Guideline Summary: Use of Epoetin and Darbepoetin in Patients With Cancer—2007 American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update

Context

An Update Committee of members from the full American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) expert panel published this clinical practice guideline update (J Clin Oncol 26:132-149, 2008). The guideline update was approved by the ASCO Board of Directors on August 15, 2007, and the Executive Committee of ASH on August 14, 2007. The previous version of this guideline was published in 2002 (J Clin Oncol 20:4083-4107, 2002).

Updated 2007 Recommendations

The guideline contains two new clinical questions concerning (1) the comparative effectiveness of epoetin and darbepoetin and (2) the thromboembolic risk of erythropoiesis-stimulating agents (ESAs). For patients with chemotherapy-associated anemia, the update committee continues to recommend initiating an ESA as hemoglobin (Hb) approaches, or falls below, 10 g/dL, to increase hemoglobin and decrease RBC transfusions. The guideline continues to recommend ESA treatment patients with low-risk myelodysplasia for similar reasons. It also continues to recommend monitoring laboratory measures of iron stores and supplementing them when indicated, to limit unnecessary, and/or ineffective ESA treatment. There is no evidence showing that ESA treatment increases survival. A table listing the guideline updates is available as a data supplement at jop.ascopubs.org.

I. General Recommendation

As in 2002, the 2007 guideline recommends that clinicians consider other correctable causes of anemia before considering ESA therapy. This consideration includes performing a thorough history and physical examination of patients with cancer and considering relevant diagnostic tests (Table 1). It is important to consider minimizing use of ESAs for patients who are at high risk of thromboembolic events.

II. Special Commentary Comparing Epoetin and Darbepoetin

Since the 2002 guideline was issued, the FDA approved a new ESA, darbepoetin alfa, for chemotherapy-induced anemia. Basing their recommendations on a systematic review comparing epoetin and darbepoetin as therapies for chemotherapy-induced anemia, the update committee concludes that the two ESAs are equivalent in effectiveness and safety when used at FDA-approved dosages. Available evidence shows no significant differences in hematologic response rates, transfusion rates, or thromboembolic events. Evidence is insufficient for conclusions about differences in quality of life (QOL), tumor response, progression, or survival. Epoetin and darbepoetin are identical with respect to (1) indications for use in chemotherapy-induced anemia, (2) hemoglobin limits for adjusting doses or discontinuing treatment, (3) warnings and cautions to consider, and (4) increased rates of thromboembolic events in the experimental arms of separate trials on each product versus controls/placebo.

III. Chemotherapy-Induced Anemia

Threshold for initiating ESA therapy (Hb concentration approaching or < 10 g/dL). A systematic review and meta-analysis on which the 2002 recommendations were based found that the strongest evidence for the effects of epoetin therapy on transfusion and QOL outcomes was from clinical trials with patients with baseline hemoglobin levels of 10 g/dL or less. In addition, the committee reviewed analyses published since 2002, some of which examined initiating treatment immediately or delaying until hemoglobin levels fell to a prespecified threshold. Three studies found transfusion rates increased in the groups receiving delayed treatment, but the differences were not statistically significant. A meta-analysis concluded that there was a decreased relative risk of transfusion with mild Hb (greater than or equal to 10 g/dL) compared with treatment at Hb less than 10 g/dL, but it was uncertain a pooled analysis was appropriate across these three trials, given their differences in treatment protocols.

Special Announcement: The US Food and Drug Administration (FDA) announced revisions to the erythropoiesis-stimulating agent (ESA) product labels on November 8, 2007 when this guideline was in press. These revisions warn that data are not sufficient to exclude the possibility of shortened survival and tumor progression in patients with cancer when ESAs are dosed to reach a hemoglobin level (Hb) between 10 and 12 g/dL. *Clinicians are advised to consider this warning, as discussed in sections IIIB and XI.* For convenience, an additional table (Table 2a) has been added to reflect the new dosing contained in the FDA label. The guideline panel strongly supports additional research to more clearly define risks of ESA usage in patients with cancer with anemia receiving chemotherapy and factors that determine those risks.

