Guideline Summary

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

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Context

Journal of Clinical Oncology and *Blood* recently jointly published the ASCO/American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer.[1,2] A previous update was published in 2007 (http://jco.ascopubs.org/content/26/1/132).

As in 2007, the current guideline update addresses safety concerns and reviews new evidence from meta-analyses, systematic reviews, and randomized controlled trials (RCTs) on erythropoiesis-stimulating agents (ESA)-related tumor progression, venous thromboembolism, and survival in adult patients with cancer. Table 1 lists the current recommendations. A table in the full guideline compares the previous and current recommendations.[1]

The associations between ESA use and adverse outcomes, which include an increase in mortality during the period of exposure and an increased risk of thromboembolic events, have led to restrictions on ESA use.[3,4]

2010 Update

This update addresses two overarching clinical questions: (1) What are the defining features of patients with a malignancy who are appropriate candidates for ESA treatment? and (2) For patients who are appropriate candidates for treatment with ESAs, what are the optimal approaches to ESA therapy?

New evidence reported since the 2007 guideline update establishes that in addition to the previously-demonstrated increases in thromboembolic event rates, ESA therapy is associated with shorter survival. However, evidence is still lacking on the mechanisms of these harms and on whether all patients are equally at risk, or some patients are at minimal risk, for the harms associated with ESA use. The Update Committee generally recommends that for patients undergoing myelotoxic chemotherapy who have hemoglobin $<$ 10 g/dL, clinicians should discuss the potential harms (thromboembolism, shorter survival) and benefits (decreased transfusions) of ESAs and compare those with potential harms (serious infections, immune-mediated adverse reactions) and benefits (rapid hemoglobin improvement) of RBC transfusions. Individual patient preferences for assumed risk should contribute to shared decisions on managing chemotherapy-induced anemia. The Update Committee cautions against ESA use under all other circumstances.

Recommendations

I. General Recommendation

Before deciding to use an ESA, clinicians should rule out causes of anemia other than chemotherapy or an underlying hematopoietic malignancy. Suggested tests are listed in Table 1. Clinicians and patients should consider demonstrated risks of thromboembolism, the possibility of death, and minimizing ESA use, particularly in patients with malignancy being treated with curative intent. The guideline notes that evidence from well-done randomized placebo-controlled double-blinded trials shows that ESA treatment decreases transfusion rates.

Since the publication of the 2007 guideline update, one individual patient data meta-analysis, four literature- or study-based meta-analyses, one systematic review, and two RCTs have published evidence relevant to the effects of ESA therapy on risk of mortality. The complete guideline summarizes results from each article (www.asco.org/guidelines/esa).

In 2008, the US Food and Drug Administration (FDA) approved revised labels that limit indications for ESA use to patients receiving myelosuppressive chemotherapy for palliative intent, not curative intent, on the basis of clinical trial data suggesting an increased risk of mortality with ESA use. The Update Committee acknowledges the FDA's assessment that the reported benefits of ESAs may be outweighed by risks considered unacceptable in patients who might otherwise expect cure from their chemotherapy. However, the Committee also notes that data are unavailable to compare outcomes of ESA therapy separately in patient subsets defined by the treatment intent of the chemotherapy regimen they are receiving.

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

Since the 2007 guideline update, there were no new studies comparing epoetin and darbepoetin, and therefore there is no

