



American Society of Clinical Oncology

*Making a world of difference in cancer care*

**2007 CLINICAL PRACTICE  
GUIDELINE UPDATE ON THE USE  
OF EPOETIN AND DARBEPOETIN**

AMERICAN SOCIETY OF ONCOLOGY/AMERICAN  
SOCIETY OF HEMATOLOGY CLINICAL PRACTICE  
GUIDELINE UPDATE

# Special Announcement

- Effective July 31, 2008, the Food and Drug Administration (FDA) mandated the following changes to the labels for the erythropoiesis stimulating agents, epoetin alfa and darbepoetin:
  - ESAs are no longer indicated for patients receiving myelosuppressive chemotherapy if the anticipated treatment outcome is cure. They remain indicated when myelosuppressive chemotherapy is intended for palliation.
  - ESAs should not be initiated if the patient's hemoglobin is above 10 g/dL. Further, the label change
    - specifies that ESA treatment should target the lowest hemoglobin concentration that will avoid transfusion,
    - removes "...or exceeds 12 g/dL" as an upper range for ESA use, and
    - removes language that allowed earlier initiation of ESAs, or treatment to higher hemoglobin targets, if the patient cannot tolerate anemia due to a co-morbid condition.
- The labels' Boxed Warnings now read: "ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers." The warning is no longer focused on studies with hemoglobin targets at or above 12 g/dL.

# Introduction

- The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) first published evidence-based clinical practice guidelines for the use of epoetin in 2002
- ASCO guidelines are updated at intervals by an Update Committee of the original Expert Panel
- For the 2007 update, the ASCO-ASH Update Committee expanded the scope of the guideline to include recommendations to address the use of darbepoetin alfa, and to address thromboembolic risk associated with the use of epoetin and darbepoetin

# Guideline Methodology: Systematic Review

- The panel completed a review and analysis of the medical literature available from 2002 through June 2007 on the use of epoetin and darbepoetin with people with cancer.

- ✓ Medline
- ✓ Cochrane

# Guideline Methodology: Panel Members

Alan E. Lichtin, MD, Co-Chair	Cleveland Clinic Foundation
J. Douglas Rizzo, MD, Co-Chair	Medical College of Wisconsin
Charles L. Bennett, MD, PhD	Northwestern University
Julia Bohlius, MD	University Hospital of Cologne
David F. Cella, PhD	Evanston Northwestern Healthcare
Benjamin Djulbegovic, MD, PhD	H. Lee Moffitt Cancer Center
Matt Goode	Patient Representative

# Guideline Methodology: Panel Members (continued)

Ann A. Jakubowski, MD, PhD	Memorial Sloan-Kettering Cancer Center
Carole B. Miller, MD	St. Agnes Healthcare
Mark U. Rarick, MD	NW Kaiser Permanente
David H. Regan, MD	US Oncology
Jerome Seidenfeld, PhD	BlueCross and BlueShield Association

# Background

- Hemoglobin – normal concentrations
  - Women: 12-16 g/dL
  - Men: 14-18 g/dL
- Anemia affects many people with cancer
  - 13-78 percent of patients undergoing treatment for solid tumors
  - 30-40 percent of patients treated for lymphoma

# Clinical Questions New to Update

1. What is the comparative effectiveness of epoetin and darbepoetin?
2. What is the thromboembolic risk of erythropoiesis stimulating agents (ESAs)?

# 2007 Categories of Recommendations for Use of Epoetin and Darbepoetin

1. Assessing causes of anemia
2. Comparing effectiveness of epoetin and darbepoetin
3. Threshold for initiating ESA therapy
4. Thromboembolism risk
5. Dosage
6. Discontinuation of ESA therapy
7. Hemoglobin target
8. Iron monitoring and supplementation
9. Anemia in patients not receiving concurrent chemotherapy
10. Anemia in patients with non-myeloid hematological malignancies receiving concurrent chemotherapy

# 2007 Recommendation I: General

- *ESA Therapy is a treatment option to increase hemoglobin and decrease transfusions for patients with chemotherapy-induced anemia*
- **Consider other correctable causes of anemia first:**
  1. Conduct appropriate history and physical
  2. Consider relevant diagnostic testing
  3. At a minimum:
    - a. Thorough drug exposure history
    - b. Peripheral blood smear (in some cases, the bone marrow)
    - c. Iron, folate, and B12 deficiency
    - d. Assess for occult blood loss and renal insufficiency

# 2007 Recommendation I: General, continued

4. Diagnostic testing (possibly appropriate) = Coomb's testing for patients with:
  - a. Chronic lymphocytic leukemia
  - b. Elderly individuals with Non-Hodgkin's lymphoma
  - c. History of auto-immune disease
5. Minimize use of epoetin or darbepoetin in patients with high risk of thromboembolic events

