SPECIAL ARTICLE

Use of Epoetin in Patients With Cancer: Evidence-Based Clinical Practice Guidelines of the American Society of Clinical Oncology and the American Society of Hematology

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Abstract: **Anemia resulting from cancer, or its treatment, is an important clinical problem increasingly treated with the recombinant hematopoietic growth factor erythropoietin. To address uncertainties regarding indications and efficacy, the American Society of Clinical Oncology and the American Society of Hematology developed an evidence-based clinical practice guideline for the use of epoetin in patients with cancer. The guideline panel found good evidence to recommend use of epoetin as a treatment option for patients with chemotherapy-associated anemia with a hemoglobin level less than 10 g/dL. Use of epoetin for patients with less severe anemia (hemoglobin < 12 g/dL but never below 10 g/dL) should be determined by clinical circumstances. Good evidence from clinical trials supports the use of subcutaneous epoetin thrice weekly (150 U/kg tiw) for a minimum of 4 weeks. Less strong evidence supports an alternative weekly (40,000 U/wk) dosing regimen, based on common clinical practice. With either administration schedule, dose escalation should be considered for those not responding to the initial dose. In the absence of response, continuing epoetin beyond 6 to 8 weeks does not appear to be beneficial. Epoetin should be titrated once the hemoglobin concentration reaches 12 g/dL. Evidence from one randomized controlled trial supports use of epoetin for patients with anemia associated with low-risk myelodysplasia not receiving chemotherapy; however, there are no published high-quality studies to support its use for anemia in other hematologic malignancies in the absence of chemotherapy. Therefore, for anemic patients with hematologic malignancies, it is recommended that physicians initiate conventional therapy and observe hematologic response before considering use of epoetin.**

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HISTORICAL BACKGROUND

ANEMIA SECONDARY to a diagnosis of cancer, or resulting from its treatment, is an important clinical problem for which new therapeutic options have recently become available. The development of chemotherapy-associated anemia is characteristically an insidious and delayed complication of treatment. Transfusion was the traditional—and only—means of therapy for symptomatic anemia, until the 1990s.

Newer chemotherapeutic agents and drug combinations have made anemia an even more clinically significant problem. In some instances, with improved cancer therapy, treatment of malignancy has come to resemble management of chronic illness. Evolution in the management of anemia has accompanied these changes in cancer therapy. Growing concern about infectious risks has led to decreased usage of RBC transfusions. Likewise, the realization that transfusion products represent a limited resource has led to strategies to optimize their use.

The identification and clinical development of the recombinant hematopoietic growth factor, erythropoietin, triggered further evolution in the management of anemia in the 1990s. Anemia caused by malignancy may be related to either (1) infiltration of marrow elements by cancer cells directly (bone marrow involvement), (2) an impaired production process directly related to treatment (the effect of cancer therapy), or (3) other nonspecific processes, such as

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the inhibitory effect of tumor necrosis factor that accounts for the "anemia of chronic disorders," iron deficiency, or low endogenous erythropoietin levels. The United States Food and Drug Administration approved epoetin, the human recombinant form of erythropoietin, as a pharmaceutical in 1989 for anemia of chronic renal failure. Since then, numerous studies have examined its potential usefulness as an alternative to transfusion in the management of anemia in the cancer population.

Initial studies explored the use of erythropoietin in a variety of clinical oncology settings, testing various dosing and scheduling regimens. These trials typically were small in size and used a variety of regimens and schedules. Some failed to demonstrate significant benefit, perhaps because of the patient populations enrolled, the study design, or the limitations of the agent as a therapy. In addition, issues that have subsequently been recognized as critical to successful therapy, such as iron repletion, baseline hemoglobin at entry, and dosing/schedule of epoetin, were not fully appreciated. These factors were increasingly considered in subsequent, larger phase II and III trials. With greater clinical experience, trial designs have focused on fine-tuning the use of epoetin to achieve clinical outcomes such as reduced transfusion requirements and improved quality of life.

Currently, the field of hematopoietic support for anemia of cancer continues to evolve. The investigation of the next generation of erythropoietin products indicates that this area will continue to change over the next several years. Nonetheless, physicians making use of current evidence confront difficult questions about the proper indications for administering epoetin in anemic patients with cancer, and confront uncertainties regarding the efficacy of this agent and the quality of the trials on which current claims of efficacy are based. Furthermore, the use of epoetin is in the context of the availability of an effective alternative form of traditional therapy, namely blood transfusion.

