs	case series	10	0	This study followed 23 mucopolysaccharidosis pts, 10 had MPS II, 3 of those 10 had HSCT.
Seto T, Japan, 2001	13460B	Inherited Metabolic Disease	MPS IV, Morquio disease		23	follow-up: up to 7 yrs	case series	4	0	This study followed 23 mucopolysaccharidosis pts, 4 had MPS IV and 1 underwent HSCT.
Shield JPH, England, 2005	6720	Inherited Metabolic Disease	GM1 gangliosidosis		1	follow-up: 7 yrs	case report	1	0	
Sivakumar P, England, 1999	16200	Inherited Metabolic Disease	MPS III, Sanfilippo syndrome		2: 1 HSCT, 1 non-HSCT	follow-up: 7.4 yrs	comparative study	2	0	comparison of one treated sibling with one untreated sibling
Stein J, Israel, 2007	4880	Inherited Metabolic Disease	Wolman disease		1	follow-up: 11 yrs	case report	1	0	

Study (Investi-gator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Takahashi, Japan, 2001	14030	Inherited Metabolic Disease	MPS II, Hunter disease		7	follow-up: 1.1 yrs	quasi-experimental	1 HSCT; 2 non-HSCT	0	This study combined several diseases, 3 had MPS II, one of which underwent HSCT, two did not.
Tokimasa, Japan, 2008	1310	Inherited Metabolic Disease	MPS II, Hunter disease		5	transplantation: Sep 2005 follow-up: 0.8 yrs	case series	1	0	This study combined several diseases, only one was MPS II.
Tolar J, US, 2009	1370	Inherited Metabolic Disease	Wolman disease		4	follow-up 0.2-11.0 yrs, thru Apr 2008	case series	4	0	
Tsai P, US, 1992	25120	Inherited Metabolic Disease	Gaucher Type 3		1	follow-up: 2 yrs	case report	1	0	
Vellodi A, England, 1999	16650	Inherited Metabolic Disease	MPS II, Hunter disease		10	transplantations: 1982-1991 follow-up: 7-14 yrs	case series	9	1	4 died <100 days post, 1 died 4 yrs post, 1 died unknown follow-up of GVHD, detailed follow-up on only 3 pts

Study (Investi-gator, country, year)	Record Number	Indica tion	Disease	Therapeutic Setting	Grou p (N)	Participant Selection (Treatment Period)	Design	n, Evaluat ed	n, Withdrawn (Lost to F/U)	Comment
Vormoor J, Germany, 2004	9420	Inherit ed Metab olic Disea ses	Farber disease		2	follow-up: 0.9-1.2 yrs	case series	2	0	
Yeager AM, US, 2000	14880	Inherit ed Metab olic Disea se	Farber disease		1	follow-up: 2.3 yrs	case report	1	0	
Styczynski, Poland, 2011	442	Inherit ed Metab olic Disea se	Wolman disease		12	between Jul 2002 - Dec 2008	case series	1		This study was conducted on pts with different diseases, only 1 of the 12 pts had Wolman disease.

Appendix Table C86. Participant characteristics: Treatment, inherited metabolic diseases

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Race (%)	Gender M, F (%)	Disease Stage/category
Arvio M, Finland, 2001	14180	5	3.04	2.75	1.6-5.5	white (100%)	M (40.0%) F (60.0%)	
Autti T, Finland, 1999	15540	2	2.3 yrs		2.0-2.6 yrs	white (100%)	M (100%)	
Chen R, Taiwan, 2007	4490	1	5.8 yrs			Asian (100%)	F (100%)	
Coppa GV, Italy, 1999	16350	1	3 yrs			White (100%)	M (100%)	
Ehlert K, Germany, 2006	4690	3	3.2 yrs	3.8 yrs	2.0-3.9 yrs		M (33.3%) F (66.7%)	Type 2/3, no CNS involvement
Goker-Alpan O, US, 2008	1790	2	1.3 yrs at dx			White (50%), Hispanic (50%)	Male (50%), Female (50%)	
Grewel S, US, 2003	9750	1	1.6 yrs				F (100%)	
Guffon N, France, 2009	680	8	5.8 yrs	4.6 yrs	7-17 yrs		M (100%)	2 attenuated1 intermediate5 severe
Hsu YS, Taiwan, 1999	16540	1	2.5 yrs			Asian (100%)	F (100%)	
Imaizumi M, Japan, 1994	23220A	1	9.8			Asian (100%)	Male (100%)	attenuated form
Imaizumi M, Japan, 1994	23220B	1	0.7 yrs			Asian (100%)	Female (100%)	CNS impairment present
Jacobs JFM, Netherlands, 2005	6740	1	3.8 yrs				F (100%)	asymptomatic
Laitinen A, Finland, 1997	19620	1	1.5 yrs			white (100%)	M (100%)	asymptomatic
Lange MC, Brazil, 2006	5690	1	6 yrs			Hispanic (100%)	F (100%)	
Li P, US, 1996	20260	1	5.0 yrs				M (100%)	severe
Lonnquist T, Finland, 2001	12960	3	0.5 yrs	0.3 yrs	0.3-0.6 yrs	white (100%)	M (33.3%) F (66.7%)	infantile neuronal form: one mildly symptomatic two asymptomatic
Malm G, Sweden, 2004	8490	2	8.1 yrs		5.8-10.4	white (100%)	M (50%) F (50%)	
McKinnis EJR, US, 1996	20560	1	2.4 yrs				M (100%)	severe

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Race (%)	Gender M, F (%)	Disease Stage/category
Morel CF, Canada, 2007	3010	1	0.25 yrs				F (100%)	
Mullen CA, US, 2000	15300	1	0.8 yrs				M (100%)	Type IIB, mild
Page KM, US, 2008	1280A	1	0.06 yrs					
Page KM, US, 2008	1280B	2	<= 0.25 yrs					
Ringden O, Sweden, 1995	22020	6	3.5 yrs	2 yrs	2-9 yrs		Male (67%); Female (33%)	2 advanced, 2 early, 2 progressive
Ringden O, Sweden, 2006	5940A	2						1 Type A and 1 Type C
Seto T, Japan, 2001	13460A	3	5.7 yrs	6.0 yrs	2.0-9.0 yrs	Asian (100%)	Male (100%)	1 intermediate2 mild
Seto T, Japan, 2001	13460B	1	15 yrs			Asian (100%)	Male (100%)	Type A
Shield JPH, England, 2005	6720	1	0.6 yrs			Asian (100%)	M (100%)	asymptomatic
Sivakumar P, England, 1999	16200	1	0.6 yrs				M (100%)	type IIIA
Stein J, Israel, 2007	4880	1	0.25 yrs			White (100%)	F (100%)	
Takahashi, Japan, 2001	14030	1	4.7 yrs			Asian (100%)		severe
Tokimasa, Japan, 2008	1310	1	5.8 yrs			Asian (100%)	M (100%)	
Tolar J, US, 2009	1370	4	0.8 yrs	1.3 yrs	0.2-2.1 yrs	White (50%)Not reported (50%)	Male (25%), Female (75%)	
Tsai P, US, 1992	25120	1	2 yrs				Female (100%)	
Vellodi A, England, 1999	16650	3	2.5 yrs	1.7 yrs	0.8-5.1 yrs		M (100%)	
Vormoor J, Germany, 2004	9420	2	3.9 yrs		3.8-3.9 yrs	white (100%)	M (50%) F (50%)	type 2/3, no CNS involvement
Yeager AM, US, 2000	14880	1	0.8 yrs				F (100%)	Type I with CNS involvement
Styczynski, Poland, 2011	442	1	16 yrs				F (100%)	stable disease

Appendix Table C87. Participant characteristics: Comparator, inherited metabolic diseases

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (med)	Age (Rng)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Arvio M, Finland, 2001	14180	12					white (100%)	M (58.3%) F (41.7%)			
Autti T, Finland, 1999	15540	6 non-HSCT, 7 non-diseased	non-HSCT: 6.0 yrs	non-HSCT: 5.8 yrs	non-HSCT: 3.0-10.0 yrs						
Banjar H, Saudi Arabia, 1998	17920	3	2.6 yrs	2.8 yrs	2.0-3.0 yrs			Male (33%), Female (67%)			
Chan LL, Malaysia, 2002	11330	1	7.6				Asian (100%)	Female (100%)			
El-Beshlawy A, Egypt, 2006	5750	11	6.14 yrs		1-16 yrs						Mean age and range are for the whole study population of 22, which includes 11 Gaucher Type 1 pts.
Erikson A, Sweden, 1995	21630	3	7.4 yrs	4.8 yrs	3.8-13.7 yrs			Male (33%), Female (67%)			
Goker-Alpan O, US, 2008	1790	30			0.2-2.5 yrs at dx		Hispanic (36.7%), Black (6.7%), White (56.7%)	Male (53.3%), Female (46.7%)			
Maegawa GHB, Canada, 2009	56590B	2	13.1 yrs	13.1 yrs	10.1-16.0 yrs			Female (100%)	juvenile form		

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Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (med)	Age (Rng)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Maegawa GHB, Canada, 2009	56590A	3	15.6 yrs	18 yrs	8.7-20.1 yrs			Male (67%), Female (33%)	juvenile form		
Muenzer J, US, 2006	57160	96	placebo, n=32: 13.1 +/- 1.22 yrs ERT EOW, n=32: 14.4 +/- 1.2 yrs ERT wkly, n=32: 15.1 +/- 1.11 yrs		placebo, n=32: 5.0-29.0 yrs ERT EOW, n=32: 5.4-30.9 yrs ERT wkly, n=32: 6.3-26.0 yrs		placebo: Asian (9.4%), Black (12.5%), White (75.0%), Other (3.1%) ERT EOW: S Amer Ind (6.3%), Asian (6.3%), Black (3.2%), White (84.3%) ERT wkly: S Amer Ind (3.1%), Black (6.3%), White (87.5%), Other (31%)		Disease score (2-6):placebo: 3 (22%), 4 (44%), 5 (28%), 6 (6%)ERT EOW: 2 (6%), 3 (19%), 4 (34%), 5 (28%), 6 (13%)ERT wkly: 2 (6%), 3 (22%), 4 (31%), 5 (31%), 6 (9%)		Age stratification: placebo: 5-11 yrs (46.9%), 12-18 yrs (31.3%), 19-31 yrs (21.9%)ERT EOW: 5-11 yrs (43.8%), 12-18 yrs (31.3%), 19-31 yrs (25.0%) ERT wkly: 5-11 yrs (43.8%), 12-18 yrs (28.1%), 19-31 yrs (28.1%)

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (med)	Age (Rng)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Muenzer J, US, 2007	57070	12	placebo: 16.7 yrs ERT .15 mg/kg: 11.0 yrs ERT .5 mg/kg: 20.0 yrs ERT 1.5 mg/kg: 10.0 yrs	placebo: 17 yrs ERT .15 mg/kg: 10 yrs ERT .5 mg/kg: 20 yrs ERT 1.5 mg/kg: 8 yrs	placebo: 13-20 yrs ERT .15 mg/kg: 9-14 yrs ERT .5 mg/kg: 20 yrs ERT 1.5 mg/kg: 6-10 yrs		White (100%)	Male (100%)	attenuated		
Paciorkowski AR, US, 2008	2980	1	3.3 yrs					Female (100%)			
Patterson MC, US, 2007	56970	12	7.2		4-11	2.5		Male (42%), Female (58%)			
Patterson MC, US, 2010	56500	12	7.2 yrs	7 yrs	4-11 yrs	2.5 yrs		Male (42%), Female (58%)			
Pineda M, Spain, 2009	56560	66	12.8 yrs	<6 yrs: n=206 -11 yrs: n=14>=12 yrs: n=27	0.6-43.0 yrs	9.5 yrs		Male (47%), Female (53%)			Cannot separate pediatric and adult pt data.

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Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (med)	Age (Rng)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Schiffman R, Netherlands, 2008	56750	30	substrate reduction therapy (n=21): 10.4 yrs no treatment (n=9): 9.9 yrs			substrate reduction therapy (n=21): 5.1 yrs no treatment (n=9): 4.0 yrs		substrate reduction therapy (n=21): Male (48%)no treatment (n=9): Male (22%)			Age distribution grps:substrate reduction therapy: 2-11 yrs (52%), 12-17 yrs (33%), >=18 yrs (14%)no treatment: 2-11 yrs (88%), 12-17 yrs (0%), >=18 yrs (11%)
Schiffmann R, Netherlands, 1997	58150	5	6.6 yrs	7.5 yrs	3.5-8.5 yrs			Male (75%), Female (25%)	aggressive systemic disease		3 had partial splenectomy prior to ERT
Seto T, Japan, 2001	13460A	7	7 yrs	6 yrs	4-12 yrs		Asian (100%)	Male (100%)	2 severe2 intermediate3 mild		
Seto T, Japan, 2001	13460B	3	11.7 yrs	13 yrs	4-18 yrs		Asian (100%)	Male (66.7%), Female (33.3%)	Type A		
Sivakumar P, England, 1999	16200	1	5 yrs					F (100%)	type IIIA		
Takahashi, Japan, 2001	14030	2	5.9 yrs		5.8-6.0 yrs		Asian (100%)				

Appendix Table C88. Treatment characteristics: Inherited metabolic diseases

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Arvio M, Finland, 2001	14180	3		allogeneic					natural history of disease		
Autti T, Finland, 1999	15540	2	related HLA-identical bone marrow	allogeneic		busulfan cyclophosphamide one pt total nodal irradiation			non-HSCT non-diseased		
Banjar H, Saudi Arabia, 1998	17920	3							pt 1: 60 units/kg every 2 wks, for 3.2 yrs pt 2: 30 units/kg every 2 wks for 3.5 yrs pt 3: 30 units/kg every 2 wks for 2.5 yrs		
Chan LL, Malaysia, 2002	11330	1							ERT	20 units/kg/dose every 2 wks	

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Chen R, Taiwan, 2007	4490	1	unrelated HLA-matched bone marrow	allogeneic	ERT for 3 yrs prior to HSCT During ERT, growth maintained, hepatosplenomegaly resolved, and hematologic and bone density abnormalities resolved. Daily activity functions were deteriorating and intellectual impairment was developing.	busulfan cyclophosphamide tecelac	cyclosporine methotrexate				Elective splenectomy prior to HSCT is standard for Gaucher disease, but was not done on this pt, and no adverse effects of spleen retention was seen.
Coppa GV, Italy, 1999	16350	1	unrelated bone marrow	allogeneic		busulfan cyclophosphamide	cyclosporin methotrexate				
Ehlert K, Germany, 2006	4690	3	2 bone marrow 1 peripheral blood	allogeneic		busulfan myeloablative	cyclosporin A methotrexate with or without anti-thymocyte globulin				

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Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
El-Beshlawy A, Egypt, 2006	5750	11			1 pt had splenectomy prior to ERT				ERT intravenously 1-2 hrs every two wks, 60 microgm/kg body weight		
Erikson A, Sweden, 1995	21630	3			pt 1: partial splenectomy at 10.7 yrs pt 2: splenectomy and HSCT at 2.1 yrs from donor father, but no engraftment				ERT	pt 1: high dose 2x wkly, at .6 yrs dose halved, at 1.8 yrs dose increased 2: high dose 2x wkly, at .5 yrs dose halved, at 1.3 yrs dose 1/4pt 3: high dose 2x wkly, at .8 yrs dose halved, at 1.8 yrs dose 1/4, at 2.3 yrs dose increased	
Goker-Alpan O, US, 2008	1790	2	bone marrow	allogeneic					ERT only		
Grewel S, US, 2003	9750	1	related HLA-identical bone marrow	allogeneic		cyclophosphamide antithymocyte globulin total body irradiation	cyclosporin A prednisone				

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Guffon N, France, 2009	680	8	6 HLA-identical related bone marrow 1 HLA-identical unrelated bone marrow 1 mismatched unrelated bone marrow	allogeneic		busulfan cyclophosphamide thymoglobulin when donor unrelated	cyclosporin A methotrexate	intravenous polyvalent immunoglobulins penicillin acyclovir trimethoprim /sulfamethoxazole			
Hsu YS, Taiwan, 1999	16540	1	related HLA-identical bone marrow	allogeneic		busulfan cyclophosphamide	cyclosporine methotrexate				
Imaizumi M, Japan, 1994	23220A	1	HLS-matched sibling bone marrow	allogeneic		busulfan cyclophosphamide	cyclosporine				
Imaizumi M, Japan, 1994	23220B	1	HLA-matched sibling bone marrow (carrier)	allogeneic		busulfan cyclophosphamide	cyclosporine				

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Jacobs JFM, Netherlands, 2005	6740	1	unrelated bone marrow	allogeneic		busulfan cyclophosphamide antithymocyte globulin	cyclosporin A				substrate reduction therapy started at 1.5 yrs post HSCT
Laitinen A, Finland, 1997	19620	1	related HLA-identical bone marrow	allogeneic		busulfan cyclophosphamide					
Lange MC, Brazil, 2006	5690	1	related bone marrow	allogeneic		busulfan cyclophosphamide	cyclosporine methotrexate				
Li P, US, 1996	20260	1	related HLA-identical bone marrow	allogeneic							
Lonnquist T, Finland, 2001	12960	3	two umbilical cord blood one bone marrow	allogeneic		busulfan cyclophosphamide antilymphocyte globulin	cyclosporin A				
Maegawa GHB, Canada, 2009	56590A	3							substrate reduction therapy orally, 100-200 mg t.i.d., adjusted to body surface area		

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Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Maegawa GHB, Canada, 2009	56590B	2							substrate reduction therapy orally 100-200 mg t.i.d. adjusted to body surface area		
Malm G, Sweden, 2004	8490	2	unrelated bone marrow	allogeneic							
McKinnis EJR, US, 1996	20560	1	related HLA-identical bone marrow	allogeneic		busulfan cyclophosphamide	methotrexate cyclosporine				
Morel CF, Canada, 2007	3010	1	umbilical cord blood	allogeneic		busulfan cyclophosphamide	cyclosporin methylprednisone				
Muenzer J, US, 2006	57160	96							ERT	placebo, n=32ERT every other week, n=32ERT weekly, n=32	
Muenzer J, US, 2007	57070	12							ERT	4 grps: placebo, ERT 0.15 mg/kg, ERT 0.5 mg/kg, ERT 1.5 mg/kg	
Mullen CA, US, 2000	15300	1	unrelated umbilical cord blood	allogeneic		busulfan cyclophosphamide antithymocyte globulin methyl prednisolone	tacrolimus methotrexate				

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Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Paciorkowski AR, US, 2008	2980	1							substrate reduction therapy	total dose = (body surface area / 1.73) X adult dose40 mg, 3 times/day, oral liquid	
Page KM, US, 2008	1280 A	1	unrelated umbilical cord blood	allogeneic		busulfan cyclophosphamide antithymocyte globulin	cyclosporin methylprednisone	IV immunoglobulin acyclovir variconozole			
Page KM, US, 2008	1280 B	2	unrelated umbilical cord blood	allogeneic		busulfan cyclophosphamide antithymocyte globulin myeloablative conditioning	cyclosporine methylprednisone	IV immunoglobulin acyclovir voriconazole			
Patterson MC, US, 2007	56970	12							substrate reduction therapy, dose adjusted to body weight		
Patterson MC, US, 2010	56500	10							substrate reduction therapy	median dose: 350 mg/day (range: 100-600 mg/day)median length of exposure: 1073 days (range: 725-1604 days)	

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Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Pineda M, Spain, 2009	56560	66							substrate reduction therapy	mean daily dose (95% CI):<6 yrs: 197.7 (138.0-257.3) mg6-11 yrs: 350.0 (266.0-433.9) mg>=12 yrs: 464.8 (403.8-525.9) mg	
Ringden O, Sweden, 1995	22020	6	4 HLA-matched related bone marrow 1 HLA-mismatched related bone marrow 1 HLA-matched unrelated bone marrow	allogeneic		pts 1, 2: cyclophosphamide and total body irradiation pts 3-6: busulfan and cyclophosphamide	pt 1: cyclosporine pts 2-6: cyclosporine and methotrexate				pt 4 did not engraft and was put on ERT
Ringden O, Sweden, 2006	5940 A	2		allogeneic		busulfan cyclophosphamide	cyclosporin	reversed isolation			
Ringden O, Sweden, 2006	5940 B	1		allogeneic		busulfan cyclophosphamide	cyclosporin	reversed isolation			

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Schiffman R, Netherlands, 2008	56750	30			29 of 30 receiving ERT simultaneously1 of 30 had HSCT at 13 and 16 yrs and engrafted				substrate reduction therapy combined with ERT (and one HSCT)	Year 1: 21 pts received substrate reduction therapy, 9 received no treatment Year 2: all pts received substrate reduction therapy pts >=12 yrs received adult dosage of 200 mg 3 times/day pts<12 yrs received lower dosages adjusted to body surface area	
Schiffmann R, Netherlands, 1997	58150	5							ERT	dosage adjusted by severity of disease, infusions weekly or every other week	
Seto T, Japan, 2001	13460A	3	related HLA-matched bone marrow	allogeneic							

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Seto T, Japan, 2001	13460B	1	related HLA-matched bone marrow	allogeneic							
Shield JPH, England, 2005	6720	1	related HLA-matched bone marrow	allogeneic							
Sivakumar P, England, 1999	16200	1	related bone marrow	allogeneic					natural history of disease		
Stein J, Israel, 2007	4880	1	unrelated umbilical cord blood	allogeneic		cyclophosphamide antithymocyte globulin total body irradiation	cyclosporin A methylprednisone	difluconazole acyclovir polymyxin gammaglobulin			
Takahashi, Japan, 2001	14030	1	bone marrow	allogeneic							
Tokimasa, Japan, 2008	1310	1	unrelated umbilical cord blood	allogeneic		busulfan cyclophosphamide fludarabine anticonvulsants mesna	methotrexate tacrolimus	laminar air flow room parenteral nutrition antibiotics heparin			

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Tolar J, US, 2009	1370	4	3 unrelated bone marrow 1 unrelated umbilical cord blood	allogeneic		1 cyclophosphamide, antithymocyte globulin, total body irradiation1 cyclophosphamide, total body irradiation 1 busulfan, fludarabine, total body irradiation1 busulfan, cyclophosphamide, antithymocyte globulin					
Tsai P, US, 1992	25120	1	HLA-matched related bone marrow	allogeneic		anti-thymocyte globulin busulfan cyclophosphamide	methotrexate				

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Vellodi A, England, 1999	16650	10	6 related non-identical bone marrow 2 related identical bone marrow 1 unrelated bone marrow 1 unknown bone marrow source	allogeneic		busulfan cyclophosphamide	cyclosporin methotrexate				
Vormoor J, Germany, 2004	9420	2	one related bone marrow, one unrelated peripheral blood	allogeneic		busulfan cyclophosphamide antithymocyte globulin	cyclosporin methotrexate				
Yeager AM, US, 2000	14880	1	related HLA-matched bone marrow	allogeneic		busulfan cyclophosphamide	cyclosporin				

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Styczynski, Poland, 2011	442	1	mismatched unrelated donor	allogeneic		reduced toxicity regimen: BU, fludarabine, and alemtuzumab	tacrolimus, MMF	HEPA filtration and reverse isolation			

Appendix Table C89. Outcome assessment: Treatment, inherited metabolic diseases

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration
Arvio M, Finland, 2001	14180	5	intellectual skills overall health	dysmorphic features	
Autti T, Finland, 1999	15540	2	MRI findings:cortex-white matter differentiation thalami signal intensity		
Chen R, Taiwan, 2007	4490	1	neuropsychologic scores	enzyme activity neurodevelopmental milestones	
Coppa GV, Italy, 1999	16350	1	enzyme activity neurocognitive scores		
Ehlert K, Germany, 2006	4690	3	number of subcutaneous nodules number of joints with limited range of motion	GVHD infections toxicity	
Goker-Alpan O, US, 2008	1790	2	neuropsychometric assessments		
Grewel S, US, 2003	9750		neuropsychologic scores neurodevelopmental milestones		
Guffon N, France, 2009	680	8	enzyme activity neuropsychologic scores		
Hsu YS, Taiwan, 1999	16540	1	neuropsychologic scores neurodevelopmental milestones	MRI findings	
Imaizumi M, Japan, 1994	23220A	1	enzyme activity neuropsychologic measurements neurodevelopmental measurements		2 yrs
Imaizumi M, Japan, 1994	23220B	1	enzyme activity neuropsychologic measurements neurodevelopmental measurements		5.6 yrs
Jacobs JFM, Netherlands, 2005	6740	1	enzyme activity MRI findings:cerebral cortical atrophy		

