

QUICK REFERENCE

**2007 Clinical Practice
Guideline Update
on the Use of
Epoetin and Darbepoetin**



**presented by the
American Society of Hematology**

**Italics indicate changes from the original 2002 document, "Use of Epoetin in Patients with Cancer: Evidence-Based Clinical Practice Guidelines of the American Society of Clinical Oncology and the American Society of Hematology"*

I. General Recommendation

- ◆ Consider correctable causes of anemia before starting an erythropoiesis-stimulating agent (ESA) for chemotherapy-induced anemia:
 - evaluate drug exposure history and peripheral blood smear (possibly bone marrow),
 - rule out or correct iron, folate, and B12 deficiencies,
 - assess for occult blood loss *and renal insufficiency*, and
 - consider Coomb's testing in cases of CLL, NHL, or history of auto-immune disease.
- ◆ Endogenous erythropoietin levels may predict response in MDS.
- ◆ *Minimize ESA use in patients with high risk of thromboembolic events (see Recommendation IV).*

II. Special Commentary on the Comparative Effectiveness of Epoetin and Darbepoetin

(Note: This topic is new to the guideline.)

- ◆ *Available evidence from a systematic review suggests epoetin and darbepoetin are equivalent with respect to effectiveness and safety.*
- ◆ *The FDA-approved package inserts list identical indications, warnings, and cautions for the two ESAs.*

IIIa. Chemotherapy-Induced Anemia: Threshold for Initiating ESA Therapy (Hb concentration approaching or < 10 g/dL)

- ◆ ESA therapy can be initiated as a treatment option in patients with chemotherapy-associated anemia *as declining hemoglobin (Hb) concentration approaches, or falls below, 10 g/dL.*
- ◆ Red blood cell (RBC) transfusion is also an option.

† IIIb. Chemotherapy-Induced Anemia: Initiation Threshold > 10 g/dL but < 12 g/dL

- ◆ For declining Hb that has not fallen near 10 g/dL (those with hemoglobin concentration < 12 g/dL, but who have never fallen *near* 10 g/dL), the decision of whether to use epoetin or darbepoetin immediately or to wait until the hemoglobin levels fall closer to 10 g/dL should be determined by clinical circumstances (*including but not limited to elderly individuals with limited cardiopulmonary reserve, those with underlying coronary artery disease or symptomatic angina, or substantially reduced exercise capacity, energy, or ability to carry out activities of daily living*).
- ◆ RBC transfusion is also an option when warranted by clinical conditions.

† FDA Label Change

The FDA announced revisions to the product labels for ESAs on November 8, 2007. These revisions warn that risks of shortened survival and tumor progression have not been excluded in cancer patients when ESAs are dosed to reach a hemoglobin < 12 g/dL and suggest dosing modification to avoid transfusion. Clinicians are advised to consider this warning.

IV. Thromboembolic Risk

(Note: This topic is new to the guideline.)

- ◆ Carefully weigh risks of thromboembolism before starting ESA therapy, since available evidence shows ESAs increase that risk.
- ◆ Risk factors for thromboemboli include history of:
 - thrombosis,
 - surgery,
 - prolonged periods of immobilization or limited activity, and
 - multiple myeloma treated with thalidomide or lenalidomide plus doxorubicin or corticosteroids.
- ◆ Data are lacking on modulating risk with anticoagulants or aspirin.

V. Starting and Escalating Doses

- ◆ FDA-approved starting doses are:
 - Epoetin, 150 U/kg TIW *or* 40,000 U weekly subcutaneously (subQ), *or*
 - Darbepoetin, 2.25 microgram/kg weekly *or* 500 micrograms every 3 weeks subQ.
- ◆ *There is no evidence for improved outcomes with alternative dosing regimens.*
- ◆ *Dose escalation for no initial response should follow FDA recommendations:*
 - *Epoetin to 300 U/kg TIW or 60,000 U weekly subQ, or*
 - *Darbepoetin to 4.5 microgram/kg weekly.*

VI. Discontinuing Therapy for No Response

- ◆ Assuming appropriate dose increase was attempted, there is no evidence of benefit from continuing ESA treatment beyond 6-8 weeks in absence of response (i.e., < 1-2 g/dL rise in hemoglobin *or no diminution of transfusion requirements*); therefore, *ESAs should be discontinued.*
- ◆ These patients should be investigated for underlying tumor progression, iron deficiency, *or other etiologies for anemia.*

VII. Hemoglobin Target

†See FDA Label Change at IIIb

- ◆ Hb can be raised to or near 12 g/dL, and titrated to avoid the patient falling below 10 g/dL.
- ◆ *Reduce dose (epoetin by 25%, darbepoetin by 40%) when Hb rise exceeds 1 g/dL in any 2 week period or when Hb exceeds 11 g/dL.*
- ◆ Withhold dose if Hb reaches or exceeds 12 g/dL, and re-start at reduced doses when falls below 11 g/dL.
- ◆ *Risk of venous thromboembolism should also be considered.*

VIII. Iron Monitoring and Supplementation

- ◆ Measure:
 - baseline iron,
 - total iron-binding capacity, and
 - transferrin saturation or ferritin levels.
- ◆ Consider periodic monitoring; institute iron repletion when indicated.
- ◆ Evidence is inadequate to specify the optimal timing, periodicity, or testing regimen for such monitoring.

IX. Anemia in Patients Not Receiving Concurrent Chemotherapy

- ◆ Evidence supports ESA use for anemia associated with low-risk myelodysplasia, but evidence is lacking to support its *exclusive* use in anemic myeloma, NHL, or CLL patients in the absence of concurrent chemotherapy.
- ◆ *The use of ESAs is not indicated for anemia associated with malignancy, or the anemia of cancer, among patients with either solid or non-myeloid hematological malignancies who are not receiving concurrent chemotherapy.*

X. Treatment of Anemia in Patients with Non-Myeloid Hematological Malignancies Who Are Receiving Concurrent Chemotherapy

- ◆ For patients with newly diagnosed myeloma, NHL, or CLL, begin chemotherapy and/or corticosteroids and observe hematologic outcomes from tumor reduction before considering ESA treatment.
- ◆ *If Hb does not increase, treat chemotherapy-associated anemia as recommended above.*
- ◆ *Exercise caution in ESA use with chemotherapeutic agents and diseases associated with higher risks of thromboemboli (see Recommendation IV).*
- ◆ Blood transfusion is also an option.

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This document summarizes recommendations from: Rizzo JD, Somerfield M, Hagerty K, et al. American Society of Hematology/American Society of Clinical Oncology 2007 clinical practice guideline update on the use of epoetin and darbepoetin. *Blood*. Prepublished on October 23, 2007, as DOI 10.1182/blood-2007-08-109488.

Guidelines provide the practitioner with clear principles and strategies for quality patient care and do not establish a fixed set of rules that preempt physician judgment.

For further questions, please refer to the Practice Guidelines section of the ASH Web site at www.hematology.org/policy/resources/guidelines, or contact the ASH Policy & Practice Department at 202-776-0544.

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