CLINICAL PRACTICE GUIDELINES

To address these uncertainties, the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) began discussions in 1997 to develop an evidence-based clinical practice guideline on the use of epoetin in cancer patients. At that time, the Agency for Healthcare Research and Quality (AHRQ) solicited topic nominations for evidence reviews that were to be based on systematic, rigorous, and unbiased methods for selecting the literature and synthesizing the data through its network of 12 evidence-based practice centers.[1] The evidence reviews can serve as a scientific foundation for developing and implementing clinical practice guidelines and related products. ASH and ASCO submitted to AHRQ a formal proposal for an evidence-based practice center review on the use of epoetin in cancer patients.

AHRQ selected erythropoietin as one of the topics to be reviewed. The undertaking was awarded to the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) in Chicago, IL.[2] ASH and ASCO established an independent panel of experts in clinical medicine, clinical research, health services research and related disciplines to develop an evidence-based guideline from the evidence review. A draft of the TEC report was made available to the panel in late 2000, and the final report was released publicly in May 2001. The full-text TEC evidence report, *Use of Epoetin for Anemia in Oncology*,[3] and the Executive Summary can be obtained in print form from the AHRQ Publications Clearinghouse (800-358-9295) or online at www.ahrq.gov/clinic/epcix.htm. This report should be consulted by those interested in a more detailed treatment of the state of the evidence supporting the use of epoetin in clinical oncology practice than the information provided in this guideline.

This document is the evidence-based clinical practice guideline developed by ASH and ASCO that is based on the review. The guideline is a blend of evidence, the opinions of experienced practitioners, and their interpretation of the evidence. **ASH and ASCO acknowledge that guidelines cannot always account for individual variations among patients. Guidelines are not intended to supplant physician judgment with respect to particular patients or special clinical situations, and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, ASCO and ASH consider adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. In addition, these guidelines describe administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a clinical situation where better therapy is needed.** In that guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy could be considered as an option.

The following sections detail the methods used by the panel to develop its recommendations, the recommendations and the findings of the TEC report that influenced the panel's conclusions, as well as suggestions for future

Table 1. Summary of Recommendations

1. The use of epoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin concentration that has declined to a level ≤ 10 g/dL. RBC transfusion is also an option depending upon the severity of anemia or clinical circumstances.
2. For patients with declining hemoglobin levels but less severe anemia (those with hemoglobin concentration < 12 g/dL, but who have never fallen below 10 g/dL), the decision of whether to use epoetin immediately or to wait until hemoglobin levels fall closer to 10 g/dL should be determined by clinical circumstances. RBC transfusion is also a therapeutic option when warranted by severe clinical conditions.
3. The recommendations are based on evidence from trials in which epoetin was administered subcutaneously thrice weekly. The recommended starting dose is 150 U/kg thrice weekly for a minimum of 4 weeks, with consideration given for dose escalation to 300 U/kg thrice weekly for an additional 4 to 8 weeks in those who do not respond to the initial dose. Although supported by less strong evidence, an alternative weekly dosing regimen (40,000 U/wk), based on common clinical practice, can be considered. Dose escalation of weekly regimens should be under similar circumstances to thrice weekly regimens.
4. Continuing epoetin treatment beyond 6 to 8 weeks in the absence of response (eg, < 1-2 g/dL rise in hemoglobin), assuming appropriate dose increase has been attempted in nonresponders, does not appear to be beneficial. Patients who do not respond should be investigated for underlying tumor progression or iron deficiency. As with other failed individual therapeutic trials, consideration should be given to discontinuing the medication.
5. Hemoglobin levels can be raised to (or near) a concentration of 12 g/dL, at which time the dosage of epoetin should be titrated to maintain that level or restarted when the level falls to near 10 g/dL. Insufficient evidence to date supports the "normalization" of hemoglobin levels to above 12 g/dL.
6. 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.
7. There is evidence from one well-designed, placebo-controlled, randomized trial that supports the use of epoetin in patients with anemia associated with low-risk myelodysplasia, but there are no published high-quality studies to support its use in anemic myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients in the absence of chemotherapy. Treatment with epoetin for myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anemia should follow the recommendations outlined above.
8. 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 a rise in hemoglobin is not observed after chemotherapy, epoetin should be used in accordance with the criteria outlined above for chemotherapy-associated anemia if clinically indicated. Blood transfusion is also a therapeutic option.

research. A summary of the guideline recommendations can be found in Table 1.