Table 1. Summary of Recommendations

Recommendation Category	2010 Recommendations
I. General	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 B12 deficiency; assessment of reticulocyte count, occult blood loss, and renal insufficiency. 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.* *Special Note: Although the FDA label now limits the indication for ESA use to patients receiving chemotherapy for palliative intent, as described in the section Literature update: Weighing harms versus benefits (of the 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.*
II. Special Commentary on the Comparative Effectiveness of Epoetin and Darbepoetin	*(Unchanged from 2007)* Based on a comprehensive systematic review comparing outcomes of epoetin and darbepoetin in patients with chemotherapy-induced anemia and on identical cancer-related indications, warnings, and cautions in the relevant FDA-approved package inserts, the Update Committee considers these agents to be equivalent with respect to effectiveness and safety.
IIIa. Chemotherapy-Induced Anemia: Threshold for Initiating ESA Therapy	The use of epoetin or darbepoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and an 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.
IIIb. Chemotherapy-Induced Anemia: Initiation Threshold ≥ 10 g/dL but < 12 g/dL	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.
IV. Thromboembolic Risk	*(Unchanged from 2007)* Clinicians should carefully weigh the risks of thromboembolism in patients for whom epoetin or darbepoetin are prescribed. Randomized clinical trials and systematic reviews of available randomized clinical trials demonstrate an increased risk of thromboembolism in patients receiving epoetin or darbepoetin. Specific risk factors for thromboembolism have not been defined in these trials; therefore, clinicians should use caution and clinical judgment when considering use of these agents. Established, general risk factors for thromboembolic events include history of thromboses, surgery, and prolonged periods of immobilization or limited activity. *Some diseases and treatment regimens have also been associated with higher risk of venous thromboembolic events.*
V. Starting and *Modifying* Doses	It is recommended that starting and *modifying* doses of ESA follow FDA guidelines: FDA-approved starting dose of epoetin is 150 U/kg three times a week, or 40,000 U weekly subcutaneously; FDA-approved starting dose of darbepoetin is 2.25 μg/kg weekly or 500 μg every 3 weeks subcutaneously; dose modification should follow FDA recommendations as outlined in Table 2 of the full guideline; discontinue ESA treatment when chemotherapy concludes. Evidence does not exist to support improved effectiveness or safety with alternative starting doses, dose schedules, or dose-modifying schedules.
VI. Discontinuing Therapy for No Response	*(Unchanged from 2007)* Continuing epoetin or darbepoetin treatment beyond 6 to 8 weeks in the absence of response (eg, a < 1 to 2 g/dL increase in Hb or no diminution of transfusion requirements) does not seem to be beneficial, assuming an appropriate dose increase has been attempted in nonresponders as per the FDA-approved label, and ESA therapy should be discontinued. Patients who do not respond should be investigated for underlying tumor progression, iron deficiency, or other etiologies for anemia.
VII. Hemoglobin Target	Hb 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, *and 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.
VIII. Iron Monitoring and Supplementation	*(Unchanged from 2007)* Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels and instituting iron repletion when indicated may help to reduce the need for ESAs, maximize symptomatic improvement for patients, and determine the reason for failure to respond adequately to ESA therapy. There is inadequate evidence to specify the optimal timing, periodicity, or testing regimen for such monitoring. Although iron replacement is generally recommended to augment response for ESA recipients with iron deficiency, there is insufficient evidence to consider the use of intravenous iron as a standard of care.
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 lower-risk myelodysplastic syndrome to avoid transfusions is an exception to this recommendation.
X. Treatment of Anemia in Patients With Nonmyeloid Hematological Malignancies Who Are Receiving Concurrent Chemotherapy	*(Unchanged from 2007)* Physicians caring for patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin. If an increase in Hb is not observed after chemotherapy, treatment with epoetin or darbepoetin for patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia experiencing chemotherapy-associated anemia should follow recommendations I through VIII. 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 Note: Although the FDA label now limits the indication for ESA use to patients receiving chemotherapy for palliative intent, as described in the section Literature update and discussion: Weighing harms versus benefits, 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.*

NOTE: The intended use of ESAs is to reduce RBC transfusion requirements. All recommendations are consistent with the FDA labels.
Abbreviations: ESA, erythropoiesis-stimulating agent; FDA, US Food and Drug Administration; Hb, hemoglobin.

change from the previous recommendation; the guideline considers the agents equivalent with respect to effectiveness and safety.

III. Initiation Thresholds

IIIa. Chemotherapy-induced anemia: Threshold for initiating ESA therapy. The use of epoetin or darbepoetin is recommended as a treatment option that may be considered for patients with chemotherapy-associated anemia and a hemoglobin 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.

The two recent RCTs, and three others cited in the 2007 guideline, compared immediate (Hb $\geq$ 10) versus delayed (Hb $<$ 10) ESA administration. FDA-approved labels for ESAs now state that "therapy should not be initiated at hemoglobin levels $\geq$ 10 g/dL" and recommend that dosing should be ". . . titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for blood transfusion . . ."[4(p30)]

The guideline concludes there is insufficient evidence to demonstrate either fewer transfusions or more frequent harm when initiating ESA therapy at Hb $\geq$ 10 g/dL versus Hb $<$ 10 g/dL. The Update Committee accepts that, although evidence is lacking to establish an optimally safe and beneficial Hb threshold for starting ESA therapy, it is clinically prudent in light of the new evidence to wait until Hb concentration falls below 10 g/dL. This recommendation is updated to acknowledge the revised FDA labels and stronger evidence of increased mortality.