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Table 1. Relevant Diagnostic Tests

Indication	Test
General	Drug exposure history
	Review of the peripheral blood smear (and in some cases, the bone marrow)
	Iron
	Folate
	B_{12} deficiency
	Assess for occult blood loss
	Assess for renal insufficiency
Chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and for those with a history of autoimmune disease	Coomb's testing
Myelodysplasia	Endogenous erythropoietin levels (may predict response)

The body of research on changes in QOL associated with ESA use has grown, through many gaps remain. The systematic review found that some clinical trials reported statistically significant QOL improvements, but with small effect sizes. Measuring QOL in clinical trials is more difficult than measuring Hb or transfusion changes. When possible, future clinical trials should strive to limit missing QOL assessments, and should continue to report the data needed to calculate effect sizes and clinically meaningful QOL changes.

Threshold for initiating ESA therapy (Hb concentration > 10 g/dL but < 12 g/dL). Clinical circumstances should determine whether to use epoetin or darbepoetin immediately or to wait until the hemoglobin levels fall closer to 10 g/dL for patients with declining hemoglobin levels but less severe anemia (those with hemoglobin concentration < 12 g/dL, but who have never fallen near 10 g/dL). Since 2002, this recommendation expanded to include clinical circumstances such as substantially reduced exercise capacity, energy, or ability to carry out activities of daily living (ADLs). Clinicians can consider initiating a trial of an ESA at higher hemoglobin levels for a subset of patients who might include older individuals with limited cardiopulmonary reserve, those with underlying coronary artery disease, symptomatic angina, or those with impaired physical functioning. Clinicians should very carefully weigh the risks and benefits of initiating ESAs in this range of anemia and stop ESAs for patients who do not receive the desired benefit in the appropriate timeframe.

IV. Thromboembolic Risk

There is increased risk of thromboembolic events for patients receiving ESAs. Established, general risk factors for thromboembolic events include previous history of thromboses, surgery, and prolonged periods of immobilization or limited activity. Patients with multiple myeloma receiving thalidomide or lenalidomide and doxorubicin or corticosteroids are at increased risk. Concern increased in 2003, when sponsors discontinued three trials after finding 25% rates of thromboembolic events. A review of these and other phase III licensing trials in the United States and Europe in 2004 led to the addition of a warning to the package inserts advising physicians of increased thromboembolic event risks with ESAs in the oncology setting. Meta-analysis results estimated one event would occur for every 75 patients receiving ESAs. The 2006 Cochrane Collaboration meta-analysis reported that epoetin or darbepoetin treatment was statistically significantly associated with increased risk for thromboembolic events, including deep vein thromboses, pulmonary emboli, strokes, myocardial infarctions, or transient ischemic attacks.[1] Because there is now strong and consistent evidence of increased thromboembolic risk, the 2007 update committee urges caution in the use of these agents with patients judged to be at high risk for thromboembolic events.

V. Starting and Escalating Doses

More than 18 trials looked at dosing strategies that differed from those recommended in the 2002 guideline and the (March 2007) FDA-approved label; evidence does not support recommending these alternative doses or dosing schedules. A clinical evidence review found few differences in safety or efficacy among different dosing strategies. At the highest doses studied, some trials reported more frequent thromboembolic events, but the differences were not statistically significant. Due to infrequent and incomplete reporting of adverse events across trials, it is not possible to reach conclusions concerning the relative safety of the alternate dosing strategies.

VI. Discontinuation

If a patient does not respond to ESAs after 6 to 8 weeks, despite a dose increase, the clinician should investigate possible underlying tumor progression, iron deficiency, or other causes of the anemia. While studies have looked for early indicators and predictors of response, the predictive power of such testing appears insufficient for clinical use. Measuring endogenous erythropoietin to select patients or predict response to ESAs is not supported by data, except in myelodysplasia.

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Table 2. ESA Dosing (The doses contained in the FDA label as of March 2007 [shown below] have been revised. The November 8, 2007 FDA label is shown in Table 3.)

Dose & Modifications	Epoetin Alfa		Darbepoetin Alfa	
Initial Dose	150 U/kg SC TIW	40,000 U SC Weekly	2.25 mcg/kg SC Weekly	500 mcg SC Q3W
Dose Increases	Increase dose to 300 U/kg TIW if no reduction in transfusion requirements or rise in Hb after 8 wk	Increase dose to 60,000 U SC weekly if no increase in Hb by ≥1 g/dL after 4 wk of therapy, in the absence of a RBC transfusion	Increase dose to 4.5 mcg/kg if there is <1 g/dL increase in Hb after 6 wk	N/A
Dose Reductions	Decrease dose by 25% when Hb approaches 12 g/dL or Hb increases > 1 g/dL in 2 wk		Decrease dose by 40% of previous dose when Hb exceeds 11 g/dL or Hb increases > 1 g/dL in 2 wk	
Dose Withholding	If Hb exceeds 12 g/dL, withhold dose until Hb < 11 g/dL; restart dose at 25% below previous dose		If Hb exceeds 12 g/dL, withhold dose until Hb = 11 g/dL; restart dose at 40% below previous dose	

NOTE. Table appears as Table 6 in the full guideline.
Abbreviations: ESA, erythropoiesis-stimulating agent; FDA, US Food and Drug Administration; SC, subcutaneous; TIW, three times per week; Q3W, every 3 weeks; Hb, hemoglobin; wk, week.

