Comparative Effectiveness Review
Number 113

Effective Health Care Program

Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment: Comparative Effectiveness Update

Executive Summary

Background

Anemia, a deficiency in the concentration of hemoglobin-containing red blood cells, is prevalent among cancer patients, depending on the type of malignancy and treatment. Transfusion is one option for treating anemia related to cancer and cancer treatment. Transfusion carries a very low risk of infection and other adverse events, including transfusion reactions, alloimmunization, overtransfusion, and immune modulation with theoretically possible adverse effects on tumor growth. (For example, adverse events that could be definitively attributed to transfusions were not reported in any trial included in this review for adverse event outcomes.)

Erythropoietin, a hormone produced in the kidney, is the major regulator of red blood cell production (erythropoiesis). Commercially produced recombinant human erythropoietins have been extensively studied and used clinically for more than a decade to treat anemia in association with various diseases, reducing the need for transfusion. These include epoetin alfa (Epogen®, Procrit®) and epoetin beta (not available in the United States); they have similar clinical efficacy. Darbepoetin alfa (Aranesp®), more recently developed, produces a similar physiologic response and is commercially available in the United States. All erythropoietic-stimulating agents (ESAs) increase the number of red blood cells within about 2 to 3 weeks when given to individuals with functioning erythropoiesis.

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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Effective Health Care

The development of intensified antineoplastic therapies has increased the risk for anemia and the likelihood of treatment. Initially, adverse effects that could be conclusively attributed to erythropoietin treatment had been reported in very few patients; more recently, randomized controlled trials have reported increased incidence of thrombotic events and reduced survival. This resulted in multiple pooled analyses of ESA trial data over several years, as well as regulatory actions by the U.S. Food and Drug Administration (FDA). The Blue Cross and Blue Shield Association Technology Evaluation Center, an Evidence-based Practice Center funded by the Agency for Healthcare Research and Quality, conducted a systematic review of epoetin use in oncology (2001)[1] and a comparative effectiveness review, "Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment" (2006).[2]

This update includes new evidence that was not available in 2006. In particular, we incorporated results from a recently published meta-analysis[3] of individual patient data from studies enrolling more than 50 patients per arm; inclusion for this update was limited to studies of similar size. In contrast, the previous report[2] included studies enrolling 10 or more patients per arm. Sensitivity analyses performed for each outcome with data from studies excluded because of size showed no differing results.

This report addresses the following Key Questions:

Key Question 1. What are the comparative benefits and harms of erythropoiesis-stimulating agent strategies and non-ESA strategies to manage anemia in patients undergoing chemotherapy or radiation for malignancy (excluding myelodysplastic syndrome and acute leukemia)?

Key Question 2. How do alternative thresholds for initiating treatment compare regarding their effect on the benefits and harms of erythropoietic stimulants?

Key Question 3. How do different criteria for discontinuing therapy or for optimal duration of therapy compare regarding their effect on the benefits and harms of erythropoietic stimulants?

Conclusions

Evidence from three groups of trials were summarized and analyzed for Key Question 1. Five trials directly compared darbepoetin with epoetin (pooled N=1,080 darbepoetin, N=989 epoetin); 40 trials compared epoetin with control (pooled N=5,959 epoetin, N=5,417 control); and 7 trials compared darbepoetin with control (pooled N=1,654 darbepoetin, N=1,520 control). There was considerable variability among trials, such as trial duration, tumor types, cancer therapy, trial quality, iron supplementation, baseline hemoglobin, ESA dosing frequency (and therefore amount per dose), and ESA dose escalation.

Hematologic Response

ESAs reduced the proportion of patients receiving transfusions (overall strength of evidence moderate) without meaningful difference between epoetin and darbepoetin (overall strength of evidence moderate). Table A shows data on transfusion risk.