IIIb. Chemotherapy-induced anemia: Initiating when Hb is $\geq$ 10 g/dL but less than 12 g/dL. The Update Committee continues to conclude that an optimal level at which to initiate ESA therapy in patients with cancer with anemia and hemoglobin between 10 g/dL and 12 g/dL cannot be definitively determined.

Considering the evidence showing that ESA use is associated with a statistically significant increased risk of mortality and venous thromboembolism and the inability to identify any particular patient subgroups that experience greater benefits or increased risk as a result of ESA therapy initiation, the Update Committee advises caution when considering ESA therapy for any patient whose hemoglobin concentration is $\geq$ 10 g/dL. Decisions about ESA therapy should be based on clinical judgment of individual risks, benefits, and treatment goals, and discussions with patients. This is also consistent with current FDA labeling for both, which state that ESA use ". . . should not be initiated at hemoglobin levels $\geq$ 10 g/dL" and that it ". . . has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being."[3(p5),4(p5)] There may be some rare clinical circumstances that warrant careful consideration when Hb $\geq$ 10 g/dL (eg, severe pulmonary or cardiovascular comorbidities).

ESAs and Quality of Life

The previous guideline update considered that a substantially enhanced health-related quality of life (QOL) from reduced anemia might be a potential benefit of ESA treatment when Hb was 10 to 12 g/dL. However, evidence published since then has not conclusively shown improved QOL with ESA therapy. Assessment of QOL remains challenging, and experts disagree about whether the measured effect sizes reach psychometrically defined thresholds for clinically meaningful changes. Furthermore, although some evidence suggests that treatment with ESAs in this setting may increase scores on some QOL measures, any benefits must be considered in the context of increasing evidence of risks associated with ESA treatment. Therefore, avoidance of transfusions, not improvement in QOL, should be the goal of ESA therapy.

IV. Thromboembolic Risk

This recommendation is unchanged, and the Update Committee continues to urge clinicians to use caution when considering ESAs. Since 2007, three literature-based meta-analyses and five RCTs have been published that evaluate the rates of thromboembolic events among patients treated with ESAs and substantiate the findings of increased risk of these events among those who received ESAs. Patients with multiple myeloma who are receiving thalidomide or lenalidomide and doxorubicin or corticosteroids are at particularly increased risk of thromboembolic events.

V. Starting and Modifying Doses and VI. Discontinuing Therapy for No Response

There were two trials relevant to Recommendation V; no new data were relevant for Recommendation VI. Both of these recommendations remain unchanged. The ESA Adult Dosing Table, showing the doses from the FDA-approved labels, is available as Appendix Table A1 (online only). The recommendation stresses that starting doses and dose modification should follow the FDA-approved labels. Modification includes dose increases, dose reduction, and dose withholding. ESA therapy should be discontinued in patients who do not respond after 6 to 8 weeks of treatment that includes one dose increase, as the labels recommend.

VII. Hemoglobin Target

The 2007 update summarized emerging (but at that time inconclusive) evidence suggesting that ESA therapy might increase the risk of mortality in patients with cancer and anemia. Although it suggested that Hb could be raised to or near 12 g/dL, an optimal target hemoglobin concentration cannot be definitively determined from the current available evidence. Given this lack of evidence, combined with the mounting evidence that ESA therapy is accompanied by increased risk of mortality, the Committee concludes that the Hb target should be as low as possible to avoid transfusions and that health care providers should avoid steep increases in hemoglobin with ESA treatment.

VIII. Iron Monitoring and Supplementation

This recommendation is unchanged since 2007. Since the 2007 update, three RCTs have been published that evaluated the

effects of intravenous (IV) iron in combination with darbepoetin in patients with chemotherapy-induced anemia.

Although published studies suggest that use of IV iron may augment ESA response, study limitations led the Committee to recommend that currently available clinical evidence is insufficient to support IV iron as a standard of care for adjuvant therapy in patients with cancer and anemia receiving ESA therapy.

