

American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer

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Purpose: To update American Society of Hematology/American Society of Clinical Oncology recommendations for use of erythropoiesis-stimulating agents (ESAs) in patients with cancer. **Methods:** An Update Committee reviewed data published between January 2007 and January 2010. MEDLINE and the Cochrane Library were searched. **Results:** The literature search yielded one new individual patient data analysis and four literature-based meta-analyses, two systematic reviews, and 13 publications reporting new results from randomized controlled trials not included in prior or new reviews. **Recommendations:** For patients undergoing myelosuppressive chemotherapy who have a hemoglobin (Hb) level less than 10 g/dL, the

Update Committee recommends that clinicians discuss potential harms (eg, thromboembolism, shorter survival) and benefits (eg, decreased transfusions) of ESAs and compare these with potential harms (eg, serious infections, immune-mediated adverse reactions) and benefits (eg, rapid Hb improvement) of RBC transfusions. Individual preferences for assumed risk should contribute to shared decisions on managing chemotherapy-induced anemia. The Committee cautions against ESA use under other circumstances. If used, ESAs should be administered at the lowest dose possible and should increase Hb to the lowest concentration possible to avoid transfusions. Available evidence does not identify Hb levels ≥ 10 g/dL

either as thresholds for initiating treatment or as targets for ESA therapy. Starting doses and dose modifications after response or nonresponse should follow US Food and Drug Administration–approved labeling. ESAs should be discontinued after 6 to 8 weeks in nonresponders. ESAs should be avoided in patients with cancer not receiving concurrent chemotherapy, except for those with lower risk myelodysplastic syndromes. Caution should be exercised when using ESAs with chemotherapeutic agents in diseases associated with increased risk of thromboembolic complications. Table 1 lists detailed recommendations.

Introduction

Use of erythropoiesis-stimulating agents (ESAs) has consistently been shown to reduce transfusions and increase the hemoglobin (Hb) level in patients with anemia that arises during or shortly after myelotoxic chemotherapy.¹⁻⁷

The American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) first published a joint evidence-based clinical practice guideline for the use of epoetin in adults with chemotherapy-induced anemia in 2002.³ ASCO guidelines are updated at intermittent intervals by an Update Committee of the original Expert Panel to assess whether there is new evidence that warrants adding to, deleting from, or modifying prior recommendations.

Since the 2002 guideline, awareness has grown of risks associated with ESAs, including increased mortality, venous thromboembolism, tumor progression, and stroke.⁸⁻²⁵ Thus, specific guidance on the safe and optimal use of ESAs is warranted. The initial guideline was updated and expanded in 2007 to include recommendations to address the use of darbepoetin alfa and emerging safety concerns.¹⁸

The current document is intended to update the 2007 guideline and examines the totality of data on ESA use, inclusive of data published since the 2007 guideline. It provides updated recommendations collectively for ESAs and reviews currently available information on ESA-associated tumor progression, venous thromboembolism, and/or survival, but does not revisit the effectiveness of ESAs to reduce transfusions or increase Hb in detail because the evidence on these outcomes is robust.

Two overarching questions clinicians are faced with when considering using ESAs are as follows.

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

This guideline attempts to address these questions within the limitations of available evidence. As in the previous update, the term epoetin is used in this document to refer to both epoetin alfa

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and epoetin beta (see the 2007 update for more detailed information).¹⁸ This guideline focuses on epoetin alfa, epoetin beta, and darbepoetin alfa and excludes products under development or no longer commercially available (eg, epoetin delta).

Table 1 provides a summary of the guideline recommendations. Data supplements, a patient guide, and other clinical tools and resources to help clinicians implement this guideline are available at <http://www.hematology.org/guidelines/esa> and www.asco.org/guidelines/esa.

Methodology

For the 2010 guideline update, the ASCO/ASH Update Committee completed a systematic review and analysis of data published since 2007. The Update Committee's literature review focused attention on available systematic reviews and meta-analyses of published phase III randomized controlled trials (RCTs) of ESAs. Computerized literature searches of MEDLINE and the Cochrane Collaboration Library were performed. Searches of the English-language literature from January 1, 2007, to January 31, 2010, were conducted to address each of the recommendation domains in the 2007 update. Relevant practice guidelines from other oncology and national organizations were identified through a search of MEDLINE and of the National Guideline Clearinghouse Web site. The literature search strategy is available in the Appendix. The literature search terms can be found in Data Supplement DS13. A summary of the literature search results is provided in a QUORUM diagram in Figure 1. For meta-analyses from a particular study group that were reported as updates during the study period, only the most recent report from that study group was included.

Panel composition and consensus development based on evidence

The ASCO Clinical Practice Guidelines Committee convened the ASCO/ASH Update Committee to lead the 2010 update. The Update Committee met via a series of teleconferences to review evidence collected from the systematic review and make revisions to the guideline recommendations as warranted. A draft of the guideline document was developed by a steering group of the Update Committee and ASCO and ASH staff. As per standard ASCO practice, the guideline was submitted to *Journal of Clinical Oncology* for peer review. It also underwent peer review before acceptance by *Blood*. Feedback from external reviewers was also solicited. The guideline was reviewed and approved by the entire Update Committee, ASCO's Clinical Practice Guidelines Committee, ASH's Committee on Practice, ASH's Subcommittee on Quality of Care, the ASCO Board of Directors, and the ASH Executive Committee.

Guideline policy

The ASCO/ASH practice guidelines reflect expert consensus on the basis of clinical evidence and literature available at the time they are written and are intended to assist physicians in clinical decision making and identify questions and settings for further research. Because of the rapid flow of scientific information in oncology, new evidence may have emerged since the time a guideline was submitted for publication. Guidelines are not continually updated and may not reflect the most recent evidence. Guidelines address only the topics specifically identified in the guideline and are not applicable to interventions, diseases, or stages of disease not

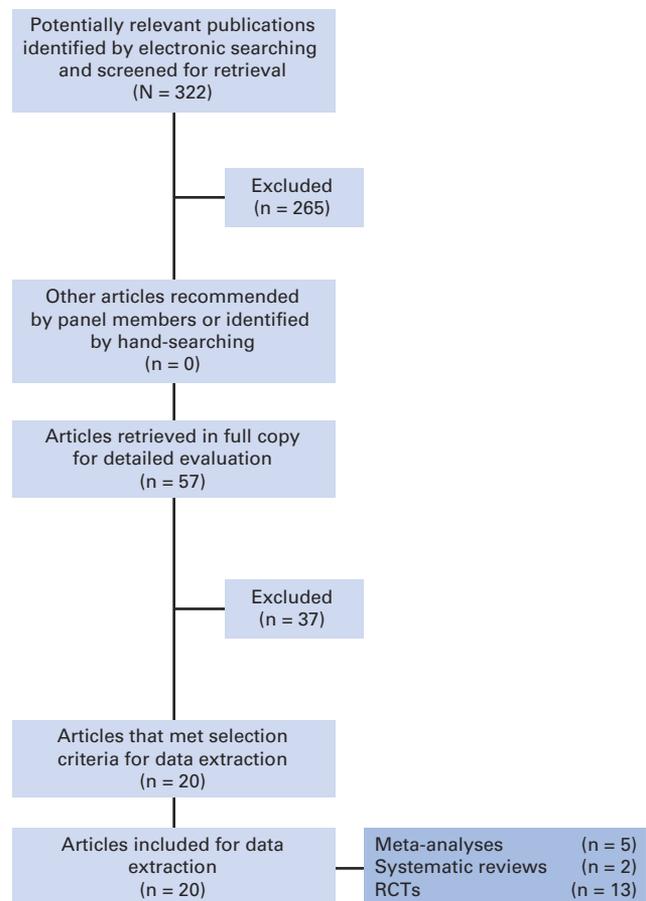


Figure 1. Exclusions and inclusions of publications identified for this systematic review. Literature search date parameter was January 1, 2007, to January 31, 2010 (inclusive). RCTs, randomized clinical trials.

specifically identified. Guidelines cannot account for individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge of the patient, to determine the best course of treatment for the patient. Accordingly, adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances and preferences. ASCO/ASH guidelines describe the use of procedures and therapies in clinical practice and cannot be assumed to apply to the use of these interventions in the context of clinical trials. ASCO and ASH assume no responsibility for any injury or damage to persons or property arising out of or related to any use of the ASCO/ASH guidelines or for any errors or omissions.

Guideline and conflict of interest

The ASCO/ASH Update Committee was assembled in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines ("Procedures," summarized at www.asco.org/guidelinescoi). Members of the Update Committee completed ASCO's disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories

Table 1. Guideline recommendations

Recommendation category	2007 Recommendations*	2010 Recommendations†
I. General Recommendation	<p>As in any medical situation, it is essential to consider other correctable causes of anemia before initiating therapy with stimulants of erythropoiesis. Therefore, it is advisable to conduct an appropriate history and physical and to consider relevant diagnostic testing aimed at identifying causes of anemia aside from chemotherapy or underlying hematopoietic malignancy. At a minimum, one should take a thorough drug exposure history, carefully review the peripheral-blood smear (and in some cases, the bone marrow), consider iron, folate, and vitamin B₁₂ deficiency where indicated, and assess for occult blood loss and renal insufficiency. Coombs' testing may be appropriate for patients with chronic lymphocytic leukemia or non-Hodgkin's lymphoma and for those with a history of autoimmune disease; endogenous erythropoietin levels may predict response in patients with myelodysplasia. Consideration should be given to minimize use of ESAs in patients with high risk of thromboembolic events, as further discussed in Recommendation IV.</p>	<p>It is recommended that before any decision regarding use of ESA is made, appropriate history, physical examination, and diagnostic tests be conducted to identify alternative causes of anemia aside from chemotherapy or an underlying hematopoietic malignancy.</p> <p>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; and assessment of reticulocyte count, occult blood loss, and renal insufficiency.</p> <p>It may also include the following: Coombs' testing for patients with chronic lymphocytic leukemia, non-Hodgkin's lymphoma, or a history of autoimmune disease; and assessment of endogenous erythropoietin levels for patients with myelodysplastic syndrome.</p> <p>Consideration must be given to demonstrated risks of thromboembolism (see Recommendation IV), <i>the possibility of death, and minimizing ESA use, particularly in patients with malignancy being treated with curative intent.</i></p> <p><i>Special Note: Although the 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, 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.</i></p>
II. Special Commentary on the Comparative Effectiveness of Epoetin and Darbeпоetin	<p>Based on a comprehensive systematic review comparing outcomes of epoetin and darbeпоetin in patients with chemotherapy-induced anemia and on identical 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.</p>	<p>(Unchanged from 2007) Based on a comprehensive systematic review comparing outcomes of epoetin and darbeпоetin 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.</p>
IIIa. Chemotherapy-Induced Anemia: Threshold for Initiating ESA Therapy	<p>The use of epoetin or darbeпоetin is recommended as a treatment option for patients with chemotherapy-associated anemia and an Hb concentration that is approaching, or has decreased to less than, 10 g/dL to increase Hb and decrease transfusions. RBC transfusion is also an option, depending on the severity of the anemia or clinical circumstances.</p>	<p>The use of epoetin or darbeпоetin 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.</p>
IIIb. Chemotherapy-Induced Anemia: Initiating When Hb Is ≥ 10 g/dL but < 12 g/dL	<p>For patients with declining Hb levels but less severe anemia (those with Hb < 12 g/dL, but who have never had Hb decrease to near 10 g/dL), the decision of whether to use epoetin or darbeпоetin immediately or to wait until the Hb level decreases 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 those with 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.</p>	<p>An optimal level at which to initiate ESA therapy in patients with anemia and Hb between 10 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.</p>

NOTE. The intended use of ESAs is to reduce RBC transfusion requirements. All recommendations are consistent with the FDA labels. Editorial revisions or condensations of earlier text that leave the substance of 2007 recommendations unaltered have been made but are not indicated by font changes.

