American Society of Clinical Oncology

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American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer

The guideline update - resources

- Abridged version – JCO publication (http://jco.ascopubs.org/misc/specialarticles.dtl)
- Unabridged version (www.asco.org/guidelines/esa)
- Clinical Tools & Resources (www.asco.org/guidelines/esa)

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 and updated them in 2007
- The scope of the 2007 update was expanded to address the use of darbepoetin alfa as well as emerging safety concerns
- The current update reviews new evidence published since 2007 on ESA-related tumor progression, venous thromboembolism, and/or survival

Guideline Methodology: Systematic Review

- The Update Committee completed a review and analysis of the medical literature available between January 2007 and January 2010
  - Databases searched:
    - ✓Medline
    - ✓Cochrane Library

Clinical Questions

Two overarching questions were addressed:

- What are the defining features of patients with a malignancy who are appropriate candidates for ESA treatment?
- For patients who are appropriate candidates for treatment with ESAs, what are the optimal approaches to ESA therapy?

2010 Recommendation I

It is recommended that before any decision regarding use of ESA is made, an appropriate history, physical and diagnostic tests be conducted to identify alternative causes of anemia aside from chemotherapy or an underlying hematopoietic malignancy.

At a minimum, this would include the following:

- thorough drug exposure history
- review of a peripheral-blood smear (and in some cases, a bone marrow examination)
- analyses, where indicated, for iron, folate, or vitamin B_{12} deficiency
- assessment of reticulocyte count, occult blood loss and renal insufficiency

2010 Recommendation I, cont'd

It may also include the following:

- Coombs' testing for patients with chronic lymphocytic leukemia, non-Hodgkin's lymphoma, or a history of auto-immune disease
- assessment of endogenous erythropoietin levels for patients with myelodysplastic syndrome

Consideration must be given to demonstrated risks of thromboembolism (see Recommendation IV), the possibility of death, and minimizing ESA use, particularly in patients with malignancy being treated with curative intent.

Recommendation I: Special Note

- *Special Note: Although the U.S. Food and Drug Administration (FDA) label now limits the indication for ESA use to patients receiving chemotherapy for palliative intent, as described in Literature update and discussion: weighing harms versus benefits (in full guideline), no study has evaluated outcomes of ESA therapy by subgroups defined by chemotherapy intent. Determination of the goal of treatment requires clinical judgment in many cases.*

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2010 Recommendation II

- **Special Commentary on the Comparative Effectiveness of Epoetin and Darbepoetin**
  - No change from 2007
  - The Update Committee considers these agents to be equivalent with respect to effectiveness and safety
  - Basis: comprehensive systematic review comparing outcomes in patients with chemotherapy-induced anemia and identical cancer-related indications, warnings and cautions (see FDA-approved package inserts)

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2010 Recommendation IIIa: Threshold for Initiating ESA Therapy

IIIa: Chemotherapy-induced anemia: Initiation threshold

In brief:

- Treatment option for patients with chemotherapy-induced anemia whose Hemoglobin (Hb) has decreased to less than 10 g/dL
- Red blood cell (RBC) transfusion also an option

Recommendation: The use of epoetin or darbepoetin is recommended as a treatment option that may be considered for patients with chemotherapy-associated anemia and a Hb concentration that has decreased to less than 10 g/dL, to decrease transfusions. RBC transfusion is also an option, depending on the severity of the anemia or clinical circumstances.

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2010 Recommendation IIIb: Threshold for Initiating ESA Therapy

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

In brief:

- Determine by clinical judgment, risks and benefits, and patient preference
- RBC transfusion is an option when warranted by clinical conditions

- An optimal level at which to initiate ESA therapy in patients with anemia and Hb between 10 g/dL and 12 g/dL cannot be definitively determined from the available evidence. Under these circumstances, whether or not to initiate ESA treatment should be determined by clinical judgment, consideration of the risks and benefits of ESAs, and patient preferences (see Recommendations I and IV). RBC transfusion is an option when warranted by clinical conditions.

2010 Recommendation IV: Thromboembolic Risk

- No change since 2007
- Carefully weigh the risks of thromboembolism for patients when prescribing ESA
- Data demonstrate increased risk of thromboembolism for patients receiving ESAs
- Use caution and clinical judgment
- Established, general risk factors for thromboembolism:
  - History of thromboses
  - Surgery
  - Prolonged periods of immobilization or limited activity
  - Some diseases and treatment regimens have also been associated with higher risk of venous thromboembolic events

2010 Recommendation V: Starting and Escalating Doses

Starting and Modifying Doses: Use FDA guidelines (see Adult Dosing Table at http://www.asco.org/guidelines/esa)

- Starting:
  - epoetin: 150 units/kg three times a week or 40,000 units weekly subcutaneously
  - darbepoetin: 2.25 micrograms/kg weekly or 500 micrograms every 3 weeks subcutaneously
- Dose modification should follow FDA recommendations
- Discontinue ESA treatment when chemotherapy concludes
- No evidence to support improved effectiveness or safety with alternative starting doses, dose schedules, or dose-modifying schedules

2010 Recommendation V: Starting and Escalating Doses (continued)

- Dose escalation: follow FDA-approved label (see Adult Dosing Table at http://www.asco.org/guidelines/esa)
  - epoetin
    - When initial dose 150 units/kg three times per week: If no reduction in transfusion requirements or increase in Hb after 4 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 ≥ 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 ug/kg
    - When initial dose 500 micrgrams every three weeks: N/A

2010 Recommendation VI: Discontinuing for No Response

- No change since 2007*
- Discontinue ESA after 6-8 weeks when absence of response (e.g., a <1 to 2 g/dL increase in Hb or no diminution of transfusion requirements), assuming an 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

*(see http://www.asco.org/guidelines/esa)

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2010 Recommendation VII: Hemoglobin Target

- Hemoglobin can be increased to the lowest concentration needed to avoid transfusions, which may vary by patient and condition.
- *Qualifying Statement:* An optimal target Hb concentration cannot be definitively determined from the available literature. Modification to reduce the ESA dose is appropriate when Hb reaches a level sufficient to avoid transfusion or the increase exceeds 1 g/dL in any 2-week period to avoid excessive ESA exposure (see Recommendation V), considering the risks of ESAs (see Recommendation I). Specific dose reduction recommendations are listed in *Table 2* of the full guideline (www.asco.org/guidelines/esa).

