Topic Brief: Colony-Stimulating Factors for Cancer Patients

Date: 5/27/2022
Nomination Number: 0984

Purpose: This document summarizes the information addressing a nomination submitted May 11, 2022, through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue: The evidence on the benefits and risks of colony-stimulating factors (CSFs) in people with cancer continues to evolve, and the current guidelines from the American Society of Clinical Oncology (ASCO) are from 2015. The nominator for this topic has requested a systematic review of the literature to inform the update of this guideline.

Findings: The scope of this topic met all EHC Program selection criteria and was considered for a systematic review. However, it was not selected.

Background

In 2019, approximately five percent of the United States population was cancer survivors, and this percentage is expected to increase by just over 30 percent by 2023.[1] Chemotherapy, a treatment for cancer, can cause neutropenia.[2] Neutropenia is a decrease in the body's white blood cells, which provide defense against infection. Febrile neutropenia (fever during neutropenia) has been shown to occur in six percent of adults with solid tumors treated with myelosuppressive chemotherapy,[3] and is associated with increased morbidity, mortality, and treatment costs.[4] Risk factors for developing febrile neutropenia include advanced age, female sex, poor performance status, poor nutritional status, high chemotherapy dose intensity, and low baseline and first-cycle nadir blood cell counts.[5] Neutropenic complications are treated with antibiotics and often require hospitalization.[6]

The addition of colony-stimulating factors (CSFs) following chemotherapy treatment can facilitate the regeneration of white blood cells damaged by chemotherapy, reducing duration and severity of neutropenia. A type of cytokine chemical, CSFs control the growth and activity of other immune and blood cells.[7] CSFs are commonly administered as a subcutaneous injection. Common side effects include bone or muscle pain, headaches, fatigue, bruising, bleeding gums or nosebleeds, diarrhea, nausea, fever, and anemia.[8]

Scope

1. What is the effectiveness and harms of using a colony-stimulating factor (CSF) for primary prophylaxis of neutropenic complications?
    a. in adults with a solid tumor or hematologic malignancy?

b. in children with a solid tumor or hematologic malignancy?

2. What is the effectiveness and harms of using a CSF for secondary prophylaxis of neutropenic complications?
    a. in adults with a solid tumor or hematologic malignancy
    b. in children with a solid tumor or hematologic malignancy

3. What is the effectiveness and harms of using a CSF to treat neutropenia?
    a. in adults with a solid tumor or hematologic malignancy
    b. in children with a solid tumor or hematologic malignancy

4. What is the effectiveness and harms of CSFs as adjuncts to hematopoietic stem cell transplantation?
    a. in adults with a solid tumor or hematologic malignancy
    b. in children with a solid tumor or hematologic malignancy

Table 1. Questions and PICO (population, intervention, comparator, outcome)

Questions	1. Primary prophylaxis	2. Secondary prophylaxis
Population	a. Adults with solid tumor or hematopoietic malignancy without neutropenia b. Children with solid tumor or hematopoietic malignancy without neutropenia Subgroups: age, type of cancer, type and dosing of chemotherapy	a. Adults with solid tumor or hematopoietic malignancy without neutropenia b. Children with solid tumor or hematopoietic malignancy without neutropenia Subgroups: age, type of cancer, type and dosing of chemotherapy
Interventions	G-CSFs or GM-CSFs, including biosimilars to prevent neutropenia during chemotherapy Consider timing, dose, and duration of G-CSF or GM-CSF Exclude use of CSF for other indications such as immunotherapy, adjuvant to vaccination, perioperative use, prevention of mucositis, for wound healing	G-CSFs or GM-CSFs, including biosimilars to prevent neutropenia during chemotherapy Consider timing, dose, and duration of G-CSF or GM-CSF Exclude use of CSF for other indications such as immunotherapy, adjuvant to vaccination, perioperative use, prevention of mucositis, for wound healing
Comparators	• No CSF • Other CSF	• No CSF • Other CSF
Outcomes	Febrile neutropenia, infection-related outcomes, hospitalization, mortality, chemotherapy dose intensity, progression-free survival, and overall survival Other harms	Febrile neutropenia, infection-related outcomes, hospitalization, mortality, chemotherapy dose intensity, progression-free survival, and overall survival Other harms

Abbreviations: CSF=colony-stimulating factors; G=granulocyte; GM=granulocyte-macrophage.

