Number 3

Effective Health Care

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

Executive Summary

Background

Anemia (deficiency of red blood cells) occurs in 13-78 percent of patients undergoing treatment for solid tumors and 30-40 percent of patients treated for lymphoma. Tumor type, treatment regimen, and history of prior cancer therapy influence the risk and severity of anemia. For example, among patients with solid tumors, the frequency of anemia severe enough to require red blood cell transfusion is highest for those with lung, gynecologic, and genitourinary tumors. This report focuses on use of epoetin or darbepoetin to manage anemia in patients undergoing cancer treatment with chemotherapy and/or radiation.

Anemia severity is defined by hemoglobin (Hb) concentration. Normal ranges are 12-16 g/dL for women and 14-18 g/dL for men. Mild anemia is defined as Hb from 10 g/dL to the lower limit of normal ranges, while moderate anemia is 8-10 g/dL. Patients are usually transfused if Hb falls to or below 8 g/dL, defined as severe anemia.

Transfusion quickly increases Hb concentration. Serious transfusion-related adverse events are uncommon. For example, in the United States, adverse events due to errors in transfusion are

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.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**

AHRQ
Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Effective Health Care

estimated to occur in only 1 in 14,000 units. Risk of hepatitis B infection is estimated to be 1 in 220,000 per unit of blood transfused.

Erythropoietin, a hormone produced primarily in the kidney, participates in regulating red blood cell production (erythropoiesis) and thus Hb concentration. Two erythropoietic stimulants are available commercially in the United States, epoetin alfa (Epogen®, Procrit®) and darbepoetin alfa (Aranesp®), which is a newer and longer acting drug. Epoetin beta, which is pharmacologically and clinically similar to epoetin alfa, is commercially available in Europe and elsewhere. Erythropoietic stimulants are widely used in clinical practice to manage anemia of patients undergoing cancer treatment and to reduce the need for transfusion.

Although it is well established that erythropoietic stimulants improve anemia in patients undergoing cancer treatment, the comparative effectiveness of epoetin and darbepoetin has not been evaluated in a systematic review. Moreover, trials varied substantially in how erythropoietic stimulants have been used, including Hb concentration at start of treatment, doses given, treatment duration, and target Hb concentrations they sought to maintain. A review of these various trials may help maximize benefit, optimize drug usage, and minimize adverse effects from using erythropoietic stimulants to manage anemia in patients undergoing cancer treatment.

The report addresses the following questions:

1. What are the comparative efficacy and safety of epoetin (alfa or beta) and darbepoetin?
2. How do alternative dosing strategies affect the comparative efficacy and safety of epoetin and darbepoetin?
3. How do alternative thresholds for initiating treatment or alternative criteria for discontinuing therapy or duration of therapy affect the efficacy and safety of erythropoietic stimulants?
4. Are any patient characteristics at baseline or early hematologic changes useful to select patients or predict responses to treatment with erythropoietic stimulants?

Conclusions

Comparative efficacy and safety of epoetin and darbepoetin

Three sets of trials were summarized and analyzed: 7 randomized direct comparisons of darbepoetin versus epoetin (pooled N=1,415 patients randomized to epoetin, 1,087 to darbepoetin); 48 randomized controlled trials (RCTs) of epoetin versus control[a] (pooled N=4,518 patients randomized to epoetin, 3,743 to control); and 4 RCTs of darbepoetin versus control[a] (pooled N=598 patients randomized to darbepoetin, 396 to control).

The evidence does not show any clinically significant difference between epoetin and darbepoetin in hemoglobin response, transfusion reduction, and thromboembolic events. (See Table A for details.)

- For hematologic response, five of six trials comparing darbepoetin to epoetin showed no statistically significant difference between these drugs. Pooled results of trials comparing epoetin to control and darbepoetin to control showed no difference; over 50 percent of patients treated with epoetin or darbepoetin had a Hb increase >2 g/dL, compared with fewer than 20 percent of untreated patients.
- For rates of transfusion, trials comparing darbepoetin to epoetin showed no statistically significant difference between these drugs. Pooled results of trials comparing epoetin or darbepoetin to control showed approximately 30 percent of patients treated with epoetin or darbepoetin were transfused, compared with 50 percent of untreated patients. However, patients varied widely in how likely they were to need a transfusion; the proportion of untreated patients undergoing transfusion ranged from 0 percent to 100 percent in the studies reviewed.
- For thromboembolic events,[b] trials comparing darbepoetin to epoetin showed no statistically significant difference between these drugs. Pooled results of trials comparing epoetin or darbepoetin to control showed that approximately 7 percent of

[a] Controls received placebo or no erythropoietic stimulant, and each group (treated or control) was transfused as necessary.