Table A. Transfusion risk				
Variable	**Darbepoetin vs. Epoetin**	**Epoetin vs. Control**	**Darbepoetin vs. Control**	**Epoetin or Darbepoetin vs. Control**
Number of trials	5	31	7	38
Patients analyzed	2,005	8,003	2,806	10,809
Pooled RR (95% CI)	1.14	0.58	0.58	0.58
	(0.82 to 1.59)	(0.52 to 0.65)	(0.51 to 0.65)	(0.53 to 0.64)
I^2	43%	60%	0%	51%

CI = confidence interval; RR = relative risk

There is a consistent body of evidence, although somewhat limited by trial quality, that ESAs reduce the probability of transfusion in the setting of cancer treatment. These agents do not eliminate the chance of receiving transfusions.

Survival Outcomes

ESAs did not affect survival over the longest available followup (overall strength of evidence low). Table B shows data on overall survival.

Table B. Overall survival			
Variable	**Epoetin vs. Control**	**Darbepoetin vs. Control**	**Epoetin or Darbepoetin vs. Control**
Number of trials	37	7	44
Patients analyzed	11,131	3,147	14,278
Pooled HR (95% CI)	1.04[a]	1.04	1.04[b]
	(0.98 to 1.11)	(0.94 to 1.17)	(0.99 to 1.10)
I^2	35%	51%	38%

[a]Excludes the single trial enrolling pediatric patients.
[b]Excludes the single trial enrolling pediatric patients. Excluding 5 trials classified here as radiotherapy or predominantly radiotherapy yielded an HR of 1.03 (95% CI, 0.97 to 1.09).
CI = confidence interval; HR = hazard ratio

ESAs increased mortality during and shortly following treatment (in this review, referred to as "on-study mortality"; overall strength of evidence moderate). Table C shows on-study mortality data.

Table C. On-study mortality				
Variable	**Darbepoetin vs. Epoetin**	**Epoetin vs. Control**	**Darbepoetin vs. Control**	**Epoetin or Darbepoetin vs. Control**
Number of trials	2	31	6	37
Patients analyzed	1,567	8,618	2,648	11,266
Pooled HR (95% CI)	0.90	1.19[a]	1.05	1.17[b]
	(0.67 to 1.20)	(1.05 to 1.36)	(0.80 to 1.38)	(1.04 to 1.31)
I^2	72%	3%	0%	0%

[a]Excludes single trial enrolling pediatric patients.
[b]Excludes single trial enrolling pediatric patients. Excluding 3 trials classified here as radiotherapy or predominantly radiotherapy yielded an HR of 1.16 (95% CI, 1.03 to 1.30).
CI = confidence interval; HR = hazard ratio

ESAs increased mortality during the active treatment or "on-study period" (median study duration 3 months) without apparent difference between epoetin and darbepoetin. There was one additional death for every 59 treated patients when the control arm on-study mortality was 10 percent, and there was one additional death for every 588 treated patients when the control arm on-study mortality was 1 percent. While there was no discernible increase in mortality with ESA use over the longest available followup, many trials did not include an overall survival endpoint and potential time-dependent confounding was not considered.

Thromboembolic Events

ESA treatment increased the risk of thromboembolic events (overall strength of evidence moderate). Epoetin and darbepoetin conferred similar risks. Table D shows data on thromboembolic events.

Table D. Thromboembolic events				
Variable	**Darbepoetin vs. Epoetin**	**Epoetin vs. Control[a]**	**Darbepoetin vs. Control**	**Epoetin or Darbepoetin vs. Control**
Number of trials	3	31	6	37
Patients analyzed	1,873	9,585	2,869	12,570
Pooled RR (95% CI)	0.86	1.50	1.53	1.51
	(0.61 to 1.21)	(1.26 to 1.77)	(1.18 to 2.00)	(1.30 to 1.74)
I^2	0%	0%	0%	0%

[a]One trial reporting no events in either treatment arm not included in totals or pooled results.
CI = confidence interval; RR = relative risk

Rates of thromboembolic events were consistently higher in ESA-treated patients. In included trials, the number needed to harm was 50 or fewer in 50 percent of trials and 20 or fewer in 21 percent of trials.