Questions	3. Neutropenia treatment	4. Adjunct to stem cell transplant
Population	a. Adults with solid tumor or hematopoietic malignancy and neutropenia	a. Adults with solid tumor or hematopoietic malignancy undergoing stem cell transplant

	b. Children with solid tumor or hematopoietic malignancy and neutropenia Subgroups: level of neutropenia, presence of fever, type of infection (pneumonia, fungal infection), presence/absence of sepsis, etc.	b. Children with solid tumor or hematopoietic malignancy undergoing stem cell transplant Subgroups: age, type of cancer, type of transplant (autologous vs allogeneic)
Interventions	G-CSFs or GM-CSFs, including biosimilars to treat neutropenia during chemotherapy Consider timing, dose, and duration of G-CSF or GM-CSF Exclude use of CSF for other indications such as immunotherapy, adjuvant to vaccination, perioperative use, prevention of mucositis, for wound healing	G-CSFs or GM-CSFs, including biosimilars to mobilize stem cells or to reduce the duration of neutropenia after stem cell transplantation Consider timing, dose, and duration of G-CSF or GM-CSF Exclude use of CSF for other indications such as immunotherapy, adjuvant to vaccination, perioperative use, prevention of mucositis, for wound healing
Comparators	• No CSF • Other CSF	• No CSF • Other CSF • CSF in combination with another agent (e.g., plerixafor)
Outcomes	Febrile neutropenia, infection-related outcomes, hospitalization, mortality, chemotherapy dose intensity, progression-free survival, and overall survival Other harms	Stem cell mobilization, duration of neutropenia, duration of severe neutropenia, febrile neutropenia, infection-related outcomes, hospitalization, mortality, graft-versus-host disease, progression-free survival, and overall survival Other harms

Abbreviations: CSF=colony-stimulating factors; G=granulocyte; GM=granulocyte-macrophage.

Assessment Methods

See Appendix A.

Summary of Literature Findings

We found no relevant systematic reviews published in the last 3 years. We found 19 primary studies for Key Question (KQ) 1, and very few studies for the remainder of the KQs. The most frequently represented condition was breast cancer.

For KQ 1, we found a total of 15 completed and four ongoing primary studies. In one of the completed studies, the participants were children.[9] In three of the 15 completed studies, the type of CSF investigated was epflapegrastim, which is not FDA-approved, but has a target date of September 9, 2022 to begin the approval process.
Nine[10-17] of the 15 completed studies and one[18] of the four ongoing studies were of breast cancer patients. The remaining completed studies were in colon cancer,[19] leukemia,[20] lymphoma,[21] lung,[22] and carcinoma patients,[23] and any cancer in children.[9] The remaining ongoing studies were in lymphoma[24] and gynecological malignancy[25, 26] patients.

For KQ 2, we found only one study, which was an RCT in patients with esophageal cancer.[27]

For KQ 3, we found only one study, which was a non-randomized controlled study in patients with breast cancer.[28]

For KQ 4, we found two studies, one RCT and one non-randomized controlled study of multiple melanoma, Hodgkin's and non-Hodgkin's lymphoma,[29] and multiple melanoma,[30] respectively.

Table 2. Literature identified for each Key Question

Question	Systematic reviews (5/2019-5/2022)	Primary studies (5/2017-5/2022)
KQ 1: Primary prophylaxis	Total: 0 • Cochrane • AHRQ • Other	Total: 19 • RCT: 7[10, 12-15, 19, 29] • Non-randomized controlled: 8[9, 11, 16, 17, 20-23] Clinicaltrials.gov: 4 RCT[18, 24-26]
KQ 2: Secondary prophylaxis	Total: 0 • Cochrane • AHRQ • Other	Total: 1 • RCT:0 • Non-randomized controlled: 1[27] Clinicaltrials.gov: 0
KQ 3: Neutropenia treatment	Total: 0 • Cochrane • AHRQ Other	Total: 1 • RCT • Non-randomized controlled: 1[28] Clinicaltrials.gov: 0
KQ 4: Adjunct to stem cell transplant	Total: 0 • Cochrane • AHRQ Other	Total: 2 • RCT: 1[29] • Non-randomized controlled: 1[30] Clinicaltrials.gov: 0

Abbreviations: AHRQ=Agency for Healthcare Quality and Research; KQ=key question; RCT=randomized controlled trial.

See Appendix B for detailed assessments of all EPC selection criteria.