Abbreviations: ESA, erythropoiesis-stimulating agent; FDA, US Food and Drug Administration; Hb, hemoglobin.

*Substantive deletions from 2007 guideline appear as bolded text.

†Substantive additions in the 2010 guideline recommendations appear as italicized text.

Table 1. Guideline recommendations (continued)

Recommendation category	2007 Recommendations*	2010 Recommendations†
IV. Thromboembolic Risk	Clinicians should carefully weigh the risks of thromboembolism in patients for whom epoetin or darbepoetin is 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 previous history of thromboses, surgery, and prolonged periods of immobilization or limited activity. Multiple myeloma patients who are being treated with thalidomide or lenalidomide and doxorubicin or corticosteroids are at a particularly increased risk. There are no data regarding concomitant use of anticoagulants or aspirin to modulate this risk.	(Unchanged from 2007) Clinicians should carefully weigh the risks of thromboembolism in patients for whom epoetin or darbepoetin is 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. <i>Some diseases and treatment regimens have also been associated with higher risk of venous thromboembolic events.</i>
V. Starting and Modifying Doses	The FDA-approved starting dose of epoetin is 150 U/kg 150 U/kg three times a week or 40,000 U weekly subcutaneously. The FDA-approved starting dose of darbepoetin is 2.25 µg/kg weekly or 500 µg every 3 weeks subcutaneously. Alternative starting doses or dosing schedules have shown no consistent difference in effectiveness on outcomes, including transfusion and Hb response, although they may be considered to improve convenience. Dose escalation should follow FDA-approved labeling (Table 2); no convincing evidence exists to suggest that differences in dose-escalation schedules are associated with different effectiveness.	It is recommended that starting and <i>modifying</i> 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 <i>modification</i> should follow FDA recommendations as outlined in Table 2; 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	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.	(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. Hb Target	Hb can be increased to (or near) a concentration of 12 g/dL, at which time the dosage of epoetin or darbepoetin should be titrated to maintain that level. Dose and dose-modification recommendations recorded in the package insert as of March 2007 and approved by the FDA can be found in Table 2. Dose reductions are also recommended when Hb increase exceeds 1 g/dL in any 2-week period or when the Hb exceeds 11 g/dL. Risk of venous thromboembolism should also be considered when determining dose-reduction schedules.	Hb can be increased to <i>the lowest concentration needed to avoid transfusions</i> , which may vary by patient and condition. Qualifying Statement: <i>An optimal target Hb concentration cannot be definitively determined from the available literature.</i> Modification to reduce the ESA dose is appropriate when Hb <i>reaches a level sufficient to avoid transfusion</i> or the increase exceeds 1 g/dL in any 2-week period <i>to avoid excessive ESA exposure (see Recommendation V), considering the risks of ESAs (see Recommendation I).</i> Specific dose-reduction recommendations are listed in Table 2.
VIII. Iron Monitoring and Supplementation	Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels and instituting iron repletion when indicated may be valuable in limiting the need for epoetin, maximizing symptomatic improvement for patients, and determining the reason for failure to respond adequately to epoetin. There is inadequate evidence to specify the optimal timing, periodicity, or testing regimen for such monitoring.	(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.

NOTE. The intended use of ESAs is to reduce RBC transfusion requirements. All recommendations are consistent with the FDA labels. Editorial revisions or condensations of earlier text that leave the substance of 2007 recommendations unaltered have been made but are not indicated by font changes.

Abbreviations: ESA, erythropoiesis-stimulating agent; FDA, US Food and Drug Administration; Hb, hemoglobin.

*Substantive deletions from 2007 guideline appear as bolded text.

†Substantive additions in the 2010 guideline recommendations appear as italicized text.

Table 1. Guideline recommendations (continued)

Recommendation category	2007 Recommendations*	2010 Recommendations†
IX. Anemia in Patients Not Receiving Concurrent Chemotherapy	There is evidence that supports the use of epoetin or darbepoetin in patients with anemia associated with low-risk myelodysplasia. There are no published high-quality studies to support the exclusive use of ESAs in anemic patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia in the absence of concurrent chemotherapy. Analyses of primary data from study 20010103 submitted to the FDA in March of 2007 support a stronger recommendation against the use of ESAs to treat anemia associated with malignancy, or the anemia of cancer, among patients with either solid or nonmyeloid hematologic malignancies who are not receiving concurrent chemotherapy. This recommendation is consistent with the black box warning that was added to the prescribing information for both epoetin alfa and darbepoetin in March of 2007, as follows: "Use of ESAs increased the risk of death when administered to a target Hb of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated in this population."	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 patients with lower risk myelodysplastic syndrome to avoid transfusions is an exception to this recommendation.
X. Treatment of Anemia in Patients With Nonmyeloid Hematologic Malignancies Who Are Receiving Concurrent Chemotherapy	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 the recommendations outlined earlier. 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.	(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. <i>Special Note: Although the 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, 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.</i>

NOTE. The intended use of ESAs is to reduce RBC transfusion requirements. All recommendations are consistent with the FDA labels. Editorial revisions or condensations of earlier text that leave the substance of 2007 recommendations unaltered have been made but are not indicated by font changes.

Abbreviations: ESA, erythropoiesis-stimulating agent; FDA, US Food and Drug Administration; Hb, hemoglobin.

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for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Update Committee did not disclose any such relationships.

ASH reviewed each potential member of the guideline Update Committee before beginning the guideline work to determine whether conflicts of interest were present. Each potential member completed a form on which he or she was asked to note relationships with any drug or device company and to provide the name of the company, drug, or device involved; the nature of the conflict; and relevant dates. As needed, staff conferred with the potential Update Committee members to discuss the relationship(s) and to clarify the presence of any conflict. After discerning that a member would not be conflicted, his or her service on the Committee was approved. The rationale behind ASH's conflict of interest policy is to assure the integrity of ASH and to avoid bias arising from conflicts of interest by the individuals involved with

activities. During the final stages of guideline preparation, conflict of interest forms were updated. An inadvertent omission of disclosure was noted by a Committee member (J.L.S., for a single event). The nature of the relationship was clarified, and the Update Committee co-chairs and the chair of the ASH Quality of Care Subcommittee reviewed the contributions of the individual and determined that they were not biased by conflicted interests. The Update Committee membership is listed in Appendix Table A1.

RESULTS

The literature search conducted for this guideline update yielded one new individual patient data meta-analysis, six new literature-based meta-analyses and/or systematic reviews of RCTs, and an additional 13 publications reporting results from RCTs that were not included in any of the meta-analyses or systematic reviews. Note also that since the 2007 update, the US Food and Drug

Administration (FDA) and the companies who manufacture and market ESAs in the United States have created a Risk Evaluation and Mitigation Strategy (REMS). More detailed information is available online from the US FDA.²⁶

Meta-analyses and/or systematic reviews of RCTs

Characteristics of the meta-analyses and systematic reviews are provided in Data Supplement DS1.

Individual patient data meta-analysis. Bohlius et al^{9,27} conducted a meta-analysis of survival outcomes using individual patient data from 53 ESA trials (13,933 patients) in a range of cancer populations.

Literature-based meta-analyses and systematic reviews. Six new literature-based meta-analyses and systematic reviews were found that met the inclusion criteria, including the Bennett et al^{8,28} meta-analyses of survival outcomes and venous thromboembolic events in patients with nonmyeloid malignancies and chemotherapy-induced anemia; the Glaspy et al²⁹ meta-analyses of survival outcomes, disease progression, and risk of venous thromboembolic events in patients with cancer; the Lambin et al³⁰ meta-analyses of survival outcomes, local tumor recurrence, and toxicity of treatment in patients with head and neck cancer; the Tonelli et al³¹ meta-analyses of survival outcomes, cardiovascular events and hypertension, health-related quality of life (QOL), transfusion rates, tumor response, and serious adverse events in patients with cancer-related anemia; the Ross et al³² systematic review (and meta-analysis of Hb response rates from controlled trials) on studies of ESA use in patients with myelodysplastic syndromes (MDS); and the Newland and Black³³ systematic review of survival outcomes and tumor progression in patients with head and neck, breast, cervical, non-small-cell lung, nonmyeloid, or lymphoproliferative malignancies. A systematic review by Shehata et al^{20,34} also met the inclusion criteria but was not included in the data extraction because the review was essentially the same as an earlier online version²⁰ included in the ASCO/ASH 2007 guideline update. These results are not discussed in detail in this update.

Several studies included in the meta-analyses that were previously available only as meeting abstracts or in reports published online in 2007 have now been published in full in peer-reviewed journals.³⁵⁻³⁹ Data from these studies were not extracted, and they will not be discussed or summarized individually.

RCTs

Thirteen newly published articles reporting results from RCTs that met the inclusion criteria and were not included in any of the meta-analyses or systematic reviews are described in the Literature Update and Discussion sections in the recommendations, as appropriate.⁴⁰⁻⁵² Characteristics of these trials are provided in Data Supplement DS2.

Primary evidence base for the guideline update

The individual patient data meta-analysis and other meta-analyses/systematic reviews serve as the primary evidence base for this guideline update. The consensus of the Update Committee was that, in general, all of these meta-analyses and systematic reviews are methodologically sound, although they differed in the totality of the trials and patients available at the time they were completed. Further comments about methodologic quality of individual meta-analyses and systematic reviews are provided in Data Supplement DS1. The Bohlius et al^{9,27} meta-analysis, for example, used

individual patient data from all trials included in the analyses, whereas Glaspy et al²⁹ used individual patient data from trials supported by two of the three manufacturers (a majority of the patients and trials they analyzed) and published aggregate data for remaining trials. For this reason, the Update Committee placed more weight in its deliberations on results from the Bohlius et al^{9,27} individual patient data meta-analysis. A summary of the data on the outcomes reported is provided in Data Supplement DS3-DS8.

2010 Guideline recommendations

New evidence reported since the 2007 guideline update (summarized in Literature Update and Discussion for Recommendation I) 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, most importantly, on whether all patients are equally at risk or whether some patients may actually be at minimal risk for the harms associated with ESA use (with transfusion as necessary) compared with RBC transfusion alone. The Update Committee generally recommends that for patients undergoing myelotoxic chemotherapy who have Hb less than 10 g/dL, clinicians should discuss the potential harms (eg, thromboembolism, shorter survival) and benefits (eg, decreased transfusions) of ESAs and compare those with the potential harms (eg, serious infections, immune-mediated adverse reactions) and benefits (eg, rapid Hb improvement) of transfusion. Individual patient preferences for assumed risk should contribute to shared decisions on managing chemotherapy-induced anemia in these patients. The Update Committee cautions against ESA use under all other circumstances.

The guideline recommendations are summarized in Table 1, with substantive changes from the 2007 guideline noted in the table. The intended use of ESAs, as recommended in Table 1, is to reduce RBC transfusion requirements. All recommendations in the guideline are consistent with the FDA labels. The recommendations presented here provide further detail and summarize supportive evidence.

I. General recommendation

2010 recommendation. It is recommended that before any decision regarding use of ESA is made, appropriate history, physical examination, 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:

- 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:

- Coombs' testing for patients with chronic lymphocytic leukemia, non-Hodgkin's lymphoma, or a history of autoimmune disease
- Assessment of endogenous erythropoietin (EPO) levels for patients with MDS

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 Literature update and discussion: weighing harms versus benefits, 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.

Literature update and discussion. As of the date of this publication, the FDA-approved labels state that the goal of ESA therapy for patients with chemotherapy-induced anemia is to reduce transfusion requirements. The only benefit of ESA therapy that has been unequivocally and consistently demonstrated in RCTs and meta-analyses is to reduce the need for transfusions as a result of increased Hb concentration. Transfusions will not be addressed in detail in this guideline update.