METHODS

Panel Composition

ASH and ASCO established a joint guideline panel of experts in clinical medicine, clinical research, and health services research. Each organization nominated a cochair (A.E.L., M.S.G.), who then selected the panel members in consultation with the relevant officers of both organizations to achieve an appropriate distribution of content experts and practitioners. The first meeting of the 12 panel members was in May 1999. The panel included six academically affiliated and two community-based practicing hematology/oncology specialists, two experts in quality-of-life research, a practice guideline methodologist, and a patient representative. Two ex-officio members represented the relevant practice guideline committees of ASH and ASCO, and the project director for the TEC review joined the panel as an ex-officio member (Appendix A). One quality-of-life expert resigned and was replaced, and the first patient representative died during the project.

Conflict of Interest

Potential conflicts of interest were handled through full disclosure and according to the policies of ASH and ASCO (Appendix A). As part of the conflicts of interest consideration, the relationship of TEC to the Blue Cross and Blue Shield Association was addressed.

Definition of Topic

At its first meeting, the panel determined that the guideline would focus on the role of epoetin in the treatment of anemia caused by chemotherapy or radiation therapy, anemia associated with cancer, and anemia with bone marrow failure (myelodysplasia and aplastic anemia). The objective of the guideline was to delineate, according to the best available evidence, which patients should receive epoetin, the appropriate dosages and routes of administration, and the duration of treatment. Predictors of response and evaluation of response were also included when possible.

The outcomes of interest in evaluating the effectiveness of epoetin were to include requirements for transfused RBCs, changes in hemoglobin or hematocrit concentration, and quality of life. Although recommendations were not to be based on economic considerations, the panel did consider it important to review existing literature on the costs and cost-effectiveness of epoetin.

Review of Evidence

The review of evidence on which this guideline is based consists largely of the rigorous systematic review of the

literature conducted by the TEC, whose process and procedures have been reviewed in detail by the AHRQ. Details of this review can be found in the full report to AHRQ available in print[3] and at www.ahrq.gov/clinic/epcix.htm, or in the condensed summary published in a journal article.[4]

In summary, the TEC searched MEDLINE, Cancerlit, and Embase databases for all relevant articles published since 1985. The TEC supplemented the above strategy by searching issues of *Current Contents on Diskette* and *Medscape Oncology*[5] through October 30, 1999, to identify recently published articles that had not yet been indexed by the online databases. The reviewers also examined abstracts presented at the 1999 annual meeting of ASCO, bibliographic information and reprints of clinical studies provided by Ortho Biotech, Inc, and reference lists from relevant review articles, editorials, and letters published after 1994. Subsequently, the panel also reviewed emerging evidence on a new agent, darbepoetin, and kept abreast of other important emerging evidence that is cited in this document.

Admissible evidence included controlled trials (randomized and nonrandomized) that compared the outcomes of managing anemia with and without the use of epoetin. All trials that met study selection criteria compared epoetin plus RBC transfusion as necessary with RBC transfusion alone. Studies had to include at least 10 similarly treated assessable patients in each arm, relevant strata, and relevant epoetin dose level. Studies that used nonrandomized concurrent or historical controls were included only if the reviewers were satisfied that patients in the treatment and control groups were comparable at baseline and that obvious selection bias was absent; however, it is acknowledged that the nature of such designs cannot completely protect against such biases. Two reviewers independently conducted each step in the review process. Disagreements were resolved by consensus. The TEC also conducted a pooled statistical analysis (meta-analysis) of the effect of epoetin on the odds of transfusion for patients with anemia or at risk of anemia primarily because of cancer therapy.

The guideline panel relied mainly on the evidence review performed by TEC in developing the guideline. However, the panel, with acknowledgment of their design limitations, also included large community studies excluded by TEC because of methodologic concerns. A summary and critical appraisal of the studies reviewed for this guideline can be found in Tables 2 through 5 (chemotherapy-induced anemia) and Appendix B.

Process Overview

The cochairs and a planning committee of ASH and ASCO representatives developed a joint operating structure for coordinating the work of the panel under the auspices of both organizations. Coordinated procedures were developed for defining the role of the cochairs, for panel selection, for addressing conflicts of interest, and for peer review and final approval of the document.