VII. Hemoglobin Target

Studies conducted since the 2002 guideline support an increased attention to safety and the importance of titrating the ESA dose to maintain hemoglobin at or near 12 g/dL. These trials primarily included patients who had baseline Hb greater than 10 g/dL, were not receiving chemotherapy, and/or for whom the Hb target was greater than 12 g/dL. Three randomized controlled trials showed worsened survival and/or tumor outcomes, including increased mortality, shorter locoregional progression-free survival, and time to locoregional progression. One of those trials was stopped early because of increased deaths of patients on the ESA arm. Based on these and more recent clinical studies, the FDA approved a black box warning on ESA labels highlighting the risk of death and serious cardiovascular events when the Hb target is greater than 12 g/dL, in March 2007. The labels direct clinicians to use the lowest possible ESA dose to reach the lowest hemoglobin level possible to avoid RBC transfusions. (Note: Dose and dose modification recommendations recorded in the package insert as of March 2007 and approved by the US FDA can be found in Table 2 [Table 6 of the full guideline] and Table 3 [Table 6a based on November 8, 2007, FDA label announcement].[2])

VIII. Iron Monitoring and Supplementation

This recommendation has not changed since 2002. Three new randomized controlled trials have looked at the role of iron supplementation. These trials suggest that IV iron given in conjunction with ESAs may enhance hemoglobin response to ESAs. However, clinicians should factor in the limitations of these studies, such as small sample sizes, when interpreting the results. Some studies suggest that if iron is given to

Table 3. ESA Dosing (This table includes new doses contained in the FDA-approved label as released on November 8, 2007.)

Dose and Modifications	Epoetin Alfa		Darbepoetin Alfa	
Initial dose	150 U/kg SC TIW	40,000 U SC weekly	2.25 mcg/kg SC weekly	500 mcg SC Q3W
Dose increase	Increase dose to 300 U/kg TIW if no reduction in transfusion requirements or rise in Hb after 8 wks	Increase dose to 60,000 U SC weekly if no increase in Hb by ≥ 1 g/dL after 4 wks of therapy, in the absence of a RBC transfusion	Increase dose to 4.5 mcg/kg if there is < 1 g/dL increase in Hb after 6 wks	—
Dose reductions	Decrease dose by 25% when Hb **reaches a level needed to avoid transfusion** or Hb increases >1 g/dL in 2 wks		Decrease dose by 40% of previous dose when **Hb reaches a level needed to avoid transfusion** or Hb increases > 1 g/dL in 2 wks	
Dose withholding	If Hb exceeds 12 g/dL, withhold dose **until Hb approaches a level where transfusions may be required**; restart dose at 25% below previous dose		If Hb exceeds 12 g/dL, withhold dose **until Hb approaches a level where transfusions may be required**; restart dose at 40% below previous dose	

NOTE. Table appears as Table 6A in the full guideline. New label text is shown in bold type.
Abbreviations: ESA, erythropoiesis-stimulating agent; FDA, US Food and Drug Administration; SC, subcutaneous; TIW, three times per week; Q3W, every 3 weeks; Hb, hemoglobin; wk, week.

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patients undergoing chemotherapy, IV administration may enhance response to ESAs better than the oral route. There are currently insufficient data to recommend one specific form of iron over another.

IX. Anemia in Patients Not Receiving Concurrent Chemotherapy

Recommendation for use of ESAs for patients with low-risk myelodysplasia is based on evidence from two randomized trials (one published since 2002). Evidence is lacking to support use of ESAs for patients with anemia with solid or nonmyeloid hematological malignancies not receiving chemotherapy and/or radiotherapy. The 2007 guideline also addresses ESA use for anemia of cancer for patients with solid tumors. In phase III data recently submitted to the US Food and Drug Administration (FDA), patients with solid tumors (and other nonmyeloid malignancies) with anemia of cancer who were not receiving chemotherapy or radiotherapy experienced no decrease in transfusion risk, but did experience more deaths and increased thromboembolic events in the ESA arm. These unpublished data, cited in the March 2007 FDA black-box warning, support a stronger recommendation against using ESAs to treat anemia associated with malignancy, or the anemia of cancer, among patients with either solid or nonmyeloid hematological malignancies who are not receiving concurrent chemotherapy. This recommendation is consistent with the FDA black-box warning.