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Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration
Laitinen A, Finland, 1997	19620	1	identification of gene mutations	enzyme activity	
Lange MC, Brazil, 2006	5690	1	overall survival GVHD		
Li P, US, 1996	20260	1	enzyme activity neuropsychologic scores neurodevelopmental milestones		
Lonnquist T, Finland, 2001	12960	3	neuropsychologic scores enzyme activity	MRI findings:cerebral cortical atrophy periventricular white matter hyperintensity	neuropsychologic testing every 0.5 yrs
Malm G, Sweden, 2004	8490	2	neuropsychologic scores enzyme activity		
McKinnis EJR, US, 1996	20560	1	neuropsychologic scores neurodevelopmental milestones enzyme activity		
Morel CF, Canada, 2007	3010	1	enzyme activity neurologic measurements neurodevelopmental milestones		
Mullen CA, US, 2000	15300	1	enzyme activity	adverse events	
Paciorkowski AR, US, 2008	2980				
Page KM, US, 2008	1280B	2	event-free survival	GVHD development of autoimmune cytopenias	
Page KM, US, 2008	1280A	1	event-free survival	GVHD development of autoimmune cytopenias	
Patterson MC, US, 2007	56970	12			
Ringden O, Sweden, 1995	22020	6	enzyme activity liver size skeletal symptoms growth		
Ringden O, Sweden, 2006	5940A	2	cumulative overall survival cumulative treatment-related mortality	cumulative incidence of cGVHD	
Ringden O, Sweden, 2006	5940B	1	cumulative overall survival cumulative treatment-related mortality	cumulative incidence of cGVHD	
Seto T, Japan, 2001	13460A	10	MRI findings in MPS pts		
Seto T, Japan, 2001	13460B	4	MRI findings in MPS pts		
Shield JPH, England, 2005	6720	1	MRI findings neurodevelopmental milestones	enzyme activity	
Sivakumar P, England, 1999	16200	2	neuropsychologic scores neurodevelopmental milestones		

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration
Stein J, Israel, 2007	4880	1	enzyme activity MRI findings		
Takahashi, Japan, 2001	14030	3	magnetic resonance spectroscopy measurement of mucopolysaccharides in the central nervous system		
Tokimasa, Japan, 2008	1310	1	engraftment GVHD		
Tolar J, US, 2009	1370	1	overall survival neuropsychologic scores	enzyme activity GVHD	
Tsai P, US, 1992	25120	1	neurocognitive scores growth enzyme activity		
Vellodi A, England, 1999	16650	10	TRM neurocognitive scores		
Vormoor J, Germany, 2004	9420	2	number of subcutaneous nodules number of joints with limited range of motion		
Yeager AM, US, 2000	14880	1	enzyme activity neuropsychologic scores	MRI findings joint measurements	
Styczynski, Poland, 2011	442	1	aGVHD, cGVHD	overall survival	0.3 yrs

Appendix Table C90. Outcome assessment: Comparator, inherited metabolic diseases

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Comment
Arvio M, Finland, 2001	14180	12				
Autti T, Finland, 1999	15540	6 non-HSCT7 non-diseased				
Banjar H, Saudi Arabia, 1998	17920	3	pulmonary involvement	skeletal changes		
Chan LL, Malaysia, 2002	11330	1	organomegaly growth			
El-Beshlawy A, Egypt, 2006	5750	11	skeletal changes			
Erikson A, Sweden, 1995	21630	3	neuropsychologic scores glucosylceramide levels (lower is better)	growth		
Goker-Alpan O, US, 2008	1790	30	neuropsychometric assessments			
Maegawa GHB, Canada, 2009	56590B	2	neurological assessments neuropsychological tests, 2 types depending on severity of impairment		neurological assessments at baseline and every 3 mos neuropsychological tests at baseline and every 6 mos	
Maegawa GHB, Canada, 2009	56590A	3	neurological assessments neuropsychological tests, 2 types depending on severity of impairment		neurological assessments at baseline and every 3 mos neuropsychological tests at baseline and every 6 mos	
Malm G, Sweden, 2004	8490	2				
Muenzer J, US, 2006	57160	96	6-minute walk test forced vital capacity		baseline, 18 wks, 36 wks, 53 wks	
Muenzer J, US, 2007	57070	12	change in urinary glucosaminoglycans	liver and spleen size 6-minute walk test pulmonary function joint mobility heart size and function sleep study	baseline, wk 13, wk 24, wk 25, wk 51	
Paciorkowski AR, US, 2008	2980	1	gait analysis neurologic exams growth parameters		gait every 6 mos neurologic exams every 3 mos	

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Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Comment
Patterson MC, US, 2007	56970	12	change in horizontal saccadic eye movement-alpha (HSEM-alpha)	mini-mental status examination ambulatory index difficulty in swallowing		HSEM-alpha is an indicator of disease severity
Patterson MC, US, 2010	56500	10	horizontal saccadic eye movement (correlates well with disease progression)	neurological assessments swallowing ambulation		
Pineda M, Spain, 2009	56560	66	4 disease disability scales: ambulation, manipulation, language, swallowing (the lower the score, the better)		at diagnosis, at start of treatment, last clinical contact	Psychiatric impairment was not part of the disability scales because most psychiatric impairment in this disease starts in adolescence or adulthood.
Schiffman R, Netherlands, 2008	56750	30	change in vertical saccadic eye movement velocity (VSEM)	neurological assessments pulmonary function liver and spleen volume hematological assessments safety evaluations		VSEM chosen end point because supranuclear gaze palsy is the only universal neurological symptom of Gaucher Type 3
Schiffmann R, Netherlands, 1997	58150	5	neurocognitive scores lumbar puncture (3 of 5 pts)		lumbar puncture every 3-6 mos for 3 yrs	
Seto T, Japan, 2001	13460A	7	MRI findings in MPS pts			
Seto T, Japan, 2001	13460B	3	MRI findings in MPS pts			
Sivakumar P, England, 1999	16200	1	neuropsychologic scores neurodevelopmental milestones			
Takahashi, Japan, 2001	14030	2	magnetic resonance spectroscopy measurement of mucopolysaccharides in the central nervous system			

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Appendix Table C91. Time to event outcomes: Treatment, inherited metabolic diseases

Study (Investigator, country)	Record Number	Group (N)	Outcome	Comment
Arvio M, Finland, 2001	14180	3	alive:pt 1: 7.6 yrs pt 2: 5.4 yrs pt 3: 1.8 yrs	
Autti T, Finland, 1999	15540	2	alive:pt 1: 7 yrs pt 2: 4 yrs	
Banjar H, Saudi Arabia, 1998	17920			
Chan LL, Malaysia, 2002	11330			
Chen R, Taiwan, 2007	4490	1	alive at 1.5 yrs post	
Coppa GV, Italy, 1999	16350	1	alive at 4 yrs post	
Ehlert K, Germany, 2006	4690		alive:pt 1: 1.2 yrs pt 2: 0.5 yrs pt 3: 0.7 yrs	
El-Beshlawy A, Egypt, 2006	5750			
Erikson A, Sweden, 1995	21630			
Goker-Alpan O, US, 2008	1790	2	alive at 19-21 yrs	
Grewel S, US, 2003	9750	1	alive at 5 yrs post	
Guffon N, France, 2009	680	8	7 alive at 12.7 yrs avg post1 dead at 6.1 yrs post	cause of death unrelated to transplant
Hsu YS, Taiwan, 1999	16540	1	alive at 0.8 yrs post	
Imaizumi M, Japan, 1994	23220A	1	alive at 2 yrs	
Imaizumi M, Japan, 1994	23220B	1	dead at 5.6 yrs follow-up	died of natural progression of disease
Jacobs JFM, Netherlands, 2005	6740	1	alive at 2.0 yrs post	
Laitinen A, Finland, 1997	19620	1	alive at 4 mos post	
Lange MC, Brazil, 2006	5690	1	alive at 3.3-14.2 yrs post (for total study pop of 8)	follow-up time for single MPS III pt not given
Li P, US, 1996	20260	1	alive at 5.0 yrs post	
Lonnquist T, Finland, 2001	12960	3	alive:pt 1: 4 yrs pt 2: 3 yrs pt 3: 2 yrs	
Maegawa GHB, Canada, 2009	56590A			
Maegawa GHB, Canada, 2009	56590B			
Malm G, Sweden, 2004	8490	2	alive:pt 1: 5 yrs pt 2: 5 yrs	
McKinnis EJR, US, 1996	20560	1	alive at 5.6 yrs post	
Morel CF, Canada, 2007	3010		alive at 2.7 yrs post	
Muenzer J, US, 2006	57160			
Muenzer J, US, 2007	57070			
Mullen CA, US, 2000	15300		alive at 2.2 yrs	
Paciorkowski AR, US, 2008	2980			
Page KM, US, 2008	1280A	1	dead at 4.6 yrs post	cause of death unknown, probably infection
Page KM, US, 2008	1280B	1	1 alive at 5.1 yrs post1 dead at 1.8 yrs post	cause of death: multi-system organ failure
Patterson MC, US, 2007	56970			

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Study (Investigator, country)	Record Number	Group (N)	Outcome	Comment
Patterson MC, US, 2010	56500			
Pineda M, Spain, 2009	56560			
Ringden O, Sweden, 1995	22020	6	6 alive, 5-11 yrs follow-up	
Ringden O, Sweden, 2006	5940A	2	1 alive at 14 yrs follow-up (Type C), without engraftment1 dead at 0.4 yrs post (Type A)	Cause of death: pneumonia
Ringden O, Sweden, 2006	5940B	1	1 dead, unknown follow-up	Cause of death: progressive disease
Schiffman R, Netherlands, 2008	56750			
Schiffmann R, Netherlands, 1997	58150			
Seto T, Japan, 2001	13460A	3	3 alive, 1 at 3 yrs post, 1 at 8 yrs post, 1 unknown follow-up	
Seto T, Japan, 2001	13460B	1	alive, unknown follow-up	
Shield JPH, England, 2005	6720		alive at 7 yrs post	
Sivakumar P, England, 1999	16200	1	alive at 7.4 yrs post	
Stein J, Israel, 2007	4880	1	alive at 4 yrs post	
Takahashi, Japan, 2001	14030	1	alive at 1.1 yrs post	
Tokimasa, Japan, 2008	1310	1	dead at 0.8 yrs post	cause of death: post-transplant lymphoproliferative disorder
Tolar J, US, 2009	1370	4	2 dead at 0.2 and 0.7 yrs post2 alive at 4 and 11 yrs post	
Tsai P, US, 1992	25120	1	dead at 2 yrs post	s. pneumoniae sepsis
Vellodi A, England, 1999	16650	10	2 alive at 7-14 yrs post1 dead 11.8 yrs post from natural progression of disease4 dead <100 days post, 2 from aGVHD, 2 from sepsis1 dead 4 yrs post from bronchiolitis1 dead unknown follow-up of GVHD	Authors attribute high mortality to poor donor selection.
Vormoor J, Germany, 2004	9420	2	alive:pt 1: 1.2 yrs pt2: 0.9 yrs	
Yeager AM, US, 2000	14880	1	dead at 2.3 yrs post	cause of death: pulmonary failure after aspiration pneumonitis (disease-related, not treatment-related)
Styczynski, Poland, 2011	442	1	alive, 0.3 yrs	

Appendix Table C92. Time to event outcomes: Comparator, inherited metabolic diseases

Study (Investigator, country, year)	Record Number	Group (N)	Outcome	1 yr	2 yr	3 yr	4 yr	5 yr	Outcome_2	Med (mos)_2	3 yr_2	5 yr_2
Abu-Ghosh 2002 USA	45610	11		~73 %	63.6 +/- 14.5 %	63.6 +/- 14.5 %	63.6 +/- 14.5 %	63.6 +/- 14.5 %	PFS		63.6 +/- 14.5 %	
Park, Korea, 2006	5450	7	DOD n=5 median 15 mos (2-30 mos) A NED n=1 20+ mos A with D n=1 130+ mos						EFS	median 8 months (2-20 mos)		
Tucci, Brazil, 2007	3910	10				83.3 %		42.8 %	DFS		66.6 %	42.8 %

Appendix Table C93. Neurocognitive/neuropsychological outcomes: Inherited metabolic diseases

Study (Investi-gator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Arvio M, Finland, 2001	14180	3 HSCT 12 non-HSCT			3 HSCT: developmental age was on average 5 yrs lower than real age 12 non-HSCT: developmental age was on average 3.4 yrs lower than real age						
Autti T, Finland, 1999	15540	2 HSCT		both HSCT pts: gross motor clumsiness, slight balance problems			2 HSCT		frequent respiratory and ear infections	no reports of respiratory and ear infections	
Banjar H, Saudi Arabia, 1998	17920	3			No changes in skeletal symptoms were found.		3		all 3 have diffuse reticular pattern on chest x-rays	2 improved and 1 had no change in lung involvement	
Chan LL, Malaysia, 2002	11330	1		height <3rd percentile	improved growth		1		spleen volume: 1592 cu cm liver: 3 cm below coastal margin mild anemia thrombocytopenia	spleen volume: 856 cu cm liver: 2 cm below coastal margin anemia corrected thrombocytopenia corrected	

Study (Investigator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Chen R, Taiwan, 2007	4490	1			stable growth and improved bone density						
Coppa GV, Italy, 1999	16350	1		significant joint limitations in hands, knees, elbows sensorineural hearing loss	mild joint limitations at 0.7 yrs post minimal joint limitations at 2.6 yrs post		1		hepatosplenomegaly mild mitral and tricuspid insufficiency	hepatosplenomegaly resolved 2.6 yrs post slight improvements in valve abnormalities at 2.6 yrs post	
Ehlert K, Germany, 2006	4690	3		no. subcutaneous nodules:pt 1: 58pt 2: 39pt 3: 18no. joints with limited motion:pt 1: 26pt 2: 24pt 3: 10	no. subcutaneous nodules:pt 1: 8 at 1.2 yrs post pt 2: 14 at 0.5 yrs post pt 3: 0 at 0.7 yrs post no. joints with limited motion:pt 1: 2 at 1.2 yrs post pt 2: 4 at 0.5 yrs post pt 3: 4 at 0.7 yrs post	all 3 pts showed improvement in mobility, less pain, and considerable gain in function					

Study (Investigator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
El-Beshlawy A, Egypt, 2006	5750	11		Grading severity level of marrow involvement: 0A level: 3 pts, 2A level: 6 pts, 3A level: 1 pt, 3B level: 1 pt	0A level:0A level: 1 constant and 2 worsened, 2A level: 5 complete improvement and 1 constant, 3A level: 1 constant, 3B level: 1 constant	3B pt had prior splenectomy	11	radiography of both femora	7 no abnormal osseous changes2 single lesions2 complex lesion	7 no abnormal osseous changes remained same2 single lesions had complete improvement2 complex lesions had 1 remain same and 1 partial improvement	
Erikson A, Sweden, 1995	21630	3	stunted growth skeletal deformities	pt 2: grew 2 cm/yr pt 3: grew 4 cm/yr	pt 2: grew 9 cm 1 yr post pt 3: grew 12 cm 1 yr post	pt 1 had femur deformity, kyphosis, cortex thinning and pt 3 had femur deformity; no change in skeletal deformities found	3	liver size spleen size	liver: pt 1: 4.3% body wt, pt 2: 6.2% body wt, pt 3: 8.3% body wt spleen:pt 1: 4.6% body wt, pt 2: splenectomy, pt 3: 14.6% body wt	liver: pt 1: 2.7% at 2.1 yrs, pt 2: 3.6% at 2 yrs, pt 3: 4.3% at 1.9 yrs spleen:pt 1: 1.0% at 2.1 yrs, pt 2: splenectomy, pt 3: 3.3% at 1.9 yrs	

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Study (Investi-gator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Goker-Alpan O, US, 2008	1790	2		bone abnormalities in 1 pt (50%)	bone abnormalities stable	or whole grp, 2 HSCT followed by ERT, and 30 ERT only: 100% slowing of horizontal saccadic eye movement					
Grewel S, US, 2003	9750	1		real age: 1.4 yrs developmental age: 0.9 yrs	real age: 3.0 yrs, gross motor age: 1.2 yrs real age: 3.5 yrs, gross motor age: 1.3 yrs real age: 4.7 yrs, gross motor age: 1.5 yrs real age: 5.7 yrs, gross motor age: 1.5 yrs real age: 6.7 yrs, gross motor age: 1.5 yrs	gross motor skills impaired fine motor skills slowly growing	1		echocardiograph showed trivial aortic insufficiency frequent respiratory infections	echocardiograph showed no further progression of cardiac symptoms no respiratory infections during follow-up	surgery for cataracts, bilateral carpal tunnel, 8 trigger digit releases multiple dental extractions insertion of bilateral ear tubes

Study (Investi-gator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Guffon N, France, 2009	680	8			8 showed improvement in joint stiffness2 no kyphosis5 mild kyphosis1 severe kyphosis2 no carpal tunnel syndrome6 carpal tunnel syndrome requiring surgery		8		8 valvular abnormalities detected by echocardiography5 hearing problems3 no hearing problems8 hepatosplenomegaly	cardiovascular abnormalities stabilized1 with hearing problems improved7 hearing remain same8 hepatosplenomegaly resolved in 3 mos post	
Hsu YS, Taiwan, 1999	16540	1		1.2 yrs: sat without support and crawled2.4 yrs: became bed-ridden during conditioning phase			1		frequent respiratory infections hepatosplenomegaly lipid-filled foamy cells among hematopoietic cells	chest CT at 0.5 and 0.8 yrs post show resolution of lung infiltrates hepatosplenomegaly resolved at 0.5 yrs post normal cellular marrow with no foamy cells at 0.5 yrs post	

Study (Investi-gator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Imaizumi M, Japan, 1994	23220A	1		moderate to severe joint contractures nodular hypertrophy present	improved joint contractures nodular hypertrophy absent		1		cardiac valvular thickness hepatomegaly at 12 cm moderate hearing loss	no change in cardiac valvular thickness hepatomegaly at 4 cm no change in hearing loss	
Imaizumi M, Japan, 1994	23220B	1		moderate to severe joint contractures marked short stature dystosis multiplex present	no change in joint contractures marked short stature dystosis multiplex still present		1		high dependence on respirator and frequent infections left ventricular hypertrophy mild corneal cloudiness hepatomegaly at 6 cm	low dependence on respirator and less frequent infections left ventricular hypertrophy same mild corneal cloudiness hepatomegaly at 0 cm	at 5 yrs, infections began increasing again and at 5.6 yrs post transplant, pt died of pneumonia
Jacobs JFM, Netherlands, 2005	6740	1			motor skills deteriorating at 0.5 yrs post	Deterioration of this pt similar to deterioration of untreated older sister.	1			ophthalmological deterioration at 1.5 yrs post	
Laitinen A, Finland, 1997	19620	1					1		mild hepatomegaly recurrent respiratory infections	clinically well	

Study (Investigator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Li P, US, 1996	20260	1		multiple bone abnormalities	improvements in joint range of motion improvements in fine and gross motor skills		1		hepatosplenomegaly cardiac enlargement with normal function	hepatosplenomegaly resolved cardiac status unimproved	
Lonnquist T, Finland, 2001	12960	3		one pt mildly symptomatic and two pts asymptomatic	all three pts by end of follow-up at 2-4 yrs of age were hypotonic and spastic, with some head control remaining		3		no optic atrophy or retinopathy	optic atrophy: development of one severe and one mild retinopathy: development of one mild	
Maegawa GHB, Canada, 2009	56590A	3		pt 1: muscle wasting, fully dependent for feeding and ambulation pt 2: moderate skeletal muscle weakness, independent ambulation, feeding, bathing pt 3: independent ambulation, feeding, and bathing	pt 1: 3 mos incoordination progressed, 15 mos wheelchair, 21 mos can't stand pt 2: at 18 mos gait disturbance progressed & muscle strength reduced pt 3: 6 mos gait disturbance, 16 mos notable wt loss	pt 2 and pt 3 stopped tx at 21 mos due to excessive weight loss					

Study (Investigator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Maegawa GHB, Canada, 2009	56590B	2		pt 1: mild muscle weakness, moderate muscle impairment, independent feeding and ambulation pt 2: needs support for ambulation	pt 1: at 6 mos handwriting deteriorated, at 12 mos fine tremor in hands, from 12-24 mos, progressive muscle atropy pt 2: at 15 mos muscle bulk decreased markedly, at 24 mos wheelchair dependent						
Malm G, Sweden, 2004	8490	2			pt 1: can walk, ride bike, dress self pt 2: can walk, ride bike, drive tractor, some fine motor skills						
McKinnis EJR, US, 1996	20560	1		real age: 1.9 yrs developmental age: 1.3-1.5 yrs	persistent skeletal deformities reversion in balance and coordination though can still walk and ride tricycle		1		hearing deficits hepatomegaly	hearing deficits persist, but have not progressed hepatomegaly resolved	

Study (Investigator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Morel CF, Canada, 2007	3010	1			alert, active, interactive, rolling back to front to back at 0.6 yrs post head lag and hypotonic at 1 yr post significant developmental delay, limited social interaction, unable to sit or stand at 1.7 yrs post		1		hepatosple nomegaly	splenomegaly resolved cherry red spots and worsening vision at 0.6 yrs post recurrent respiratory infections failure to thrive gastronomy feeding at 1.3 yrs post sleep apnea at 1.7 yrs post exclusively g-tube fed at 2.3 yrs post	

Study (Investi-gator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Muenzer J, US, 2006	57160	96	6-minute walk test, meters	placebo: 392 +/- 19ERT EOW: 401 +/- 18ERT wkly: 392 +/- 19	Changes in 6-minute walk test:placebo: 7.3 +/- 9.5ERT EOW: 30.3 +/- 10.3 (p=0.07)ERT wkly: 44.3 +/- 12.3 (p=0.01)		96	Forced vital capacity (L)	placebo: 1.09 +/- 0.09ERT EOW: 1.17 +/- 0.10ERT wkly: 1.19 +/- 0.10	Changes in forced vital capacity (p-value):placebo: 0.06 +/- 0.03ERT EOW: 0.07 +/- 0.03 (p=0.37)ERT wkly: 0.22 +/- 0.05 (p=0.001)	Liver volume % change:placebo: -0.8 +/- 1.6ERT EOW: -24.0 +/- 1.7 (p<0.0001)ERT wkly: -25.3 +/- 1.6 (p<0.0001)Spleen volume % change:placebo: 7.2 +/- 4.2ERT EOW: -19.8 +/- 3.2 (p<0.0001)ERT wkly: -25.1 +/- 2.4 (p<0.0001)

Study (Investigator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Muenzer J, US, 2007	57070	12	6-minute walk test, meters	placebo: 374.7ERT .15 mg/kg: 448.7ERT .5 mg/kg: 324.3ERT 1.5 mg/kg: 439.7	6 mos: no change12 mos: 8 improved, 4 no change	pooled 6-minute walk test, including placebo which received ERT after 6 mos:baseline: 398 +/- 1171 yr: 445 +/- 124 (p=0.013)	12		12 hepatosplenomegaly	pooled 1 yr: 11 reduced liver and spleen size, changes in size not dose-related	forced vital capacity: pooled 1 yr data did not show significant change, measurements difficult and unreliable sleep study:6 of 7 pts eligible experienced decrease in O2 desaturation events/hr (from 19.2 to 2.4)
Mullen CA, US, 2000	15300	1			growing and developing normally		1		hepatomegaly	hepatomegaly resolved	

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Study (Investi-gator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Paciorkowski AR, US, 2008	2980	1		proximal weakness in extremities ataxic hand tremor ataxic gait motion analysis: walked 0.24 m/sec, 62 steps/min	3 mos: hand tremor diminished9-12 mos: lost ability to walk motion analysis at 6 mos: walked 0.12 m/sec, 32.4 steps/min		1		splenomegaly	unchanged splenomegaly	
Patterson MC, US, 2007	56970	12	horizontal saccadic eye movement -alpha		mean decrease of -0.465 ms/deg p=0.028 for whole grp (including >=12 yr grp)	improvement in ambulation seen for whole grp including pts >=12:p=0.052					
Patterson MC, US, 2010	56500	10	Standard Ambulation Index	2.0 (0.7-3.3)	1 yr: 2.3 (0.6-4.0)2 yrs: 2.6 (0.7-4.5)	8 of 10 pts are considered stable in ambulation	9	Horizontal Saccadic Eye Movement, alpha and beta	HSEM alpha mean (95% CI): 2.181 (1.3-3.0)HSEM beta mean (95% CI): 28.96 (13.9-44.0)	1 yr HSEM alpha mean (95% CI): 1.692 (1.0-2.4)2 yr HSEM alpha mean (95% CI): 2.106 (1.3-2.9)1 yr HSEM beta mean (95% CI): 33.66 (18.3-49.0)2 yr HSEM beta mean (95% CI): 33.47 (17.9-49.1)	no improvement, but overall stability of disease

Study (Investigator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Pineda M, Spain, 2009	56560	57	Disability scale component scores	at diagnosis:ambulation: 0.18 (0.16,0.20)manipulation: 0.27 (0.24,0.30)language: 0.16 (0.14,0.18)swallowing: 0.12 (0.10,0.15)at start of treatment: overall deterioration of scores	at last clinical visit, % with stable/improved scores:ambulation: 76.6%manipulation: 76.2%language: 77.0%swallowing: 81.0%		57	Annual change in composite score, by age grp		<6 yrs: -0.070 (-0.275,0.136)6-11 yrs: -0.0157 (-0.394,0.080)>=12 yrs: -0.162 (-0.329,0.006)	most improvement seen in older grps (6-11 yrs and >=12 yrs)
Ringden O, Sweden, 1995	22020	6		pts 1, 5, 6: kyphosis pts 2, 3, 4: no kyphosis	pts 1, 5, 6: kyphosis pts 2, 3, 4: no kyphosis all experienced growth spurt	pt 4 who did not engraft and is on ERT, has decreased motor skills	6		hepatomegaly	hepatomegaly resolved	