[b] Studies usually did not provide a detailed definition of thromboembolic events; those that did included thrombosis and related complications such as thrombophlebitis, transient ischemic attacks, stroke, pulmonary embolism, and myocardial infarctions.

patients treated with epoetin or darbepoetin experienced a thromboembolic event, compared with 4 percent of untreated patients. However, trials varied widely in thromboembolic event rates: 0 percent to 30 percent among treated patients and 0 percent to 23 percent among untreated patients. Several studies sought to maintain Hb levels higher than recommended in product labels (≤12 g/dL); however, evidence is insufficient to determine if risk is lower when treatment conforms to Food and Drug Administration (FDA) label recommendations.

- For each of the above outcomes, more evidence is available on epoetin than darbepoetin.

Table A. Summary of Rates of Hematologic Response, Transfusion, and Thromboembolic Events

Parameter	Darbepoetin vs. epoetin	Epoetin vs. control	Darbepoetin vs. control
Hb response rates:			
Number of studies reporting	6	15	3
Patients analyzed	2,205	3,293	659
Pooled relative risk of Hb increase >2 mg/dL (95% CI)	Meta-analysis not done[1]	3.42 (3.03, 3.86)[2]	3.36 (2.48, 4.56)
Pooled event rates (range across studies)	Meta-analysis not done[1]	Epo: 58% (21%-73%) Control: 17% (3%-32%)	Darb: 54% (25%-84%) Control: 17% (9%-18%)
Transfusion rates:			
Number of studies reporting	6	34	4
Patients analyzed	2,158	5,210	950
Pooled relative risk (95% CI)	1.10 (0.93, 1.29)[2]	0.63 (0.59, 0.67)[2]	0.61 (0.52, 0.72)
Pooled event rates (range across studies)	Darb: 22% (3%-28%) Epo: 20% (12%-43%)	Epo: 30% (0-91%) Control: 47% (0-100%)	Darb: 29% (13%-34%) Control: 51% (25%-67%)
Thromboembolic events:			
Number of studies reporting	3	30	1
Patients analyzed	1,879	6,092	314
Pooled relative risk (95% CI)	0.86 (0.61, 1.21)	1.69 (1.36, 2.10)	1.44 (0.47, 4.43)[3]
Pooled event rates (range across studies)	Darb: 6% (3%-9%) Epo: 7% (3%-11%)	Epo: 7% (0-30%) Control: 4% (0-23%)	Darb: 5% Control: 3%

[1] Trials defined response differently and initiated and adjusted doses differently; only one randomized controlled trial (n=352) reported significant difference favoring epoetin, but results may be biased since dose was adjusted differently in each arm; five trials (N=1,853) reported no significant differences between arms.

[2] Tests of heterogeneity (I^2) indicated excessive variability among individual study results. Results of this fixed-effects meta-analysis were compared with random-effects meta-analysis; results were not meaningfully different.

[3] Since there was only one trial, this result is a single-study (not pooled) relative risk.

Abbreviations: CI: confidence interval; Hb: hemoglobin.

The evidence is not sufficient for conclusions on effects of either epoetin or darbepoetin on quality of life, tumor response and progression, survival, or adverse outcomes other than thromboembolic events.

- Trials did not completely or consistently report quality of life (QoL) results, so 12 potentially relevant studies were unusable for this analysis, and quantitative analysis could not be performed for the 15 remaining studies. Overall, QoL measures tended to favor treatment with epoetin or darbepoetin. However, the degree of change varied widely across studies and not all positive changes were statistically significant.

  Numeric changes on QoL instrument scales must be empirically evaluated to determine whether the degree of change is perceptible and meaningful to the patient. Currently, there is not enough evidence to quantify the minimum changes that are clinically meaningful on the most commonly used QoL instrument, Functional Assessment of Cancer Therapy-Anemia (FACT-An) and its subscales. Additional limitations of the evidence are potential bias due to substantial missing data; concerns regarding study validity, including lack of blinding and lack of information on QoL instrument administration; and incomplete reporting of numerical results.

- The limited evidence available (five studies, N=688) does not suggest that erythropoietic stimulants improve solid tumor response to a concurrent course of cancer therapy. Whether erythropoietic stimulants accelerate progression of some cancers, as reported by one study (n=351), is uncertain.

- Of 40 (N=8,249) RCTs reporting on survival, only seven (N=2,188) were actually designed to assess effects on survival (progression free or overall). No studies designed to test survival[c] used epoetin or darbepoetin as currently recommended; rather, all seven trials sought to maintain Hb levels >12 g/dL. Two of the seven trials, one on metastatic breast cancer (n=939) and one on head and neck cancer (n=351), showed poorer overall survival for patients treated with epoetin; this prompted an FDA safety review in May 2004 and revised product labeling to indicate that clinicians should avoid targeting Hb concentrations above 12 g/dL. Of the other five trials, survival appeared poorer with erythropoietic stimulant in three (N=471) and better in two (N=427), but most results were not statistically significant.