In rare circumstances, patients with cancer and renal insufficiency may have concurrent indications for the use of ESAs. Clinicians should also consider guidelines on ESA use for renal anemia under these circumstances (eg, National Kidney Foundation Disease Outcome Quality Initiative).⁵³

In 2008, the FDA approved revised labels that limited the indication for ESA administration to patients receiving chemotherapy for palliative intent. ESAs are not indicated for patients receiving chemotherapy for curative intent. This change was made based on results of eight randomized trials and one meta-analysis available at that time, which suggested an increased risk of mortality with ESA use. Subsequent meta-analyses of RCTs and new data published from RCTs investigating differences in mortality with ESA use report similar findings.

Since the 2007 guideline update, one individual patient data meta-analysis,^{9,27} four literature-based or study-level meta-analyses,^{8,28-31} one systematic review of RCTs without a meta-analysis,³³ and two individual placebo-controlled RCTs^{46,48} have published evidence relevant to the effects of ESA therapy on risk of mortality.

Literature update and discussion: new evidence on potential harms. Bohlius et al^{9,27} conducted various meta-analyses of survival data (measured either over the study duration only or over all available follow-up) using individual patient data from 53 RCTs (pooled N = 13,933). They identified 10 additional trials, from which individual patient data were unavailable. ESA therapy was found to increase on-study mortality (hazard ratio [HR], 1.17; 95% CI, 1.06 to 1.30; $P = .003$) and mortality among patients in trials with chemotherapy ($n = 10,441$; HR, 1.10; 95% CI, 0.98 to 1.24; $P =$ not significant). Estimation of the number needed to treat for an additional harmful outcome (in this case, the number of patients treated that would lead to one extra death) depends on the underlying survival probability in the absence of ESA treatment. For patients with an underlying survival probability of 95% at 1 year, the resulting estimate is that one additional person may die for every 121 participants randomly assigned to receive ESAs (number needed to harm [NNH], 121; 95% CI, 69 to 343), whereas the estimate based only on trials that included chemotherapy is that one additional person may die for every 206 participants randomly assigned to receive ESAs (NNH, 206; 95% CI, 86 to 1,026).²⁷ If the underlying survival probability is 80%, the estimated NNH for all patients would be 34 (95% CI, 19 to 94), and if the underlying survival probability is 70%, the estimated NNH would be 24 (95%

CI, 14 to 67). For trials that included chemotherapy, if the underlying survival probability is 80%, the estimated NNH would be 57 (95% CI, 24 to 279), and if the underlying survival probability is 70%, the estimated NNH would be 41 (95% CI, 17 to 200). ESA therapy also worsened survival over all available follow-up (HR, 1.06; 95% CI, 1.00 to 1.12; $P = .046$). There was no evidence for statistically significant heterogeneity across trials ($I^2 = 0\%$, $P = .87$ for on-study mortality, and $I^2 = 7.1\%$, $P = .33$ for survival over all available follow-up). Sensitivity analyses in which published or investigator-provided aggregate data for six of the 10 missing studies were added to the available individual patient data showed no major changes in HRs or CIs. A range of subgroups were also analyzed (eg, by patient characteristics, tumor characteristics, chemotherapy treatment) to determine whether there was any evidence of patient subgroups who were not at an increased risk of mortality. Meta-regression and statistical tests for interaction of potential modifying variables with the ESA treatment effect did not identify a set of factors that could be used to reliably select patients for whom the increased risk of mortality was minimal or negligible.

Findings from two literature-based meta-analyses^{8,28,31} are consistent with the results of the individual patient data analyses by Bohlius et al.^{9,27} Bennett et al^{8,28} conducted a literature-based meta-analysis of survival outcomes in 53 RCTs in patients (N = 14,164) with nonmyeloid malignancies taking ESAs for chemotherapy-induced anemia. They found a significantly increased risk of mortality in patients taking ESAs compared with controls (HR, 1.09; 95% CI, 1.01 to 1.18), although they note that most trials had limited ability to evaluate survival or tumor progression. The literature-based meta-analysis by Tonelli et al³¹ included RCTs in adults with cancer-related anemia. Twenty-eight RCTs (N = 6,525) were included in their analysis, which found that all-cause mortality during treatment was significantly higher in the group receiving ESAs compared with the control group (relative risk [RR], 1.15; 95% CI, 1.03 to 1.29).

The most recently published meta-analyses by Glaspy et al²⁹ used a mix of published, updated, and individual patient data to examine whether ESA use affects survival, disease progression, or risk of venous thromboembolic events. These analyses included 41 ESA oncology trials identified from the 2006 Cochrane Review meta-analysis of survival,¹¹ 13 additional trials published subsequently, and six unpublished trials with data obtained from ESA manufacturers. Glaspy et al²⁹ had access to certain individual patient data, and to manufacturers' proprietary data that updated published reports, only from studies sponsored by two of the three commercial sources for ESAs (ie, Amgen, Thousand Oaks, CA, and Centocor Ortho Biotech, Horsham, PA). The 60 trials they included (N = 15,323) were grouped by treatments patients received for their malignancy—chemotherapy/chemoradiotherapy, radiotherapy alone, or none (anemia of cancer).

The random effects meta-analysis of overall survival in all patients with cancer reported by Glaspy et al²⁹ yielded results (odds ratio [OR], 1.06; 95% CI, 0.97 to 1.15) similar to those reported by Bohlius et al²⁷ (HR, 1.06; 95% CI, 1.00 to 1.12) but with wider CIs that did not reach the conventional level ($P = .05$) for statistical significance. Results of random effects meta-analyses also were similar for trials in patients receiving chemotherapy (OR, 1.03; 95% CI, 0.93 to 1.13 reported by Glaspy et al²⁹ v HR, 1.04; 95% CI, 0.97 to 1.11 reported by Bohlius et al²⁷). Glaspy et al²⁹ did not report meta-analysis results for on-study mortality, except for a sensitivity analysis that compared OR with HR using data from a subset of 20 trials with more than 6 months of follow-up. Thus,

results for meta-analysis of on-study mortality that could be compared with those reported by Bohlius et al^{9,27} are unavailable from Glaspy et al.²⁹

Several factors may contribute to the difference between the meta-analyses reported by Glaspy et al²⁹ and Bohlius et al^{9,27} with respect to the statistical significance of increased mortality among patients randomly assigned to ESA treatment. First, the analyses differed in the number of trials and patients included. For example, Glaspy et al²⁹ included some smaller studies (planned N < 100) excluded by Bohlius et al^{9,27} and also included one trial completed after the analysis by Bohlius et al^{9,27} closed. Second, the analysis by Bohlius et al^{9,27} used patient-level data for all included studies, whereas Glaspy et al²⁹ did not. This may explain why Glaspy et al²⁹ did not use meta-regression and formal tests of interaction terms to evaluate patient, tumor, and treatment characteristics as variables that might modify the effects of ESA treatment on mortality. Of note, Bohlius et al^{9,27} used this type of analysis, which requires patient-level data and is crucial for evaluating the impact of baseline factors on a treatment effect,⁵⁴ and found that none of the potentially explanatory variables defined a patient subset with minimally increased risk.

However, the most important difference between these analyses might be in their respective approaches to intent-to-treat analyses. Bohlius et al^{9,27} analyzed all patients in the treatment groups to which they were allocated (a strict intent-to-treat analysis), whereas Glaspy et al²⁹ limited inclusion of patients randomly assigned to ESA therapy (and possibly those allocated to placebo in blinded studies) to those who received at least one dose of study drug (a modified intent-to-treat analysis) and also excluded studies in which patients in the control arms were permitted to cross over to ESA treatment. Using patient-level data, Bohlius et al^{9,27} reported (see their online appendix⁹) that patients randomly assigned to an ESA arm who never received a first dose of ESA were at greater risk for mortality than the remaining patients randomly assigned to the same arm, whereas patients in the control arms who crossed over to ESA were at lower risk for mortality than other controls. This difference in baseline risk for patients removed from the ESA and control arms might have biased results of a modified intent-to-treat analysis. Therefore, the Update Committee placed greater weight on results of the Bohlius et al^{9,27} meta-analysis when developing this recommendation.

The literature-based meta-analysis by Lambin et al³⁰ assessed a more narrowly focused question—whether combined treatment with radiotherapy and EPO is better than standard radiotherapy for the treatment of patients with head and neck cancer. Five RCTs (N = 1,397) were included in their analysis and showed significantly worse overall survival for patients receiving radiotherapy and EPO compared with those who received only radiotherapy (OR, 0.73; 95% CI, 0.58 to 0.91; P = .005). These studies had targeted a higher Hb concentration than that currently recommended in FDA-approved labels. Readers should note that this meta-analysis presents the point estimate and CI for survival (hence is < 1.0), whereas the other meta-analyses all calculate point estimates and CIs for mortality (hence are all > 1.0).

In addition to the series of meta-analyses, Newland and Black³³ published a systematic review that summarized and critiqued 10 RCTs reporting increased tumor progression or death from disease progression with ESA use (Data Supplement DS4). They drew attention to methodologic limitations of the available studies and the impact of those limitations on conclusions. Despite these limitations, Newland and Black³³ agree that ESAs should be used in accordance with current FDA-approved labeling while addi-

tional well-designed trials further elucidate mechanisms of ESA effects on tumor progression.

None of the three new RCTs published since the 2007 guideline update demonstrated a statistically significant increased risk in mortality with ESA therapy compared with placebo.^{37,46,48} It should be noted that the relevant analysis for one of those trials⁴⁶ was on a subset of patients with renal disease with malignancy (Data Supplement DS2). There were limitations with all three trials, and the small effect sizes likely reflect the small samples.

Evidence concerning thromboembolic risks associated with ESA use is summarized in the Literature Update and Discussion section of Recommendation IV.

Given the consistent results from the Bohlius et al^{9,27} individual patient meta-analyses and three of the four literature-based meta-analyses, the Update Committee placed more weight on these data than on the other reports (one literature-based meta-analysis, a systematic review, and three individual RCTs; Data Supplement DS4).

Literature update and discussion: evidence on potential benefits. There is evidence from well-performed, randomized, placebo-controlled, double-blinded trials that ESA treatment decreases transfusion rates.¹⁹ This is the only benefit of ESA treatment that has been consistently demonstrated in RCTs and meta-analyses.

In 2006, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of epoetin and darbepoetin.¹⁹ They found that the majority of trials reported fewer transfusions among patients randomly assigned to epoetin compared with patients assigned to control (RR, 0.63; 95% CI, 0.59 to 0.67). Results from a subset analysis that compared meta-analytic results separately in high-quality versus low-quality trials comparing epoetin versus control are reported in the AHRQ review. High-quality trials were double-blinded RCTs and met at least one of the following conditions: less than 10% of patients within each study arm were excluded from analysis and the ratio of patients excluded from analysis in each arm was less than 2:1, or less than 5% of patients were excluded in each study arm. There were statistically significantly fewer transfusions in the epoetin arms in both the high-quality and low-quality subsets (RR, 0.69; 95% CI, 0.63 to 0.76; and RR, 0.58; 95% CI, 0.52 to 0.63, respectively).

The AHRQ review found transfusion rates to be statistically significantly lower in patients in the darbepoetin arms compared with patients in the control arms (RR, 0.61; 95% CI, 0.52 to 0.72) in a fixed effects meta-analysis of four RCTs.¹⁹ The pooled transfusion rates were 30% (range, 0% to 91%) in patients treated with epoetin versus 47% (range, 0% to 100%) in controls. In patients treated with darbepoetin, the pooled transfusion rate was 29% (range, 14% to 34%), whereas it was 51% (range, 25% to 67%) in controls.