Study (Investigator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Schiffman R, Netherlands, 2008	56750	26 (4 withdrew during extension phase of study)	vertical saccadic eye movement (VSEM)		No treatment effect on VSEM.	Study may not have been long enough for neurological defects to improve, or neurological defects are irreversible.	30	forced vital capacity	substrate reduction therapy: 75.1 (62.0-88.2)no treatment: 79.5 (61.3-97.6)	81.1 (65.7-96.5)no treatment: 81.3 (62.7-99.9)	No difference between groups detected, but in subgroup analysis on pts with abnormal forced vital capacity, improvement was seen with substrate reduction therapy.
Seto T, Japan, 2001	13460B	1 HSCT, 3 non-HSCT		HSCT pt: mild bone deformities	HSCT pt: no follow-up post HSCT	3 non-HSCT pts:#1: bone deformities 1 yr, overflexion of neck becoming quadriplegic 9 yrs#2: decreased tendon reflexes 14 yrs#3: increased deep tendon reflexes 4 yrs					

Study (Investigator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Shield JPH, England, 2005	6720	1			walking at 0.6 yrs post became clumsy at 1.7-2.1 yrs post limited motor skills at 4.0 yrs post wheelchair at 6.0 yrs post						
Sivakumar P, England, 1999	16200	2: 1 HSCT, 1 non-HSCT			HSCT pt: immobile at 7.4 yrs post non-HSCT pt: immobile at 10 yrs of age		2: 1 HSCT, 1 non-HSCT			both treated and untreated pts have swallowing dysfunction	
Stein J, Israel, 2007	4880	1		weight, height, and head circumference at <3rd percentile	at 4 yrs post:weight 10th percentile height 3rd percentile head circumference 3rd percentile		1		hepatosplenomegaly	hepatosplenomegaly resolved by 0.5 yrs post	
Tokimasa, Japan, 2008	1310										

Study (Investi-gator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Tolar J, US, 2009	1370	4		pt 1: considerable developmental delay	pt 1 at 11 yrs post: motor function improved pt 4 at 4 yrs post: fine motor skills below avg, gross motor skills avg		4		pt 1: hepatosplenomegaly	pt 1: hepatosplenomegaly resolved	
Tsai P, US, 1992	25120	1		failure to thrive, height < 3rd percentile	height 10th percentile at 9 mos post height 50th percentile at 2 yrs post		1	expected liver volume based on body wt	300%	225% at .2 yrs post 136% at .7 yrs post116% at 1.1 yrs post125% at 2 yrs post	
Vellodi A, England, 1999	16650	3		Griffiths Mental Development Scale:pt 1: locomotor 63, eye-hand 58pt 2: locomotor 55, eye-hand 58pt 3: locomotor 110, eye-hand 93	Griffiths Mental Development Scale:pt 1 at 10 yrs post: locomotor 11, eye-hand 8pt 2 at 2.7 yrs post: locomotor 6.5, eye-hand 2.5	significant neurodevelopmental decline in pts 1 and 2					

Study (Investigator, country, year)	Record Number	Group (N) (NDP)	Normal Level (NDP)	Pre-Transplant (NDP)	Post-Transplant (NDP)	Comments (NDP)	Group (N) (OOI)	Normal Level (OOI)	Pre-Transplant (OOI)	Post-Transplant (OOI)	Comments (OOI)
Vormoor J, Germany, 2004	9420	2		no. subcutaneous nodules:pt 1: 58pt 2: 39no. joints with limited range of motion:pt 1: 26pt 2: 24	no. subcutaneous nodules:pt 1: 8pt 2: 12no. joints with limited range of motion:pt 1: 2pt 2: 2	dramatic improvement in motor activity	2				
Yeager AM, US, 2000	14880	1		wt, ht, and head circumference:10th-25th percentile	wt, ht, and head circumference:5th percentile at 0.8 yrs post<5th percentile at 1.5 yrs post		1		subcutaneous nodules present	subcutaneous nodules:nodules resolved 0.1 yrs post increased joint range of motion at 1.5 yrs post swallowing: no swallowing dysfunction at 0.7 yrs post severe gastroesophageal reflux at 1.3 yrs post	

Appendix Table C93. Neurocognitive/neuropsychological outcomes: Inherited metabolic diseases Continued

Study (Investi-gator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Arvio M, Finland, 2001	14180						3 HSCT 12 non-HSCT				Dysmorphic Facial and Body Features remained unchanged following HSCT
Autti T, Finland, 1999	15540	2 HSCT			2 HSCT: reached heterozygous activity level		2 HSCT, 6 non-HSCT		2 HSCT:poor cortex-white matter differentiation decreased thalami signal intensity	2 HSCT:decline from poor to evident cortex-white matter differentiation improvement in thalami signal intensity improvement in concentration and cooperation6 non-HSCT:poor cortex-white matter differentiation decreased thalami signal intensity	True clinical effect of HSCT will not be seen until pts reach puberty, which is when rapid mental decline usually occurs with aspartylglucosaminuria.
Chan LL, Malaysia, 2002	11330						1				Behavioral and learning difficulties developed after stopping ERT. Recurrent seizures occurred 2.6 yrs after stopping ERT.

Study (Investi-gator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Chen R, Taiwan, 2007	4490	1	26 +/- 5 nmol/h/mg protein	1.2 nmol/h/mg protein	16.2, 22.7 nmol/h/mg protein at 0.5 yrs, 0.8 yrs post		1		Weschler Intelligence Scales:performance: 67verbal: 69complete: 67	at 1.5 yrs post, Weschler Intelligence Scales:performance: 60verbal: 69complete: 62	
Coppa GV, Italy, 1999	16350	1	2.6-20.4 U/mg	0.2 U/mg	2.3, 1.0, and 3.3 U/mg at 0.25 yrs, 1.6 yrs, and 3.6 yrs post		1		IQ: 72	IQ: 69, 70, and 70 at 0.7 yrs, 2.6 yrs, and 4.0 yrs post	attends kindergarten, sociable, can speak simple sentences, writes a few letters
Ehlert K, Germany, 2006	4690										
El-Beshlawy A, Egypt, 2006	5750	11	1-5 micromol/hr/gm protein	mean: 0.4 +/- 0.3 micromol/hr/gm protein range: 0.0-0.9 microml/hr/gm protein		measurements for whole grp, Gaucher Type 1 and 3 combined					

Study (Investi-gator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Erikson A, Sweden, 1995	21630	3	level of accumulated glucosylceramide in plasma (micromol/liter plasma) (lower is better)	pt 1: 15 pt 2: 21 pt 3: 13	pt 1: 8,10,8,9,8,9,10 at 3,6,9,12,13,15,18 mos pt 2: 11,6,11,12,11,13,12 at 3,6,9,12,15,18,21 mos pt 3: 11,5,8,7,7,7,8 at 3,6,9,12,18,21,23 mos	normal levels (5-10) were reached by those with intact spleen	3	EEG Wechsler Intelligence Scale and Griffith mental development scale	EEG normal pt 1: 82-88 on Wechsler Scale pt 2: 82-88 on Griffith Scale pt 3: 104-111 on Griffith Scale	EEG normal pt 1: 89-96 on Wechsler Scale at 1.3 yrs post pt 2: 74-81 on Griffith Scale at 1 yr post pt 3: 97-103 on Griffith Scale at 1 yr post	all 3 pts became more active and needed less sleep pts 2 and 3 were tired and slow and became active pre-schooler post treatment
Goker-Alpan O, US, 2008	1790						2		nr	borderline mental retardation	for whole grp, 2 HSCT followed by ERT, and 30 ERT only: 12.5% cognitive and neurological decline

Study (Investigator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Grewel S, US, 2003	9750	1		6.5% of control	20-24% of control at 0.2 yrs, 0.3 yrs, and 0.5 yrs post		1		real age: 1.4 yrs developmental age, expressive language, and receptive language: 0.9 yrs	real age: 3.0 yrs, developmental age: 1.6 yrs real age: 3.5 yrs, developmental age: 2.1 yrs real age: 4.7, developmental age: 3.3 yrs real age: 5.7 yrs, developmental age: 4.3 yrs real age: 6.7 yrs, developmental age: 5.3 yrs	attends school with individualized education program; slow progress in communication, daily living, socialization, and expressive language; mild to moderate cognitive impairment
Guffon N, France, 2009	680	8		<= 1% of day control	at latest evaluation: 6 100% of day control1 57% of day control1 50% of day control	The two pts at <100% enzyme activity had carrier donors.	8		IQ/DQ:pt 1: 125pt 2: 72pt 3: 87pt 4: 70pt 5: 70pt 6: 65pt 7: 100pt 8: 100	IQ/DQ:pt 1: 110, normal language pt 2: 60, very poor language pt 3: 65, poor language pt 4: <50, no language pt 5: <50, speech loss 3 yrs post pt 6:<50, speech loss 8 yrs post, pt 7: 100, normal language pt 8: <50, poor language	2 attend normal schools5 attend special schools1 attends special apprenticeship3 very poor social adjustment2 poor social adjustment2 good social adjustment1 very good social adjustment

Study (Investi-gator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Hsu YS, Taiwan, 1999	16540	1		40% of normal control			1		real age: 2.4 yrs developmental age: 0.8-1.2 yrs	developmental age decreasing steadily:real age: 2.6 yrs, developmental age: 0.4-0.7 mos real age: 2.9 yrs, developmental age: 0.3-0.4 yrs real age: 3.3 yrs, developmental age: 0.2-0.3 yrs	MRI pre-transplant showed normal myelination and no obvious brain atrophy MRI 0.5 yrs post-transplant showed normal myelination and evident brain atrophy
Imaizumi M, Japan, 1994	23220A	1		4% of normal controls	34.9% of normal controls		1		no CNS involvement, attends normal school	no change	
Imaizumi M, Japan, 1994	23220B	1		not detectable	63.3% of normal control		1		severe psychomotor retardation	severe, gained development of 4-8 month old: sit by self, use walker, exhibited emotional expressions	

Study (Investi-gator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Jacobs JFM, Netherlands, 2005	6740	1		44-50 nmol/h/mg protein	919, 728, 133, 115, 126, and 128 at 0.1 yrs, 0.5 yrs, 1.25 yrs, 1.3 yrs, 1.6 yrs, and 1.9 yrs post		1		MRI shows cerebral atrophy at 0.5 yrs post worsening neuropsychological tests at 0.5 yrs post speech deteriorating at 0.5 yrs post		Deterioration of this pt similar to deterioration of untreated older sister.
Laitinen A, Finland, 1997	19620	1		0% of normal control	30.8%, 19.0%, 21.0% of normal control at 6 wks, 3 mos, 4 mos		1		mild global delay		
Lange MC, Brazil, 2006	5690						1			no significant neuropsychological improvement	
Li P, US, 1996	20260	1	4-18 cpm x 1000/hr/mg protein	0 cpm x 1000/hr/mg protein	0.3, 2.5, 2.4 cpm x 1000/hr/mg protein at 1.0, 3.0, 4.0 yrs post		i		IQ: 44	IQ: 44 at 3 yrs post	

Study (Investi-gator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Lonnquist T, Finland, 2001	12960	3	in leukocytes: 24-100 nmol/h/mg in cerebrospinal fluid: 8-24 nmol/h/mg	in leukocytes in all 3 pts: decreased in cerebrospinal fluid in 1 pt: decreased	in leukocytes in all 3 pts: normal in cerebrospinal fluid: 1 normal, 2 decreased		3			cerebral cortical atrophy: from moderate to severe in one pt, from not detectable to moderate in two pts periventricular white matter hyperintensity: from mild to severe in one pt, from not detectable to moderate in two pts	
Maegawa GHB, Canada, 2009	56590A						3		pt 1: severe cognitive dysfunction, hallucinations, agitation, scores 1.5 yrs below age pt 2: episodic psychosis, cognitive function well-preserved, works part time pt 3: 2 episodes of psychosis, IQ=75	pt 1: neuropsych scores unchanged pt 2: 18 mos post, neuropsych scores stable, speech less intelligible, hallucinations reduced, anxiety ongoing pt 3: at 16 mos post, spasticity developed, anxiety aggravated, neuropsych scores stable	

Study (Investi-gator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Maegawa GHB, Canada, 2009	56590B						2		pt 1: mild cognitive impairment, attends regular school with assistance pt 2: severe cognitive impairment, generalized seizures	pt 1: at 15 mos acute psychotic event pt 2: at 15 mos marked increase in seizures, alertness deteriorated, at 24 mos spasticity increased	
Malm G, Sweden, 2004	8490	2	0.8-2.2 microkat/kg	pt 1: 0.10 microkat/kgpt 2: 0.09 microkat/kg	pt 1: 0.98, 1.10 at 3 mos, 60 mos pt 2: 1.59, 0.80 at 3 mos, 60 mos		2		pt 1: developmental age 4.7 yrs below real age	pt 1 and 2: development al age stabilizing at 5 yrs over time	pt 1 and 2: mentally retarded, speaks in sentences, understands Swedish and Finnish words
McKinnis EJR, US, 1996	20560	1	23-45 units/mg protein	undetectable	38 units/mg protein		1		intelligence ratio (age equivalent/real age): 0.68, 0.51, 0.48, 0.54, 0.50, 0.42, 0.29, 0.17, 0.12, 0.09 at 2.8, 3.3, 3.4, 3.9, 4.2, 5.0, 5.9, 6.0, 6.9, 8.0 yrs of age	Along with decreasing intelligence ratio, pt went from mild behavioral difficulties pre-transplant to increased behavioral problems post-transplant. Reversion in language, communication, concentration, cooperation, and attention span also seen.

Study (Investigator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Morel CF, Canada, 2007	3010	1	0.6-1.8 nmol/h/mg protein	0.1	5.7, 1.3, 8.4, 2.2, 1.4, 0.6, 1.7 at 0.2 yrs, 0.4 yrs, 0.5 yrs, 0.6 yrs, 1 yr, 1.3 yrs, 2.7 yrs post		1		neurologically intact	neurological regression:bilateral cerebral atrophy at 0.6 yrs postseizure disorder developed at 1.7 yrs post	
Muenzer J, US, 2006	57160	96	Urine GAG levels (in micrograms/mg creatinine)	placebo: 419 +/- 34ERT EOW: 338 +/- 21ERT wkly: 326 +/- 26	Percent change (p-value):placebo: 21.4 +/- 11.6ERT EOW: -44.7 +/- 4.0 (p<0.0001)ERT wkly: -52.5 +/- 5.3 (p<0.0001)						

Study (Investigator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Muenzer J, US, 2007	57070	12	Urine GAG, in micrograms/mg creatinine	placebo: 371.3ERT .15 mg/kg: 386 +/- 124ERT .5 mg/kg: 364+/- 50ERT 1.5: 445 +/- 101	6 mos post:ERT .15 mg/kg: 230 +/- 76ERT .5 mg/kg: 211 +/- 110ERT 1.5: 168 +/- 611 yr post:ERT .15 mg/kg: 203 +/- 55ERT .5 mg/kg: 209 +/- 98ERT 1.5 mg/kg: 178 +/- 32	pooled urine GAG measurements, including placebo which received ERT after 6 mos:baseline: 398 +/- 946 mos: 203 +/- 821 yr: 200 +/- 18					
Mullen CA, US, 2000	15300	1		< 1% of normal control	8%, 22%, and 55% of normal control at 0.2 yrs, 0.7 yrs, and 2.2 yrs post		1			growing and developing normally	
Paciorkowski AR, US, 2008	2980						1		modest cognitive abilities	3 mos: some improvement in adaptive social domains6 mos: regression, speech decline12 mos: <0.1 percentile in developmental scales	

Study (Investi-gator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Patterson MC, US, 2007	56970						29	mini-mental status examination		mean change in score:1.2 for treatment grp-0.3 for non-treatment grp p=0.165	only results for those >=12 provided
Pineda M, Spain, 2009	56560						57	Annual change in composite score, by age grp		in subset with neurological disease (n=43): -0.210 (-0.336,0.085)in whole grp: -0.125 (-0.235,0.115)	A greater treatment effect was seen in subset of those with neurological disease.
Ringden O, Sweden, 1995	22020	6			5 who engrafted were within normal range		6	Weschler Intelligence Scale	pt 1: stanine 7	pt 1: stanine 7, 5, 6, 7, 7 at 1 yr, 3 yrs, 5 yrs, 8 yrs, and 10 yrs follow-up; IQ=112-120 pt 2: stanine 7 at 6 yrs pt 3: 3 at 4 yrs pt 4: below age pt 5: at age pt 6: below age at 1 yr	

Study (Investi-gator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Schiffman R, Netherlands, 2008	56750						30				No statistically significant differences between study grps using Purdue Peg Board test, Wechsler Scale, Benton visual retention test, Rey auditory verbal learning test, d2 test of attention, continuous performance test, and Trail Making Test.
Schiffmann R, Netherlands, 1997	58150	5	0.585 nmol/ml (0.399-0.764)		0.741 nmol/ml (0.04-2.363)		5		3 mild-moderate mental retardation 2 normal IQ	no change in IQ, 1 showed clinical function deterioration	4 stable 9or slightly improved, 1 deteriorated cerebrospinal fluid measurements showed that glucocerebrosidase delivery to the cerebrospinal fluid was minimal (not significantly different)

Study (Investi-gator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Seto T, Japan, 2001	13460A						10: 3 HSCT, 7 non-HSCT		HSCT:#1: lesions in white matter and corpus callosum#2: enlargement of perivascular spaces at basal ganglia, intensity changes in periventricular white matter#3: lesions in parietal and occipital lobes, intensity in white matter	HSCT:#1: no follow-up MRI#2: no change at 7 yrs post#3: lesions slightly diminished at 2.5 yrs post	non-HSCT:#1: cortical atrophy, white matter lesions & intensity#2: brain atrophy 9 yrs, cerebrum atrophy 15 yrs#3: brain atrophy 12 yrs#4: white matter lesions#5: ventricular dilation, white matter intensity 18 yrs#6: normal 18 yrs#7: normal 16 yrs
Seto T, Japan, 2001	13460B						1 HSCT, 3 non-HSCT		HSCT pt: no pathological findings in brain or spinal cord	HSCT pt: no MRI following HSCT	3 non-HSCT pts:#1: brain image normal, intellect fairly good, severe spinal cord compression 19 yrs#2: normal intellect, spinal cord compression 13 yrs#3: spinal cord compression, remainder CNS normal 4 yrs

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Study (Investi-gator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Shield JPH, England, 2005	6720	1		8 nmol/h/mg protein	246 nmol/h/mg protein at 7 yrs post		1			normal language development at 0.6 yrs post language declining at 1.7-2.1 yrs post demyelination and diffuse cerebral function at 2.4 yrs post no language at 4.0 yrs post	
Sivakumar P, England, 1999	16200	1 HSCT pt	875-1716 pmol/h/mg protein	4 pmol/h/mg protein	280-666 pmol/h/mg protein over 7 yrs follow-up	no enzyme data for 1 non-HSCT pt	2: 1 HSCT, 1 non-HSCT			developmental quotient scores for HSCT pt: 99, 72, 55, 43, 24, 11, 6 at 1.5, 2.5, 3.5, 4.5, 6, 7, 8, 10 yrs of age developmental quotient scores for non-HSCT pt: 25, 21, 10, 5 at 6, 7, 8, 10 yrs of age	developmental quotients decreasing with age for both treated and untreated pts
Stein J, Israel, 2007	4880	1	8 nmol/mg protein/h	0	7 nmol/mg protein/h at 1.5 yrs post		1		MRI showed 0.5 yr delay in myelination	MRI showed appropriate myelination for age at 1 yr post	at 4 yrs post, pt has normal intellectual development, attends regular school, and speaks Russian and Hebrew

Study (Investigator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Takahashi, Japan, 2001	14030	1 HSCT, 2 non-HSCT		1 HSCT pt: non-detectable 2 non-HSCT pts: non-detectable	1 HSCT pt: 6.7 and 6.7 nmol/hr/mg protein at 0.5 and 1.1 yrs post	measurements for non-HSCT given only once	1 HSCT, 2 non-HSCT		DQ:1 HSCT pt: 722 non-HSCT pts: 94 and 124	DQ:1 HSCT pt: 61 and 54 at 0.5 yrs and 1.1 yrs post2 non-HSCT pts: no follow-up measurement	MRI findings:1 HSCT pt:ventricular dilatation present pre-transplant and worsened post-transplant lesions in white matter present both pre-transplant and post-transplant 2 non-HSCT pts:no ventricular dilatation lesions in white matter
Tokimasa, Japan, 2008	1310						1		mental retardation		
Tolar J, US, 2009	1370	4		pt 1: 0pt 2: 6% of normal pt 3: 3.8% of normal pt 4: 12.5% of normal	pt 1: 50%, 80-90%, 100% of normal at 0.1, 2.0, 3.5 yrs post pt 2: 50% of normal pt 3: 4.1 (normal)pt 4: 5.9 (normal)		4			pt 1 at 11 yrs post: mildly impaired cognitive abilities, sustained visual attention impaired, verbal fluency avg, attends special school, mostly homeschooled, no behavior problems, English and Spanish language development	pt 4 at 4 yrs post: cognition improved from baseline, receptive and expressive language high avg, adaptive skills avg, emotional and social behavior avg, attends special education preschool, speaks 3 languages

Study (Investi-gator, country, year)	Record Number	Group (N)	Normal Level	Pre-Transplant	Post-Transplant	Comments	Group (N) (NNO)	Normal Level (NNO)	Pre-Transplant (NNO)	Post-Transplant (NNO)	Comments (NNO)
Tsai P, US, 1992	25120	1			near normal	measured in liver, lung, lymph nodes, brain	6		RA: 22 mos; DA: 15 mos;DQ=68	RA: 33 mos; DA: 21 mos;DQ=64RA: 39 mos; DA: 25 mos; DQ=64bilingual at 1.6 yrs post	
Vellodi A, England, 1999	16650	3			pt 1: consistently reduced compared to control, donor was carrier pt 2: normal reference at 6.5 yrs post pt 3: normal reference range		3		Griffiths Mental Development Scale: pt 1: social 61, speech 61 pt 2: social 71, speech 71 pt 3: social 93, speech 93	Griffiths Mental Development Scale:pt 1 at 10 yrs post: social 10, speech 10 pt 2: social 2, speech 2 pt 3: full IQ 78, verbal IQ 80 performance IQ 81	steady deterioration in pts 1 and 2pt 3 attends mainstream school, has difficulty with concentration, but is otherwise doing well
Vormoor J, Germany, 2004	9420	2					2				
Yeager AM, US, 2000	14880	1	6% of normal control		44%, 53%, 52%, 18%, 41%, 47%, 48%, and 53% at 0.1 yrs, 0.3 yrs, 0.5 yrs, 0.7 yrs, 0.8 yrs, 1.1 yrs, 1.4 yrs, and 2.3 yrs		1		normal myelination at 0.75 yrs	normal myelination at 0.3 yrs post loss of grey and white matter differentiation at 0.7 yrs post poor grey and white matter contrast at 1.3 yrs post	Bayley Scales of Infant Development:developmental age and real age equivalent at time of transplant (0.75 yrs)development age plateaued at 0.6 yrs at real age of 1.3 yrs and 2.1 yrs

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Appendix Table C94. Adverse events: Treatment, inherited metabolic diseases

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	F/U (mos)	%	Group (N) AGVHD	Severity or Grade AGVHD	F/U (mos)_2	%_2
Arvio M, Finland, 2001	14180	3				3			
Autti T, Finland, 1999	15540	2				2			
Chen R, Taiwan, 2007	4490	1	staphylococcus epidermis sepsis		1 (100%)	1	grade 1		1 (100%)
Coppa GV, Italy, 1999	16350	1			0 (0%)	1			0 (0%)
Ehlert K, Germany, 2006	4690	3	cytomegalovirus (2 pts)mucositis (2 pts)colitis (1 pt)clostridium difficile enteritis (1 pt)		3 (100%)	3	grade I (1 pt)grade II (2 pts)		3 (100%)
Grewel S, US, 2003	9750					1	grade 2 gastrointestinal		1 (100%)
Guffon N, France, 2009	680					8			0 (0%)
Hsu YS, Taiwan, 1999	16540	1			0 (0%)	1	grade 1	0.5 yrs	1 (100%)
Imaizumi M, Japan, 1994	23220A					1			0 (0%)
Imaizumi M, Japan, 1994	23220B					1			0 (0%)
Laitinen A, Finland, 1997	19620	1				1			
Lange MC, Brazil, 2006	5690					1			0 (0%)
Lonnquist T, Finland, 2001	12960	3				3			
Malm G, Sweden, 2004	8490	2	shingles		1 (50%)	2	pt 1: severe skin, gastrointestinal, liver pt 2: grade I skin		2 (100%)
McKinnis EJR, US, 1996	20560					1			0 (0%)
Morel CF, Canada, 2007	3010					1	skin		1 (100%)

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	F/U (mos)	%	Group (N) AGVHD	Severity or Grade AGVHD	F/U (mos)_2	%_2
Mullen CA, US, 2000	15300	1	2 episodes of gram-positive bacteremia, one of limited gastrointestinal bleeding while thrombocytopenic, and one mucositis requiring total parenteral nutrition for several wks		1 (100 %)	1	grade 3 skin and grade 2 gastrointestinal skin rash	2 wks post17 wks post	1 (100 %)
Page KM, US, 2008	1280A					1	grade 2		1 (100 %)
Ringden O, Sweden, 1995	22020	6	pt 2: pneumococcal meningitis at 7 mos pt 3: pneumonia, 3 mos in hospital pt 4: strep septicemia at day 10pt 5: septicemia day 6		4 (67%)	6	grade I		4 (67%)
Sivakumar P, England, 1999	16200					1	mild		1 (100 %)
Stein J, Israel, 2007	4880	1	cytomegalovirus antigenemia		1 (100 %)	1	mild skin rash	0.2 yrs	1 (100 %)
Takahashi, Japan, 2001	14030								
Tokimasa, Japan, 2008	1310	1	septicemia (MRSA)		1 (100 %)	1	stage 1		1 (100 %)
Tolar J, US, 2009	1370	4	sepsis	0.2 and 0.7 yrs	2 (50%)	4	pt 1: grade 3 skin, liver pt 3: grade 3 skin, liver pt 4: grade 3 skin		3 (75%)
Tsai P, US, 1992	25120	1	bilateral pneumonia	18-21 mos	1 (100 %)	1			0 (0%)
Vellodi A, England, 1999	16650	3	rotavirus gastroenteritis leading to severe hypoalbuminaenemia and cerebral edema	1 mo	1 (33.3 %)	3	moderate		1 (33.3 %)