Summary of Selection Criteria Assessment

The evidence on the benefits and risks of white blood cell growth factors in people with cancer is evolving, and an update to the current 2015 ASCO guidelines is needed. We found a small number of studies published in the last 5 years for inclusion in a new systematic review, intended to inform an updated guideline.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years May 25, 2019 - May 25, 2022 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
    - AHRQ Evidence Reports https://www.ahrq.gov/research/findings/evidence-based-reports/index.html
    - EHC Program https://effectivehealthcare.ahrq.gov/
    - US Preventive Services Task Force https://www.uspreventiveservicestaskforce.org/
    - AHRQ Technology Assessment Program https://www.ahrq.gov/research/findings/ta/index.html
- US Department of Veterans Affairs Products publications
    - Evidence Synthesis Program https://www.hsrd.research.va.gov/publications/esp/
    - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program https://www.healthquality.va.gov/
- Cochrane Systematic Reviews https://www.cochranelibrary.com/
- University of York Centre for Reviews and Dissemination database https://www.crd.york.ac.uk/CRDWeb/
- PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
- PubMed https://www.ncbi.nlm.nih.gov/pubmed/
- Joanna Briggs Institute http://joannabriggs.org/

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a limited literature search in PubMed for the last five years May 25, 2017- May 25, 2022. We reviewed all studies identified titles and abstracts for inclusion. We classified identified studies by question and study design to estimate the size and scope of a potential evidence review.

Search strategy
Ovid MEDLINE(R) ALL 1946 to May 24, 2022
Date searched: May 25, 2022

1 exp Leukocytes/ (801545)
2 ("white blood cell*" or leukocyt*).ti,ab,kf. (208607)
3 or/1-2 (923575)
4 granulocyte colony-stimulating factor/ or filgrastim/ or lenograstim/ or granulocyte-macrophage colony-stimulating factor/ (30234)
5 (((granulocyte or granulocyte-macrophage) adj3 (CSF or CSFs or "colony-stimulating")) or GCSF or GMCSF or "G-CSF*" or "GM-GSF*" or Neupogen or Granix or Zarxio or filgrastim or lenograstim or Neulasta or Udenyca or Nyvepria or PegFilBS or PegFilOR or pegfilgrastim or Leukine or "Emgrast-M" or Sargramostim).ti,ab,kf. (38595)
6 or/4-5 (46380)
7 Chemotherapy-Induced Febrile Neutropenia/ or Neutropenia/ or Hematopoietic Stem Cell Transplantation/ or Peripheral Blood Stem Cell Transplantation/ (71519)
8 (chemo* or neutropen* or neutropaen* or (("stem cell" or "stem cells") adj3 transplant*)).ti,ab,kf. (827345)
9 or/7-8 (848378)
10 and/3,6,9 (4645)
11 limit 10 to english language (4299)
12 11 not ((animals/ not humans/) or (canine or cat or cats or dog or dogs or feline or mice or mouse or rat or rats or rattus or rodent*).ti.) (3580)
13 12 not (case or "COVID-19" or dermatitis or endometriosis or lichen or obesity or "sickle cell" or tuberculosis).ti. (3478)
14 limit 13 to yr="2019 -Current" (253)
15 meta-analysis/ or systematic review/ or (meta-analy* or metaanaly* or ((evidence or scoping or systematic) adj3 (review or synthesis))).ti,ab,kf. (439527)
16 and/14-15 (4)
17 limit 13 to yr="2017 -Current" (399)
18 randomized controlled trials as topic/ or random allocation/ or double-blind method/ or single-blind method/ or exp clinical trial as topic/ or placebos/ or research design/ or comparative study/ or exp evaluation studies/ or follow up studies/ or prospective studies/ (3672288)
19 ("randomized controlled trial" or "controlled clinical trial" or "clinical trial").pt. (912020)
20 ((clin* adj25 trial*) or ((single* or doubl* or trebl* or tripl*) adj25 (blind* or mask*)) or control* or placebo* or prospective* or random* or volunteer*).ti,ab. (5951235)
21 or/18-20 (8318213)
22 and/17,21 (158)
23 17 not (16 or 22) (240)

Ovid EBM Reviews - Cochrane Central Register of Controlled Trials April 2022
Date searched: May 25, 2022
1 exp Leukocytes/ (10260)
2 ("white blood cell*" or leukocyt*).ti,ab,kf. (11698)
3 or/1-2 (20579)
4 granulocyte colony-stimulating factor/ or filgrastim/ or lenograstim/ or granulocyte-macrophage colony-stimulating factor/ (2081)
5 (((granulocyte or granulocyte-macrophage) adj3 (CSF or CSFs or "colony-stimulating")) or GCSF or GMCSF or "G-CSF*" or "GM-GSF*" or Neupogen or Granix or Zarxio or filgrastim or lenograstim or Neulasta or Udenyca or Nyvepria or PegFilBS or PegFilOR or pegfilgrastim or Leukine or "Emgrast-M" or Sargramostim).ti,ab,kf. (6421)
6 or/4-5 (6696)
7 Chemotherapy-Induced Febrile Neutropenia/ or Neutropenia/ or Hematopoietic Stem Cell Transplantation/ or Peripheral Blood Stem Cell Transplantation/ (3176)