The panel considered it essential to use a systematic review of the evidence as its foundation for making recommendations. This process includes a systematic weighting of the level of evidence and a systematic grading of the evidence for making a recommendation.[6,7] The hierarchical grading system gives greater weight to well-designed randomized controlled trials and meta-analyses and progressively less weight to studies with weaker internal validity. When evidence was lacking, the panel determined that it was appropriate to reach conclusions based on expert opinion as long as it was acknowledged explicitly. The panel determined that consensus would be reached by majority vote. The strength of evidence and grade of recommendations were assigned according to the coding scheme in use by ASCO (Table 6).[8] However, for clarity these are supplemented by narrative descriptions of the state of the evidence.

The panel met on several occasions. After developing procedures and reviewing the evidence as presented by the TEC report, draft recommendations were prepared and discussed in a face-to-face meeting before the completion of a full draft report. All panel members reviewed all iterations of the guideline, contributing feedback to the levels of evidence and the systematic grading of the data supporting the recommendations.

Independent review from three external experts was obtained. The final content of the guidelines and the manuscript were reviewed and approved by the ASCO Health Services Research Committee and Board of Directors, as well as the Executive Committee of ASH.

RECOMMENDATIONS

General Recommendation

As in any medical situation, it is essential to give consideration to other correctable causes of anemia before proceeding to 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 B12 deficiency where indicated, and assess for occult blood loss. Coomb's testing may be appropriate for patients with chronic lymphocytic

Table 2. Assessment of Study Quality

First Author/Year	Blinding (required)	% of Excluded Subjects Below Specified Threshold?* (required)	Accounted for Excluded Patients?	Allocation Concealed?	Transfusion Trigger?	R/O Other Anemia Causes?†	Iron Status Confirmed?‡	Patients Blinded to Hb Levels?§
Mean/median baseline Hb ≤ 10 g/dL; adult patients								
Silvestris, 1995‖	Nonblinded	Yes	No/NS	Yes	NA¶	No	Yes	
Oberhoff, 1998	Nonblinded	No	No/NS	No/NS	No	No	No	
Case, 1993	**Double-blinded**	**Yes**	**No**	**No/NS**	**Yes**	**Yes**	**No**	**No/NS**
Henry, 1995	**Double-blinded**	**Yes**	**No**	**No/NS**	**Yes**	**Yes**	**No**	**No/NS**
Cascinu, 1994	**Double-blinded**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	
Kurz, 1997	**Double-blinded**	**Yes**	**No**	**Yes**	**Yes**	**No**	**Yes**	**No/NS**
Littlewood, 1999 (abstract/slides)	**Double-blinded**	**Yes**	**No/NS**	**No/NS**	**Yes**	**No**	**No**	**No/NS**
Mean/median baseline Hb ≤ 10 g/dL; pediatric patients								
Varan, 1999	Nonblinded	Yes	Yes	No/NS	Yes	No	No	
Leon, 1998	*Nonblinded#*	*Yes*	*Yes*	*No/NS*	*Yes*	*Yes*	*Yes*	*No/NS*
Porter, 1996	Double-blinded	No	No/NS	Yes	Yes	No	Yes	
Mean/median baseline Hb > 10 and < 12 g/dL; adult patients								
Markman, 1993	*Nonblinded*	*No*	*No*	*No/NS*	*Yes*	*NA***	*No*	
Dusenbery, 1994	*Nonblinded#*	*Yes*	*Yes*	*No/NS*	*Yes*	*No*	*Yes*	
Lavey, 1993	*Nonblinded*	*Yes*	*Yes*	*No/NS*	*NA¶*	*No*	*Yes*	
Wurnig, 1996	**Double-blinded**	**Yes**	**Yes**	**No/NS**	**Yes**	**Yes**	**No**	
Mean/median baseline Hb > 10 and < 12 g/dL; adult patients								
Henke, 1999	Nonblinded	Yes	Yes	No/NS	NA¶	No	Yes	
Quirt, 1996 (abstract)	Single-blinded	Yes	No/NS	No/NS	No	No	No	No/NS
ten Bokkel Huinink, 1998	Nonblinded	Yes	Yes	Yes	Yes	No	No	
Mean/median baseline Hb ≥ 12 g/dL; adult patients								
Gamucci, 1993	Nonblinded	Yes	No/NS	No/NS	NA¶	NA**	Yes	
Sweeney, 1998	Nonblinded	Yes	Yes	No/NS	NA¶	Yes	Yes	No/NS
Del Mastro, 1997	Nonblinded	Yes	Yes	Yes	Yes	NA	Yes	No/NS
Thatcher, 1999	Nonblinded	Yes	Yes	No/NS	Yes	Yes	No	No
Welch, 1995	Nonblinded	Yes	Yes	No/NS	Yes	NA	Yes	No/NS