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infection	F/U (mos)	%	Group (N) AGVHD	Severity or Grade AGVHD	F/U (mos)_2	%_2
Vormoor J, Germany, 2004	9420	2	mucositis:pt 1: grade 2pt 2: grade 3		2 (100%)	2	pt 1: grade II pt 2: grade I		2 (100%)
Yeager AM, US, 2000	14880					1			0 (0%)
Styczynski, Poland, 2011	442	1				1	skin, grade III gut, grade III	0.3 yrs	1 (100%)

Appendix Table C94: Adverse events: Treatment, inherited metabolic diseases Continued

Study (Investigator, country, record#)	Record Number	Group (N) CGVHD	Severity or Grade CGVHD	F/U (mos)_3	%_3	Comment_3
Arvio M, Finland, 2001	14180	3				
Autti T, Finland, 1999	15540	2				
Chen R, Taiwan, 2007	4490	1			0 (0%)	
Coppa GV, Italy, 1999	16350	1			0 (0%)	
Ehlert K, Germany, 2006	4690	3			0 (0%)	
Guffon N, France, 2009	680	8	grade 1, lung		1 (12.5%)	chronic pulmonary disease developed
Imaizumi M, Japan, 1994	23220A	1			0 (0%)	
Imaizumi M, Japan, 1994	23220B	1			0 (0%)	
Lange MC, Brazil, 2006	5690	1			0 (0%)	
Malm G, Sweden, 2004	8490	2			0 (0%)	
McKinnis EJR, US, 1996	20560	1			0 (0%)	
Mullen CA, US, 2000	15300	1	severe hemolytic anemia	0.75 yrs post	1 (100%)	
Page KM, US, 2008	1280A	1			0 (0%)	
Ringden O, Sweden, 1995	22020	6	pancreatitis		1 (17%)	
Sivakumar P, England, 1999	16200	1			0 (0%)	
Stein J, Israel, 2007	4880	1			0 (0%)	
Tolar J, US, 2009	1370	4			2 (50%)	pt 1 and pt 4
Vellodi A, England, 1999	16650	3			0 (0%)	
Yeager AM, US, 2000	14880	1			0 (0%)	
Styczynski, Poland, 2011	442	1		0.3 yrs	0 (0%)	

Appendix Table C94. Adverse events: Treatment, inherited metabolic diseases Continued

Study (Investigator, country, year)	Record Number	Group (N) Engraftment Failure	Severity or Grade_4	F/U (mos)_4	%_4	Comment_4
Arvio M, Finland, 2001	14180	5			3 (60.0%)	1 was re-transplanted and was successful
Autti T, Finland, 1999	15540	2			0 (0%)	
Chen R, Taiwan, 2007	4490	1			0 (0%)	
Coppa GV, Italy, 1999	16350	1			0 (0%)	
Ehlert K, Germany, 2006	4690	3			0 (0%)	
Grewel S, US, 2003	9750	1			0 (0%)	
Guffon N, France, 2009	680	8			0 (0%)	
Hsu YS, Taiwan, 1999	16540	1			0 (0%)	
Imaizumi M, Japan, 1994	23220A	1			0 (0%)	
Imaizumi M, Japan, 1994	23220B	1			1 (100%)	engraftment incomplete for 1st 4 yrs, then complete engraftment at 5 yrs
Jacobs JFM, Netherlands, 2005	6740	1			0 (0%)	
Laitinen A, Finland, 1997	19620	1			0 (0%)	
Lange MC, Brazil, 2006	5690	1			0 (0%)	
Li P, US, 1996	20260	1			0 (0%)	
Lonnquist T, Finland, 2001	12960	3			1 (33.3%)	second transplant in engraftment failure pt was successful
Malm G, Sweden, 2004	8490	2			0 (0%)	
McKinnis EJR, US, 1996	20560	1			0 (0%)	
Morel CF, Canada, 2007	3010	1			0 (0%)	
Mullen CA, US, 2000	15300	1			0 (0%)	
Page KM, US, 2008	1280A	1			0 (0%)	
Ringden O, Sweden, 1995	22020	6	was put on ERT	rejected bone marrow at 3 mos	1 (17%)	
Ringden O, Sweden, 2006	5940A	2			2 (100%)	
Seto T, Japan, 2001	13460A	3			0 (0%)	
Seto T, Japan, 2001	13460B					
Sivakumar P, England, 1999	16200	1			1 (100%)	

Study (Investigator, country, year)	Record Number	Group (N) Engraftment Failure	Severity or Grade_4	F/U (mos)_4	%_4	Comment_4
Stein J, Israel, 2007	4880	1			0 (0%)	
Takahashi, Japan, 2001	14030	1			0 (0%)	
Tokimasa, Japan, 2008	1310					
Tolar J, US, 2009	1370	4			1 (25%)	pt 3 had 2 failures at 1.6 yrs and 1.7 yrs prior to successful engraftment at 2.1 yrs
Vellodi A, England, 1999	16650	10			2 (20.0%)	
Vormoor J, Germany, 2004	9420	2			0 (0%)	
Yeager AM, US, 2000	14880	1			0 (0%)	
Styczynski, Poland, 2011	442	1		0.3 yrs	0 (0%)	

Appendix Table C94. Adverse events: Treatment, inherited metabolic diseases Continued

Study (Investigator, country, year)	Group (N) TRM	Severity or Grade TRM	F/U (mos) TRM	% TRM	Comment TRM	Group (N) Secondary Malignancies	Severity or Grade SM	F/U (mos) SM	% SM	Comments SM	Record Number
Arvio M, Finland, 2001	3			0 (0%)		3					14180
Autti T, Finland, 1999	2			0 (0%)		2					15540
Chen R, Taiwan, 2007	1			0 (0%)							4490
Coppa GV, Italy, 1999	1			0 (0%)							16350
Ehlert K, Germany, 2006	3			0 (0%)							4690
Grewel S, US, 2003	1			0 (0%)		1	EBV-positive B-cell lymphoma	0.7 yrs	1 (100%)	successfully treated by withdrawal of immunosuppression and one donor lymphocyte infusion	9750
Guffon N, France, 2009	8			0 (0%)							680

Study (Investi-gator, country, year)	Group (N) TRM	Severity or Grade TRM	F/U (mos) TRM	% TRM	Comment TRM	Group (N) Second-ary Malignan-cies	Severity or Grade SM	F/U (mos) SM	% SM	Comments SM	Record Number
Hsu YS, Taiwan, 1999	1			0 (0%)							16540
Imaizumi M, Japan, 1994	1			0 (0%)							23220A
Imaizumi M, Japan, 1994	1			0 (0%)							23220B
Jacobs JFM, Netherlands, 2005	1			0 (0%)							6740
Laitinen A, Finland, 1997	1			0 (0%)		1					19620
Lange MC, Brazil, 2006	1			0 (0%)							5690
Li P, US, 1996	1			0 (0%)							20260
Lonnquist T, Finland, 2001	3			0 (0%)		3					12960
Malm G, Sweden, 2004	2			0 (0%)		2					8490
McKinnis EJR, US, 1996	1			0 (0%)							20560
Morel CF, Canada, 2007	1			0 (0%)							3010
Mullen CA, US, 2000	1			0 (0%)							15300
Page KM, US, 2008	1				dead at 4.6 yrs post, unknown cause, probable infection						1280A
Ringden O, Sweden, 2006	2			1 (50%)	Type A pt, died of pneumonia 0.4 yrs post						5940A
Seto T, Japan, 2001	3			0 (0%)							13460A
Seto T, Japan, 2001	1			0 (0%)							13460B

Study (Investi-gator, country, year)	Group (N) TRM	Severity or Grade TRM	F/U (mos) TRM	% TRM	Comment TRM	Group (N) Second-ary Maligna n-cies	Severity or Grade SM	F/U (mos) SM	% SM	Comments SM	Record Number
Sivakumar P, England, 1999	1			0 (0%)							16200
Stein J, Israel, 2007	1			0 (0%)							4880
Takahashi, Japan, 2001	1			0 (0%)							14030
Tokimasa, Japan, 2008	1	PTLD		1 (100%)		1	post-transplant lymphoproliferati ve disease	0.8 yrs	1 (100%)	cause of death	1310
Tolar J, US, 2009	4		0.2 and 0.7 yrs	2 (50%)	pt 2: hepatorenal failure, pulmonary failure, coagulopath y, sepsis pt 3: sepsis and liver failure						1370
Tsai P, US, 1992	1	s. pneumonia e sepsis		1 (100%)							25120
Vellodi A, England, 1999	10			4 (40%)	4 < 100 days post, 2 of sepsis, 2 of aGVHD						16650
Vormoor J, Germany, 2004	2			0 (0%)		2					9420
Yeager AM, US, 2000	1			0 (0%)							14880
Styczynski, Poland, 2011	1		0.3 yrs	0 (0%)							442

Appendix Table C95. Adverse events: Comparator, inherited metabolic diseases

Study (Investigator, country, year)	Record Numbe r	Gro up (N)	Severity or Grade Infectious	F/U (mo s)	%	Comme nt	Group (N) AGVHD	Severity or Grade_2	%_ 2	Group (N) CGVHD	Severity or Grade_3	%_ 3	Group (N) Engraftme nt failure	%_4

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Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infectious	F/U (mos)	%	Comment	Group (N) AGVHD	Severity or Grade_2	%_2	Group (N) CGVHD	Severity or Grade_3	%_3	Group (N) Engraftment failure	%_4
Arvio M, Finland, 2001	14180	12												
Banjar H, Saudi Arabia, 1998	17920													
Chan LL, Malaysia, 2002	11330													
El-Beshlawy A, Egypt, 2006	5750													
Erikson A, Sweden, 1995	21630													
Muenzer J, US, 2006	57160													
Muenzer J, US, 2007	57070													
Paciorkowski AR, US, 2008	2980	1	viral infection (fever, transient leukopenia, thrombocytopenia)	11 mos	1 (100%)									
Page KM, US, 2008	1280B	2				other complications (not infectious):2 developed autoimmune hemolytic anemia2 thrombocytopenia	2	1 grade 1 1 grade 2	2 (100%)	2	1 extensive cytopenia 1 limited cytopenia (skin)	2 (100%)	2	0 (0%)
Patterson MC, US, 2007	56970													
Patterson MC, US, 2010	56500													

Study (Investigator, country, year)	Record Number	Group (N)	Severity or Grade Infectious	F/U (mos)	%	Comment	Group (N) AGVHD	Severity or Grade_2	%_2	Group (N) CGVHD	Severity or Grade_3	%_3	Group (N) Engraftment failure	%_4
Pineda M, Spain, 2009	56560													
Schiffman R, Netherlands, 2008	56750													
Schiffmann R, Netherlands, 1997	58150													

Appendix Table C95. Adverse events: Comparator, inherited metabolic diseases Continued

Study (Investigator, country, year)	Record Number	Group (N) TRM	Severity or Grade TRM	F/U (mos) TRM	% TRM	Group (N)Developmental Delay	Severity or Grade DD	% DD	Comments DD	Group (N)_9	Severity or Grade SSGR	% SS GR
Arvio M, Finland, 2001	14180											
Banjar H, Saudi Arabia, 1998	17920	3			0 (0%)							
Chan LL, Malaysia, 2002	11330	1			0 (0%)							
El-Beshlawy A, Egypt, 2006	5750	11			0 (0%)							
Erikson A, Sweden, 1995	21630	3			0 (0%)							
Muenzer J, US, 2006	57160	96			0 (0%)							
Muenzer J, US, 2007	57070											
Paciorkowski AR, US, 2008	2980											
Page KM, US, 2008	1280B	2	1 multi-system organ failure	1.8 yrs	1 (50%)							
Patterson MC, US, 2007	56970	12			0 (0%)	12	lethargy, memory impairment, depression	1 (8%)	withdrew from study	12	severe weight loss	3 (25%)
Patterson MC, US, 2010	56500	10			0 (100%)							
Pineda M, Spain, 2009	56560	66			0 (0%)							
Schiffman R, Netherlands, 2008	56750	30			0 (0%)							

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Study (Investigator, country, year)	Record Number	Group (N) TRM	Severity or Grade TRM	F/U (mos) TRM	% TRM	Group (N)Developmental Delay	Severity or Grade DD	% DD	Comments DD	Group (N)_9	Severity or Grade SSGR	% SS GR
Schiffmann R, Netherlands, 1997	58150					5		1 (20%)	One pt experienced precocious puberty due to human chorionic gonadotropin used in ERT preparation			

Appendix Table C96. Design, participant selection and enrollment: Autoimmune disease

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Brunner et al, Austria, 2002	11910	Non-hematologic autoimmune	Systemic lupus erythematosus (SLE)	Refractory	Case report	WHO class IV nephritis, pneumonitis, cutaneous vasculitis	Case report	1		
Chen et al, China, 2005	7790	Non-hematologic autoimmune	Systemic lupus erythematosus	Refractory	SLE (2)	class III or IV lupus nephritis (1996, 2001)	case reports	2		
Connor et al, UK, 2008	2220	Hematologic autoimmune	Evans syndrome	Refractory	Evans syndrome case report					
Couri et al, Brazil, 2009	290	Non-malignant autoimmune	Type 1 diabetes mellitus	Newly diagnosed	18	Inclusion: both sexes, age 13-21 yrs, clinical and laboratory diagnosis of type 1 DM during previous 6 wks Exclusion: positive serology for HIV, HBV, HCV, underlying disease precluding HSCT, pregnancy (11/2003-04/2008)	Prospective phase I/II	18	0	
Crino et al, Italy, 2005	62110	Non-hematologic autoimmune	Type 1 diabetes mellitus	Newly diagnosed	nicotinamide plus intensive insulin therapy (25) intensive insulin therapy (27)	recent onset type 1 diabetes mellitus (< 4 wks duration from dx) (NR)	retrospective	25 27	0 0	
Daikeler et al, Switzerland, 2009	740	Hematologic autoimmune	Evans syndrome	Refractory	Evans syndrome (5)	unselected (1984-2007)	EBMT registry report	5	0	All cases reported to EBMT registry 1984-2007
Daikeler et al, Switzerland, 2009	740A	Hematologic autoimmune	Autoimmune hemolytic anemia	Refractory	Autoimmune hemolytic anemia (7)	unselected (1984-2007)	EBMT registry reports	7		All cases reported to EBMT registry 1984-2007

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
de Kleer et al, Netherlands, 2004	8350	Non-hematologic autoimmune	Juvenile idiopathic arthritis	Refractory	Juvenile idiopathic arthritis (34)	all patients with refractory JIA who underwent autologous HSCT since 1997 29 systemic 5 polyarticular	Registry	34 of 41 pts	7 without sufficient data to allow evaluation	
De Stefano et al, Italy, 1999	16180	Hematologic autoimmune	Autoimmune hemolytic anemia	Refractory	Autoimmune hemolytic anemia case report					
Elhasid et al, Israel, 2004	9050	Non-hematologic autoimmune	Diffuse calcinosis	Refractory, severe disease	1		case report	1		
Fagius et al, Sweden, 2009	1270	Non-hematologic autoimmune	Multiple sclerosis (MS)	Refractory, malignant progressive MS of short duration	MS (2)	very frequent (> 4/yr) and severe EDSS > 6.0) relapses; disease duration < 1.5 yrs; absence of irreversible CNS damage with documented recent improvement suggesting HSCT can benefit patient	case series	2 pediatric cases of 9 total cases		
Farge et al, France, 2004	8600	Non-hematologic autoimmune	Systemic sclerosis (SSc)	Refractory	SSc (5)	Rapidly progressing, early diffuse life-threatening SSc (< 3 yrs duration) or limited SSc if life-threatening	open, multicenter phase I/II	5 pediatric cases out of total 41 cases		Patients included from record #s 11400, 13740, 16270
Huhn et al, USA, 2003	11550	Hematologic autoimmune	Autoimmune thrombocytopenia	Refractory	Autoimmune thrombocytopenia case report					
Jones et al, USA, 2004	9110	Non-hematologic autoimmune	Overlap syndrome	Refractory, severe	1	1998	case report	1		
Kimiskidis et al, Greece, 2008	3020	Non-hematologic autoimmune	Multiple sclerosis (MS)	Refractory, malignant progressive MS of short duration	MS (1)		case report	1		
Kishimoto et al, Japan, 2003	9500	Non-hematologic autoimmune	Juvenile idiopathic arthritis	Refractory	Juvenile idiopathic arthritis (3)	Not reported	Case reports	3	0	Japanese experience

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Lisukov et al, Russia, 2004	9190	Non-hematologic autoimmune	Systemic lupus erythematosus (SLE)	Refractory	SLE (4)	refractory WHO class III-IV glomerulonephritis, CNS, lung, heart involvement, life-threatening cytopenias	case series	4		4 of 6 were pediatric pts
Mancardi et al, Italy, 2005	7110	Non-hematologic autoimmune	Malignant multiple sclerosis (MS)	Life-threatening, progressive, refractory	MS (2)	Malignant life-threatening MS, refractory to alternative therapies	case reports	2		
Mastrandrea et al, USA, 2009	40050	Non-hematologic autoimmune	Type 1 diabetes mellitus	Newly diagnosed	etanercept plus intensive insulin therapy	10/2002-10/2007	RCT	10		Using one arm of an RCT
Musso et al, Italy, 2001	13570	Non-hematologic autoimmune	Systemic lupus erythematosus (SLE)	Refractory	SLE (2)	life-threatening severe, refractory disease, SLICC/ACR damage index score < 3,	case series	2		
Nakagawa et al, Japan, 2001	13910	Non-hematologic autoimmune	Juvenile idiopathic arthritis	Refractory	Juvenile idiopathic arthritis (1)	1998	Case report	1		
Oyama et al, USA, 2005	7570	Non-hematologic autoimmune	Crohn's Disease (CD)	Refractory	CD (4)	Clinical and histologic evidence of CD, < 60 yrs old, failed treatment with corticosteroids, mesalamine, metronidazole, azathioprine, 6-mercaptopurine, infliximab, CDAI of 250-400	Case series	4		
Burt et al, USA, 2010	273	autoimmune	Crohn's disease	refractory	3	NR	phase I/II	3	0	Long term followup of Oyama et al, 2005
Paillard et al, 2000, France	14650	Hematologic autoimmune	Autoimmune hemolytic anemia	Refractory	Autoimmune hemolytic anemia case report					

Study (Investigator, country, year)	Record Number	Indication	Disease	Therapeutic Setting	Group (N)	Participant Selection (Treatment Period)	Design	n, Evaluated	n, Withdrawn (Lost to F/U)	Comment
Rabusin et al, Italy, 2000	13940	Non-hematologic autoimmune	Juvenile idiopathic arthritis	Refractory systemic or polyarticular disease	Juvenile idiopathic arthritis (5)	1996-2000	Case series	5		
Raetz et al, USA, 1997	18920	Hematologic autoimmune	Evans syndrome	Refractory	Evans syndrome case report					
Statkute eta, USA, 2005	7370	Non-hematologic autoimmune	Systemic lupus erythematosus (SLE)	Refractory	SLE (9)	SLE refractory to pulse cyclophosphamide and > 20 mg prednisone daily, , 4 of 11 ACR criteria for SLE, class III or IV GN, lung, CNS, or visceral involvement (1997-2004)	Case series	9		9 of 28 in the series were pediatric age
Strober et al, USA, 2009	230	Non-hematologic autoimmune	Myasthenia gravis (MG)	Refractory	MG (1)		case report	1		
Trysberg et al, Sweden, 2000	15570	Non-hematologic autoimmune	Systemic lupus erythematosus (SLE)	Refractory	1	CNS lupus, bilateral opticus neuritis, transverse myelitis	case report	1		
Urban et al, Austria, 2006	5970	Hematologic autoimmune	Evans syndrome	Refractory	Evans syndrome case report					
Wulffrat et al, Netherlands, 2001	13970	Non-hematologic autoimmune	Systemic lupus erythematosus (SLE)	Refractory	Case reports (2)	Severe, WHO class IV glomerulonephritis, polyarthritis, malar rash	case reports	2		

Appendix Table C97. Participant characteristics: Treatment, autoimmune disease

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
Brunner et al, Austria, 2002	11910	SLE case report	18 yrs					F			
Chen et al, China, 2005	7790	SLE (2)			13, 18 yrs				severe, refractory to corticosteroids, 6-mercaptopurine, cyclophosphamide		
Connor et al, UK, 2008	2220	Evans syndrome case report	7 yrs					F			
Couri et al, Brazil, 2009	290	18		18	13-21		white (75)	67, 33			
Daikeler et al, Switzerland, 2009	740	Evans syndrome (5)		11	2-21 yrs			M 5 (100)			All cases reported to EBMT registry 1984-2007
Daikeler et al, Switzerland, 2009	740A	Autoimmune hemolytic anemia (7)		7	2-14			5 M (71)			All cases reported to EBMT registry 1984-2007
de Kleer et al, Netherlands, 2004	8350	Juvenile idiopathic arthritis (34)	8.9 yrs		4-18 yrs	3.6 yrs	NR	19 M, 15 F (56/44)	refractory	29 systemic5 polyarticular	

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Comment
De Stefano et al, Italy, 1999	16180	Autoimmune hemolytic anemia case report	6 yrs					M			
Elhasid et al, Israel, 2004	9050	Diffuse calcinosis (1)	15 yrs					F	Severe, progressive		
Fagius et al, Sweden, 2009	1270	MS (2)	9, 16 yrs					1 M, 1 F	EDSS 4.0, 8.0; annualized relapse rate 15, 18, respectively		
Farge et al, France, 2004	8600	SSc (5)		12 yrs	9-17 yrs			F 4, M 1		scleroderma lung disease, 4 diffuse, 1 limited	
Huhn et al, USA, 2003	11550	Autoimmune thrombocytopenia case report	17 yrs					M			
Jones et al, USA, 2004	9110	1	10					F	Severe, refractory with small vessel vasculitis		
Kimiskidis et al, Greece, 2008	3020	MS (1)	17 yrs					M	Malignant MS, EDSS score 5.0		
Kishimoto et al, Japan, 2003	9500	Juvenile idiopathic arthritis (2)	3, 13, 21 yrs					1 M, 2 F	Systemic disease, refractory to conventional therapies		
Lisukov et al, Russia, 2004	9190	SLE (4)	19 yrs		15-21 yrs	2.8 yrs		F (100)	refractory to pulse cyclophosphamide, corticosteroids, azathioprine		
Mancardi et al, Italy, 2005	7110	MS (2)	16, 18 yrs					1 M, 1 F		Paralyzing lesions within CNS	

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Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (median)	Age (Range)	Age (SD)	Race (%)	Gender M, F (%)	Disease Stage/category	Disease Histology/Site (%)	Com ment
Musso et al, Italy, 2001	13570	SLE (2)	17, 20 yrs					F (100)	severe refractory		
Nakagawa et al, Japan, 2001	13910	Juvenile idiopathic arthritis (1)	15 yrs						Refractory disease		
Oyama et al, USA, 2005	7570	CD (4)	17 yrs		15-21 yrs	2.7 yrs	white	M (n = 3)	severe refractory		
Burt et al, USA, 2010	273	HSCT (3)			16, 18, 21 years		NR	2 M, 1 F	refractory to all standard treatments	NR	
Paillard et al, 2000, France	14650	Autoimmun e hemolytic anemia case report	8 yrs					M			
Rabusin et al, Italy, 2000	13940	Juvenile idiopathic arthritis (5)	14.6 yrs		9-20 yrs	3.9 yrs		1 M (20)	Refractory, 3-12 yrs duration		
Raetz et al, USA, 1997	18920	Evans syndrome case report	5 yrs					M			
Statkute eta, USA, 2005	7370	SLE (9)	19 yrs		15-21 yrs	2yrs		F (100)	Refractory		
Strober et al, USA, 2009	230	MG (1)	17 yrs					M	Severe, refractory		
Trysberg et al, Sweden, 2000	15570	SLE (1)	18 yrs					F	Severe, refractory		
Urban et al, Austria, 2006	5970	Evans syndrome case report	2 yrs					M			
Wulffrat et al, Netherlands, 2001	13970	SLE (2)	14 yrs					1 M, 1 F	Severe, refractory		

Appendix Table C98. Participant characteristics: Comparator, autoimmune disease

Study (Investigator, country, year)	Record Number	Group (N)	Age (mean)	Age (Range)	Age (SD)	Gender M, F (%)
Crino et al, Italy, 2005	62110	nicotinamide plus intensive insulin therapy (25) intensive insulin therapy (27)	14.7 14	NR	5 4.3	
Mastrandrea et al, USA, 2009	40050	etanercept plus intensive insulin therapy (10)	12.5 yrs	3-18 yrs	3.3 yrs	8 (80)