8 (chemo* or neutropen* or neutropaen* or (("stem cell" or "stem cells") adj3 transplant*)).ti,ab,kf. (97419)
9 or/7-8 (97992)
10 and/3,6,9 (440)
11 limit 10 to english language (385)
12 11 not ((animals/ not humans/) or (canine or cat or cats or dog or dogs or feline or mice or mouse or rat or rats or rattus or rodent*).ti.) (384)
13 12 not (case or "COVID-19" or dermatitis or endometriosis or lichen or obesity or "sickle cell" or tuberculosis).ti. (379)
14 limit 13 to yr="2017 -Current" (49)

Epistemonikos
Date searched: May 25, 2022
(title:((title:(("white blood cell*" OR leukocyt*)) OR abstract:(("white blood cell*" OR leukocyt*))) AND (title:((((granulocyte OR granulocyte-macrophage) adj3 (CSF OR CSFs OR "colony-stimulating")) OR GCSF OR GMCSF OR "G-CSF*" OR "GM-GSF*" OR Neupogen OR Granix OR Zarxio OR filgrastim OR lenograstim OR Neulasta OR Udenyca OR Nyvepria OR PegFilBS OR PegFilOR pegfilgrastim OR Leukine OR "Emgrast-M" OR Sargramostim)) OR abstract:((((granulocyte OR granulocyte-macrophage) adj3 (CSF OR CSFs OR "colony-stimulating")) OR GCSF OR GMCSF OR "G-CSF*" OR "GM-GSF*" OR Neupogen OR Granix OR Zarxio OR filgrastim OR lenograstim OR Neulasta OR Udenyca OR Nyvepria OR PegFilBS OR PegFilOR pegfilgrastim OR Leukine OR "Emgrast-M" OR Sargramostim))) AND (title:((chemo* OR neutropen* OR neutropaen* OR (("stem cell" OR "stem cells") AND transplant*))) OR abstract:((chemo* OR neutropen* OR neutropaen* OR (("stem cell" OR "stem cells") AND transplant*))))) OR abstract:((title:(("white blood cell*" OR leukocyt*)) OR abstract:(("white blood cell*" OR leukocyt*))) AND (title:((((granulocyte OR granulocyte-macrophage) adj3 (CSF OR CSFs OR "colony-stimulating")) OR GCSF OR GMCSF OR "G-CSF*" OR "GM-GSF*" OR Neupogen OR Granix OR Zarxio OR filgrastim OR lenograstim OR Neulasta OR Udenyca OR Nyvepria OR PegFilBS OR PegFilOR pegfilgrastim OR Leukine OR "Emgrast-M" OR Sargramostim)) OR abstract:((((granulocyte OR granulocyte-macrophage) adj3 (CSF OR CSFs OR "colony-stimulating")) OR GCSF OR GMCSF OR "G-CSF*" OR "GM-GSF*" OR Neupogen OR Granix OR Zarxio OR filgrastim OR lenograstim OR Neulasta OR Udenyca OR Nyvepria OR PegFilBS OR PegFilOR pegfilgrastim OR Leukine OR "Emgrast-M" OR Sargramostim))) AND (title:((chemo* OR neutropen* OR neutropaen* OR (("stem cell" OR "stem cells") AND transplant*))) OR abstract:((chemo* OR neutropen* OR neutropaen* OR (("stem cell" OR "stem cells") AND transplant*)))))) (1)

ClinicalTrials.gov
ClinicalTrials.gov Link

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change, if a partner organization would use this evidence review to influence practice, and if the topic supports a priority area of AHRQ or the Department of Health and Human Services.

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the United States?	Yes.
1b. Is the nomination a request for an evidence report?	Yes.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes. In 2019, approximately 5% of the United States population were cancer survivors, and this percentage is expected to increase by 31.4% by 2023.[1]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes. In 2019, approximately 5% of the United States population were cancer survivors, and this percentage is expected to increase by 31.4% by 2023.[1] In 2012, the total cost of cancer-related neutropenia hospitalizations was $2.3 billion for adults and $439 million for children.[31]
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes.
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. In 2012, the total cost of cancer-related neutropenia hospitalizations was $2.3 billion for adults and $439 million for children.[31]
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	Yes. We did not find recent high-quality systematic reviews to cover these questions.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. The evidence is evolving, and the most recent guideline was in published in 2015.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Clinical practice is not always consistent with the guidelines, with a tendency for CSF overuse with low-risk chemotherapies, and underuse with high-risk chemotherapy regimens.[32]
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	Size/scope of review: KQ1: 23 studies KQ2: 1 study KQ3: 1 study KQ4: 2 studies The estimated size of a new systematic review is small.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change and	Yes.

supports a priority of AHRQ or Department of Health and Human Services	
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes. The nominator plans to use a systematic review to update the 2015 ASCO guidelines.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; ASCO=American Society for Clinical Oncology.