2010 Recommendation VII: Hemoglobin Target (continued)

- Dose reduction: follow FDA-approved label
  - Epoetin
    - Decrease dose by 25% when Hb *reaches a level needed to avoid transfusion* or Hb increases > 1 g/dL in 2 weeks
  - Darbepoetin
    - Decrease dose by 40% of previous dose when Hb *reaches a level needed to avoid transfusion* or Hb increases to > 1 g/dL in 2 weeks

2010 Recommendation VIII: Iron Monitoring and Supplementation

- No change since 2007
- Baseline and periodic monitoring may help to reduce the need for ESAs, maximize symptomatic improvement, and/or determine reason for ESA response failure
- Monitor:
  - Iron
  - Total iron-binding capacity
  - Transferrin saturation
  - Ferritin levels
- Insufficient evidence on:
  - Timing, periodicity, testing regimen, or iron replacement

2010 Recommendation IX: Anemia in Patients Not Receiving Concurrent Chemotherapy

- It is recommended that ESAs not be used in treatment of anemia associated with malignancy in patients who are not receiving concurrent myelosuppressive chemotherapy
- Use of ESAs in people with lower-risk myelodysplastic syndrome to avoid transfusions is an exception to this recommendation

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2010 Recommendation X: Treatment of Anemia in Patients with Non-Myeloid Hematological Malignancies Who Are Receiving Concurrent Chemotherapy

- No change since 2007
- For patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia:
  - Begin treatment with chemotherapy and/or corticosteroids
  - Observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin
  - If an increase in Hb is not observed after chemotherapy and patient experiencing chemotherapy-associated anemia, treatment for those with these malignancies with epoetin or darbepoetin should follow recommendations I-VIII

2010 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, or 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

Recommendation X: Special Note

- *Special Note: Although the FDA label now limits the indication for ESA use to patients receiving chemotherapy for palliative intent, as described in the "Literature update and discussion: weighing harms versus benefits" of full guideline, no study has evaluated outcomes of ESA therapy by subgroups defined by chemotherapy intent.*
- *Although patients with multiple myeloma and chronic lymphocytic leukemia often respond to first- or subsequent-line therapy, because these malignancies recur in most patients, determining the treatment intent requires clinical judgment of an individual patient's circumstances.*

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Special Commentary on ESAs, Survival, and Tumor Response

- Since 2007 guideline, new RCT data available
- Some reporting adverse health effects associated with ESA use in patients with cancer (e.g. increased mortality risks, thromboembolic events)
- FDA-approved labels revised, as reflected in current guideline recommendations I-X (see above)

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NOTE

- The FDA and the pharmaceutical companies who market and/or manufacture ESAs in the U.S. created a Risk Evaluation and Mitigation Strategy (REMS) to advise clinicians and to facilitate discussions with patients. This program began 3/24/10 and will be phased in over 1 year.
- Clinicians must enroll in the ESA APPRISE Oncology program.
- Patients need to sign an acknowledgment form to confirm that they have talked with their healthcare professional about the risks of ESAs.
- More detailed information available online (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200297.htm)

2010 Recommendations: Summary Justification for Initial Therapy

Justification for initial therapy	Consider other correctable causes of anemia first	Monitor and supplement iron	ESA is an option[1]	Consider RBC transfusion	Weigh the risks of thrombo embolism
Chemotherapy-associated anemia and Hb concentration has decreased below 10 g/dL	✓	✓	✓	✓	✓
Chemotherapy-associated anemia with Hb concentration 10 g/dL and 12 g/dL	✓	✓	use clinical circumstances to determine use	✓	✓
Patients with anemia associated with low-risk myelodysplastic syndrome	✓	✓	✓	✓	✓
Anemia of cancer without myelosuppressive chemotherapy	✓	✓	No	✓	✓
Myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia treated with palliative intent	✓	✓	Only if Hb doesn't increase after chemotherapy with or without corticosteroids	✓	✓
People with multiple myeloma receiving thalidomide or lenalidomide and doxorubicin or corticosteroids	✓	✓	Use caution – at increased risk of thromboembolism	✓	✓
High risk of thromboembolism	✓	✓	Minimize use	✓	✓

2010 Recommendations: Summary
After ESA Therapy

After ESA therapy If	Then
No response within 4 (epoetin) – 6 (darbepoetin) weeks[i]	Increase if no diminution of transfusion requirements (epoetin initial
	dose 150 U/kg) or no increase by ≥1 g/dL (epoetin initial dose 40,000 U). For darbepoetin, increase if <1 g/dL increase.
If no response after chemotherapy course or after 8 weeks of ESA therapy	Discontinue
If Hb exceeds a level needed to avoid transfusion	Withhold
Hb increase > 1 g/dL in any 2 week period	Reduce dose (25% epoetin; 40% darbepoetin)

[i] 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 microgram/kg weekly

Guideline Methodology: Update Committee Members

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Guideline Methodology: Update Committee Members (continued)

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Additional ASCO Resources

- The full text of the guideline (in both abridged and unabridged versions, with evidence tables), this slide set, and additional clinical tools and resources can be found at: http://www.asco.org/guidelines/esa. 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.