Appendix Table C99. Treatment characteristics: Autoimmune disease

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Brunner et al, Austria, 2002	11910	SLE case report	PB	autologous	corticosteroids, azathioprine, cyclophosphamide, immunopheresis	cyclophosphamide plus ATG	N/A		N/A		
Chen et al, China, 2005	7790	SLE (2)	PB	autologous	corticosteroids, cyclophosphamide	ATG, cyclophosphamide	N/A	bactrim, IVIG, G-CSF in 1 pt	N/A		
Connor et al, UK, 2008	2220	1 case report	NR	allogeneic	corticosteroids, IVIG, cyclosporine, mycophenolate mofetil, rituximab	alemtuzumab, fludarabine, melphalan	cyclosporine and mycophenolate mofetil	NR	NA	NA	
Couri et al, Brazil, 2009	290	18	peripheral blood	autologous nonmyeloablative	None	cyclophosphamide, antithymocyte globulin		dexchlorpheniramine, G-CSF			
Crino et al, Italy, 2005	62110	nicotinamide plus intensive insulin therapy (25) intensive insulin therapy (27)			None				nicotinamide plus intensive insulin therapy	nicotinamide 25 mg/kg daily, plus 3-4 injections per day of regular plus intermediate-acting insulin 3-4 injections per day of regular plus intermediate-acting insulin both groups 55% carbohydrate diet	

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Daikeler et al, Switzerland, 2009	740	Evans syndrome (5)	3 BM, 1 PB, 1 CB	allogeneic	Standard therapy (NR)	various combinations, including cyclophosphamide, fludarabine, busulfan, thiotepa, ATG, TBI	cyclosporine A with either methotrexate or mycophenolate mofetil	NR	NA	NA	5 cases reported to EBMT registry between 1984 and 2007
Daikeler et al, Switzerland, 2009	740A	Autoimmune hemolytic anemia (7)		allogeneic	Standard therapy (NR)	various combinations, including cyclophosphamide, fludarabine, busulfan, thiotepa, ATG, TBI	cyclosporine A with either methotrexate or mycophenolate mofetil	NR	NA	NA	5 cases reported to EBMT registry between 1984 and 2007
de Kleer et al, Netherlands, 2004	8350	Juvenile idiopathic arthritis (34)	BM 25, PB 9	autologous	various combinations of corticosteroids, methotrexate, cyclosporin A, azathioprine, NSAIDs, sulphasalazine, cyclophosphamide, gold im, IVIG, hydroxyxchloroquine, anti-TNF agents	3 different regimens used: A = ATG, cyclophosphamide, low dose TBI B = ATG, cyclophosphamide C = fludarabine, cyclophosphamide, methylprednisolone					

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Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
De Stefano et al, Italy, 1999	16180	Autoimmune hemolytic anemia case report	bone marrow	allogeneic	autologous HSCT, splenectomy, prednisone, azathioprine, cyclosporine A,	busulfan, fludarabine, thiotepa	cyclosporine A, methotrexate, ATG	NR	NA	NA	
Elhasid et al, Israel, 2004	9050	Diffuse calcinosis (1)	PB	autologous	corticosteroids, cyclophosphamide, azathioprine, methotrexate, hydroxychloroquine, thalidomide	BEAM	N/A		N/A		
Fagius et al, Sweden, 2009	1270	MS (2)	PB	autologous	methylprednisolone, plasma exchange, beta-IFN	cyclophosphamide in 1 case, BEAM (BCNU, etoposide, ara-C, melphalan) in the second	N/A	ATG, acyclovir, bactrim	N/A		

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Farge et al, France, 2004	8600	SSc (5)	PB	autologous	NR	Combinations including cyclophosphamide alone, cyclophosphamide plus ATG and TBI, cyclophosphamide plus CAMPATH-1H	N/A	NR	N/A		
Huhn et al, USA, 2003	11550	Autoimmune thrombocytopenia case report	PB	autologous	prednisone, splenectomy, IVIG, azathioprine, danazol. Interferon-alpha, plasmapheresis	cyclophosphamide		MESNA, G-CSF, fluconazole, Bactrim			
Jones et al, USA, 2004	9110	1	BM	allogeneic	methotrexate, cyclophosphamide, corticosteroids, nifedipine, enalapril, amitriptyline, celecoxib	nonmyeloablative, fludarabine, cyclophosphamide, TBI	mycophenolate mofetil, cyclosporine A	methylprednisolone, IVIG	N/A		
Kimiskidis et al, Greece, 2008	3020	MS (1)	PB	autologous	iv methylprednisolone, IFN-beta	busulfan, ATG	N/A	G-CSF,	N/A		

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Kishimoto et al, Japan, 2003	9500	Juvenile idiopathic arthritis (2)	1 BM, 2 PBSC	autologous	corticosteroids, cyclosporine A, NSAIDs, methotrexate, cyclophosphamide	cyclophosphamide and ATG (n = 1), etoposide, thiotepa, ATG (n = 2)	N/A	Not reported	N/A		
Lisukov et al, Russia, 2004	9190	SLE (4)	PB or BM (not specified)	autologous	corticosteroids, azathioprine, cyclophosphamide	various dose regimens of BEAM with ATG, cyclophosphamide with ATG, etoposide plus melphalan, all with methylprednisolone	N/A	anti-emetics, analgesia, ciprofloxacin, fluconazole, acyclovir, G-CSF, bactrim	N/A		
Mancardi et al, Italy, 2005	7110	MS (2)	PB	autologous	high-dose corticosteroids, cyclophosphamide, plasma exchange, IFN-beta	BCNU, ara-C, etoposide, melphalan, with or without ATG		IV cyclosporine A	N/A		
Mastrandrea et al, USA, 2009	40050	etanercept plus intensive insulin therapy (10)							etanercept plus intensive insulin therapy	etanercept 0.4 mg/kg twice weekly up to max dose of 25 mg/kg three-injection insulin regimen with Humalog and NPH before breakfast	

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Musso et al, Italy, 2001	13570	SLE (2)	PB	autologous	corticosteroids, cyclophosphamide, IVIG, azathioprine, plasma exchange	cyclophosphamide plus ATG and prednisolone	N/A	ciprofloxacin, bactrim, acyclovir, itraconazole	N/A		
Nakagawa et al, Japan, 2001	13910	Juvenile idiopathic arthritis (1)	PB	autologous	corticosteroids, methotrexate, NSAIDs	ALG, cyclophosphamide,	N/A	IVIG, acyclovir, antipruritic drugs	N/A		
Oyama et al, USA, 2005	7570	CD (4)	PB	autologous	corticosteroids, mesalamine, metronidazole, azathioprine, 6-mercaptopurine, infliximab	cyclophosphamide, ATG	N/A	mesna, methylprednisolone, G-CSF, low microbial diet, ciprofloxacin, fluconazole, valacyclovir, pentamidine, bactrim	N/A		

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Burt et al, USA, 2010	273	HSCT (3)	T-cell depleted, peripheral blood CD34+ enriched	autologous	various combinations, including mesalamine, cyclosporine, corticosteroids, 6-mercaptopurine, methotrexate, infliximab, azathioprine, budesonide, interleukin 11, tacrolimus	nonmyeloablative, cyclophosphamide 50 mg/kg daily for 4 days	equine or rabbit ATG	ciprofloxacin, fluconazole, acyclovir, aerosolized pentamidine, piperacillin/tazobactam, bactrim, leukoreduced RBC and platelet transfusions until engraftment	N/A	N/A	
Paillard et al, 2000, France	14650	Autoimmune hemolytic anemia case report	PB	autologous	autologous HSCT, prednisone, IVIG, plasmapheresis, splenectomy, ATG	BCNU, etoposide, ara-C, melphalan, ATG	NA	cyclosporine A	NA	NA	
Rabusin et al, Italy, 2000	13940	Juvenile idiopathic arthritis (5)	NR, all cells treated in vitro with vincristine and methylprednisolone	autologous	Corticosteroids, NSAIDs, methotrexate, cyclosporine A, cyclophosphamide	ATG, plus cyclophosphamide or fludarabine	N/A	hyperhydration, uromitexane, cortisone, antihistamine, cyclosporine A	N/A	N/A	

Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Raetz et al, USA, 1997	18920	Evans syndrome case report	umbilical cord blood	allogeneic	prednisone, IVIG, 6-mercaptopurine, azathioprine, anti-D, cyclosporine A, vincristine	cyclophosphamide and TBI	cyclosporine A	G-CSF	NA	NA	
Statkute eta, USA, 2005	7370	SLE (9)	PB	autologous	pulse cyclophosphamide, > 20 mg prednisone daily	ATG, cyclophosphamide	N/A	G-CSF, pentamidine, fluoroquinolone, acyclovir or valacyclovir, bactrim	N/A		
Strober et al, USA, 2009	230	MG (1)	PB	allogeneic	pyridostigmine, IVIG, thymectomy, corticosteroids, mycophenolate mofetil, azathioprine, plasmapheresis, rituximab, high-dose cyclophosphamide	alemtuzumab, busulfan, fludarabine	methotrexate, cyclosporine A		N/A		
Trysberg et al, Sweden, 2000	15570	SLE (1)	PB	autologous	corticosteroids, cyclophosphamide, warfarin, aspirin, ATG,	cyclophosphamide and TBI	N/A	cyclosporin A, low dose corticosteroids, anti-herpes, anti-fungal, antibiotics	N/A		

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Study (Investigator, country, year)	Record Number	Group (N)	Stem Cell Source	Type of HSCT	Prior Treatment	Conditioning Regimen	Immunosuppressive therapy for GVHD prophylaxis	Supportive Care	Comparative Treatment	Comparative Treatment Dose/Regimen	Comment
Urban et al, Austria, 2006	5970	Evans syndrome case report	umbilical cord blood	allogeneic	2 autologous HSCT corticosteroids, IVIG, rituximab, vincristine	busulfan, ATG, thiotepa, etoposide	prednisone, cyclosporine A	NR	NA	NA	
Wulffrat et al, Netherlands, 2001	13970	SLE (2)	BM	autologous	corticosteroids, cyclophosphamide, azathioprine, hydroxychloroquine	cyclophosphamide, ATG, low-dose TBI	N/A	NR	N/A		

Appendix Table C100. Outcome assessment: Treatment, autoimmune disease

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	Independent Response Assessor	F/U Frequency/Duration	Comment
Brunner et al, Austria, 2002	11910	SLE case report	Complete remission			Complete drug-free resolution of SLE at 21 mos F/U, KPS 100%	
Chen et al, China, 2005	7790	SLE (2)	pre-post SLEDAI score~ drug-free clinical remission			Pt 1: SLEDAI 6, 0~ Pt 2: SLEDAI 12, 0~ Pt 1 in complete clinical and laboratory remission 44 mos posttransplant; Pt 2 in complete clinical and laboratory remission until 9 mos, when she was lost to F/U	
Connor et al, UK, 2008	2220	1 case report	survival			at 10 mos she was weaning immunosuppression, with full donor chimerism and no evidence of GVHD	
Couri et al, Brazil, 2009	290	18	AUC of C-peptide levels during mixed-meal tolerance test, 0,24, 36 mos~ TRM total insulin free post-HSCT (%) time free from exogenous insulin			74.5 +/- 24.8 nmol/L, 260.0 +/- 30 nmol/L, 241.0 +/-48 nmol/L (p = 0.001, 0 vs 24 mos) 0 16 of 18 (89%), range 7-52 months	AUC data includes 7 patients > 20 yrs old

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	Independent Response Assessor	F/U Frequency/Duration	Comment
Daikeler et al, Switzerland, 2009	740	Evans syndrome (5)	survival			3 alive at 36, 85 and 113 mos 1 dead from disease at 59 mos 1 dead from interstitial pneumonitis at 6 mos	
Daikeler et al, Switzerland, 2009	740A	Autoimmune hemolytic anemia (7)	survival			4 alive at 3.9, 86, 112, 124 mos 3 dead at 0.7, 1.4, 5.2 mos	Survival reported as alive or dead at follow-up time; not Kaplan-Meier curves

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	Independent Response Assessor	F/U Frequency/Duration	Comment
de Kleer et al, Netherlands, 2004	8350	Juvenile idiopathic arthritis (34)	Complete drug-free response (%) partial response (%) no response (%) OS EFS	TRM other adverse events	CR = 53%~ PR = 18%~ NR = 21%~ OS = 79% at 5 yrs~ EFS = 54% at 5 yrs~ TRM = 9%		Five of 6 rheumatological outcomes (VAS - wellbeing, CHAQ-pain, disability, active joint count, ESR) improved within 3 mos from pre-HSCT values (p < 0.04); EPM-ROM did not decline. JIA among those who relapsed was as severe and refractory as prior HSCT
De Stefano et al, Italy, 1999	16180	Autoimmune hemolytic anemia case report	survival			patient alive and well 18 mos posttransplant, weaned off immune suppressive therapy, full donor chimerism, normally functioning immune system	

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Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	Independent Response Assessor	F/U Frequency/Duration	Comment
Elhasid et al, Israel, 2004	9050	Diffuse calcinosis (1)	activities of daily living~ clinical disease			At 2 yrs post-HSCT, patient is free from laboratory and clinical evidence of disease, is able to stand, sit, and walk unaided	
Fagius et al, Sweden, 2009	1270	MS (2)	EDSS score pre-post HSCT~ clinical condition			Pt 1: 4.0, 0.0; Pt 2: 8.0, 1.0~ both patients reported without disease-modifying treatments and stable at 28 and 35 mos	Results except EDSS reported as a group
Farge et al, France, 2004	8600	SSc (5)	Outcomes for 5 patients were reported in scant detail. All 5 were alive, with 4 CR, 1 PR. TRM was reported in a 6th patient. 1 patient relapsed at about 9 mos after initial CR.			median 38 mos (range 14-68 mos)	

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	Independent Response Assessor	F/U Frequency/Duration	Comment
Huhn et al, USA, 2003	11550	Autoimmune thrombocytopenia case report	response to therapy (self-sustained platelet count > 100,000/mm3, reduced bleeding complications and transfusion requirements			no response at 39 mos follow-up	
Jones et al, USA, 2004	9110	1	complete drug-free remission~ activities of daily living			Patient's cushingoid features resolved, all immune suppressant therapies were stopped, grew 17.7 cm in 3 yrs, full-time student in a regular classroom	
Kimiskidis et al, Greece, 2008	3020	MS (1)	EDSS pre-post HSCT~ clinical remission			EDSS = 3.5 at 1 mo, 1.0 at 12 mos~drug-free clinical remission at 62 mos, able to finish college and work	

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	Independent Response Assessor	F/U Frequency/Duration	Comment
Kishimoto et al, Japan, 2003	9500	Juvenile idiopathic arthritis (3)	Disease response~ Survival			Pt 1: No response to AHSCT, subsequent allogeneic transplant was followed by patient death 48 days posttransplant~ Pt 2: Disease flares at 11 and 23 mos, medication-free at 39 mos~ Pt 3: drug-free clinical remission at > 35 mos	
Lisukov et al, Russia, 2004	9190	SLE (4)	Complete remission (SLEDAI < 3, prednisolone dose < 10 mg daily, absence of other immunosuppressive therapy) (%)			1 pt (25%) achieved CR with F/U > 60 mos; 1 pt improved functionally but did not achieve primary endpoint	
Mancardi et al, Italy, 2005	7110	MS (2)	EDSS score pre-post HSCT~ neurological improvement~ mobility			Pt 1: 7.4, 4.0; Pt 2; 9, 4.5~ Pt 1 could walk and perform activities of daily living independently at 29 mos F/U~ Pt 2 neurological condition improved dramatically (not described) at 14 mos F/U	

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	Independent Response Assessor	F/U Frequency/Duration	Comment
Musso et al, Italy, 2001	13570	SLE (2)	Corticosteroid-free complete remission~ KPS pre- and posttransplant			2 of 2 (100) at > 30 mos and > 3.8 mos F/U~ Pt 1: 40, 100; Pt 2: 60, 100	Both patients reported drug-free at F/U
Nakagawa et al, Japan, 2001	13910	Juvenile idiopathic arthritis (1)	Medication-free survival~ growth rate			15 mos posttransplant~ 16 cm/yr compared to 2 cm/yr in preceding 3 yrs	
Oyama et al, USA, 2005	7570	CD (4)	Clinical drug-free remission (%)~ survival (%)~ KPS pre-post HSCT~CDAI pre-post HSCT~ disease manifestations post-HSCT			100%~ 100% at 37, 36, 16, 7 mos F/U~ 40, 100; 50, 100; 40, 80; 60, 90~ 337, 51; 293, 59; 250, 78; 274, 74~ 2 asymptomatic (50%), 2 (50%) with occasional abdominal pain or diarrhea	
Burt et al, USA, 2010	273	HSCT (3)	immunosuppressive drug-free remission, with CDAI< 150 and CSI < 12; clinical relapse-free survival; HSCT-associated adverse events	CDAI, CSI	NR	6, 12, 24, 36, 48, 60 mos post-HSCT	
Paillard et al, 2000, France	14650	Autoimmune hemolytic anemia case report	survival			Patient in hematological remission 20 mos posttransplant	

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	Independent Response Assessor	F/U Frequency/Durati on	Comment
Rabusin et al, Italy, 2000	13940	Juvenile idiopathic arthritis (5)	Complete drug-free response 6 mos (%)~ Partial response 6 mos (%)~ Relapse (%)			CR = 4 of 5 (80) at 3 mos, 3 of 5 (60) at 6 mos~ PR = 1 of 5 (20) at 3 mos~ Relapse = 5 of 5 (100) between 6 and 18 mos (mn = 10 +/- 5.1 mos)	Disease evolution followed according to Giannini, including joint-swelling scores, pain scores, and ESR
Raetz et al, USA, 1997	18920	Evans syndrome case report	survival			patient dead 289 days posttransplant of fulminant liver failure	
Statkute eta, USA, 2005	7370	SLE (9)	SLE drug-free remission (%)~			7 of 9 (78), remission maintained for median 29 mos (rng 12-78 mos)	
Strober et al, USA, 2009	230	MG (10	Activities of daily living			At 40 mos post-HSCT pt if free of all immune suppressant and MG therapies, plays basketball, and is completely independent	
Trysberg et al, Sweden, 2000	15570	SLE (1)	CNS deficit, mobility			Neurological deficits improved promptly after HSCT, patient was able to read again, walk freely, with MRI observed regression of brain lesions	Required corticostero ids,

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	Secondary Outcomes	Independent Response Assessor	F/U Frequency/Duration	Comment
Urban et al, Austria, 2006	5970	Evans syndrome case report	survival			at 18 mos patient in good clinical condition, with 100% donor chimerism, no evidence of GVHD, weaned off immune suppressive therapy	
Wulffrat et al, Netherlands, 2001	13970	SLE (2)	Pre-post SLEDAI score~ complete drug-free clinical remission			Pt 1: 20, 0; Pt 2: 27, 8~ 2 (100) drug-free complete remission at 18 and 12 mos F/U	Post-HSCT SLEDAI score of 8 in Pt 2 is due to the presence of permanent vasculitic retinal lesions

Appendix Table C101. Outcome assessment: Comparator, autoimmune disease

Study (Investigator, country, year)	Record Number	Group (N)	Primary Outcomes	F/U Frequency/Duration
Crino et al, Italy, 2005	62110	nicotinamide plus intensive insulin therapy (25) intensive insulin therapy only (27)	glycosylated hemoglobin (%) 0, 12, 24 mos fasting C-peptide (nmol/L) 0, 12, 24 mos	nicotinamide plus intensive insulin therapy 9.6+/-2.2, 5.4+/-0.8, 6.1+/-0.9, 1.9+/-0.15, 0.25+/-0.2, 0.19+/-0.2 intensive insulin therapy 10.5+/-2.2, 6.5+/-0.9, 7.0+/-0.9, 0.16+/-0.12, 0.21+/-0.2, 0.19+/-0.13
Mastrandrea et al, USA, 2009	40050	etanercept plus intensive insulin therapy (10)	glycosylated hemoglobin (%) 0, 24 wks meal stimulated C peptide AUC (ng/mL/hr) 0, 24 wks	12.8+/-3.2, 5.9+/-0.5 3.1+/-1.2 ng/mL/hr, 3.9+/-1.6 ng/mL/hr

Appendix Table C102. Time to event outcomes: Treatment, autoimmune disease

Study (Investigator, country, year)	Record Number	Disease	Outcome Assessment Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Time to Event Outcomes Group (N)	Outcome	Outcome_2
Brunner et al, Austria, 2002	11910	Systemic lupus erythematosus (SLE)	SLE case report	Complete remission		Complete drug-free resolution of SLE at 21 mos F/U, KPS 100%			
Chen et al, China, 2005	7790	Systemic lupus erythematosus	SLE (2)	pre-post SLEDAI score~ drug-free clinical remission		Pt 1: SLEDAI 6, 0~ Pt 2: SLEDAI 12, 0~ Pt 1 in complete clinical and laboratory remission 44 mos posttransplant; Pt 2 in complete clinical and laboratory remission until 9 mos, when she was lost to F/U			
Connor et al, UK, 2008	2220	Evans syndrome	1 case report	survival		at 10 mos she was weaning immunosuppression, with full donor chimerism and no evidence of GVHD			
Couri et al, Brazil, 2009	290	Type 1 diabetes mellitus	18	AUC of C-peptide levels during mixed-meal tolerance test, 0,24, 36 mos~ TRM total insulin free post-HSCT (%) time free from exogenous insulin		74.5 +/- 24.8 nmol/L, 260.0 +/- 30 nmol/L, 241.0 +/-48 nmol/L (p = 0.001, 0 vs 24 mos) 0 16 of 18 (89%), range 7-52 months	16	100	

Study (Investigator, country, year)	Record Number	Disease	Outcome Assessment Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Time to Event Outcomes Group (N)	Outcome	Outcome_2
Daikeler et al, Switzerland, 2009	740	Evans syndrome	Evans syndrome (5)	survival		3 alive at 36, 85 and 113 mos 1 dead from disease at 59 mos 1 dead from interstitial pneumonitis at 6 mos			
Daikeler et al, Switzerland, 2009	740A	Autoimmune hemolytic anemia	Autoimmune hemolytic anemia (7)	survival		4 alive at 3.9, 86, 112, 124 mos 3 dead at 0.7, 1.4, 5.2 mos			
de Kleer et al, Netherlands, 2004	8350	Juvenile idiopathic arthritis	Juvenile idiopathic arthritis (34)	Complete drug-free response (%) partial response (%) no response (%) OS EFS	TRM other adverse events		Juvenile idiopathic arthritis (34)	OS, 1-5 years 79%	EFS, 1-5 years approx 1-54%
De Stefano et al, Italy, 1999	16180	Autoimmune hemolytic anemia	Autoimmune hemolytic anemia case report	survival		patient alive and well 18 mos posttransplant, weaned off immune suppressive therapy, full donor chimerism, normally functioning immune system			
Elhasid et al, Israel, 2004	9050	Diffuse calcinosis	Diffuse calcinosis (1)	activities of daily living~ clinical disease		At 2 yrs post-HSCT, patient is free from laboratory and clinical evidence of disease, is able to stand, sit, and walk unaided			
Fagius et al, Sweden, 2009	1270	Multiple sclerosis (MS)	MS (2)	EDSS score pre-post HSCT~ clinical condition		Pt 1: 4.0, 0.0; Pt 2: 8.0, 1.0~ both patients reported without disease-modifying treatments and stable at 28 and 35 mos			

Study (Investigator, country, year)	Record Number	Disease	Outcome Assessment Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Time to Event Outcomes Group (N)	Outcome	Outcome_2
Farge et al, France, 2004	8600	Systemic sclerosis (SSc)	SSc (5)	Outcomes for 5 patients were reported in scant detail. All 5 were alive, with 4 CR, 1 PR. TRM was reported in a 6th patient. 1 patient relapsed at about 9 mos after initial CR.		median 38 mos (range 14-68 mos)			
Huhn et al, USA, 2003	11550	Autoimmune thrombocytopenia	Autoimmune thrombocytopenia case report	response to therapy (self-sustained platelet count > 100,000/mm3, reduced bleeding complications and transfusion requirements		no response at 39 mos follow-up			
Jones et al, USA, 2004	9110	Overlap syndrome	1	complete drug-free remission~ activities of daily living		Patient's cushingoid features resolved, all immune suppressant therapies were stopped, grew 17.7 cm in 3 yrs, full-time student in a regular classroom			

Study (Investigator, country, year)	Record Number	Disease	Outcome Assessment Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Time to Event Outcomes Group (N)	Outcome	Outcome_2
Kimiskidis et al, Greece, 2008	3020	Multiple sclerosis (MS)	MS (1)	EDSS pre-post HSCT~ clinical remission		EDSS = 3.5 at 1 mo, 1.0 at 12 mos~drug-free clinical remission at 62 mos, able to finish college and work			
Kishimoto et al, Japan, 2003	9500	Juvenile idiopathic arthritis	Juvenile idiopathic arthritis (3)	Disease response~ Survival		Pt 1: No response to AHSCT, subsequent allogeneic transplant was followed by patient death 48 days posttransplant~ Pt 2: Disease flares at 11 and 23 mos, medication-free at 39 mos~ Pt 3: drug-free clinical remission at > 35 mos			
Lisukov et al, Russia, 2004	9190	Systemic lupus erythematosus (SLE)	SLE (4)	Complete remission (SLEDAI < 3, prednisolone dose < 10 mg daily, absence of other immunosuppressive therapy) (%)		1 pt (25%) achieved CR with F/U > 60 mos; 1 pt improved functionally but did not achieve primary endpoint			
Mancardi et al, Italy, 2005	7110	Malignant multiple sclerosis (MS)	MS (2)	EDSS score pre-post HSCT~ neurological improvement ~ mobility		Pt 1: 7.4, 4.0; Pt 2; 9, 4.5~ Pt 1 could walk and perform activities of daily living independently at 29 mos F/U~ Pt 2 neurological condition improved dramatically (not described) at 14 mos F/U			