The AHRQ review also reported estimates of the number needed to treat to spare one patient from transfusion at representative baseline risks of transfusion, as reported from control arms from available RCTs.¹⁹ For patients with a baseline risk for transfusion of 30%, the estimated number needed to treat to spare one patient from transfusion is nine patients (95% CI, 8.13 to 10.10) for patients who take epoetin and eight to nine patients (95% CI, 6.94 to 11.90) for patients who take darbepoetin. For patients with a baseline risk of 50%, the estimated number needed to treat is five patients for both epoetin and darbepoetin (95% CI, 4.88 to 6.06; and 95% CI, 4.17 to 7.14, respectively). For patients with a baseline risk of 70%, the estimated number needed to treat is four patients for both epoetin and darbepoetin (95% CI, 3.48 to 4.33; and 95% CI, 2.98 to 5.10, respectively). It should be noted that the baseline risk in the control arms was highly variable (0% to 100%)

across trials; thus, a single number needed to treat should not be computed. Also, the values for baseline risk were chosen to give a representative distribution across what was observed in different trials with different patient populations.

Results from three RCTs^{43,46,50} and two systematic reviews,^{31,34} published since the 2007 guideline update, were consistent with those reported in the AHRQ comparative effectiveness review; each reported fewer transfusions among patients in the ESA arms compared with patients in the control arms.

Literature update and discussion: weighing harms versus benefits. In the context of balancing the reported risks of ESAs against the reported benefits from using them as supportive care, the FDA-approved label was changed in August 2008 to state that use of ESAs is “not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.”⁵⁵ According to this product label, no studies have adequately characterized the impact of ESAs on progression-free and overall survival in the setting of curative-intent chemotherapy. The FDA-approved indication includes the option of ESA therapy, rather than transfusion support, as part of a palliative care chemotherapy regimen.

Unfortunately, as discussed in the Literature Update and Discussion sections in Recommendations I, IIIa, and IV, it cannot be determined from the available evidence whether any particular group of potential ESA recipients has a greater or lesser risk of harm than other patients with chemotherapy-induced anemia. The mechanisms of harm are also unclear. The FDA-approved label’s distinction between patients being treated with curative versus palliative intent may assist clinicians as they compare and discuss the risk-to-benefit ratios of an ESA versus RBC transfusions. However, it is worth reinforcing the point that the decision to limit the indication for ESAs to patients undergoing chemotherapy for palliation (treatment intent) is not on the basis of direct comparative analyses of data from clinical trials of ESA treatment. Available analyses of data from RCTs have not stratified results on the basis of the intent of any particular regimen used.

Note also that determining the goal of treatment requires clinical judgment. Examples of diseases for which the treatment goal should generally be considered curative include (among others) testicular cancer, first-line therapy of Hodgkin’s disease, and early-stage solid tumors treated with adjuvant chemotherapy (eg, breast, colon, early lung).

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. Clinicians are urged to exercise caution in considering ESA use in patients with malignancy being treated with curative intent. The Update Committee stresses the importance of including a detailed discussion between health care providers and their patients about the potential harms and benefits of ESA therapy.

II. Special commentary on the comparative effectiveness of epoetin and darbepoetin

2010 recommendation. This recommendation remains the same as in 2007. On the basis of a comprehensive systematic review comparing outcomes of epoetin and darbepoetin in patients with chemotherapy-induced anemia and on the basis of identical 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.

Literature update and discussion. Since the 2007 guideline update, there have been no new studies that compared outcomes of epoetin and darbepoetin in patients with chemotherapy-induced anemia. Hence, there is no new evidence that would change the 2007 recommendation.

IIIa. Chemotherapy-induced anemia: threshold for initiating ESA therapy

2010 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.

Literature update and discussion. Systematic reviews that informed the 2002 guideline and 2007 update found insufficient evidence to conclude that initiating ESA therapy at Hb levels \geq 10 g/dL either spared more patients from transfusions or decreased the number of RBC units transfused per patient when compared with starting therapy at Hb concentrations of less than 10 g/dL. The literature search for the current update identified three articles published subsequently that reported on RCTs comparing immediate versus delayed initiation of ESA therapy,^{39,42,47} with one of these³⁹ being a full publication of a meeting abstract that was included in the 2007 guideline update³⁸ (Data Supplement DS9). There are several methodologic limitations to these two new trials,^{42,47} as well as the three previously reviewed trials.^{38,56,57} Neither the two new trials nor the three previously reviewed trials blinded investigators or patients to assigned treatment. Across all five available trials, the Hb threshold to begin ESA treatment varied; Hb threshold for treatment in the delayed arm was 9 g/dL in one trial,⁵⁷ 10 g/dL in three trials,^{39,47,56} and 11 g/dL in one trial.⁴² Additionally, none of the trials treated patients in the delayed arm with a placebo before initiating ESA treatment or specified consistent transfusion triggers for either arm (they either were not reported or varied according to transfusion policies across sites). These methodologic limitations might have biased trial results and should be considered when comparing results across the trials.

Neither of the two new trials^{42,47} reported a statistically significant decrease in the proportion of patients who received transfusion in the arm randomly assigned to immediate ESA treatment compared with the arm randomly assigned to delayed treatment. One of the new trials⁴⁷ reported fewer units transfused per patient in the immediate treatment arm, but the difference was not statistically significant. Thromboembolic events were more frequent among patients treated immediately in both new trials,^{42,47} but neither trial reported test results for statistical significance of these differences (Data Supplement DS9).

Although the Update Committee continues to find available evidence insufficient to conclude that initiating ESA therapy at Hb concentrations \geq 10 g/dL decreases transfusion use relative to delaying treatment until Hb < 10 g/dL, the Committee also notes that available evidence does not demonstrate increased harms associated with starting ESA therapy at Hb concentrations \geq 10 g/dL, compared with waiting until it decreases below that threshold. Furthermore, a post hoc reanalysis of data from a randomized trial comparing different dosing regimens of darbepoetin alfa suggests the question of Hb threshold for starting ESA therapy merits further investigation.⁴⁹ These investigators (Data Supplements DS2 and DS11) randomly assigned patients with baseline Hb less than 11 g/dL to treatment with darbepoetin at either 500 μ g every 3 weeks (arm 1) or 2.25 μ g/kg weekly (arm

2) and stratified patients on the basis of Hb levels less than 10 g/dL (arm 1, n = 176; arm 2, n = 175) or ≥ 10 g/dL (arm 1, n = 177; arm 2, n = 177). The initial report⁵⁸ analyzed outcomes by darbepoetin dosing regimen (ie, arm 1 v arm 2); the more recent report⁴⁹ included analyses within each arm by Hb stratum. Fewer transfusions (with nonoverlapping 95% CIs) occurred for the less than 10 g/dL stratum than for the ≥ 10 g/dL stratum in both arms of this study (Data Supplement DS11). Results also showed more frequent thromboembolic events but fewer on-study deaths in the ≥ 10 g/dL stratum than the less than 10g/dL stratum of each arm (CIs and statistical significance were not reported).

In the ASCO/ASH update of recommendations in 2007, the Committee advised that ESA therapy might begin as a patient's decreasing Hb concentration approached 10 g/dL. This advice was particularly relevant to patients facing multiple cycles of additional myelosuppressive chemotherapy and was based on the well-documented 2- to 6-week delay between the start of ESA administration and increases in the number of circulating mature RBCs (FDA labels for epoetin alfa [Procrit; Centocor Ortho Biotech] and darbepoetin alfa [Aranesp; Amgen]).⁵⁹⁻⁶¹ However, evidence has emerged since the 2007 update showing that ESA administration is associated with a statistically significant increase in mortality risk (see Literature Update and Discussion for Recommendation I). In response to the new evidence, FDA-approved labeling for epoetin alfa and darbepoetin alfa now states that "Therapy should not be initiated at Hb levels ≥ 10 g/dL." Furthermore, FDA recommends that dosing should be "titrated for each patient to achieve and maintain the lowest Hb level sufficient to avoid the need for blood transfusion."

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 decreases to less than 10 g/dL. Thus, the Committee has revised the recommended starting Hb concentration and treatment goal to reflect the current FDA-approved labels. However, the Committee acknowledges that rare clinical circumstances (such as severe pulmonary or cardiovascular comorbidities) may warrant careful consideration of ESA use when Hb levels are ≥ 10 g/dL.

IIIb. Chemotherapy-induced anemia: initiating when Hb is ≥ 10 g/dL but less than 12 g/dL

2010 recommendation. An optimal level at which to initiate ESA therapy in patients with anemia with an Hb between 10 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.

Literature update and discussion. As discussed previously for Recommendation IIIa, conclusive evidence is lacking to show that beginning ESA therapy before Hb level decreases to less than 10 g/dL decreases transfusion use compared with waiting until Hb reaches that threshold. Evidence also is lacking to demonstrate that, for patients with either a specific combination of anemia symptoms or a particular level of severity of symptoms, ESA treatment outcomes are superior with immediate treatment.^{39,42,47,56} Similarly, available evidence does not identify specific concurrent illnesses to define patient subgroups in whom the benefits of starting ESA treatment before Hb decreases to less than 10 g/dL outweigh the risks. Note also that current FDA labeling for both epoetin alfa and

darbepoetin alfa states that ESA use "should not be initiated at Hb levels ≥ 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" (see FDA product labels for epoetin and darbepoetin).^{62,63}

Literature update and discussion: ESAs and QOL. Although transfusion avoidance is generally the rationale for ESA treatment in patients with cancer, use of ESAs when the Hb is between 10 and 12 g/dL has been considered as a treatment based on the hypothesis that it may improve QOL in patients with cancer.

Previous iterations of the ESA guideline emphasized that a substantially enhanced QOL related to reduced anemia after ESA use was a potential benefit that might justify use in some patients when the Hb was between 10 and 12 g/dL. Considerable research interest has centered on whether and by how much ESAs impact recipients' QOL. The rather modest QOL benefits reported to date must now be reconsidered in the context of more well-defined risks of death related to ESA therapy. These risks may also be related to intensity of ESA dosing in nonresponders (see Special Commentary on ESAs, Tumor Response, and Survival and see Potential Mechanisms Mediating Tumor Progression and Increased Mortality), which may be particularly true for patients considered for ESA initiation in this Hb range on the basis of clinical circumstances.

Since the last guideline update, several clinical trials^{35,42,48} and one meta-analysis³¹ have included QOL as an end point for patients with chemotherapy-induced anemia randomly assigned to treatment with ESAs or placebo. One trial³⁵ was specifically designed with QOL as the primary end point. Although there are increasing data about effects of ESAs on QOL, the more recent trials do not consistently show that ESA use, particularly at higher levels of Hb initiation, leads to substantial improvements in QOL (ie, perceived and valued by patients) as measured by the Functional Assessment of Cancer Therapy (FACT) instruments,^{35,42} even when the Hb increases and transfusion decreases are statistically significant.³⁵ One trial⁴⁸ reported that the decline in the FACT score was smaller in the ESA-treated group than in the placebo group, although the differences were not statistically significant and are marginally within the range of difference considered clinically meaningful.^{64,65}

A recent literature-based meta-analysis concludes that QOL, as measured by changes in linear analog self-assessment score (seven trials), overall FACT score (three trials), or various FACT subscales (20 trials), is improved for patients with cancer and anemia treated with ESAs compared with patients who did not receive an ESA (Data Supplement DS8).³¹ The RCTs included in this analysis were published between 2001 and 2008 and pooled results across trials separately for different instruments using a random effects model. Overall differences in QOL scores between treatment groups, pooled by QOL instrument/measure, although statistically significant, were just barely greater than the lower limit generally accepted to be clinically meaningful.^{65,66}

As discussed in the previous ASCO/ASH guideline update,¹⁸ assessment of QOL remains challenging. Reported studies continue to face methodologic limitations, including small sample sizes; sample sizes generated to detect differences in primary outcomes rather than QOL; heterogeneity of malignancies, treatment, and QOL instruments; variable ESA doses, schedules, and initiation thresholds; lack of blinding; and lack of reported power calculations for negative QOL findings. Although clinically meaningful differences in QOL have been described for some instruments,^{65,66} many studies do not clearly identify the sample size anticipated to determine this difference a priori.