IX. Anemia in Patients Not Receiving Concurrent Chemotherapy

The substance of this recommendation has not changed from the 2007 update. However, new evidence provides additional support for the continued recommendation that ESA treatment decreases the need for transfusions in patients with lower risk myelodysplastic syndrome who are not undergoing concurrent chemotherapy.

X. Treatment of Anemia in Patients With Nonmyeloid Hematological Malignancies Who Are Receiving Concurrent Chemotherapy

This recommendation remains the same as in 2007. Results from the individual patient data meta-analysis informed this decision.

Special Commentaries on ESAs, Outcomes, and Potential Mechanisms

The guideline contains a special commentary on these topics, including a section on potential molecular mechanisms by which ESAs may contribute to adverse events, including increased mortality risks, among people with cancer who take them. The guideline comments that the new randomized trials published or available in the public domain since the 2007 guideline were underpowered to detect survival outcomes and instead reported responses to ESA therapy measured by increases in Hb or transfusion avoidance. Therefore, interpretation of the results is extremely challenging because the studies are underpowered, thus masking potentially true risks or true benefits of ESA therapy.

The guideline suggests that research to further clarify the mechanisms of harm would be useful, particularly research identifying patient subgroups that may be at less risk of adverse events with ESA use.

Methodology

The ASCO/American Society of Hematology Update Committee reviewed searches of MEDLINE and the Cochrane Collaboration Library and conducted a systematic review of the literature published between January 2007 and January 2010.

Additional Resources

Journal of Clinical Oncology published an abridged version of this guideline on September 25, 2010. The guideline (both abridged and unabridged versions) is available at www.asco.org/guidelines/esa, and a slide set and other clinical tools are available as data supplements. The full guideline includes sections on patient communications and health disparities. Patient information is available at asco.org and www.cancer.net.

Note also that since the 2007 update, the FDA and companies who market ESAs in the United States created a Risk Evaluation and Mitigation Strategy. Among other requirements, health care providers who prescribe ESAs to patients with cancer must enroll in the ESA APPRISE Oncology Program. This program began March 24, 2010 and will be phased in over 1 year. More detailed information is available online from the FDA (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200297.htm).

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Appendix

Table A1. ESA Adult Dosing

	Epoetin Alfa		Darbepoetin Alfa	
Dose and Modification	**Initial Dose* of 150 U/kg SC TIW**	**Initial Dose* of 40,000 U SC weekly**	**Initial Dose* of 2.25 μg/kg SC weekly**	**Initial Dose* of 500 μg SC Q3W**
Initial dose	Increase dose to 300 U/kg TIW if no reduction in transfusion requirements or increase in Hb *after 4 weeks of therapy to achieve and maintain lowest Hb level sufficient to avoid need for RBC transfusion*	Increase dose to 60,000 U SC weekly if no increase in Hb by ≥ 1 g/dL after 4 weeks of therapy, in the absence of an RBC transfusion *to achieve and maintain lowest Hb level sufficient to avoid need for RBC transfusion*	Increase dose up to 4.5 μg/kg if there is < 1 g/dL increase in Hb after 6 weeks of therapy	NA
Dose reduction	Decrease dose by 25% when Hb reaches a level needed to avoid transfusion or Hb increases > 1 g/dL in 2 weeks		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	
Dose withholding	*If Hb exceeds a level needed to avoid transfusion; restart dose at 25% below previous dose when Hb approaches a level where transfusion may be required*		If Hb exceeds a level needed to avoid transfusion; restart dose at 40% below previous dose when Hb approaches a level where transfusion may be required	
Discontinue	Following completion of CT course or if no response after 8 weeks of therapy (measured by Hb levels or continuing need for transfusions)		Following completion of CT course or if no response after 8 weeks of therapy (measured by Hb levels or continuing need for transfusions)	

NOTE: Changes from the 2007 guideline dosing table are noted in italics.
Abbreviations: ESA, erythropoiesis-stimulating agent; SC, subcutaneous; TIW, three times per week; Q3W, every 3 weeks; Hb, hemoglobin; NA, not applicable; CT, chemotherapy.
* Therapy should not be initiated at hemoglobin levels ≥ 10 g/dL.