Study (Investigator, country, year)	Record Number	Disease	Outcome Assessment Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Time to Event Outcomes Group (N)	Outcome	Outcome_2
Musso et al, Italy, 2001	13570	Systemic lupus erythematosus (SLE)	SLE (2)	Corticosteroid-free complete remission~ KPS pre- and posttransplant		2 of 2 (100) at > 30 mos and > 3.8 mos F/U~ Pt 1: 40, 100; Pt 2: 60, 100	SLE (2)		
Nakagawa et al, Japan, 2001	13910	Juvenile idiopathic arthritis	Juvenile idiopathic arthritis (1)	Medication-free survival~ growth rate		15 mos posttransplant~ 16 cm/yr compared to 2 cm/yr in preceding 3 yrs			
Oyama et al, USA, 2005	7570	Crohn's Disease (CD)	CD (4)	Clinical drug-free remission (%)~ survival (%)~ KPS pre-post HSCT~CDAI pre-post HSCT~ disease manifestations post-HSCT		100%~ 100% at 37, 36, 16, 7 mos F/U~ 40, 100; 50, 100; 40, 80; 60, 90~ 337, 51; 293, 59; 250, 78; 274, 74~ 2 asymptomatic (50%), 2 (50%) with occasional abdominal pain or diarrhea			
Paillard et al, 2000, France	14650	Autoimmune hemolytic anemia	Autoimmune hemolytic anemia case report	survival		Patient in hematological remission 20 mos posttransplant			
Rabusin et al, Italy, 2000	13940	Juvenile idiopathic arthritis	Juvenile idiopathic arthritis (5)	Complete drug-free response 6 mos (%)~ Partial response 6 mos (%)~ Relapse (%)		CR = 4 of 5 (80) at 3 mos, 3 of 5 (60) at 6 mos~ PR = 1 of 5 (20) at 3 mos~ Relapse = 5 of 5 (100) between 6 and 18 mos (mn = 10 +/- 5.1 mos)			

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Study (Investigator, country, year)	Record Number	Disease	Outcome Assessment Group (N)	Primary Outcomes	Secondary Outcomes	F/U Frequency/Duration	Time to Event Outcomes Group (N)	Outcome	Outcome_2
Raetz et al, USA, 1997	18920	Evans syndrome	Evans syndrome case report	survival		patient dead 289 days posttransplant of fulminant liver failure			
Statkute eta, USA, 2005	7370	Systemic lupus erythematosus (SLE)	SLE (9)	SLE drug-free remission (%)~		7 of 9 (78), remission maintained for median 29 mos (rng 12-78 mos)			
Strober et al, USA, 2009	230	Myasthenia gravis (MG)	MG (10	Activities of daily living		At 40 mos post-HSCT pt if free of all immune suppressant and MG therapies, plays basketball, and is completely independent			
Trysberg et al, Sweden, 2000	15570	Systemic lupus erythematosus (SLE)	SLE (1)	CNS deficit, mobility		Neurological deficits improved promptly after HSCT, patient was able to read again, walk freely, with MRI observed regression of brain lesions			
Urban et al, Austria, 2006	5970	Evans syndrome	Evans syndrome case report	survival		at 18 mos patient in good clinical condition, with 100% donor chimerism, no evidence of GVHD, weaned off immune suppressive therapy			
Wulffrat et al, Netherlands, 2001	13970	Systemic lupus erythematosus (SLE)	SLE (2)	Pre-post SLEDAI score~ complete drug-free clinical remission		Pt 1: 20, 0; Pt 2: 27, 8~ 2 (100) drug-free complete remission at 18 and 12 mos F/U			

Appendix Table C103. Time to event outcomes: Comparator, autoimmune disease

Study (Investigator, country, year)	Record Number	Disease	Primary Outcomes	F/U Frequency/Duration
Crino et al, Italy, 2005	62110	Type 1 diabetes mellitus	glycosylated hemoglobin (%) 0, 12, 24 mos fasting C-peptide (nmol/L) 0, 12, 24 mos	nicotinamide plus intensive insulin therapy 9.6+/-2.2, 5.4+/-0.8, 6.1+/-0.9, 1.9+/-0.15, 0.25+/-0.2, 0.19+/-0.2 intensive insulin therapy 10.5+/-2.2, 6.5+/-0.9, 7.0+/-0.9, 0.16+/-0.12, 0.21+/-0.2, 0.19+/-0.13
Mastrandrea et al, USA, 2009	40050	Type 1 diabetes mellitus	glycosylated hemoglobin (%) 0, 24 wks meal stimulated C peptide AUC (ng/mL/hr) 0, 24 wks	12.8+/-3.2, 5.9+/-0.5 3.1+/-1.2 ng/mL/hr, 3.9+/-1.6 ng/mL/hr

Appendix D. Disease-Free/Event-Free Survival

Ewing's Sarcoma Family of Tumors (ESFT)

EFS or DFS was reported or generated in 13 HSCT studies (Oberlin, 2008 #2020; Meyers, 2001, #13670; Drabko, 2005, #6680; Prete, 1998, #17210; Hawkins, 2000 ,#15360; Ozkaynak, 1998, #18540; Laws, 2003, #9450; Yaniv, 2004, #9100; Kushner, 2001, #14240; Lucas, 2008, #9450; Diaz, 2010 #1212; Ilari, 2010 #1208; Ladenstein, 2010 #1209) and 4 comparative studies (Bernstein, 2006, #6290; Sari, 2010 #42790; Kushner,1995, #44560; Milano, 2006,#5960;)
.

Appendix Table D1. Event-free survival (DFS; PFS) for treatment (single and tandem auto HSCT) and comparison (conventional chemotherapy +/- radiation) groups: ESFT

	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	Study
1 year	54% (25-84)*		Yaniv, Israel, 2004 (n=11) #9100
	20% (0-45)*		Kushner, USA, 2001(n=10) #14240
	50% (0-100%)*		Laws, Germany, 2003 (n=2) #9450
	Stable disease 9 mos after HSCT		Lucas, USA, 2008 (n=1) #2450
		65% +/- 5% [isolated lung mets vs other and more than isolated lung mets 72% +/-7% and 62% +/- 6%; p=.39]	Bernstein, USA/Canada 2006 (n=110) #6290
		83% (67-98%)	Kushner, USA, 1995 (n=24) #44560
2 year	20%		Meyers, USA, 2001 (n=32) #13670
	63%		Drabko, Poland, 2005 (n=21) #6680
	63%		Prete, Italy, 1998 (n=17) #17210
	50% (0-100%)*		Laws, Germany, 2003 (n=2) #9450
		24% (+/-4%) [31% +/-7% for pts with isolated lung mets and 20% +/-5% for pts with more widespread dz; p=.39]	Bernstein, USA/Canada 2006 (n=110) #6290
3 year	36%		Hawkins, USA, 2000 (n=16) #15360

	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	Study
	51% for all pts 66% +/-19% for 1st remission 37% for 2nd remission		Ozkaynak, USA, 1998 (n=15) #18540
	18% (0-41%)*		Yaniv, Israel, 2004 (n=11) #9100
	20% (0-45)*		Kushner, USA, 2001 (n=10) #14240
		75% (55-95%)	Kushner, USA, 1995 (n=24) #44560
		74%	Milano, Italy, 2006 (n=18) #5960
	40% (SD: 0.05)		Ladenstein, Austria, France, UK, Switzerland, Netherlands, Germany, Sweden, 2010 #1209
4 year	A NED (ESFT) at 50 mos after HSCT[a]		Numata, Japan, 2006 (n=1) #12130
5 year	46%		Oberlin, France, 2008 (n=61) #2020
	32% (+/- 11%) in HyperME with median f/u 146 mos (98-190) and 40% (+/-13%) in TandemME with median f/u 68 mos (28-88 mos)		Burdach, Germany and Austria, 2003 (n=32) #10030
	18% (0-41%)*		Yaniv, Israel, 2004 (n=11) #9100
	20% (0-45)*		Kushner, USA, 2001 (n=10) #14240
	A NED 60 months after surgery		Kogawa, Japan, 2004 (n=1) #8410
		18%	Sari, Turkey, 2010 (n=36) #42790
		75% (55-95%)	Kushner, USA, 1995 (n=24) #44560
	PFS 56% (+/- 4%) with a median f/u of 92 months for survivors (range 6-168 months) by localized vs mets at dx PFS for pts with local dz:78% (+/- 8%); for mets: 27% (+/- 10%)		Diaz, Spain, 2010 (n=47) #1212
	7 year f/u 61% (95%CI 36-79)		Ilari, Italy, 2010 (n=24) #1208

[a]Numata (#12130)-pt dxd with CML, chronic phase at 50 mos

Wilm's Tumor

Event-free/disease-free survival

Sixteen studies reported event or disease-free survival (Spreafico, 2008, #2380; Malogolowkin, 2008, ##44950; Tucci, 2007, ##3910; Park, 2006, ##5450; Campbell, 2004, #8570; Valera, 2004, ##8620; Kremens, 2002, ##11240; Abu-Ghosh, 2002, #45610; Saarinen-Pihkala, 1998, ##17940; Pein,1998, ##17570; Dagher, 1998, #17840; Hempel, 1998, ##18100; Hempel, 1996, #20550; Kullendorff,1997, #19290; Brown, 2010, #1211; Lucas, 2010, #1210).

Appendix Table D2. Event-free survival (DFS; PFS) for treatment (single auto HSCT) and comparison (conventional chemotherapy +/- radiation) groups: Wilm's tumor

	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	Study
1 year	1 yr 52% [32-73] (n=23)		Kremens, 2002, #11240
		1 yr ~73% (n=11)	Abu-Ghosh, 2002, #45610
	1 yr 86% [60-100]* (n=7)		Hempel, 1996, #20550
	1 yr 75% [33-100]* (n=4)		Kullendorff, 1997, #19290
	1 yr 67% [13-100]* (n=3)		Valera, 2004, #8620
	.5 yrs (n=1)		Dagher, 1998, #17840
	DFS at 15 months after HSCT (n=1)		Brown, 2010, #1211
1 year PFS range across studies	52%-86% (Kremens, Spreafico, Hempel, Kullendorff, Valera)	~73% (Abu-Ghosh)	
2 year	2 yr 75% [33-100]* (n=4)		Kullendorff, 1997, #19290

	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	Study
	2 yr 86% [60-100]* (n=7)		Hempel,1996, #20550
	alive at 32 months after HSCT (n=1)		Hempel, 1998, #18100
	EFS at 2.5 years (n=1)		Lucas, 2010, #1210
3 year	3 yr 50% +/- 17 (n=28)		Pein, 1998, #17570
	3 yr 52% [32-73] (n=23)		Kremens, 2002, #11240
	3 yr 56% +/-12% (n=20)		Spreafico, 2008, #2380
		3 year 66.6% (n=10)	Tucci, 2007, #3910
		3 yr 64% (n=11)	Abu-Ghosh, 2002, #45610
	3 yr 67% [13-100]* (n=3)		Valera, 2004, #8620
4 year	4-year 60% (n=13)		Campbell, 2004, #8570
	median 51 months (40-53 months) (n=3)		Saarinen-Pihkala, 1998, #17940
		4 yr 48% (n=60)	Malogolowkin, 2008, #44950
5 year	5 yr 52% [32-73]* (n=23)		Kremens,2002, #11240
	A NED at 7 yr (n=1)	5 year 42.8% (n=10)	Tucci, 2007, #3910
		5 yr 64% (n=11)	Abu-Ghosh, 2002, #45610

Rhabdomyosarcoma

Event-free survival

Data on intermediate outcomes were reported in eleven studies and calculated from the raw data from two additional studies (Hara, 1998 #17950; Lucidarme, 1998 #17610). Event free survival estimates are presented below.

Appendix Table D3. Event-free survival (DFS; PFS) for treatment (single auto HSCT) and comparison (conventional chemotherapy +/- radiation) groups: Rhabdomyosarcoma

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
Metastatic Auto	1 year	~46% at 1 year (n=52)	~53% at 1 year (n=42)		Carli, Italy, 1999 #16010
			~63% at 1 year (n=152)		Sandler, USA, 2001 #12810
			~69% at 1 year (n=127)		Breneman, USA, 2003 #75360
Mixed Tumor Stage Auto		12.5 (4,35) at 1 year (n=8)			Lucidarme, France, 1998± #17610
		66.7 (28.9,100) at 1 year (n=7)			Hara, Japan, 1998± #17950
Metastatic Auto	3 year	29.7 (15.6,43.8) at 3 years (n=52)	19.2 (6.8-31.6)at 3 years (n=42)	0.3	Carli, Italy, 1999 #16010
		16.5 at 3 years (n=101)	54.9 at 3 years (n=45)		McDowell, UK, 2010 #75350
		75% (33-107) at 3 years (n=4)	15% (-4-35) at 3 years (n=13)		Williams, Canada, 2004 #9010
		35.3% (24.3-46.5) at 3 years (n=70)			Bisogno, Italy, 2009 #75340
			~28% at 3 years (n=152)		Sandler, USA, 2001 #12810
			25% (17-33) at 3 years (n=127)		Breneman, USA, 2003 #75360

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
Mixed Tumor Stage Auto		66.7 (28.9,100) at 3 years (n=7)			Hara, Japan, 1998± #17950
Metastatic Auto	5 year	14.9 at 5 years (n=101)	51.0% at 5 years (n=45)		McDowell, UK, 2010 #75350
			~20% at 5 years (n=127)		Breneman, USA, 2003 #75360
			~27% at 5 years (n=152)		Sandler, USA, 2001 #12810
Mixed Tumor Stage		36% at 5 years (n=22)			Matsubara**, Japan, 2003 #10810
Cranial Parameningeal			32% (22-42) at 10 years (n=91)		Raney, USA, 2008 #2440
Metastatic (summary)	EFS range for 3 years for studies with > 20 patients	29.7-35.3% (Carli #16010, Biosgno #75340)	19.2-28% (Carli #16010, Sandler #12810, Breneman #75360)		This range does not Include the McDowell #75350 study as the patients in the treatment arm are not comparable to other studies due to their higher risk category.
Mixed Tumor stage (summary)	EFS range for 3 years for studies with > 5 patients	66.7% (Hara #17950)	No comparator		

Retinoblastoma

Four studies reported event free survival (Namouni, 1997 #18090; Kremens, 2003 #10860; Dunkel, 2010 #28560; Dunkel, 2010 #1204), and EFS was calculated from the raw data from two studies (Galindo, 2003; Matsubara, 2005 #7580). These studies were all single arm case series. At five years the event free survival for patients without CNS involvement ranges from 66.7 to 85.7.

Appendix Table D4. Event-free survival (DFS; PFS) for treatment (single auto HSCT) and comparison (conventional chemotherapy +/- radiation) groups: Retinoblastoma

Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
Event Free no CNS	Isolated orbital disease (n=7) 85.7 (59.8-100) at 1-5 years			Namouni, 1997± #18090
	100% at 1-3 years 75% at 4-5 years[b] (n=4)			Galindo, 2003± #10420
	100% at mean Follow-up of 38 months (n=3)			Matsubara, 2005 #7580
	66.7% at mean follow-up of 8.9 years (n=5)			Kremens, 2003 # 10860
	67% (38-85) at follow-up of 5 years (DFS) 59% (31-79) at follow-up of 10 years (PFS)			Dunkel, 2010, #1204
Event Free mixed	~88% at 1 year[a] ~ 62% at 2 years ~57% at 3 years ~53% at 4-5 years (n=34)[b]			Namouni, 1997 #18090
	Patients with Trilateral retinoblastoma (n=13) ~68% at 1 year ~38% at 2-5 years			Dunkel, 2010 #28560
EFS range for 5+ years for studies with >2 patients without CNS involvement not including trilateral retinoblastoma	66.7-85.7% (Kremens 2003 # 10860,Galindo 2003 #10420, Namouni 1997 #18090)	NR		
EFS range for 5+ years for studies with >2 trilateral	~38% (Dunkel, 2010 #28560)	No comparator study identified		

retinoblastoma				

[a] estimated preceded by a ~ were estimated from published Kaplan-Meier curves. [b] this includes all patients including those who died prior to treatment. ± survival curves were constructed using the raw data published in the articles.

Neuroblastoma

Data on intermediate outcomes were reported in all seven primary studies. Six studies reported data as event-free survival (EFS), one study as disease-free survival (DFS), and another as progression-free survival (PFS). No significant differences between treatment groups in either three-year DFS or five-year EFS were identified in the two comparative studies.(Kim, 2007 [2870]; Ladenstein, 2008 [1610]) Multivariate analysis of the Sung et al. (2007) data showed the application of total body radiation and local radiotherapy during the treatment regimen, and a longer interval ($\geq$ 12 weeks) between the first and second transplant to be independent favorable predictors for EFS (HR, 9.66, 7.17, 5.73; 95% CI, 1.31-71.26, 1.69-30.38, 1.32-24.88; p = 0.026, 0.007, 0.020, respectively).(Sung, 2007 [3950]) It should be noted that five studies (71%) did not define *a priori* these outcomes.

Appendix Table D5. Event-free survival (DFS; PFS) for treatment (tandem HSCT) and comparison (single HSCT) groups: Neuroblastoma

Outcome	Intervention Tandem (%; ± 95% CI; SE) [N]	Comparator Single (%; ± 95% CI; SE) [N]	P-value	Study (record #)
3 year rate	50 (20.4) [9]	40.6 (14.7) [27]	0.50	Kim, 2007 (2870)
	61 (50-71) [82]			George, 2006 (5440)
		47 (38-55) [149]		Berthold, 2005 (6760)
5 year rate	27 (2) [455]	33 (1) [2,895]	0.19	Ladenstein, 2008 (1610)
	54 (42-64) [82]			George, 2006 (5440)
	62.1 (13.7) [52]			Sung, 2007 (3950)
		38 (21-54) [32]		Pritchard, 2005 (8030)
		30 (4) [189]		Matthay, 2009 (6210)
	51.2 (12.4) [71]		0.03	Sung, 2010 (1206)
> 5 year rate	52 (40-63) [82]			George, 2006 (5440)
EFS range for ≥5 years for studies with > 10 patients	27-62	30-38		

CI, confidence interval; DFS, disease-free survival; N, number of patients; PFS, progression-free survival; SE, standard error

Germch-Cell Tumor

Data on intermediate outcomes were reported in all four studies. The CIBMTR cohort reported data as progression-free survival (PFS) and the remaining three studies either as disease-free survival (Einhorn 2007, De Giorgi 2005) or event-free survival (Agarwal). Data were available to compute three-year rates across all studies, and five-year rates for three studies. For the CIBMTR cohort, there was a trend toward a lower probability of PFS at one-year in the tandem group compared to the single HSCT group (36% vs. 60%), although no p-values were computed due to the small number of cases. PFS did not differ between treatment groups across studies. For the CIBMTR cohort, PFS at 5 years for the tandem group remained at 36% (11%-63%) compared to 49% (26%-69%) in the single HSCT group. PFS was defined as survival without recurrence (or cancer progression) as measured by exam, radiographs, and/or an increase in serum marker levels.(CIBMTR, 2010)

Appendix Table D6. Event-free survival (DFS; PFS) for treatment (tandem HSCT) and comparison (single HSCT) groups: Germ-cell tumor

Outcome	Intervention Tandem (%; ± 95% CI) [N]	Comparator Single (%; ± 95% CI) [N]	P-value	Study (record #)
1-year rate	36 (11-63)	60 (36-78)	NR	CIBMTR, 2010
	59 (39.5-88)			Einhorn, 2007 (77230)
		50 (26-74.5)		De Giorgi, 2005 (77240)
3 year rate	36 (11-63)	49 (26-69)	NR	CIBMTR, 2010
	59 (39.5-88)			Einhorn, 2007 (77230)
		50 (7-93)		Agarwal, 2009 (72940)
		50 (26-74.5)		De Giorgi, 2005 (77240)
5 year rate	36 (11-63)	49 (26-69)	NR	CIBMTR. 2010
	59 (39.5-88)			Einhorn, 2007 (77230)
		50 (26-74.5)		De Giorgi, 2005 (77240)
EFS range for 5 years for studies with > 10 patients	36-59	49-50		

[a] EFS for stage IV patients; CI, confidence interval; DFS, disease-free survival; N, number of patients; NR, not reported; PFS, progression-free survival

CNS/Embryonal Tumors

Data on intermediate outcomes were reported in 11 (of 12) studies. For comparisons between tandem vs. single HSCT, data were available to compute two-year, three-year, and five-year rates for three studies. For Sung et al. (2007), EFS at 2 years for the tandem group was 73% (46%-99%) compared to 67% (13%-100%) in the single HSCT group [4770] The AT/RT patient reported in Gidwani et al. (2008) was disease free for two years following tandem HSCT.[71940] EFS was defined as the interval between diagnosis to progression/relapse or death from any cause.

For the conventional-care group of studies, data were available to compute three-year rates for one study and five-year rates for three studies. There were no comparative studies between single HSCT vs. conventional care. For Geyer et al. (2005) on multiple tumor types, overall five-year EFS was 27% (3%) for children under three years of age; for MB, PNET and AT/RT, the corresponding rates were 32% (5%), 17% (6%), and 14% (7%), respectively.[49990] Similar trends to OS above observed in EFS rates between studies.

Appendix Table D7. Event-free survival (DFS; PFS) for treatment (tandem HSCT) and comparison (single HSCT) groups: CNS/embryonal tumors

Outcome (Tumor type)	Intervention Tandem (%; ± 95% CI; SE) [N]	Comparator Single (%; ± 95% CI; SE) [N]	P-value	Study (record #)
2 year rate				
(MB-PNET)	73 (46-99) [11]	67 (13-100) [3]	NR	Sung, 2007 (4770)
(AT/RT)	[One patient remained disease-free]			Gidwani, 2008 (71940)
(MB-PNET)		57 (15) [13]		Perez-Martinez, 2005 (7650)
3 year rate				
(MB-PNET)	73 (46-99) [11]	NA		Sung, 2007 (4770)
(MB)		49 (27-72) [21]		Chi, 2004 (7900)
(AT/RT)		23 (11) [13]		Gardner, 2008 (71930)
(MB)	67 [2 of3 patients with complete remission]			Aihara, 2010, #1201
5 year rate				
(MB-PNET)	58 (25-91) [11]	NA		Sung, 2007 (4770)
(PNET)		39 (24-53) [43]		Fangusaro, 2008 (3420)
(MB)		52 (11) [21]		Dhall, 2008 (52130)
EFS range for 5 years for studies with > 10 patients	58	39-52		

AT/RT, atypical teratoid/rhabdoid tumor; CC, conventional care; CI, confidence interval; DFS, disease-free survival; EFS, event-free survival; MB, medulloblastoma; N, number of patients; NA, not available; PFS, progression-free survival; PNET, supratentorial primitive Neuroectodermal tumors; SE, standard error

Appendix Table D8. Event-free survival (DFS; PFS) for treatment (single HSCT) and comparison (conventional care) groups: CNS/embryonal tumors

Outcome (Tumor type)	Intervention Single (%; ± 95% CI; SE) [N]	Comparator CC (%; ± 95% CI; SE) [N]	P-value	Study (record #)
3 year rate				
(MB)	49 (27-72) [21]			Chi, 2004 (7900)
(MB)		40 (28-51) [68]		Taylor, 2005 (52760)
(AT/RT)	23 (11) [13]			Gardner, 2008 (71930)
5 year rate				
(MB)	52 (11) [21]			Dhall, 2008 (52130)
PNET	39 (24-53) [43]			Fangusaro, 2008 (3420)
(MB)		81 (2) [379]		Packer, 2006 (77250)
(MB-PNET-AT/RT-Other)		27 (3) [284]		Geyer, 2005 (49990)
(MB)		35 (23-46) [68]		Taylor, 2005 (52760)
EFS range for 5 years for studies with >10 patients	39-52	27-81		

AT/RT, atypical teratoid/rhabdoid tumor; CC, conventional care; CI, confidence interval; DFS, disease-free survival; EFS, event-free survival; MB, medulloblastoma; N, number of patients; NA, not available; PFS, progression-free survival; PNET, supratentorial primitive neuro-ectodermal tumors; SE, standard error

Glial Tumors

Data on intermediate outcomes were reported in twenty-nine studies and calculated from the raw data. Event free survival estimates are presented below.