Health-Related Quality of Life

Treating to high target hemoglobin levels (greater than 12 g/dL) was accompanied by improved health-related quality of life (HRQoL) scores (e.g., the Functional Assessment of Cancer Therapy [FACT] Fatigue score; overall strength of evidence low). Table E shows HRQoL data.

Table E. Health-related quality of life

Variable	Epoetin or Darbepoetin vs. Control
Number of trials	14
Patients analyzed	3,643
Mean difference for change in FACT-Fatigue score (95% CI)	2.74
	(1.69 to 3.78)
I^2	45%

CI = confidence interval; FACT = Functional Assessment of Cancer Therapy

Any clinical significance of the improvement in HRQoL is likely to be small. On average, the difference in change between treatment arms was less than the estimated minimal clinically important difference (a value of 3 for the FACT-Fatigue score).

Early Versus Late ESA Treatment

Evidence from five trials was summarized and analyzed; 468 and 465 patients randomized to early (when chemotherapy or radiotherapy begins) and late (when hemoglobin falls below a defined threshold) ESA treatment, respectively. Hemoglobin thresholds for initiating late treatment ranged from 9 g/dL to 11 g/dL.

There were fewer thromboembolic and on-study mortality adverse events when ESA treatment was delayed until baseline hemoglobin was less than 10 g/dL, in keeping with current treatment practice, but the difference in effect from early treatment was not significant, and the evidence was limited and insufficient for conclusions.

Evidence is lacking to determine whether immediate treatment versus delayed treatment produces better outcomes (overall strength of evidence low).

Criteria for Discontinuing Therapy or for Optimal Duration of Therapy

No randomized controlled trials were identified that fulfilled the review's inclusion criteria for studies of discontinuing therapy or defining optimal duration of therapy.

Balance of Potential Benefit and Harm

ESAs reduce the need for transfusions and increase the risk of thromboembolism. A detectable relative increase in mortality risk, which is higher with lower underlying absolute mortality risk, accompanies their use. An individual patient receiving ESAs will have, on average, better quality-of-life FACT-Fatigue scores, but of a magnitude less than the minimal clinically important difference. In a cohort decision model in which increased hemoglobin determined the utility-based measure of improvement in quality of life, ESAs were accompanied by some additional expected quality-adjusted life-years—consistent with the small difference in FACT-Fatigue scores. However, expected life-years were always lost, and the loss was greater with higher underlying absolute mortality risk.

Remaining Issues

Much of the evidence included here was obtained under treatment protocols that used higher baseline and target hemoglobin levels than those used in current practice. While it is possible that adverse event rates might be somewhat different with lower baseline and target hemoglobin levels, we found little difference in effect when baseline hemoglobin was either less than or more than 10 g/dL, the currently recommended threshold for ESA initiation. This result is similar to results from a meta-analysis of individual patient data.[3] Additionally, three trials included in Key Question 1 enrolled patients predominantly undergoing radiotherapy. Although radiotherapy is not an FDA-approved indication for ESA use, those results were included because the population of interest was patients undergoing treatment for cancer. Moreover, we did not find those trial results influential in these analyses.

Existing evidence establishes with sufficient certainty that use of ESAs to manage anemia in patients with cancer is accompanied by increased mortality risk. Whether there are subgroups at higher and lower risk of adverse events and mortality is unclear. Recent regulatory and guideline changes may have reduced ESA exposure in subsequent clinical trials and routine practice. It is unknown whether dosing practices and overall ESA exposure influence harms. However, the increased risk of mortality raises questions as to whether equipoise exists to justify enrolling patients in clinical trials. Instead, examining observational data collected during the course of usual patient care could be adequate to address unanswered questions. Finally, trial registry records for all completed studies lacking results or links to them should be appropriately updated. Trial registries should also query investigators when studies are completed and post responses in a registry record when results are unavailable.

References

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Full Report

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