Taken together with trials previously reported, treatment with ESAs in patients with chemotherapy-induced anemia leads to small, statistically significant increases in QOL. However, experts disagree on whether the magnitude of the effect size for the difference in QOL change scores (treated *v* control arms) observed in ESA RCTs meets the psychometric definition of a clinically meaningful change. Furthermore, any benefits with regard to improvements in QOL must now be considered in the context of increasing evidence of risks associated with ESA treatment in this population. The guideline Update Committee recommends that the goal of ESA use should be to avoid transfusions, as discussed in other sections of this update, without specific consideration of improvement in QOL as a target outcome.

Considering the evidence showing that ESA use is associated with a statistically significant increased risk of mortality and venous thromboembolism (see Literature Review and Discussion for Recommendations I and IV) and the inability to identify any patient subset with minimally increased risk using individual patient data meta-analysis,⁹ the Update Committee advises caution when considering ESA therapy in any patient whose Hb concentration is ≥ 10 g/dL. Decisions about ESA therapy should be based on clinical judgment of individual risks, benefits, treatment goals, and discussions with patients.

IV. Thromboembolic risk

2010 recommendation. This recommendation remains the same as in 2007. Clinicians should carefully weigh the risks of thromboembolism in patients for whom epoetin or darbepoetin is prescribed. RCTs and systematic reviews of available RCTs 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 (see Literature update and discussion).

Literature update and discussion. Since the 2007 update, three literature-based meta-analyses have been published that evaluated the rates of thromboembolic events among patients treated with ESAs (Data Supplement DS6).^{28,29,31} In an analysis by Bennett et al⁸ of 38 RCTs (8,172 patients) on ESA use in patients with cancer, therapy with epoetin or darbepoetin was statistically significantly associated with increased risk for venous thromboemboli compared with patients in control arms (7.5% *v* 4.9%, respectively; RR, 1.57; 95% CI, 1.31 to 1.87). Although these authors published an updated meta-analysis of mortality,⁸ the latter publication did not include an updated meta-analysis of venous thromboemboli. However, updated results are available from the study authors on request. Tonelli et al³¹ also reported a significantly higher rate of thrombotic events (not further defined) among patients who received ESAs compared with controls in an analysis of 13 RCTs (3,420 patients; RR, 1.69; 95% CI, 1.27 to 2.24). Finally, Glaspy et al²⁹ examined venous thromboembolic events in 44 RCTs (13,196 patients) and found an increased risk in patients treated with ESAs (OR, 1.48; 95% CI, 1.28 to 1.72). The risk was the same when the analysis was restricted to the 35 RCTs that evaluated ESA use and reported this outcome among patients who received chemotherapy (*v* anemia of cancer or radiotherapy trials). In a separate meta-analysis conducted by Glaspy et al²⁹ on a subset of 18 chemotherapy RCTs that provided data over long-term (>

6 months) follow-up, the risk of venous thromboemboli was similar (6,498 patients; OR, 1.47; 95% CI, 1.24 to 1.74).

Results of five of six RCTs published subsequently are consistent with the meta-analyses, although none of the five trials conducted tests of statistical significance (Data Supplement DS11).^{36,37,46,48,49} However, one study (N = 120) reported no thromboembolic events of any grade in either arm.⁴³

Also of interest is a recently published retrospective (post hoc) reanalysis of data on thrombovascular events from a randomized trial⁶⁷ of epoetin beta in patients undergoing chemotherapy for metastatic breast cancer that was included in several of the meta-analyses discussed earlier. The new analysis explored the impact of baseline factors on the risk of thrombovascular events. Univariate analysis identified age, number of metastatic sites, hormone receptor status, and ductal histology as potentially independent negative prognostic factors for a thrombovascular event.⁴⁰ However, adjustment for these and other covariates did not substantially modify the HR or CI for increased risk of thrombovascular events in the ESA arm compared with controls. Additionally, although subset analysis suggested that the effect of epoetin beta remained statistically significant in the subset with more than two risk factors but lost statistical significance in the subset with two or fewer risk factors, a formal test for interaction between treatment effect and number of risk factors was not statistically significant ($P = .63$). Nevertheless, this analysis suggests that further work, possibly using individual patient data meta-analysis, might help to identify patients at greatest risk for ESA-induced increases in the risk of thromboemboli and similar adverse events.

A fixed effects meta-analysis of 30 RCTs in the AHRQ comparative effectiveness review found that thromboembolic events were statistically significantly more likely to occur in patients administered epoetin compared with controls (RR, 1.69; 95% CI, 1.36 to 2.10; $P < .001$).¹⁹ The pooled event rates of thromboembolic events were 7% (range, 0% to 30%) in patients treated with epoetin versus 4% in controls (range, 0% to 23%), whereas the rates were 5% in patients treated with darbepoetin versus 3% in controls (only one darbepoetin trial reported thromboembolic event rates).

None of the more recent RCTs, systematic reviews, or meta-analyses provided estimates for NNH. The AHRQ review provides estimates, given individual baseline risk factors, for the number needed to treat to cause one additional thromboembolic event. Individual baseline risks of thromboembolic events were selected based on those reported in a review of known risk factors, such as tumor type, extent of cancer, treatment regimen, prior history of thrombosis, and presence of other risk factors such as surgery or immobilization.⁶⁸ For patients with a baseline risk of 2.5%, one additional thromboembolic event is estimated to occur for every 58 patients treated with an ESA (95% CI, 36 to 111), compared with one thromboembolic event occurring for every 29 patients treated with a baseline risk of 5% (95% CI, 18 to 56), one event occurring for every 15 patients treated with a baseline risk of 10% (95% CI, nine to 28), and one event occurring for every seven patients treated with a baseline risk of 20% (95% CI, five to 14).

The meta-analyses and individual RCTs that have been published since the 2007 update demonstrate and consistently substantiate the increased risk of thromboemboli among patients receiving ESA therapy previously reported. The Update Committee continues to urge caution in the use of ESAs for patients judged to be at increased risk for thromboemboli. Patients with multiple myeloma who are being treated with thalidomide or lenalidomide and

doxorubicin or corticosteroids are at particularly increased risk.⁶⁹ There are no data from RCTs investigating concomitant use of anticoagulants or aspirin to lessen this risk.

V. Starting and modifying doses

2010 recommendation. It is recommended that starting and modifying doses of ESAs 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.
- 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.

Literature update and discussion. The 2007 update concluded that evidence was lacking to demonstrate improved efficacy or safety using starting doses or dose modifications different from those in the FDA-approved labeling for epoetin alfa and darbepoetin alfa. Two trials were published subsequently that compared different ESA starting doses or modifications.^{44,52} In the first trial, a double-blind RCT, patients with solid tumor and Hb less than 11 g/dL facing at least 4 months of additional chemotherapy received either 30,000 U (n = 30) or 20,000 U (n = 20) of epoetin beta injected subcutaneously once weekly.⁴⁴ All patients received oral iron supplements (800 mg twice daily), but the specific iron preparation(s) administered was not reported. Hb response (defined as a ≥ 2 g/dL increase in concentration) was observed in a slightly larger proportion of patients randomly assigned to the higher initial epoetin dose versus the lower dose (78.3% v 66.7%, respectively). Study authors also reported transfusions in 16.8% of patients in the lower dose arm but none in patients in the higher dose arm during the first 4 weeks of the study. However, they did not report tests of

statistical significance for either of these differences and also did not report transfusion use after week 4.

The second trial, an open-label multicenter trial, randomly assigned patients with breast cancer or a gynecologic malignancy to two different starting regimens of epoetin beta—either 10,000 U three times a week or 20,000 U twice a week.⁵² Differences between arms with respect to Hb response rates, proportion of patients transfused, and changes in FACT-Anemia and FACT-General scores from baseline to end of study were not statistically significant. Investigators reported no events of thrombosis or embolism in the arm treated with 10,000 U three times a week, compared with nine events (15%) in the arm treated with 20,000 U twice a week.

This recommendation remains unchanged because neither of the new studies provides evidence to conclude that outcomes of ESA therapy would be improved by use of an initial dose or dose-modification regimen other than those in the FDA-approved labels. Note that some aspects of the labels' starting dose and dose-modification recommendations have changed (Table 2).

VI. Discontinuing therapy for no response

2010 recommendation. This recommendation remains the same as in 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.

Literature update and discussion. Since the 2007 guideline update, there have been no new studies that investigated indicators of response to ESAs. Hence, there is no new evidence that would change the 2007 recommendation.

Table 2. ESA adult dosing

Dose and modification initial dose	Epoetin alfa		Darbepoetin alfa	
	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
Dose increase	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 a 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 a < 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 > 1 g/dL in 2 weeks	
Dose withholding	<i>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</i>		<i>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</i>	
Discontinue	<i>After completion of CT course or if no response after 8 weeks of therapy (measured by Hb levels or continuing need for transfusions)</i>		<i>After completion of CT course or if no response after 8 weeks of therapy (measured by Hb levels or continuing need for transfusions)</i>	

NOTE. Changes from the 2007 American Society of Hematology/American Society of Clinical Oncology ESA guideline dosing table are noted in italics. Data from US Food and Drug Administration.^{62,63}

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 Hb levels ≥ 10 g/dL.

VII. Hb target

2010 recommendation. 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 to avoid excessive ESA exposure (see Recommendation V), considering the risks of ESAs (see Recommendation I). Specific dose-reduction recommendations are provided in Table 2.

Literature update and discussion. The 2007 update summarized emerging (but at that time inconclusive) evidence suggesting that ESA therapy might increase the risk of mortality in anemic patients with cancer. Since then, individual patient data⁹ and literature-based^{8,31} meta-analyses of RCTs have shown statistically significant increases in the risk of mortality for patients randomly assigned to ESA treatment compared with controls. In the individual patient data meta-analysis, the effect of ESA treatment on risk of mortality was observed whether measured over the treatment period specified in each RCT's protocol or over the entire follow-up duration available. Of note, the individual patient data meta-analysis reported that in multivariate regression analyses, tests for interaction did not show statistically significant modification of the mortality increase by planned Hb ceiling (using subsets defined as < 13 v 13 to < 15 v ≥ 15 g/dL or using subsets defined by increments of 1 g/dL between 13 and 16 g/dL). Additionally, subset analyses by target Hb concentration (comparing subsets at < 13 v 13 to < 15 v ≥ 15 g/dL) found no statistically significant differences between subsets in mortality increase from ESA treatment ($P = .98$). Similarly, a literature-based meta-analysis³¹ reported that none of the variables tested (including the achieved Hb concentration and whether ESA treatment regimen adhered to the prior ASCO/ASH guideline recommendations) significantly moderated the association between ESA treatment and mortality. None of these analyses independently evaluated the dose-intensity of ESA treatment as a possible risk factor (see Special Commentary on ESAs, Tumor Response, and Survival). Thus, available data do not identify a target Hb concentration for ESA therapy (or its upper limit) that is entirely free from increased risk of mortality. The Update Committee revised this recommendation to reflect current FDA-approved labeling advice to use ESAs to avoid transfusions and for health care providers to avoid steep increases in Hb with ESA treatment.

VIII. Iron monitoring and supplementation

2010 recommendation. This recommendation remains the same as in 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 inadequate evidence to consider the use of intravenous iron as a standard of care.