## 2007 Recommendation II

- **Special Commentary on the Comparative Effectiveness of Epoetin and Darbepoetin**
  - Basis: comprehensive systematic review comparing outcomes in patients with chemotherapy-induced anemia
  - The Update Committee considers these agents to be equivalent with respect to effectiveness and safety

# 2007 Recommendation III: Threshold for Initiating ESA Therapy

## IIIa: Chemotherapy-induced anemia: Initiation threshold

- Hemoglobin approaching, or below, 10 g/dL
- Red blood cell (RBC) transfusion also an option

## IIIb: Chemotherapy-induced Anemia: Initiation threshold > 10 g/dL but < 12 g/dL

- Options, determine use by clinical circumstances (*next slide*)
  - Use ESA immediately, or
  - Wait until the hemoglobin levels fall closer to 10 g/dL
  - Red blood cell (RBC) transfusion also an option

# 2007 Recommendation III: Chemotherapy-induced Anemia: Initiation Threshold, continued

## IIIb, Continued

- Clinical circumstances include:
  - Elderly individuals with limited cardiopulmonary reserve
  - Underlying coronary artery disease or symptomatic angina
  - Substantially reduced exercise capacity, energy, or ability to carry out activities of daily living [ADLs]

# 2007 Recommendation IV: Thromboembolic Risk

- Data demonstrate increased risk of thromboembolism for patients receiving ESAs
- Carefully weigh the risks of thromboembolism for patients when prescribing ESA
- Use caution and clinical judgment
- Those at risk of thromboembolism, in general:
  - History of thromboses
  - Surgery
  - Prolonged periods of immobilization or limited activity
  - Patients with multiple myeloma who are being treated with thalidomide or lenalidomide and doxorubicin or corticosteroids

# 2007 Recommendation V: Starting and Escalating Dose

- Starting Dose – Use FDA approved
  - Epoetin: 150 units/kg three times a week or 40,000 units weekly subcutaneously
  - Darbepoetin: 2.25 microgram/kg weekly or 500 micrograms every 3 weeks subcutaneously
  - No finding of consistent difference in outcomes from alternative starting doses or dosing schedules

# 2007 Recommendation V: Starting and Escalating Dose, (continued)

- Dose escalation: follow FDA-approved label
  - Epoetin
    - When initial dose 150 units/kg three times per week: If no reduction in transfusion requirements or rise in Hb after 8 weeks, then increase dose to 300 units/kg three times per week
    - When initial dose 40,000 units weekly: If no increase in Hb by  $\geq 1$  g/dL after 4 weeks of therapy (in the absence of a RBC transfusion), then increase dose to 60,000 units weekly
  - Darbepoetin
    - When initial dose 2.25 microgram/kg weekly: If there is  $<1$  g/dL increase in Hb after 6 weeks, then increase dose to 4.5 mcg/kg
    - When initial dose 500 mcg subcut every three weeks: N/A

# 2007 Recommendation VI: Discontinuing for No Response

- Discontinue ESA after 6-8 weeks when absence of response (e.g.,  $< 1$ - $2$  g/dL rise in hemoglobin or no diminution of transfusion requirements), assuming appropriate dose increase attempted in non-responders as per FDA-approved label
- For patients with no response, investigate for:
  - Underlying tumor progression
  - Iron deficiency
  - Other etiologies of anemia

# 2007 Recommendation VII: Hemoglobin Target

- Raise Hb to (or near) a concentration of 12 g/dL → titrate to maintain
- Reduce dose:
  - When hemoglobin rise is  $> 1$  g/dL in any 2 week period OR
  - When the hemoglobin  $> 11$  g d/L
  - Consider risk of venous thromboembolism when determining dose reduction schedules
  - Epoetin: ↓ dose by 25% when Hb approaches 12 g/dL or Hb ↑  $> 1$  g/dL in 2 weeks
  - Darbepoetin: ↓ dose by 40% of previous dose when Hb  $> 11$  g/dL or Hb ↑  $> 1$  g/dL in 2 weeks

# 2007 Recommendation VIII: Iron Monitoring and Supplementation

- May be valuable in limiting need for ESA, maximizing symptomatic improvement, determining reason for ESA response failure
- Monitor:
  - Iron
  - Total iron-binding capacity
  - Transferrin saturation
  - Ferritin levels
- Institute iron repletion when indicated
- Inadequate evidence on:
  - Timing,
  - Periodicity, or
  - Testing regimen

# 2007 Recommendation IX: Anemia in Patients Not Receiving Chemotherapy

- Evidence supports using ESAs in patients with anemia associated with low-risk myelodysplasia
- No published high-quality studies supporting exclusive ESA use in patients with anemic myeloma, non-Hodkin's lymphoma, or chronic lymphocytic leukemia in absence of chemotherapy
- Do not use ESAs to treat 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
- Recommendation IX consistent with March 2007 black-box warning:
  - “Use of ESAs increased the risk of death when administered to a target hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated in this population.”