- The remaining 33 of the 40 RCTs reporting on survival collected survival data retrospectively from trials designed only to test hematologic and transfusion outcomes. This evidence is not definitive, but might detect a large difference in survival. Analysis of mortality in all 40 trials shows no overall benefit of darbepoetin or epoetin on survival. Neither higher than recommended target Hb nor any other single patient- or treatment-related factor explained why some trials showed a detriment in survival and others did not.

- For other adverse events, reporting is incomplete, representing less than one-third of patients. Studies did not use consistent definitions of events and severity. For epoetin, 15 studies (N=1,949) reported on hypertension, 9 (N=1,422) reported on thrombocytopenia/hemorrhage, 6 (N=522) reported on rash, 3 (N=389) reported on seizures. For darbepoetin, one trial (n=122) comparing darbepoetin to epoetin reported on seizures, and one trial (n=314) comparing darbepoetin to control reported on hypertension. Overall, adverse events were more frequent with epoetin or darbepoetin than control, but pooled results did not show statistically significant differences.

- For each of the above outcomes, more evidence is available on epoetin than darbepoetin.

Alternative dosing strategies

- Twelve trials examined different dosing regimens for epoetin and seven trials examined different dosing regimens for darbepoetin. For each of the following pairs of dosing strategies,[d] one large trial

[c] To test survival, a trial should enroll sufficient numbers of patients with the same tumor (or stratify patients by tumor), and should follow them over an adequate time period.

[d] Rationales for comparing these alternative strategies are: (1) Drug concentrations with fixed-dose strategies may be inadequate for overweight patients and excessive for underweight patients. (2) More frequent dosing schedules are less convenient, but may be more effective to maintain the desired drug concentration range. (3) Front-loading refers to starting at higher dose, then reducing to a maintenance dose, which may increase the proportion of responding patients.

reported no statistically significant difference between strategies: fixed-dose compared to dose based on weight, one trial each for epoetin and darbepoetin; fixed-dose epoetin administered weekly vs. thrice weekly; fixed dose epoetin administered weekly vs. every 3 weeks; and darbepoetin using an initial loading dose versus constant weight-based dosing regimens. The remaining 14 trials were too small to interpret.

Thresholds for initiating treatment or criteria for discontinuing therapy

- Three unblinded randomized trials, not yet published, compared using erythropoietic stimulant therapy soon after mild anemia developed vs. delaying treatment until Hb had fallen below a predefined threshold of moderate anemia. Comparisons were ~11 g/dL vs. 9 g/dL (N=269); ~11 g/dL vs. 10 g/dL (N=204); and ~13 g/dL vs. 10 g/dL (N=216). All patients in the mild anemia arms were treated with an erythropoietic stimulant; of patients in whom treatment was delayed until moderate anemia developed, 19 percent, 63 percent, and 44 percent, respectively, were treated with erythropoietic stimulant. Transfusion was more frequent when treatment was delayed until moderate anemia developed, but the difference was not statistically significant in any study. One trial reported a statistically significant increase in thromboembolic events among patients who were treated for mild anemia compared with those who were treated for moderate anemia.
- No trials compared criteria for discontinuing therapy.

Factors to select patients or predict responses to treatment

- Available evidence does not identify any single factor as clinically useful to guide treatment decisions. Potential predictive factors, measured at baseline (e.g., serum erythropoietin level or observed/predicted ratio [O/P ratio], serum ferritin) or early after starting treatment (e.g., Hb increase, serum ferritin, reticulocyte increase), were evaluated in 26 studies and found to have either weak ability or no ability to discriminate between responders and nonresponders.
- Seven algorithms combining multiple factors, potentially more useful to predict Hb response, are each currently supported only by one study. The largest of these studies do not report sufficient predictive ability for any algorithm to establish clinical utility for selecting treatment.

Remaining Issues

- Considerably less evidence exists on darbepoetin than epoetin. Consequently, most conclusions concerning effects of erythropoietic stimulants as a class rest on inferences from the evidence on epoetin.
- More evidence is needed to delineate the effects on survival, tumor progression, and risk of adverse effects when erythropoietic stimulants are administered as currently recommended.
- To interpret changes in anemia-specific quality of life measures, a clear, empirically based definition of the minimum clinically important difference is needed.

Full Report

This executive summary is part of the following document: Seidenfeld J, Piper M, Bohlius J, Weingart O, Trelle S, Engert A, Skoetz N, Schwarzer G, Wilson J, Brunskill S, Hyde C, Bonnell C, Ziegler KM, Aronson N. Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment. Comparative Effectiveness Review No. 3. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-02-0026.) Rockville, MD: Agency for Healthcare Research and Quality. May 2006. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

For More Copies

For more copies of Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment: Executive Summary. No. 3 (AHRQ Pub. No. 06-EHC008-1), please call the AHRQ Clearinghouse at 1-800-358-9295 or e-mail ahrqpubs@ahrq.gov.

AHRQ Pub. No. 06-EHC008-1
May 2006