Literature update and discussion. Since the 2007 update, three RCTs have been published that evaluated the effects of intravenous iron in combination with darbepoetin in patients with

chemotherapy-induced anemia (Data Supplement DS10),^{41,45,51} In a multicenter, open-label, randomized phase III trial, Bastit et al⁴¹ evaluated hematopoietic response rate (primary outcome), transfusion rate, fatigue rating, and adverse event rate (secondary outcomes) in 396 patients with nonmyeloid malignancies who received darbepoetin with or without supplemental intravenous iron. Hematopoietic response, defined as Hb ≥ 12 g/dL or a ≥ 2 g/dL increase in Hb during the 16-week treatment period, was significantly greater for patients in the intravenous iron plus darbepoetin group than for patients in the standard practice group, who received either oral iron or no iron plus darbepoetin (86% v 73%, respectively; 95% CI [for the difference], 3% to 23%; $P = .011$). With regard to secondary outcomes, the transfusion rate was significantly lower in the intravenous iron group compared with the standard practice group (9% v 20%, respectively; 95% CI [for the difference], -18% to -3% ; $P = .005$). There was no difference in fatigue scores, as measured by the FACT-Fatigue scale, and no differences in the incidence of adverse events.

In a randomized, open-label, multicenter trial of darbepoetin with or without intravenous iron supplementation, Pedrazzoli et al⁴⁵ evaluated hematopoietic response (primary outcome), transfusion requirement, time to achieve hematopoietic response, Hb profiles over time, and time-adjusted Hb area under the curve (secondary outcomes) among 149 patients with lung, gynecologic, breast, or colorectal cancers and chemotherapy-induced anemia. Hematopoietic response was defined as either an increase in Hb ≥ 12 g/dL or the achievement of Hb ≥ 12 g/dL in the absence of an RBC transfusion in the previous 28 days. By intent-to-treat analysis, hematopoietic response was 76.7% in the darbepoetin plus iron group and 61.8% in the darbepoetin-only group ($P = .0495$). Transfusions were required in two (2.7%) of 73 patients in the darbepoetin plus iron group and in five (6.5%) of 76 patients in the darbepoetin-only group. There were no differences in adverse event rates between the study arms.

The third trial randomly assigned 67 patients with moderate anemia (defined by the investigators as Hb of 9 to 11 g/dL) with hematologic malignancies not undergoing chemotherapy to epoetin beta with versus without intravenous iron sucrose.⁵¹ The primary outcome was mean change in Hb concentration from baseline to end of treatment, whereas secondary outcomes included the proportion of patients achieving an Hb response (defined as an increase of ≥ 2 g/dL from baseline without need for transfusion until end of treatment at week 15), time to Hb response, epoetin dose, and laboratory measures of iron stores and metabolism. By intent-to-treat analysis, a significantly larger proportion of patients in the intravenous iron arm achieved Hb response than in the arm not given intravenous iron (87% v 53%, respectively; $P < .001$). Transfusions were required for two patients (6%) in the arm that received iron and for one patient (3%) in the arm that did not receive iron. Mortality was 11.8% in the arm that did not receive iron and 0% in the arm that received iron.

Literature update and discussion: limitations to studies of iron supplementation. Several studies have suggested that intravenous iron should be used universally in support of recombinant EPO therapy in anemic patients with cancer. However, there are limitations to these studies that may modify such a recommendation. First, there is significant heterogeneity across the published clinical trials, which affects their generalizability. Sources of heterogeneity include patient populations (myeloid and nonmyeloid malignancies), use of concomitant chemotherapy, differing ESA and iron formulations and schedules in the treatment groups, different control groups, and different reported primary outcomes

(Hb response, transfusion avoidance, and QOL). Second, transfusion use was generally not standardized in these studies. Third, the trial arms were not blinded, leaving them open to observer bias. Fourth, in some of the trials, the results from analysis per protocol were superior to intent-to-treat analysis. Response rates for the most universally reported outcome, Hb response, vary between absolute differences of 13% and 40% between treatment and control groups across clinical trials. Fifth, despite random assignment, several trials had an imbalance with respect to the larger number of women with breast or gynecologic tumors, who may be more likely to be iron deficient, in the intravenous iron arm. Sixth, a control arm of intravenous iron alone without recombinant EPO is lacking in all of the studies.⁷⁰ Finally, all of these trials sought to increase the Hb to greater than 12 g/dL, a goal that is less relevant given current clinical guidance. It is also noteworthy that little difference was observed between oral or no iron use and intravenous iron use during the first 6 to 8 weeks, suggesting that iron therapy may be most appropriately considered at 6 to 8 weeks for patients who are not obviously iron deficient at the onset of ESA therapy.

In summary, although the published studies suggest that use of intravenous iron may augment ESA response, study limitations lead the Committee to recommend that currently available clinical evidence is insufficient to support intravenous iron as standard of care for adjuvant therapy in anemic patients with cancer receiving recombinant EPO therapy.

IX. Anemia in patients not receiving concurrent chemotherapy

2010 recommendation. 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 patients with lower risk MDS to avoid transfusions is an exception to this recommendation.

Literature update and discussion. The substance of this recommendation has not changed from the 2007 update. The 2002 guideline recommended against ESA therapy for anemia in patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia who were not receiving chemotherapy because most patients in trials of these hematologic malignancies received chemotherapy and available data were insufficient for conclusions on patients not treated concurrently.³ The 2007 Update Committee reaffirmed this recommendation because conclusive evidence was still unavailable on outcomes of ESA therapy for such patients.¹⁸ In March 2007, the FDA Oncologic Drugs Advisory Committee reviewed unpublished evidence of a statistically significant increase in mortality and no decrease in transfusion risk in the ESA arm of a large RCT for patients with mostly stage III or IV solid tumors not receiving concurrent chemotherapy. In response, the FDA issued a warning against ESA therapy for anemia in patients with cancer (solid tumors or nonmyeloid hematologic malignancies) who were not receiving concurrent chemotherapy. ESA manufacturers and the FDA also warned clinicians to discontinue ESA treatment when a patient's chemotherapy course was completed, and current FDA-approved labeling retains the same warnings.

ASCO/ASH's 2007 Update Committee also recommended against ESA treatment for patients with solid tumors not receiving chemotherapy, on the basis of data from the same large RCT, available on the FDA's Web site. Evidence reported since the 2007 update on outcomes of ESA therapy in patients with a malignancy not receiving concurrent chemotherapy is insufficient to change the

2007 recommendation. The following paragraphs summarize the new evidence on outcomes of ESA therapy in this population.

The individual patient data meta-analysis reported by Bohlius et al⁹ included five trials in which patients with anemia and cancer received no anticancer therapy (combined n = 1,690). Subset analyses showed that ESA treatment increased the risk of mortality for these patients during the active study period (HR, 1.33; 95% CI, 1.06 to 1.66) and also over the full duration of follow-up available (HR, 1.22; 95% CI, 1.04 to 1.44). Other subsets included patients receiving chemotherapy (n = 10,441), chemoradiotherapy (n = 737), or radiotherapy alone (n = 799) and a subset categorized as other (n = 266). Meta-regression and tests for interaction found that the variable of type of treatment did not statistically significantly modify the effect of ESA treatment on mortality (P = .42 for on-study mortality; P = .11 for overall survival over all available follow-up). Although results of these analyses confirm that ESA treatment increases risk for mortality in patients with anemia and cancer not receiving concurrent chemotherapy, they also show that the increased risk of death is not limited to this patient subset.

The updated literature-based meta-analysis reported by Bennett et al⁸ included a subset of six trials defined as anemia of cancer because patients did not receive either chemotherapy or radiation therapy. The effect of ESA therapy on mortality was statistically significant in this subset (HR, 1.19; 95% CI, 1.01 to 1.40) and also in the other 47 trials in which patients received either chemotherapy or radiation therapy for their malignancy (HR, 1.09; 95% CI, 1.00 to 1.18). These point estimates and CIs were similar to those obtained for the complete set of 53 trials included in this updated meta-analysis (pooled N = 14,164; HR, 1.09; 95% CI, 1.01 to 1.18). Bennett et al^{8,28} did not report meta-regression and formal statistical tests for interaction of potentially modifying variables with the effect of ESAs.

A subsequent literature-based meta-analysis³¹ reported that use of chemotherapy, type of cancer, and all other variables tested did not modify the association between ESA use and mortality. However, the authors did not report HRs or CIs in any of the subsets they analyzed.

Finally, the literature-based meta-analysis reported by Glaspy et al²⁹ defined a subset of nine studies (n = 1,901) on anemia of cancer and another subset of four studies (n = 1,314) on patients administered radiotherapy alone for their malignancy. They reported that ESA treatment did not have a statistically significant effect on mortality in either the anemia of cancer (OR, 1.09; 95% CI, 0.87 to 1.36) or radiotherapy-only (OR, 1.18; 95% CI, 0.95 to 1.47) subsets. Nevertheless, for reasons detailed under Recommendation I, including availability of patient-level data for a greater proportion of studies and patients, use of meta-regression and formal tests of interactions terms, and use of a strict intent-to-treat analysis, where analytic results conflicted, the 2010 Update Committee placed greater weight on results from the individual patient data meta-analysis.⁹

In a meta-analysis that compared the ORs for increased rates of thromboembolic events associated with ESA therapy in subsets of trials on chemotherapy-induced anemia versus trials on anemia of cancer,²⁹ the OR point estimates for these two subsets were not that different (1.48 v 1.36, respectively), and the 95% CIs overlapped (1.27 to 1.72 v 0.68 to 2.74, respectively). Thus, although the subset analysis was statistically significant for chemotherapy-induced anemia trials but was not statistically significant for anemia of cancer trials, the similarity in point estimates and overlapping CIs does not suggest major

differences in the effects of ESAs on thromboembolic events in these two groups of patients.

The literature search did not identify any new RCTs published since the 2007 update and not included in any of the new systematic reviews or meta-analyses identified for this update that were limited to patients not receiving concurrent chemotherapy.

Literature update and discussion: patients with lower risk MDS. The updated literature search identified one new RCT⁵⁰ and a meta-analysis and systematic review of RCTs³² that reported outcomes of ESA therapy for patients with lower risk MDS. In the first step of their study, Greenberg et al⁵⁰ randomly assigned patients (84% in the low or intermediate-1 risk groups by International Prognostic Scoring System criteria) to treatment with epoetin plus supportive care (n = 53; 60% previously transfused) or to supportive care alone (n = 57; 61% previously transfused). Patients were stratified by endogenous EPO level of less than 200 mU/mL versus more than 200 mU/mL at random assignment. Additionally, some patients crossed over from best supportive care to EPO 4 months after random assignment. In a subgroup analysis that pooled results of patients randomly assigned to EPO initially with those of patients who crossed over, response was greater (45%) for the subgroup with endogenous EPO less than 200 mU/mL at random assignment than for the subgroup with EPO more than 200 mU/mL (5%). At the end of 4 months (step 1), fewer patients in the arm randomly assigned to epoetin remained transfusion dependent (29%) compared with the arm randomly assigned to supportive care alone (51%). These investigators also reported a significantly higher rate of erythroid response (using International Working Group criteria^{71,72}) among patients randomly assigned to epoetin versus patients assigned to supportive care alone (34% v 5.8%, respectively; $P = .001$). The fact that some patients in the control arm crossed over to EPO after 4 months may explain why the difference in median survival between these groups (3.1 years for patients on epoetin v 2.6 years for controls, after 5.8 years of median follow-up) was not statistically significant. Notably, erythroid response in step 1 was significantly associated with longer median survival (5.5 years for responders v 2.3 years for nonresponders; $P = .004$).