Appendix Table D9. Event-free survival (DFS; PFS) for treatment (single auto HSCT) and comparison (conventional chemotherapy +/- radiation) groups: Glial tumors

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
Astrocytoma	**1 year**	AA/GBM PFS: ~30% (These HSCT and chemotherapy estimates are grouped EFS for astrocytoma and glioblastoma multiforme) (N=27)	AA/GBM year PFS ~10% (N=56)	Chemo versus ABMR unstratified comparison of event-free survival: P=0.014	Finlay, 2008
			2 patients progressed at 1.5 and 8.5 mo (N=2)		Shih, 2008
			3 patients progressed at 3,3, and 8 mo (N=3)		Sio, 2006
			1 astrocytoma patient progressed at 4 months, and one patient was progression free at 10 months (N=2)		Koronoes, 2006
		Other Glioma ~ 73 (9 AA and 2 Oligodendroglioma) (N=11)		PFS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse P=.008	Massimino, 2005
			Median AA PFS 21.2mo (1.2-49.3) (N=4)		Hurwitz, 2001
			1 OA patient progressed shortly after chemotherapy and received irradiation (33% of OA) (N=6)		Doireau, 1999
		2 patients progressed at 4.5 and 5.5 months (N=2)			Jakacki, 1999
		1 patient progressed at 11 mo (N=1)			Busca, 1997

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
	3 Year	AA/GBM PFS: 22±7% (These HSCT and chemotherapy estimates are grouped EFS for astrocytoma and glioblastoma multiforme) (N=27)	AA/GBM year PFS 0% (N=56)	Chemo versus ABMR unstratified comparison of event-free survival: P=0.014	Finlay, 2008
		Other Glioma ~ 73 (9 AA and 2 Oligodendroglioma) (N=11)		PFS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse P=.008	Massimino, 2005
	5 Year	AA/GBM PFS: 22±7% (These HSCT and chemotherapy estimates are grouped EFS for astrocytoma and glioblastoma multiforme) (N=27)	AA/GBM year PFS 0% (N=56)	Chemo versus ABMR unstratified comparison of event-free survival: P=0.014	Finlay, 2008
		Other Glioma ~ 73 (9 AA and 2 Oligodendroglioma) (N=11)		PFS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse P=.008	Massimino, 2005
Glioblastoma Multiforme	**1 Year**	AA/GBM PFS: 22±7% (These HSCT and chemotherapy estimates are grouped EFS for astrocytoma and glioblastoma multiforme) This AA PFS remained constant up to 5-years follow up (N=27)	1 AA/GBM year PFS 0% (N=56)	Chemo versus ABMR unstratified comparison of event-free survival: P=0.014	Finlay, 2008
			2 patients progressed at 1 and 4.2 mo (N=2)		Shih, 2008
			Median 6 mo (5-12) (86) 1 patient is alive without progression at 15+ mo (N=5)		Korones, 2006
			1 patient progressed at 11mo (N=1)		Sio, 2006
		~40 (N=10)		PFS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse P=.008	Massimino, 2005
		64±14 (N=11)			Grovas, 1999

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
		4 patients progressed at 2, 3, 4 and 7 months (N=4)			Jakacki, 1999
		1 patient was alive with no progression at last FU (N=1)			Busca, 1997
	3 Year	AA/GBM PFS: 22±7% (These HSCT and chemotherapy estimates are grouped EFS for astrocytoma and glioblastoma multiforme) This AA PFS remained constant up to 5-years follow up (N=27)	1 AA/GBM year PFS 0% (N=56)	Chemo versus ABMR unstratified comparison of event-free survival: P=0.014	Finlay, 2008
		~20 (N=10)		PFS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse P=.008	Massimino, 2005
		2 year PFS: 46±14 (N=11)			Grovas, 1999
		1 patient progressed at 34months (N=1)			Mahoney, 1996
	5 Year	AA/GBM PFS: 22±7% (These HSCT and chemotherapy estimates are grouped EFS for astrocytoma and glioblastoma multiforme) This AA PFS remained constant up to 5-years follow up (N=27)	1 AA/GBM year PFS 0% (N=56)	Chemo versus ABMR unstratified comparison of event-free survival: P=0.014	Finlay, 2008
		0 (N=10)		PFS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse P=.008	Massimino, 2005

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
Anaplastic Ependymoma	**1 Year**		91% (76-100%) (N=12)	Neurosurgical estimate of GTR vs. < GTR, P=.0001 Post-op radiographic residual tumor $1.5cm^2$ vs < $1.5cm^2$, P<.0001 No difference found for anaplastic vs. non-anaplastic progression	Robertson, 1998
		1 patient progressed at 27 mo (25) (N=4)			Ayan, 1995
	3 Year		65% (38-93%) (N=12)	Neurosurgical estimate of GTR vs. < GTR, P=.0001 Post-op radiographic residual tumor $1.5cm^2$ vs < $1.5cm^2$, P<.0001 No difference found for anaplastic vs. non-anaplastic progression	Robertson, 1998
	5 Year		35.2±11.0% (N=23)	Grade II vs. anaplastic P=.005	Jaing, 2004
			~14% (N=31)		Horn, 1999
			Complete resection 70% (± 14) (N=10) incomplete resection 36% (± 15) I (N=11) 52% (±11) all anaplastic ependymoma (N=21)	Resection: P=.09	Kuhl, 1998

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
			47% (17-61%) (N=12)	Neurosurgical estimate of GTR vs. < GTR, P=.0001 Post-op radiographic residual tumor 1.5cm^2 vs < 1.5cm^2, P<.0001 No difference found for anaplastic vs. non-anaplastic progression	Robertson, 1998
Non-anaplastic, mixed, or unspecified Ependymoma	**1 Year**		~88 (N=23)	Complete vs. partial resection not significant	Conter, 2009
			2 patients progressed at 1 mo and 1 at 1.4 mo (N=2)		Shih, 2008
			Non-metastatic: ~87% (N=80) Metastatic ~62.5% (N=9)		Grundy, 2007
		~63% (N=29)		EFS across the three age groups: <18 months, 18–35 months and 36 months significant difference P=0.04 GTR vs <GTR not significant	Zacharoulis, 2007
			2 patients progressed at 2 and 3 mo (N=2)		Sio, 2006
			~92% (N=64)		Merchant, 2002
			Median 2.1mo (.0-30.3) (N=13)		Hurwitz, 2001

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
			56% (N=73)	Posterior Fossa Tumor RR 2.1 (1-2.5) P=.05 Postoperative radiologic documented residuum RR 2.9 (1.6-5.1) P=.0004	Grill, 2001
		~22 (N=15)			Mason, 1998
		57 (31-83 95% CI) (N=14)			Grill, 1996
		1 patient progressed at 12 mo (N=7)			Mahoney, 1996
		75% (56-95%) (N=20)		Neurosurgical estimate of GTR vs. < GTR, P=.0001 Post-op radiographic residual tumor $1.5cm^2$ vs $< 1.5cm^2$, P<.0001 No difference found for anaplastic vs. non- anaplastic progression	Robertson, 1995
	3 Year		3 year PFS: 62.5 54.2 (N=23)	Complete vs. partial resection not significant	Conter, 2009
			metastatic: ~46% (N=80) Metastatic 0% (N=9)		Grundy, 2007
		~28% (N=29)		EFS across the three age groups: <18 months, 18– 35 months and 36 months significant difference P=0.04 GTR vs <GTR not significant	Zacharoulis, 2007

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
			:~71% (N=64)		Merchant, 2002
			23% (N=73)	Posterior Fossa Tumor RR 2.1 (1-2.5) P=.05 Postoperative radiologic documented residuum RR 2.9 (1.6-5.1) P=.0004	Grill, 2001
		0% (N=15)			Mason, 1998
		27 (0-55 95% CI) (N=14)			Grill, 1996
		54% (31-76%) (N=20)		Neurosurgical estimate of GTR vs. < GTR, P=.0001 Post-op radiographic residual tumor 1.5cm^2 vs < 1.5cm^2, P<.0001 No difference found for anaplastic vs. non-anaplastic progression	Robertson, 1995
	5 Year		54.2% (N=23)	Complete vs. partial resection not significant	Conter, 2009
			Non-metastatic: ~39% (N=80) Metastatic 0% (N=9)		Grundy, 2007

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
			Grade II: 67.5±11.0% (N=20) Age<3 (N=9) 22.2±13.9 Age>3 (N=34): 52.2±9% GTR (N=18): 71.8±10.7% STR (N=19): 30.7±11.3 Biopsy (N=6): 16.7±15.2% RT involved field (N=31) 52.3±9.3% RT without involved field (N=12): 31.3±14%	Gr II vs. Anaplastic P=.002 Age: P=.005 Surgical Resection: P<.001 Radiotherapy: P=.029	Jaing, 2004
			12% (N=73)	Posterior Fossa Tumor RR 2.1 (1-2.5) P=.05 Postoperative radiologic documented residuum RR 2.9 (1.6-5.1) P=.0004	Grill, 2001

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
			Overall: 42.2±5.5% (N=83) <3 years (N=29) ~18 >3 years (N=54): ~56 <GTR (N=48): ~23 GTR (N=35): ~71 Grade II (N=51): ~53	Age<3, Age >3: P<.01 Gender: P<.01 GTR: P<.01 Residual Disease by scan: P<.01 Histology Gr II vs Gr III: P<.01	Horn, 1999
			54% (31-76%) (N=20)	Neurosurgical estimate of GTR vs. < GTR, P=.0001 Post-op radiographic residual tumor $1.5cm^2$ vs < $1.5cm^2$, P<.0001 No difference found for anaplastic vs. non-anaplastic progression	Robertson, 1998
		2 patients alive with no disease progression at last follow up (N=2)			Busca, 1997
		14 (0-37 95% CI) (N=14)			Grill, 1996
CPC	1 Year		28.9% (9.0-48.0)% (N=15)		Grundy, 2010
			~56% (N=29)	CPC vs. CPP/APP HR=15.2, P<.0001 Chemotherapy yes vs. no, HR=6.4, P=.004	Wrende, 2009

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
		1 patient progressed at 4 months (N=1)			Gururangan, 1998
	3 Year		28.9% (9.0-48.0)% (N=15)		Grundy, 2010
			~56% (N=29)	CPC vs. CPP/APP HR=15.2, P<.0001 Chemotherapy yes vs. no, HR=6.4, P=.004	Wrende, 2009
	5 Year		21.7(5.3-45.1)% (N=15)	CPC vs. CPP/APP HR=15.2, P<.0001 Chemotherapy yes vs. no, HR=6.4, P=.004	Grundy, 2010
			~36% (N=29)	28 (7-100)% (N=29)	Wrende, 2009
Other Glioma	1 Year		HGG: 52.6 (33.2-763) (N=19)		Grundy, 2010
		1 patient with oligodendroglioma progressed at 8 mo. (N=1) 1 patients with anaplastic glioma progressed at 3 mo(N=3)			Thorarinsdottir, 2007
			BSG Median 1 mo (0-5 mo 95% CI) BSG 13 (0-35% 95% CI) (N=8)		Sio, 2006
			1 BSG patient progressed at 4 months, one at 8 months (N=2)		Korones, 2006
		1 year PFS: Other Glioma ~ 73 (9 AA and 2 Oligodendroglioma) (N=11)		PFS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse P=.008	Massimino, 2005

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Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
			BSG median 2.9mo (.1-19.8) (N=15) Malignant glioma Median 1.4mo (.4-7.2) (N=13) Miscellaneous glioma median 2.1mo (.6-12.9) (N=12)		Hurwitz, 2001
		1 year PFS Pontine glioma ~3 (N=35)			Bouffet, 1999
		5 Pontine glioma patients progressed Median 5 mo (3-12) (N=6) 1 patient was progression free at 12 months. (N=6)			Jakacki, 1999
		1 ODG patient was alive and progression free at last follow up (N=1)			Busca, 1997
		1 BSG patient progressed at 1 mo (N=1)			Mahoney, 1996
	3 Year		HGG: 24.1(7.8-45.1) (N=19)		Grundy, 2010
		2 patients with anaplastic glioma progressed at 17, and 33.5 mo (N=3)			Thorarinsdottir, 2007
			BSG 0		Sio, 2006
		3 year PFS: Other Glioma ~ 73 (9 AA and 2 Oligodendroglioma) (N=11)		PFS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse P=.008	Massimino, 2005
	5 Year		HGG: 18.1 (4.6-38.6) (N=19)		Grundy, 2010
		1 patient with ganglioma progressed at 59 mo (N=1)			Thorarinsdottir, 2007

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
		5 year PFS: Other Glioma ~ 73 (9 AA and 2 Oligodendroglioma) (N=11)		PFS for glioblastoma multiforme compared to other histotypes (AA and ODG) were significantly worse P=.008	Massimino, 2005
			Malignant Glioma 36 ± 10 (N=22)		Kuhl, 1998
Astrocytoma	1 year PFS N ≥ 10	Recurrent/Progressive: ~30% (Finlay N=27) [This estimate includes glioblastoma multiforme tumor types] Measured from time of myeloablative chemotherapy	Recurrent/Progressive: ~10 (Finlay N=56) [This estimate includes glioblastoma multiforme tumor types] Finlay et al measured from time of tumor recurrence		
Astrocytoma	1 year PFS N ≥ 10	**Newly Diagnosed: ~73%* (Massimo, 2005) [*This study included 9 Anaplastic Astrocytoma patients and 2 lower-grade oligodendroglioma patients.] Massimo measured from time of diagnosis**			
Glioblastoma Multiforme	1 year PFS N ≥ 10	Recurrent/Progressive: ~30% (Finlay N=27*) [*This estimate includes anaplastic astrocytoma tumor types] Measured from time of myeloablative chemotherapy	Recurrent/Progressive: ~10-42% (Finlay* N=56, Korones** N=7) [*This estimate includes glioblastoma multiforme tumor types, ** 1 patient DOD before progression] Finlay et al measured from time of tumor recurrence Korones time measurement uncertain		

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
Glioblastoma Multiforme	1 year PFS N ≥ 10	**Newly Diagnosed:** Grovas measured from time of stem cell rescue Massimo considered OS from date of chemotherapy 64 Grovas (N=11) ~40 Massimo (N=10)	**Recurrent/Progressive: (Korones N=7) 14%**		
Ependymoma	5 year PFS for studies with N ≥10 patients	**Newly Diagnosed** 12% (Zacharoulis (N=29)) Zacharoulis estimated PFS from date of diagnosis	**Newly Diagnosed Non-anaplastic, mixed, or unspecified Ependymoma:** 12-67% (Conter (N=23), Grill,2001 (N=73), Horn (N=51), Jaing (N=20), Robertson (N=20)) Conter and Jaing estimated OS from date of surgery, Grill measured from date of chemotherapy, Robertson measured from date of randomization, and horn measured from date of diagnosis. **Newly Diagnosed Anaplastic Ependymoma**: 14-52% (Jaing (N=23) , Horn (N=31), Kuhl (N=21), Robertson (N=12)) Jaing used date of surgery for PFS calculation, Horn used date of diagnosis, Kuhl used date of chemotherapy, and Robertson used date of randomization		Grundy *et al*. was not included in this estimate because the study stratified by metastasis finding a 5 year PFS of 0% for metastatic ependymoma and 46% for non-metastatic disease and measured the PFS from date of surgery.

Setting	Outcome	Intervention Single (%; ± 95% CI)	Comparator Chemo (%; ± 95% CI)	P-value	Study
Ependymoma	5 year PFS for studies with N ≥10 patients	**Recurrent/Progressive:** 14% (Grill, 1996 (N=14)) Grill measured PFS from date of autologous bone marrow transplant			Grundy *et al.* was not included in this estimate because the study stratified by metastasis finding a 5 year PFS of 0% for metastatic ependymoma and 46% for non-metastatic disease and measured the PFS from date of surgery.
CPC	5 Year PFS All studies:	1 patient progressed at 4 mo (Gururangan (N=1)) Gururangan assessed EFS after myeloablative chemotherapy	21.7-36% (Grundy (N=15) and Wrede (N=29)) Wrede measured EFS from date of diagnosis and Grundy used date of surgery		
AA= anaplastic ependymoma, AWD= Alive with disease, BSG, Brain stem glioma; CPC, Choroid plexus carcinoma; DOD=Dead of disease, GBM=Glioblastoma multiforme; HGG, high-grade glioma					

Appendix E. Neurodevelopmental and Neurocognitive Outcomes

Appendix Table E1. Neurocognitive and neurodevelopmental outcomes for treatment (HSCT) of inherited metabolic diseases with rapid progression

Disease	Neurocognitive Pre-Intervention	Neurocognitive Post-Intervention	Neurodevelopmental Pre-Intervention	Neurodevelopmental Post-Intervention	Study treatment, study design (N)
Wolman disease	nr	pt 1 at 11 yrs post: mildly impaired cognitive abilities, sustained visual attention impaired, verbal fluency avg, attends special school, mostly homeschooled, no behavior problems, English and Spanish language development pt 4 at 4 yrs post: cognition improved from baseline, receptive and expressive language high avg, adaptive skills avg, emotional and social behavior avg, attends special education preschool, speaks 3 languages	pt 1: considerable developmental delay pt 4: nr	pt 1 at 11 yrs post: motor function improved pt 4 at 4 yrs post: fine motor skills below avg, gross motor skills avg	Tolar J, US, 2009 (1370), HSCT, case series (N=4)
	nr	nr	failure to thrive	nr	Gramatges MM, US, 2009 (83290), HSCT, case report (N=1)
	MRI showed 0.5 yr delay in myelination	MRI showed appropriate myelination for age at 1 yr post at 4 yrs post, pt has normal intellectual development, attends regular school, and speaks Russian and Hebrew	weight, height, and head circumference at <3rd percentile	at 4 yrs post: weight 10th percentile, height 3rd percentile, head circumference 3rd percentile	Stein J, Israel, 2007 (4880), HSCT, case report (N=1)

Disease	Neurocognitive Pre-Intervention	Neurocognitive Post-Intervention	Neurodevelopmental Pre-Intervention	Neurodevelopmental Post-Intervention	Study treatment, study design (N)
Niemann-Pick Type A	neurologically intact	neurological regression: alert, socially engaged, verbalizing appropriately for age at 0.6 yrs post brain CT shows bilateral cerebral atrophy at 0.6 yrs post limited social interaction , seizure disorder developed at 1.7 yrs post	nr	alert, active, interactive, rolling back to front to back at 0.6 yrs post head lag and hypotonic at 1 yr post significant developmental delay, unable to sit or stand at 1.7 yrs post	Morel CF, Canada, 2007 (3010), HSCT, case report
	pt 1 and 2: normal MRI/CAT, EEG pt 1: Denver Developmental Exam, 2-3 mos (real age 10 mos) pt 2: Gessell Schedules, appropriate for age at 4 mos	pt 1 and 2: neurological deterioration seen in MRI/CAT, EEG pt 2 at 6 mos post: mild developmental delay, cognitive skills at 7-8 mos (real age 11 mos) pt 2 at 12 mos post: moderate developmental delay, cognitive skills 12 mos (real age 167mos)	pts 1 and 2: hyponic, depressed reflexes	pt 2 at 6 mos post: moderate developmental delay, motor skills at 6 mos (real age 11 mos) pt 2 at 12 mos post: severe developmental delay, motor skills at 6 mos (real age 17 mos)	Bayever E, US, 1995 (25460), HSCT, case series (N=2)
Mucolipidosis II (I-cell disease)	nr	nr	failure to thrive	nr	Li CK, China, 2004 (9070), HSCT, case series (n=1)
	real age: 1.4 yrs expressive language and receptive language: 0.9 yrs	real age: 3.0 yrs, developmental age: 1.6 yrs real age: 3.5 yrs, developmental age: 2.1 yrs real age: 4.7, developmental age: 3.3 yrs real age: 5.7 yrs, developmental age: 4.3 yrs real age: 6.7 yrs, developmental age: 5.3 yrs attends school with individualized education program; slow progress in communication, daily living, socialization, and expressive language; mild to moderate cognitive impairment	real age: 1.4 yrs developmental age: 0.9 yrs	real age: 3.0 yrs, gross motor age: 1.2 yrs real age: 3.5 yrs, gross motor age: 1.3 yrs real age: 4.7 yrs, gross motor age: 1.5 yrs real age: 5.7 yrs, gross motor age: 1.5 yrs real age: 6.7 yrs, gross motor age: 1.5 yrs gross motor skills impaired fine motor skills slowly developing	Grewel S, US, 2003 (9750), HSCT, case report

Disease	Neurocognitive Pre-Intervention	Neurocognitive Post-Intervention	Neurodevelopmental Pre-Intervention	Neurodevelopmental Post-Intervention	Study treatment, study design (N)
	nr	exhibiting emotional expressions	moderate to severe joint contractures, marked short stature, dystosis multiplex severe psychomotor retardation	no change in joint contractures still severe psychomotor retardation, but gained 4-8 mo-old skills of sitting up and using walker	Imaizumi M, 1994, Japan, (23220B), HSCT, case series (n=1)

Appendix Table E2. Neurocognitive and neurodevelopmental outcomes for treatment (HSCT) and comparators (ERT, substrate reduction therapy) of inherited metabolic diseases with slow progression

Disease	Neurocognitive Pre-Intervention	Neurocognitive Post-Intervention	Neurodevelopmental Pre-Intervention	Neurodevelopmental Post-Intervention	Study treatment, study design (N)
MPS II (Hunter's disease)	**Severe form:** IQ/DQ: pt 2: 72 pt 4: 70 pt 5: 70 pt 6: 65 pt 8: 100	**Severe form:** IQ/DQ: pt 2: 60, very poor language pt 4: <50, no language pt 5: <50, speech loss 3 yrs post pt 6:<50, speech loss 8 yrs post, pt 8: <50, poor language all 5 attend special schools	**Severe form:** nr	**Severe form:** 2 no motor problems 3 bedridden	Guffon, France, 2009 (680), HSCT, case series (N=8)
	Attenuated form: IQ/DQ: pt 1: 125 pt 3: 87 pt 7: 100	**Attenuated form:** IQ/DQ: pt 1: 110, normal language pt 3: 65, poor language pt 7: 100 2 attend mainstream school, 1 attends special apprenticeship 3 sociable	**Attenuated form:** nr	**Attenuated form:** 3 no motor problems	
	Form not specified: nr	**Form not specified:** nr	**Form not specified:** nr	**Form not specified:** nr	Page, US, 2008 (1280B), HSCT, case series (n=2)
	Form not specified: real age: 5.9 yrs mental age: 2.3 yrs MRI: brain atrophy	**Form not specified:** real age: 6.5 yrs mental age: 2.5 yrs at autopsy: brain cells distended from accumulation of substrate	**Form not specified:** nr	**Form not specified:** nr	Tokimasa, Japan, 2008 (1310), HSCT, case series (n=1)
	Attenuated form: pt 1: lesions in white matter and corpus callosum pt 2: enlargement of perivascular spaces at basal ganglia, intensity changes in periventricular white matter pt 3: lesions in parietal and occipital lobes, intensity in white matter	**Attenuated form:** pt 1: no follow-up MRI pt 2: no change at 7 yrs post pt 3: lesions slightly diminished at 2.5 yrs post	**Attenuated form:** nr	**Attenuated form:** nr	Seto, Japan, 2001 (13460A), HSCT, case series (n=3)

Disease	Neurocognitive Pre-Intervention	Neurocognitive Post-Intervention	Neurodevelopmental Pre-Intervention	Neurodevelopmental Post-Intervention	Study treatment, study design (N)
	Severe form: DQ and MRI findings: 1 HSCT pt: 72, ventricular dilatation present, white matter lesions 2 non-HSCT pts: 94 and 124, no ventricular dilatation, lesions in white matter	**Severe form:** DQ and MRI findings: 1 HSCT pt: 61 and 54 at 0.5 yrs and 1.1 yrs post, ventricular dilatation worsened, white matter lesions 2 non-HSCT pts: no follow-up measurement	**Severe form:** nr	**Severe form:** nr	Takahashi, Japan, 2001 (14030), HSCT, comparative study (n=1)
	Attenuated form: nr	**Attenuated form:** "developing and growing normally"	**Attenuated form:** nr	**Attenuated form:** "growing and developing normally"	Mullen, US, 2000 (15300), HSCT, case report
	Attenuated form: IQ: 72	**Attenuated form:** IQ: 69, 70, and 70 at 0.7 yrs, 2.6 yrs, and 4.0 yrs post	**Attenuated form:** significant joint limitations in hands, knees, elbows	**Attenuated form:** mild joint limitations at 0.7 yrs post minimal joint limitations at 2.6 yrs post	Coppa, Italy, 1999 (16350), HSCT, case report
	Form not specified: Griffiths Mental Development Scale: pt 1: social 61, speech 61 pt 2: social 71, speech 71 pt 3: social 93, speech 93	**Form not specified:** Griffiths Mental Development Scale: pt 1 at 10 yrs post: social 10, speech 10; steady deterioration pt 2: social 2, speech 2, steady deterioration pt 3: full IQ 78, verbal IQ 80 performance IQ 81; attends mainstream school, trouble with concentration	**Form not specified:** Griffiths Mental Development Scale: pt 1: locomotor 63, eye-hand 58 pt 2: locomotor 55, eye-hand 58 pt 3: locomotor 110, eye-hand 93	**Form not specified:** Griffiths Mental Development Scale: pt 1 at 10 yrs post: locomotor 11, eye-hand 8 pt 2 at 2.7 yrs post: locomotor 6.5, eye-hand 2.5 pt 3: nr	Vellodi, England, 1999 (16650), HSCT, case series (N=9)
	Severe form: IQ: 44	**Severe form:** IQ: 44 at 3 yrs post	**Severe form:** multiple bone abnormalities	**Severe form:** improvements in joint range of motion improvements in fine and gross motor skills	Li, US, 1996 (20260), HSCT, case report