# 2007 Recommendation X: Treatment of Anemia in Patients with Non-Myeloid Hematological Malignancies Who Are Receiving Concurrent Chemotherapy

- Patients with Myeloma, Non-Hodgkin's lymphoma, Chronic lymphocytic leukemia:
  - Begin treatment with chemotherapy and/or corticosteroids
  - Observe the hematologic outcomes achieved solely through tumor reduction first
  - If a rise in hemoglobin is not observed following chemotherapy, treatment with epoetin or darbepoetin should follow recommendations I-IX

## 2007 Recommendation X: Treatment of Anemia in Patients with Non-Myeloid Hematological Malignancies Who Are Receiving Concurrent Chemotherapy, (continued)

- Patients with Myeloma, Non-Hodgkin's lymphoma, Chronic lymphocytic leukemia, (continued)
  - *Particular caution should be exercised in the use of epoetin or darbepoetin concomitant with chemotherapeutic agents and diseases where risk of thromboembolic complications is increased. (Refer to Recommendation IV.)*
  - Blood transfusion is also a therapeutic option

# *Special Commentary on ESAs, Survival, and Tumor Response*

- Since the 2002 guideline, a number of published studies on ESAs for patients with cancer have raised safety concerns. Additional studies-complete data not yet available. Other data non-peer reviewed.
- Due to the designs of the trials discussed in guideline, there is difficulty in interpreting their results and applying them to current clinical practice.
- It is unknown whether these results apply to a population of chemotherapy-treated patients with cancer receiving ESAs at doses titrated to achieve and maintain a Hb level of close to 12.
- Adequately-powered, well-designed trials designed to detect differences in tumor response or survival are lacking in patients in whom ESAs are prescribed in order to decrease the need for transfusion secondary to myelosuppressive chemotherapy.

# 2007 Recommendations: Summary

## Justification for Initial Therapy

	Consider other correctable causes of anemia first	Monitor and supplement iron	ESA <sup>1</sup>	Consider RBC transfusion	Weigh the risks of thromboembolism
<b>Justification for initial therapy</b>					
Chemotherapy-associated anemia and a Hb concentration approaching or below 10 g/dL	✓	✓	✓	✓	✓
Chemotherapy-associated anemia with Hb concentration >12 g/dL but never fallen near 10 g/dL	✓	✓	use clinical circumstances to determine use	✓	✓
Patients with anemia associated with low-risk MDS	✓	✓	✓	✓	✓
Anemia of cancer without chemotherapy -with either solid or non-myeloid hematological malignancies	✓	✓	No	✓	✓
Myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia with concurrent chemotherapy	✓	✓	Only if Hb doesn't rise after chemotherapy and/or corticosteroids. Use caution, especially with people with multiple myeloma receiving thalidomide or lenalidomide and doxorubicin or corticosteroids.	✓	✓
High risk of thromboembolism	✓	✓	Minimize use	✓	✓

# 2007 Recommendations: Summary After ESA Therapy

After ESA therapy					
Reach to or near 12 g/dL	-	✓	Titrate to maintain	n/a	✓
No response within 4-8 weeks <sup>†</sup>	✓	✓	Increase if rise < 1-2 g/dL (but not if >1 increase in 2 week period) and no diminution of transfusion requirements	✓	✓
If no response 6-8 weeks after dose increase attempted	✓	✓	Discontinue	✓	✓
Hb rise > 1 g/dL in any 2 week period	n/a	✓	Reduce dose	n/a	✓
Hb > 11 g d/L	n/a	✓	Reduce dose until Hb <11 g/dL	n/a	✓

<sup>†</sup> For Epoetin alfa – starting dose 40,000 units weekly or 150 units/kg thrice times weekly if no response after 8 weeks; for Darbepoetin alfa – Starting dose 2.25 mc/kg weekly

# Additional ASCO Resources

- The full text of the guideline, this slide set, and additional clinical tools and resources can be found at: <http://www.asco.org/guidelines/epo>
- A patient guide on Epoetin and Darbepoetin Treatment can be found at <http://www.cancer.net>



# ASCO Guidelines

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 the 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.