Ross et al³² conducted a systematic review and meta-analysis of studies on ESA use in patients with MDS. They identified five controlled trials (pooled N = 354; four of five were RCTs) and 54 single-arm studies (pooled N = 1,752). The primary efficacy outcome of interest for meta-analysis, the proportion of patients with an Hb response, was significantly greater in the ESA-treated arms than in the control arms for the four controlled studies that reported this outcome (OR, 5.2; 95% CI, 2.5 to 10.8). However, only one of the controlled trials they reviewed reported effects of ESA treatment on transfusion use (78% of ESA-treated patients v 90% of controls). Two other meta-analyses identified in the literature search were excluded because they either pooled data from single-arm studies⁷³ or analyzed studies comparing ESA use with versus without a granulocyte or granulocyte-macrophage colony-stimulating factor.⁷⁴

The new RCT⁵⁰ and meta-analysis,³² along with evidence reviewed in earlier editions of this guideline,^{75,76} support the continued recommendation for using ESA treatment to decrease need for transfusions in patients with lower risk MDS who are not undergoing concurrent chemotherapy.

X. Treatment of anemia in patients with nonmyeloid hematologic malignancies who are receiving concurrent chemotherapy

2010 recommendation. This recommendation remains the same as in 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, who are being treated with palliative intent and who are 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 (see 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 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.

Literature update and discussion. Since the 2007 guideline update, Bohlius et al^{9,27} published results from their individual patient data meta-analyses of mortality and survival data, which included subset analyses of patients with nonmyeloid hematologic malignancies who were receiving concurrent chemotherapy.

Of the 53 trials that informed the meta-analyses of Bohlius et al,^{9,27} four studies were restricted to patients with various hematologic malignancies,^{13,77-79} and 15 studies included patients with a wide range of different malignancies, including patients with solid cancer and hematologic malignancies.⁸⁰⁻⁹³ Subset analyses, using individual patient data from patients with hematologic malignancies receiving chemotherapy (n = 1,832), showed no significant differences in mortality over the active study period between patients in ESA arms compared with patients in control arms (HR, 1.12; 95% CI, 0.81 to 1.54).⁹ There were also no significant differences between arms for survival over all available follow-up in patients with hematologic malignancies who were receiving chemotherapy (HR, 1.13; 95% CI, 0.96 to 1.33).⁹ However, meta-regression and tests for interaction found that the variable of malignancy type did not statistically significantly modify the effect of ESA treatment on mortality ($P = .18$ for on-study mortality; $P = .33$ for overall survival over all available follow-up).

Special commentary on ESAs, tumor response, and survival

Since the publication of the 2007 guideline, the results of several randomized trials have either been published or become available in the public domain, with some additional studies reporting

adverse health effects associated with ESA use in patients with cancer. In response, the labels for ESAs were revised by the manufacturers and approved by the FDA to alert physicians to shortened survival and/or increased risk of tumor progression or recurrence in eight RCTs involving patients with cancer of the head and neck, breast, or uterine cervix; non-small-cell lung cancer; or various lymphoproliferative malignancies or mixed nonmyeloid cancers.⁵⁹⁻⁶¹

Six of these RCTs were abstracted in detail in the 2007 guideline update.^{13-16,22,88,94} This commentary briefly summarizes the results of several RCTs that evaluated survival or tumor progression since the 2007 guideline update.

Virtually all studies reported here demonstrated responses to ESA therapy measured by increases in Hb or transfusion avoidance as anticipated. Common limitations of some of the trials recently completed are early trial closure, insufficient numbers of participants, and/or inadequate follow-up to determine adverse events (eg, tumor progression and survival). This makes interpretation of the results extremely challenging because the studies are ultimately underpowered to detect the outcomes of interest (survival), thus masking potentially true risks or true benefits of ESA therapy.

Literature review

Head and neck cancer. Since the 2007 guideline update, one new RCT³⁷ was published, and one meta-analysis of five RCTs (that included this trial) was identified that addressed the role of ESA in patients with head and neck cancer (Data Supplements DS1 and DS2). The data from Hoskin et al³⁷ were included (as trial EPO-GBR-7) in previously reported meta-analyses.^{9,27,29} The Cochrane Collaboration's Ear, Nose and Throat Disorders Group reviewed five RCTs^{14,16,30,37,95,96} comparing radiation therapy plus ESA with radiation therapy alone in a total of 1,397 patients with head and neck cancer.³⁰ There was a statistically significant increase in death and worse locoregional progression-free survival in the radiation therapy plus ESA group compared with the group who received radiation therapy alone.

Breast cancer. The Breast Cancer-Anemia and the Value of Erythropoietin (BRAVE) trial was an open-label, randomized, multicenter study in women with metastatic breast cancer and baseline Hb of less than 12.9 g/dL randomly assigned to treatment with chemotherapy and epoetin beta (30,000 U weekly) or to a control group.⁶⁷ The primary outcome was overall survival. Of the 463 patients enrolled, 123 patients withdrew, and 340 patients completed the study treatment period. There were no significant differences in survival or disease progression between the groups at 4, 12, or 18 months.

The results of the Preoperative Epirubicin Paclitaxel Aranesp Study (PREPARE) trial involving 733 patients with early breast cancer have not yet been published in peer-reviewed form.^{24,25} The PREPARE study was an open-label, randomized trial comparing survival and relapse-free survival between preoperative standard chemotherapy and a sequential dose-intense neoadjuvant regimen for 12 weeks. The patients in each arm were randomly assigned to receive darbepoetin alfa (4.5 µg/kg every 2 weeks during chemotherapy to maintain Hb ≥ 13 g/dL) or transfusion as necessary. Comparison of relapse-free and overall survival between the darbepoetin alfa and transfusion groups was a secondary end point. An interim analysis after a median follow-up of 3 years reported increased mortality in the darbepoetin-treated groups compared with the transfusion groups

(14% v 10%, respectively; HR, 1.42; 95% CI, 0.93 to 2.18) and lower relapse-free survival (72% v 78%, respectively; HR, 1.33; 95% CI, 0.99 to 1.79). Neither result was statistically significant. Although results of tumor progression were reported, they were not formally compared statistically.

Lung cancer. N93-004 was a randomized, double-blind, placebo-controlled trial that evaluated the effects of epoetin alfa on tumor response to chemotherapy and survival in patients with limited or extensive-stage small-cell lung cancer.⁹⁷ Patients with Hb ≤ 14.5g/dL were treated with epoetin alfa 150 U/kg three times weekly or placebo for a median of 13.4 weeks without dose escalation. The trial was terminated prematurely because of slow recruitment after 224 of the planned 400 patients were accrued. The overall mortality rate was 91.7% in the epoetin alfa group and 87.8% in the placebo group, and the median survival time was similar in the epoetin alfa (10.5 months) and placebo (10.4 months) groups. Disease progression was similar in both groups. Differences in survival and disease progression were not statistically significant.

Study 20010145 was a randomized, double-blind, placebo-controlled, multicenter trial comparing survival and Hb response in 600 previously untreated patients with extensive-stage small-cell lung cancer receiving chemotherapy and randomly assigned to darbepoetin alfa or placebo.⁹⁸ Darbepoetin alfa 300 µg or placebo was administered once per week for 4 weeks and then every 3 weeks for a total of 24 weeks to a target Hb of 13 g/dL (dose was withheld at Hb ≥ 14 g/dL). There was no significant difference in overall survival (HR, 0.93; 95% CI, 0.78 to 1.11) or progression-free survival (HR, 1.02; 95% CI, 0.86 to 1.21) between darbepoetin alfa and placebo.

Cancer of the uterine cervix. The Gynecologic Oncology Group 191 trial compared patients with stage IIB to IVA cancer of the uterine cervix and Hb less than 12 g/dL treated with chemoradiotherapy and randomly assigned to receive either epoetin alfa 40,000 U weekly to an Hb target of ≥ 13 g/dL or transfusions to maintain Hb more than 10 g/dL.^{23,99} The primary clinical end points were progression-free and overall survival and local control. The study was closed prematurely after enrolling 114 of the planned 460 patients because of increased thromboembolic events in the epoetin alfa group (19.3% in the epoetin alfa group v 7.7% in the control group). At 3 years, progression-free survival and overall survival were lower in the epoetin alfa group compared with the control group (progression-free survival: 59% v 65%, respectively; HR, 1.06; 95% CI, 0.58 to 1.91; overall survival: 61% v 73%, respectively; HR, 1.28; 95% CI, 0.68 to 2.42); however, these differences were not statistically significant.

Mixed nonmyeloid solid cancers. Study 20010103 was a multicenter, randomized, placebo-controlled trial in 989 patients with active nonmyeloid solid cancer and anemia (Hb ≤ 11 g/dL) not receiving chemotherapy or radiotherapy and randomly assigned to placebo or darbepoetin alfa (6.5 µg/kg every 4 weeks) for 16 weeks plus an additional 16 weeks of treatment for patients who completed the first 16 weeks.⁸⁸ The primary end point was transfusions, and there was no statistically significant difference between transfusions in the treatment group compared with the placebo group. There was a significant difference in survival, with an increased risk of death reported in the darbepoetin group compared with the placebo group (HR, 1.22; 95% CI, 1.03 to 1.45; $P = .022$).

Potential mechanisms mediating tumor progression and increased mortality

The association between ESA use and adverse outcomes in patients with anemia and cancer, which include an increase in mortality during the period of exposure and an increased risk of thromboembolic events,^{10,11} has led to restrictions on ESA use in this patient population. Given the clinical effectiveness of ESAs in alleviating anemia and reducing transfusion requirements in patients with anemia and cancer, understanding the mechanisms for the adverse effects of ESAs is essential to optimizing the benefits of these agents while avoiding their hazards.

EPO physiology (and that of its recombinant congeners, the ESAs) is central to the issue of potential harms. EPO is normally constitutively produced, and its plasma concentration is maintained at a constant level subject only to diurnal variation.¹⁰⁰ Hypoxia is the only physiologic stimulus for increasing the EPO production, but because erythroid progenitor cell proliferation is exponential, EPO production is tightly regulated even in situations of extreme hypoxia.¹⁰¹ The mechanisms for this are several and include relief of tissue hypoxia by increased RBC number, increased EPO catabolism by its target cells because they express the highest concentrations of EPO receptors (EpoRs),¹⁰² increased blood viscosity as a result of the increase in RBC number,¹⁰³ and a concomitant decline in plasma volume associated with EPO activity.^{104,105}

Impairment of any of these compensatory mechanisms can result in harm. When the RBC mass is increased by any means (eg, transfusion, excess EPO exposure from any cause, androgen use, chronic carbon monoxide exposure), there is a concomitant reduction in plasma volume^{104,105} because the body's natural tendency is to maintain the total blood volume at a constant level. The consequences of this tendency, if left unchecked, are an increase in blood viscosity, an increase in systemic and pulmonary pressures, endothelial cell and platelet activation,¹⁰⁶ increased nitric oxide scavenging by the increased RBC mass leading to vasoconstriction and increased platelet adhesiveness,¹⁰⁷ increased inflammatory cytokine production,^{108,109} enhanced leukocyte-platelet interactions and enhanced interactions between leukocytes/platelets and the vessel wall,¹¹⁰ generation of platelet microparticles,¹¹¹ and circulatory stasis leading to a hypercoagulable state. Such stasis can also be detrimental because it may cause tumor hypoxia because tumor vessels are anatomically abnormal¹¹² and tumor hypoxia can enhance tumor aggressiveness.¹¹³ Confounding the situation is the fact that there is no correlation between the peripheral hematocrit and the absolute RBC mass because the distribution of RBCs and plasma in the circulation are independent of each other.¹¹⁴ Thus, a hematocrit measurement does not adequately represent the actual number of RBCs in the vasculature once there is a deviation from normal. Importantly, mortality risk in general is narrowly distributed around a hematocrit of 36% in women and 40% in men.¹¹⁵ Given these facts, it is not surprising that ESAs have the potential to do harm if not used judiciously.