Disease	Neurocognitive Pre-Intervention	Neurocognitive Post-Intervention	Neurodevelopmental Pre-Intervention	Neurodevelopmental Post-Intervention	Study treatment, study design (N)
	Severe form: Mild behavioral difficulties	**Severe form:** Decreasing intelligence ratio (age equivalent/real age) from 0.68 at 2.8 yrs of age to 0.09 at 8.0 yrs of age Increased behavioral problems, reversion in language, communication, concentration, cooperation, and attention span.	**Severe form:** real age: 1.9 yrs developmental age: 1.3-1.5 yrs	**Severe form:** persistent skeletal deformities reversion in balance and coordination though can still walk and ride tricycle	McKinnis, US, 1996 (20560), HSCT, case report
	Form not specified: DQ: normal	**Form not specified:** DQ not reported	**Form not specified:** stiff joints dystosis multiplex	**Form not specified:** joint mobility improved dystosis multiplex stabilized	Hoogerbrugge PM, Netherlands, 1995 (21780B), HSCT, case series (n=1)
	Form not specified: Brunet-Lezine scales: mental age: 25 mos real age: 31 mos good socialization	**Form not specified:** Brunet-Lezine scales: at 3 mos post: mental age: 2 yrs real age: 3 yrs worsening of verbal capabilities, measured at 10 mos level at 20 mos post: mental age: 2.5 yrs real age: 4.5 yrs no change in verbal capabilities	**Form not specified:** mild flexion contractures good motor capabilities	**Form not specified:** joint mobility improved growth in ht and wt	Coppa GV, Italy, 1995 (21950), HSCT, case report
	Attenuated form: Stanford-Benet scales: within normal range, attends regular school	**Attenuated form:** no decrease in school performance, has plans for college	**Attenuated form:** moderate mobility impairment due to deformed bones, joints energy & activity normal ht: <5th percentile, wt: 5th-10th percentile, head circumference: 98th percentile	**Attenuated form:** moderate improvement in joint flexibility growth spurt	Bergstrom SK, US, 1994 (22650), HSCT, case report

Disease	Neurocognitive Pre-Intervention	Neurocognitive Post-Intervention	Neurodevelopmental Pre-Intervention	Neurodevelopmental Post-Intervention	Study treatment, study design (N)
	Attenuated form: no CNS involvement, attends regular school	**Attenuated form:** no change	**Attenuated form:** moderate to severe join contractures nodular hypertrophy present	**Attenuated form:** improvement in joint contractures nodular hypertrophy absent	Imaizumi, Japan, 1994 (23220A), HSCT, case series (n=1)
	Attenuated form: nr	**Attenuated form:** nr	**Attenuated form:** 6-minute walk test: placebo: 374.7 ERT .15 mg/kg: 448.7 ERT .5 mg/kg: 324.3 ERT 1.5 mg/kg: 439.7	**Attenuated form:** Changes in 6-minute walk test: 6 mos: no change 12 mos: 8 improved, 4 no change	Muenzer, US, 2007 (57070), ERT, open label extension (N=12)
	Attenuated form: nr	**Attenuated form:** nr	**Attenuated form:** 6-minute walk test: placebo: 392 +/- 19 ERT EOW: 401 +/- 18 ERT wkly: 392 +/- 19	**Attenuated form:** Changes in 6-minute walk test: placebo: 7.3 +/- 9.5 ERT EOW: 30.3 +/- 10.3 (p=0.07) ERT wkly: 44.3 +/- 12.3 (p=0.01)	Muenzer, US, 2006 (57160), ERT, RCT (N=96)
MPS III (Sanfilippo disease)	nr	nr	nr	nr	Ringden, Sweden, 2006 (5940B), HSCT, case series (n=1)
	nr	no significant neuropsychological improvement	nr	nr	Lange, Brazil, 2006 (5690), HSCT, case series (n=1)
	nr	developmental quotients decreasing with age from 99 at 1.5 yrs of age to 6 at 10 yrs of age	nr	pt immobile at 7.4 yrs post, wheelchair bound like sibling who was untreated	Sivakumar, England, 1999, (16200), HSCT, comparative study (n=1)
	DQ: pt 1: 72, hyperactive pt 2: 80, monosyllabic pt 3: 38, dystonic, dysarthric	DQ: pt 1:41, dysarthric pt 2: 50, hypotonic pt 3: 26, no speech	nr	nr	Hoogerbrugge PM, Netherlands, 1995 (21780A), HSCT, case series (n=3)

Disease	Neurocognitive Pre-Intervention	Neurocognitive Post-Intervention	Neurodevelopmental Pre-Intervention	Neurodevelopmental Post-Intervention	Study treatment, study design (N)
	Ruth Griffiths Mental Development: pt 1: 82 pt 2: 95 functioning in low-average range Social skills: pt 1 and 2: normal	Ruth Griffiths Mental Development: pt 1: 35-40 pt 2: 15-25 significant developmental delays, both attend special school though scores decreased, it is unknown if the decreases would have been greater without HSCT; untreated brothers are severely retarded Social skills: pt 1: normal pt 2: anti-social	Overall growth: pt 1 and 2: normal	Overall growth: pt 1: pubertal development pt 2: has no pubertal development Untreated brothers are wheelchair-bound; unclear if neurodevelopment better for treated sisters due to treatment or if differences due to heterogeneic variations of disease	Vellodi A, England, 1992, (25600), HSCT, case series (N=2)
MPS IV (Morquio syndrome)	no pathological findings in brain or spinal cord MRI	nr	mild bone deformities	nr	Seto, Japan, 2001 (13460B), HSCT, case series (n=1)
	nr	nr	aortic stenosis left ventricular dilatation	no change	Gatzoulis MA, England, 1995 (21610), HSCT, case series (n=1)
Gaucher Type 3	nr	borderline mental retardation in 2 pts	bone problems in 1 pt	bone problems stable in 1 pt	Goker-Alpan 2008, US, HSCT followed by ERT, case series (n=2)
	Weschler Intelligence Scales: performance: 67 verbal: 69 complete: 67	Weschler Intelligence Scales at 1.5 yrs post: performance: 60 verbal: 69 complete: 62	nr	stable growth and improved bone density	Chen R, Taiwan, 2007 (4490), HSCT, case report

Disease	Neurocognitive Pre-Intervention	Neurocognitive Post-Intervention	Neurodevelopmental Pre-Intervention	Neurodevelopmental Post-Intervention	Study treatment, study design (N)
	Weschler Intelligence Scales: pt 1: stanine 7	Weschler Intelligence Scales: pt 1: stanine 7, 5, 6, 7, 7 (at 1 yr, 3 yrs, 5 yrs, 8 yrs, 10 yrs post); IQ=112-120 pt 2: stanine 7 (at 6 yrs post) pt 3: stanine 3 (at 4 yrs post) pt 4: below age (did not engraft, on ERT) pt 5: RA**: 5; DA**: 5 pt 6: RA: 5; DA: 3 (at 1 yr post) pre-transplant data not given for pts 2, 5, and 6, but authors state psychological development was excellent in these 3 pts	Skeletal involvement: pts 1, 5, 6: kyphosis pts 2, 3, 4: no kyphosis Growth: below average	Skeletal involvement pts 1, 5, 6: kyphosis pts 2, 3, 4: no kyphosis Growth: All 6 have growth spurt, even pt 4 who did not engraft and is on ERT	Ringden O, Sweden, 1995 (22020), HSCT, case series (N=6)
	RA**: 22 mos; DA**: 15 mos Developmental Quotient=68	RA: 33 mos; DA: 21 mos; DQ=64 at 0.7 yrs post RA: 39 mos; DA: 25 mos; DQ-=64 at 1.1 yrs post bilingual at 1.6 yrs post	Failure to thrive, height < 3rd percentile	Height at 10th percentile at 9 mos post Height at 50th percentile at 2 yrs post	Tsai P, US, 1992, (25120), case report
	nr	No statistically significant differences between study grps using Purdue Peg Board test, Wechsler Scale, Benton visual retention test, Rey auditory verbal learning test, d2 test of attention, continuous performance test, and Trail Making Test.	nr	No treatment effect on Vertical Saccadic Eye Movement Study may not have been long enough for neurological defects to improve, or neurological defects are irreversible.	Schiffman R, Netherlands, 2008 (56750), substrate reduction therapy with ERT, RCT (N=30)
	nr	nr	Grading severity level of marrow involvement: 0A level: 3 pts 2A level: 6 pts 3A level: 1 pt 3B level: 1 pt	0A level: 1 constant and 2 worsened 2A level: 5 complete improvement and 1 constant 3A level: 1 constant 3B level: 1 constant	El-Beshlawy A, Egypt, 2006 (5750), ERT, case series (n=11)
	nr	Behavioral and learning difficulties developed after stopping ERT Recurrent seizures 2.6 yrs after stopping ERT	height <3rd percentile	improved growth	Chan LL, Malaysia, 2002 (11330), ERT, case report

Disease	Neurocognitive Pre-Intervention	Neurocognitive Post-Intervention	Neurodevelopmental Pre-Intervention	Neurodevelopmental Post-Intervention	Study treatment, study design (N)
	nr	nr	nr	no change in skeletal deformities	Banjar H, Saudi Arabia, 1998 (17920), ERT, case series (n=3)
	3 mild-moderate mental retardation 2 normal IQ	no change in IQ 1 showed clinical function deterioration cerebrospinal fluid measurements showed that glucocerebrosidase delivery to the cerebrospinal fluid was minimal (not significantly different)	nr	nr	Schiffmann R, Netherlands, 1997 (58150), ERT, case series (n=5)
	EEG normal for all pts Weschler Intelligence Scales: pt 1: 82-88 Griffith Scale: pt 2: 82-88 pt 3: 104-111	EEG normal for all pts Weschler Intelligence Scales: pt 1: 89-96 at 1.3 yrs post Griffith Scale: pt 2: 74-81 at 1 yr post pt 3: 97-103 at 1 yr post all 3 pts became more active and needed less sleep pts 2 and 3 were tired and slow and became active pre-schooler post treatment	pt 1: femur deformity, kyphosis, cortex thinning pt 2: grew 2 cm/yr pt 3: grew 4 cm/yr, femur deformity	pt 1: no change in skeletal deformities pt 2: grew 9 cm 1 yr post pt 3: grew 12 cm 1 yr post, no change in skeletal deformities	Erikson A, Sweden, 1995 (21630), ERT, case series (n=3)
Aspartyl-glucos-aminuria	pt 1: developmental age 4.7 yrs below real age pt 2: nr	pt 1 and 2: developmental age stabilizes at 5 yrs pt 1 and 2: mentally retarded, speaks in sentences, understands Swedish and Finnish words	nr	pt 1: can walk, ride bike, dress self pt 2: can walk, ride bike, drive tractor, some fine motor skills	Malm G, Sweden, 2004 (8490), HSCT, case series (N=2)
	nr	5 HSCT: developmental age was on average 5 yrs lower than real age 12 non-HSCT: developmental age was on average 3.4 yrs lower than real age HSCT pts may have lower developmental ages because 2 pts with more severe disease were chosen for HSCT	nr	Dysmorphic Facial and Body Features remained unchanged following HSCT	Arvio M, Finland, 2001 (14180), HSCT, comparative study (n=5)

Disease	Neurocognitive Pre-Intervention	Neurocognitive Post-Intervention	Neurodevelopmental Pre-Intervention	Neurodevelopmental Post-Intervention	Study treatment, study design (N)
	2 HSCT: poor cortex-white matter differentiation, decreased thalami signal intensity 6 non-HSCT: poor cortex-white matter differentiation, decreased thalami signal intensity	2 HSCT: slight improvement from poor to evident cortex-white matter differentiation, improvement in thalami signal intensity, improvement in concentration and cooperation	both HSCT pts: gross motor clumsiness, slight balance problems	nr	Autti T, Finland, 1999 (15540), HSCT, comparative study (n=2)
	mild global delay	nr	nr	nr	Laitinen A, Finland, 1997 (19620), HSCT, case report
Niemann-Pick Type C	real age: 2.4 yrs developmental age: 0.8-1.2 yrs developmental regression began prior to transplant, no speech development in previous yr MRI pre-transplant showed normal myelination and no obvious brain atrophy	real age: 2.6 yrs, developmental age: 0.4-0.7 yrs real age: 2.9 yrs, developmental age: 0.3-0.4 yrs real age: 3.3 yrs, developmental age: 0.2-0.3 yrs MRI 0.5 yrs post-transplant showed normal myelination and evident brain atrophy	1.2 yrs: sat without support and crawled 2.4 yrs: pt became bed-ridden during conditioning phase	6-9 mos post: head lag, could not raise body	Hsu YS, Taiwan, 1999 (16540), HSCT, case report
	MRI: normal brain activity	MRI: developing neurologically, but with delayed speech	mildly hypotonic normal developmental milestones (standing)	fine motor coordination (can hold pencil, draw) at 1.7 yrs post tolerates normal activity walks independently	Bonney DK, England, 2009, (81700) HSCT, case report
	nr	nr	Standard ambulation index: 2.0 (0.7-3.3)	Standard ambulation index: 1 yr: 2.3 (0.6-4.0) 2 yrs: 2.6 (0.7-4.5) 8 of 10 pts are considered stable in ambulation	Patterson MC, US, 2010 (56500), substrate reduction therapy, open label extension (N=12)

Disease	Neurocognitive Pre-Intervention	Neurocognitive Post-Intervention	Neurodevelopmental Pre-Intervention	Neurodevelopmental Post-Intervention	Study treatment, study design (N)
	nr	Change in composite disability score combined pediatric and adult pts: greater treatment effect was seen in subset of those with neurological disease	at diagnosis, mean scores: ambulation: 0.18, manipulation: 0.27, language: 0.16, swallowing: 0.12 at start of treatment: overall deterioration of scores	at last clinical visit, % with stable/improved scores: ambulation: 76.6%, manipulation: 76.2%, language: 77.0%, swallowing: 81.0%	Pineda M, Spain, 2009 (56560)*, substrate reduction therapy, retrospective cohort (N=66)
	modest cognitive abilities	3 mos: some improvement in adaptive social domains 6 mos: regression, speech decline 12 mos: <0.1 percentile in developmental scales	proximal weakness in extremities ataxic hand tremor motion analysis: walked 0.24 m/sec, 62 steps/min	3 mos: hand tremor diminished 9-12 mos: lost ability to walk motion analysis at 6 mos: walked 0.12 m/sec, 32.4 steps/min	Paciorkowski AR, US, 2008 (2980), substrate reduction therapy, case report
	nr	Mini-mental status examination data only provided for pts >=12 yrs: difference between treated and untreated groups, p=0.165	nr	Ambulatory index data only provided for pts >=12 yrs: difference between treated and untreated groups, p=0.052	Patterson MC, US, 2007 (56970)*, substrate reduction therapy, RCT (n=12)

*cannot separate adult and pediatric data within this study
**RA: real age, DA: developmental age

Appendix Table E3. Neurocognitive and neurodevelopmental outcomes for treatment (HSCT) and comparators (ERT, substrate reduction therapy) of inherited metabolic diseases with both rapid and slow progression

Disease	Neurocognitive Pre-Intervention	Neurocognitive Post-Intervention	Neurodevelopmental Pre-Intervention	Neurodevelopmental Post-Intervention	Study (record #), treatment, study design (N)
Farber disease	**Type 2/3, with no CNS involvement** nr	**Type 2/3, with no CNS involvement** nr	**Type 2/3, with no CNS involvement** # subcutaneous nodules: pt 1: 58 pt 2: 39 pt 3: 18 # joints with limited motion: pt 1: 26 pt 2: 24 pt 3: 10	**Type 2/3, with no CNS involvement** # subcutaneous nodules: pt 1: 8 at 1.2 yrs post pt 2: 14 at 0.5 yrs post pt 3: 0 at 0.7 yrs post # joints with limited motion: pt 1: 2 at 1.2 yrs post pt 2: 4 at 0.5 yrs post pt 3: 4 at 0.7 yrs post	Ehlert K, Germany, 2006 (4690), HSCT, case series (N=3)
	Type 2/3, with no CNS involvement nr	**Type 2/3, with no CNS involvement** nr	**Type 2/3, with no CNS involvement** # subcutaneous nodules: pt 1: 58 pt 2: 39 # joints with limited motion: pt 1: 26 pt 2: 24	**Type 2/3, with no CNS involvement** # subcutaneous nodules: pt 1: 8 pt 2: 12 # joints with limited motion: pt 1: 2 pt 2: 2	Vormoor J, Germany, 2004 (9420), HSCT, case series (N=2)
	Type 1, with CNS involvement normal myelination at 0.75 yrs Bayley Scales of Infant Development: developmental age and real age equivalent at time of transplant (0.75 yrs)	**Type 1, with CNS involvement** normal myelination at 0.3 yrs post, decrease in grey and white matter differentiation at 0.7 yrs post, poor grey and white matter contrast at 1.3 yrs post development age plateaued at 0.6 yrs at real age of 1.3 yrs and 2.1 yrs	**Type 1, with CNS involvement** wt, ht, and head circumference: 10th-25th percentile	**Type 1, with CNS involvement** wt, ht, and head circumference: 5th percentile at 0.8 yrs post <5th percentile at 1.5 yrs post	Yeager AM, US, 2000 (14880), HSCT, case report
	Type 1, with CNS involvement mental regression	**Type 1, with CNS involvement** mental regression worsened, cerebral atrophy seen in brain imaging	**Type 1, with CNS involvement** unable to stand decreased tendon reflexes	**Type 1, with CNS involvement** regression of motor abilities increasing tremor	Hoogerbrugge, PM, Netherlands, 1995 (21780D), HSCT, case series (n=1)

Disease	Neurocognitive Pre-Intervention	Neurocognitive Post-Intervention	Neurodevelopmental Pre-Intervention	Neurodevelopmental Post-Intervention	Study (record #), treatment, study design (N)
GM$_1$ ganglio-sidosis	**juvenile form:** nr	**juvenile form:** normal language development at 0.6 yrs post language declining at 1.7-2.1 yrs post demyelination and diffuse cerebral function at 2.4 yrs post no language at 4.0 yrs post	**juvenile form:** nr	**juvenile form:** walking at 0.6 yrs post became clumsy at 1.7-2.1 yrs post limited motor skills at 4.0 yrs post wheelchair at 6.0 yrs post	Shield JPH, England, 2005 (6720), HSCT, case report
Tay-Sachs disease	**form not specified:** nr	**form not specified:** nr	**form not specified:** nr	**form not specified:** nr	Page KM, US, 2008 (1280A), HSCT, case series (n=1)
	form not specified: mental regression brain imaging showed widened subarachnoidal spaces	**form not specified:** vegetative state no brain imaging follow-up	**form not specified:** psychomotor retardation myoclonic jerks	**form not specified:** vegetative state	Hoogerbrugge PM, Netherlands, 1995 (21780C), HSCT, case series (n=1)
	juvenile form: nr	**juvenile form:** MRI shows cerebral atrophy at 0.5 yrs post worsening neuropsychological test scores at 0.5 yrs post speech deteriorating at 0.5 yrs post	**juvenile form:** nr	**juvenile form:** motor skills deteriorating at 0.5 yrs post Deterioration of this pt similar to deterioration of untreated older sister	Jacobs JFM, Netherlands, 2005 (6740), HSCT with substrate reduction therapy added at 2 yrs post, case report
	juvenile form: pt 1: mild cognitive impairment, attends regular school with assistance pt 2: severe cognitive impairment, generalized seizures	**juvenile form:** pt 1: at 15 mos acute psychotic event pt 2: at 15 mos marked increase in seizures, alertness deteriorated, at 24 mos spasticity increased	**juvenile form:** pt 1: mild muscle weakness, moderate muscle impairment, independent feeding and ambulation pt 2: needs support for ambulation	**juvenile form:** pt 1: at 6 mos handwriting deteriorated, at 12 mos fine tremor in hands, from 12-24 mos, progressive muscle atrophy pt 2: at 15 mos muscle bulk decreased markedly, at 24 mos wheelchair dependent	Maegawa GHB, Canada, 2009 (56590B), substrate reduction therapy, single arm (n=2)

Disease	Neurocognitive Pre-Intervention	Neurocognitive Post-Intervention	Neurodevelopmental Pre-Intervention	Neurodevelopmental Post-Intervention	Study (record #), treatment, study design (N)
ceroid lipo-fuscinosis	cerebral cortical atrophy: moderate in one pt, not detectable in 2 pts periventricular white matter hyperintensity: mild in 1 pt, not detectable in 2 pts	cerebral cortical atrophy: moderate became severe in one pt, not detectable became moderate in two pts periventricular white matter hyperintensity: mild became severe in one pt, not detectable became moderate in two pts	one pt mildly symptomatic and two pts asymptomatic	all three pts by end of follow-up at 2-4 yrs of age were hypotonic and spastic, with some head control remaining	Lonnquist T, Finland, 2001 (12960), HSCT, case series (N=3)
Sandhoff's disease	nr	nr	nr	nr	Ringden O, Sweden, 2006 (5940B), HSCT, case series (n=1)
	pt 1: severe cognitive dysfunction, hallucinations, agitation, scores 1.5 yrs below age pt 2: episodic psychosis, cognitive function well-preserved, works part time pt 3: 2 episodes of psychosis, IQ=75	pt 1: neuropsych scores unchanged pt 2: 18 mos post, neuropsych scores stable, speech less intelligible, hallucinations reduced, anxiety ongoing pt 3: at 16 mos post, spasticity developed, anxiety aggravated, neuropsych scores stable	pt 1: muscle wasting, fully dependent for feeding and ambulation pt 2: moderate skeletal muscle weakness, independent ambulation, feeding, bathing pt 3: independent ambulation, feeding, and bathing	pt 1: 3 mos incoordination progressed, 15 mos wheelchair, 21 mos can't stand pt 2: at 18 mos gait disturbance progressed & muscle strength reduced pt 3: 6 mos gait disturbance, 16 mos notable wt loss pt 2 and pt 3 stopped tx at 21 mos due to excessive weight loss	Maegawa GHB, Canada, 2009 (56590A), substrate reduction therapy, single arm (n=3)

Appendix F. C-Peptide and HbA1c Outcomes

In all studies, serum C-peptide levels were measured using radioimmunoassay. To accommodate differences in data presentation and analysis, they are presented in the tables as a percentage change from values at study entry.

C-Peptide Level

Data on C-peptide levels were reported in all three studies included in this review, at follow-up times that range from 6 months in one IIT study (Crino et al, 2005, rec#23080) to more than 4 years in the HSCT study (Couri et al, 2009, rec#290) (Table F1). The proportional change in C-peptide levels in the HSCT study refer only to patients who remained continuously insulin free.

AppendixTable F1. C-peptide levels following autologous HSCT or IIT in pediatric patients

Outcome	Intervention % Δ in Mean Value	Comparator % Δ in Mean Value	p-value (vs Mean Baseline Value)	Study (rec#)
6 months	+ ~ 113 (n = 11)		< 0.001	Couri et al, 2009 (290)
1 year	+ ~ 100 (n = 12)		0.001	
2 year	+ 249 (n = 8)		< 0.001	
3 year	+ 224 (n = 3)		0.001	
4 year	NR (n = 1)		NR	
1 year		+ 131 (n = 27)	NS	Crino et al, 2005 (23080)
2 year		+ 119 (n = 27)		
6 months		- 20 (n = 8)	0.05	Mastrandrea et al, 2009 (40050)

The data in Table F1 show that C-peptide levels following a mixed-meal tolerance test were significantly increased above baseline values in the HSCT study (Couri et al, 2009, rec#290) for more than two years in 8 of 12 patients who became continuously insulin free following the procedure. In one IIT study, mean fasting C-peptide levels were not changed significantly at 1 or 2 years following initiation of treatment from that at study entry (Crino et al, 2005, rec#23080). In the

second IIT study, the mean C-peptide level following a Boost meal test was slightly lower at 6 months following initiation of treatment than that at study entry (Mastrandrea et al, 2009, rec#40050).

Hemoglobin A1C Levels

Table F2 shows HbA1C levels in patients treated with nonmyeloablative autologous HSCT (Couri et al, 2009, rec#290) or IIT (Crino et al, 2005, rec#23080; Mastrandrea et al, 2009, rec#40050).

Hemoglobin A1C (HbA1C) levels pretransplant ranged from 5.4% to 11.6% (mean 8.4 ± 1.6%) among 18 pediatric patients in the HSCT study (Couri et al, 2009, rec#290). Among those who became continuously insulin-free, HbA1C declined from a mean 8.0% to 5.7%, 5.7%, 5.5%, and 6.0%, respectively, at 12, 24, 36, and 48 months after transplantation (p < 0.001 at all time points versus pretreatment value).

In one IIT study, HbA1C did not change significantly from a mean 10.5 ± 2.2% at diagnosis to 5.4 ± 0.8% and 6.5 ± 0.9% at 12 and 24 months, respectively (Crino et al, 2005, rec# 23080). In the second IIT study, mean HbA1C at study entry (12.4 ± 2.5%) declined to an average 7.0 ± 1.2% (p-value NR) (Mastrandrea et al, 2009, rec#40050).

AppendixTable F2. HbA1C levels following autologous HSCT or IIT in pediatric patients

Outcome	Intervention % Δ in Mean Value	Comparator % Δ in Mean Value	p-value (vs Mean Baseline Value)	Study (rec#)
3 months	- 32		< 0.001	Couri et al, 2009 (290)
1 year	- 29			
2 year	- 29			
3 year	- 31			
4 year	- 25			
1 year		- 48	NS	Crino et al, 2005 (23080)
2 year		- 38		
6 months		- 44	NR	Mastrandrea et al, 2009 (40050)