X. Nonmyeloid Hematologic Malignancies

Since 2002, three systematic reviews found ESA use decreased the risk of transfusion for patients with nonmyeloid hematologic malignancies who were receiving chemotherapy. Overall, there were no statistically significant differences in survival between treatment and control arms. A pooled analysis found increased thromboembolic events in the ESA arm. As previously mentioned, patients with multiple myeloma receiving certain treatments are at increased risk; therefore, this recommendation added a caution regarding ESA use together with therapies that increase risk of thromboembolic events.

XI. Special Commentary, Survival, and Tumor Response

Concerns have arisen since 2002 about safety, survival, and tumor response, based on several published studies and data provided to the FDA. The FDA convened a meeting of its Oncologic Drugs Advisory Committee (ODAC) in May 2004 to discuss concerns about ESAs raised by three studies. By 2007, there were data from six randomized clinical trials showing higher mortality in the ESA treatment arms. Five had findings on decreased survival and two had findings on poorer locoregional control and progression-free survival. Three trials were stopped early because of increased deaths, disease progression, or thromboembolic events. In five of the six trials, the target hemoglobin was above 12 g/dL and patients' baseline Hb levels were greater than 10 g/dL. In addition, four of the six studies included patients not receiving chemotherapy, solely radiotherapy. In March 2007, FDA added the warnings described under Recommendation VII. In May 2007, FDA convened the ODAC again to discuss data available since 2004, including data from these randomized controlled trials, during which ODAC members voted on additional recommendations. The results of recent studies are difficult to interpret and apply to clinical practice because of design issues and ESA usage that diverges from FDA labeling and published guidelines. It is unknown whether the trials' results apply to a population of patients with cancer treated with chemotherapy who receive ESAs at doses titrated to achieve and maintain Hb levels of close to 12 g/dL and initiated when Hb levels are below or approaching 10 g/dL. Adequately-powered, well-designed trials designed to detect differences in tumor response or survival are lacking with patients for whom ESAs are prescribed to decrease the need for transfusion secondary to myelosuppressive chemotherapy. Randomized trials could further define which patients are most likely to benefit from ESA use and which are at greatest risk of adverse responses.

Methodology

The ASCO/ASH Update Committee completed an updated review and analysis of data published since 2002 through June 2007. They reviewed searches of MEDLINE and the

It is important to realize that many management questions have not been comprehensively addressed in randomized trials, and guidelines cannot always account for individual variation among patients. A guideline is not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results.

Accordingly, ASCO considers adherence to this guideline to be voluntary, with ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

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Cochrane Library. For the 2007 update, the Update Committee expanded the scope of the guideline to address the use of darbepoetin alfa and thromboembolic risk associated with using epoetin and darbepoetin.

Additional Resources

The full-text version of the guideline was published in the Journal of Clinical Oncology (J Clin Oncol 26:132-149, 2008). In addition to the full-text of the guideline update available at www.asco.org/guidelines/EPO, other ASCO resources include a patient guide, summary slide set, and orders and flow sheet.

Authors

The Use of Epoetin and Darbepoetin in Patients With Cancer: 2007 American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update was developed and written by Douglas Rizzo, Mark R. Somerfield, Karen L. Hagerty, Jerome Seidenfeld, Julia Bohlius, Charles L. Bennet, David F. Cella, Benjamin Djulbegovic, Matthew Goode, Ann A. Jakubowski, Mark U. Rarick, David H. Regan, and Alan E. Lichtin for the American Society of Clinical Oncology/American Society Epoetin and Darbepoetin Update Panel.

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References

1. Bohlius J, Langensiepen S, Schwarzer G, et al: Erythropoietin for patients with malignant disease (review). The Cochrane Library Issue 2, 2006
2. FDA Approved labels as of 11-08-07. Epoetin alfa: available at http://www.fda.gov/cder/foi/label/2007/103234s5158lbl.pdf and darbepoetin alfa: available at http://www.fda.gov/cder/foi/label/2007/103951s5164lbl.pdf

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