Role of cytokines

The potential hazards of ESAs are, of course, compounded by the disorders in which they are used. For example, both cancer and end-stage renal disease are disorders in which inflammatory cytokine production is increased,^{108,116} and in patients with cancer, this effect is compounded by chemotherapy. What has not been

sufficiently appreciated is that EPO can also increase inflammatory cytokine production. For example, patients with anemia and end-stage renal disease receiving an ESA have high inflammatory cytokine levels, which are higher than the levels in patients with end-stage renal disease who are not anemic and in those who are ESA naive.¹⁰⁸ The ability of EPO to enhance cytokine production was apparent in its initial clinical trials where intravenous administration of large quantities of the recombinant hormone provoked flu-like symptoms and conjunctivitis.¹¹⁷ Additional studies demonstrated that EPO could enhance the production of marrow myeloid and megakaryocytic progenitor cells, even though these cells lack EpoRs,¹⁰⁹ indicating that this effect of the hormone was mediated by other cytokines. This also seems to be true for other intriguing non-erythroid cell effects of the ESAs, including tissue injury response and regeneration.¹¹⁸

Role of EpoRs

The mechanisms of ESA-related adverse effects on tumor progression are not well characterized. Hypotheses that have been considered include the following: potential direct effects of ESAs on tumors via a putative functional EpoR expressed in tumor cells or cells in the tumor microenvironment; and systemic effects of ESAs that may indirectly impact tumor biology, as discussed earlier. Laboratory studies have demonstrated that ESAs may induce tumor signaling and affect tumor cell behavior, and knocking down the EpoR on tumor cells may delay their growth in animal models.¹¹⁹⁻¹²¹ The clinical applicability of preclinical experimental models of EPO biology in cancer has not been resolved, and limited correlative tumor biology data have emerged from completed clinical RCTs.¹²² In retrospective analyses of a subgroup of archival tumor specimens from the Evaluation of Neorecormon on Outcome in Head And Neck Cancer (ENHANCE) trial, the worse progression-free survival in the epoetin beta group was limited to the cohort of patients whose tumor cells expressed EpoR protein by immunohistochemistry, although the commercially available antibody used in protein expression assays can nonspecifically bind other proteins.¹²³⁻¹²⁵ In a more recent study, quantitative analysis of EpoR mRNA expression in archival tumors from the ENHANCE trial revealed that worse locoregional progression-free survival was limited to patients in the epoetin beta group with residual tumors that expressed relatively high levels of EpoR mRNA.¹²⁶ Although these retrospective analyses suggest that ESAs may exert direct effects on tumor growth and thereby impair progression-free survival only if EpoR is expressed in the tumors, no human clinical studies have demonstrated that these tumors are ESA responsive. Further investigation in larger prospective studies and in other cancer types will be required to confirm these preliminary findings.

Much attention has been directed at the potential interaction of ESAs with tumor cell EpoRs to promote the growth and survival of these cells.¹²⁷ It is also relevant to consider the adverse effect of plasma ESA concentrations greater than that which saturates the physiologic EpoRs present on erythroid progenitor cells. It has been well documented that nonresponse of patients with anemia and cancer to an ESA is associated with reduced survival,¹²⁸ and importantly, in two studies of patients with end-stage renal disease, it was not reaching the desired hematocrit that was associated with increased mortality but failure to reach the desired hematocrit.¹²⁹ In a third study in patients with renal failure, an increased mortality risk was associated with the ESA dose alone; the higher the dose, the greater were the morbidity and mortality independent of the hematocrit level.^{129,130} Thus, it is clear that some adverse effects of ESAs are independent of EPO receptors.

In the individual patient data meta-analysis of 13,933 patients with anemia and cancer receiving ESAs, it was found that patients receiving an ESA three or more times a week had a lower mortality than patients receiving an ESA once a week or every 2 weeks.^{9,27} Given the pharmacokinetics of EPO, lower doses of an ESA given three times weekly do not exceed a plasma concentration (approximately 100 mU/mL) that saturates the EpoRs on erythroid progenitor cells,¹³¹ and thus, the hormone is not available to interact with other cells. When given at higher doses less frequently, physiologic clearance mechanisms for the hormone become saturated, and it has a longer plasma residence time. This can only enhance non-erythroid cell interactions because it is known, for example, that EpoRs are expressed by endothelial cells but at a copy number and Kd value that cannot compete with erythroid cells at physiologic plasma concentrations.¹³² Thus, it can be hypothesized that judicious ESA dosing may be a simple means of avoiding the toxicities associated with ESA administration, which is a hypothesis that cannot be adequately evaluated in existing studies as a result of confounding with several related cofactors.

In all eight RCTs that reported increased tumor progression and/or worse mortality associated with ESA use, the target Hb levels were greater than 12 g/dL, and ESA dose escalation was permitted in some studies. The impact of ESAs on tumor progression and survival in patients receiving myelosuppressive chemotherapy and treated with ESAs initiated at Hb \leq 10 g/dL to reduce transfusion requirements and not to exceed 12 g/dL has not been evaluated in well-designed, prospective, randomized, adequately powered trials. In patients with cancer, characterization of the relationship between adverse outcomes and ESA dose, dosing schedule, or ESA responsiveness will require further investigation.

Patient communication

Patient counseling regarding the risks and benefits of ESA therapy is essential to ensure that patients are making informed decisions. The Update Committee encourages health care providers to have an open dialogue with their patients to help them make informed decisions by considering the scientific evidence and weighing their individual risks with potential harms and benefits of ESA therapy.

In addition to providing a medication guide, health care providers should discuss the following with patients considering ESA therapy:

- The goal of ESA therapy for patients with chemotherapy-induced anemia is to reduce RBC transfusion requirements.
- The FDA has indicated that ESAs should not be given to patients who are being treated for cancer when the goal is to cure the patients (of cancer). There are potential harms and benefits of ESAs versus RBC transfusions, and patients may have specific risk factors.
- ESAs have been found to shorten overall survival and/or speed tumor growth in some patients with cancer.
- ESAs have risks of adverse events, such as blood clots, so individual risk factors need to be considered.
- ESAs are not recommended for patients with cancer who are not receiving chemotherapy or who are receiving radiotherapy because ESAs have been associated with an increased risk of death in these patients.
- Although there are some suggestions that ESA treatment may improve fatigue or QOL in some patients, the primary goal of ESA therapy should be to reduce transfusion requirements.

- An acknowledgment form needs to be signed by patients to confirm that they have talked with their health care professional about the risks of ESAs.

The US FDA and the pharmaceutical companies that market ESAs in the United States have put in place an REMS to advise clinicians and to facilitate discussions with patients about the use of ESAs. The REMS requires health care professionals to provide a medication guide that explains the risks and benefits of ESAs to patients who receive ESAs. For more details, refer to the medication guide for epoetin alfa⁶⁰ and the medication guide for darbepoetin alfa.⁵⁹ Health care providers who prescribe ESAs to patients with cancer are also required to enroll in the ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe Use of ESAs) Oncology Program.²⁶

Health disparities

ASCO/ASH clinical practice guidelines represent expert recommendations derived from critical appraisal of the best available evidence relevant to prospectively formulated, well-focused clinical questions on optimal practices in management of oncologic diseases. However, racial, ethnic, and socioeconomic disparities in quality of health care exist and persist in the United States. Members of racial and ethnic minority groups and patients with fewer financial resources tend to have a higher burden of comorbid illness, are more likely to be uninsured or underinsured, face more challenges in accessing care, and are at greater risk of receiving care of poor quality than other Americans.¹³³⁻¹³⁷

Analysis of observational data from the Surveillance, Epidemiology, and End Results–Medicare database (on patients treated between 1991 and 2002 for colon, non-small-cell lung, or breast cancer or diffuse large B-cell lymphoma) suggests that, with respect to socioeconomic status, ESAs might have been used more frequently for patients above the median than for patients in the lowest quartile.¹³⁸

It is possible that out-of-pocket costs of ESAs pose a barrier to patients with little or no prescription coverage or who are subject to cost-sharing strategies (ie, copayments). The guideline Update Committee encourages health care providers to include direct and indirect costs in their discussions with patients who are considering ESA therapy. ASCO and ASH support the development of resources to facilitate patient-provider communication about costs of cancer care.¹³⁹

Estimated costs for darbepoetin and epoetin on the basis of Medicare Plan B average sales price, with no administration fees or other adjustments made, are provided in Data Supplement DS12. These prices were estimated from a third-party payor perspective, on the basis of reimbursement rates from the Centers for Medicare and Medicaid Services that are widely accepted by providers, computed at the manufacturer's average sales price. Other treatment-related direct and indirect costs were not considered, such as diagnostic laboratory tests. Actual treatment costs and reimbursement will vary considerably across regions, payors, institutions, and practices, as well as over time, and the reader should consult current local cost information specific to his or her practice setting.

The guideline Update Committee believes that patients with cancer should have equal access to ESAs, after consideration of their risks and benefits. However, current data do not help us understand whether differences in patterns of use reflect differences in access, whether disparities exist in patients' access to ESAs, or

whether there are any particular groups who benefit more or less from their use. Awareness of possible disparities in quality of care and efforts to mitigate these disparities should be considered in the context of this clinical practice guideline.

Future directions

There is clear evidence regarding the ability of ESAs to increase Hb and avoid transfusions. There is also evidence of harm associated with their use. Perhaps the most pressing need for additional research is studies that further clarify the mechanisms of harm and, particularly, the groups of patients or circumstances of clinical use that are least associated with these risks. This understanding is paramount to the ability of clinicians to extend the benefit of these drugs while reducing the risks.

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Appendix

Literature search strategy

For the 2010 guideline update, pertinent published information was reviewed to address each of the guideline questions. As noted in the Results, one meta-analysis using individual patient data and six comprehensive systematic reviews and meta-analyses of randomized controlled trials (RCTs) served as the primary evidentiary basis for this update. An additional 13 papers met the inclusion criteria and reported results from RCTs that were not included in any of the meta-analyses or systematic reviews. Supplementary searches of the MEDLINE database (National Library of Medicine, Bethesda, MD) were conducted to identify relevant information (January 2007 through January 2010) from additional published RCTs, systematic reviews, meta-analyses, and practice guidelines for this update. A series of searches was conducted using the medical subject headings or text words “erythropoietin, recombinant,” “epoetin alfa,” “epoetin beta,” “darbepoetin alfa,” and “neoplasms,” and variants thereof. (Details of the searches can be obtained from guidelines@asco.org on request.) Search results were limited to human studies and English-language articles. Search terms can be found in Data Supplement DS13. Only trials that reported clinical outcomes in nonpediatric populations were included in the systematic review. Trials were excluded if they only reported hematologic response rates and/or Hb concentration. Publications were included if they reported retrospective analyses of previously published RCTs. Extraction and review of quality-of-life (QOL) data were limited to studies and systematic reviews that included a control arm not treated with an ESA, reported QOL results separately for each arm, and reported overall QOL scores (in addition to any subscale scores that may have been reported) from standardized, validated QOL instruments. Editorials, letters, and commentaries were excluded from consideration, as were systematic reviews and meta-analyses that were limited to single agents, on the basis of the US Food and Drug Administration’s position that available ESAs are members of the same pharmacologic class. The Cochrane Library was searched for available systematic reviews and meta-analyses with the phrases “erythropoietin,” “epoetin,” “darbepoetin,” “cancer,” and “malignancies.” Directed searches on the basis of the bibliographies of primary articles were also performed. Finally, Update Committee members and ASCO staff contributed articles from their personal collections.

Table A1. Update committee membership

Update committee members	Affiliation/institution
Melissa Brouwers, PhD, co-chair	McMaster University, Department of Oncology
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