NOTE. "Higher quality" trials in bold font; nonrandomized studies in italics. Source: Seidenfeld J, Aronson N, Piper M, et al: Uses of Epoetin for Anemia in Oncology: Evidence Report/Technology Assessment No. 30 (AHRQ Publication No. 01-E009). Rockville, MD, Agency for Healthcare Research and Quality, June 2001, p 87, Table 14.

Abbreviations: R/O, ruled out; Hb, hemoglobin; NA, not applicable; NS, not specified.

*Less than 5% of subjects were excluded in each study arm OR < 10% of subjects were excluded in each study arm AND the ratio between arms for the percentage of subjects excluded from the analysis was < 2:1.

†Ruled out all of the following: iron, B_{12}, and folate deficiencies, occult bleeding, and hemolytic anemia.

‡Epoetin arm supplemented OR serum iron, ferritin, and transferrin saturation all monitored and reported in results.

§Only evaluated for studies reporting quality-of-life outcomes.

‖Mean/median baseline hemoglobin not specified, but patients with baseline hemoglobin > 10 g/dL excluded.

¶Not applicable because transfusion outcomes were not reported.

#Historical controls only; all other nonrandomized studies used concurrent controls.

**Not applicable because enrollment limited to nonanemic patients.

leukemia; endogenous erythropoietin levels may predict response in patients with myelodysplasia.

Chemotherapy-Induced Anemia

Recommendation: **The use of epoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin concentration that has declined to a level ≤ 10 g/dL. RBC transfusion is also a treatment option depending on the severity of anemia or clinical circumstances.**

Level of evidence (status of evidence): II (several small and one larger [N = 375] placebo-controlled, randomized trials and nonblinded trials with generally consistent results favoring the use of epoetin).

Grade of recommendation: B.

Rationale: Improvement in hemoglobin concentration: Reviewed studies were grouped into three categories based on subjects' mean baseline hemoglobin concentration at study entry (≥ 12 g/dL, > 10 g/dL but < 12 g/dL, or ≤ 10 g/dL). This categorization was performed in order to provide recom-

Table 3. Hematologic Outcomes for Studies Grouped by Baseline Hemoglobin Levels

First Author/Year	Transfusion Trigger or mn Hb at Transf.*	Baseline Hb	Study Arm	No. Enrolled	No. Assessable	EPO Dose (U/kg/wk) Start	EPO Dose (U/kg/wk) Final
Mean/median baseline Hb ≤ 10 g/dL; adult patients							
Silvestris, 1995	NA	–†	Control	24	22	0	
		–†	Epoetin	30	27	450	900
Oberhoff, 1998	NA	10.3‡	Control	110	88	0	
		9.6‡	Epoetin	117	101	~450	
Case, 1993	**8.2**	**9.8**	**Control**	**76**	**74**	**0**	
	8.2	**9.5**	**Epoetin**	**81**	**79**	**450**	
Henry, 1995	**8.5**	**9.5**	**Control**	**65**	**61**	**0**	
	8.2	**9.8**	**Epoetin**	**67**	**64**	**450**	
Cascinu, 1994	**8.0**	**8.7**	**Control**	**50**	**49**	**0**	
		8.6	**Epoetin**	**50**	**50**	**300**	
Kurz, 1997	**8.0**	**9.85**	**Control**	**12**	**12**	**0**	
		9.88	**Epoetin**	**23**	**23**	**450**	**900**
Littlewood, 1999 (abstract/slides)	**NA**	**9.7**	**Control**	**124**	**115**	**0**	
		9.9	**Epoetin**	**251**	**244**	**450**	**900**
Mean/median baseline Hb ≤ 10 g/dL; pediatric patients							
Varan, 1999	6.0	8.48	Control	17	17	0	
		8.5	Epoetin	17	17	450	
Leon, 1998	*6.0*	*9.5*	*Control*	*25*	*25*	*0*	
		9.8	*Epoetin*	*25*	*25*	*750*	
Porter, 1996	8.0	9.4‡	Control	12	10	0	
		9.7‡	Epoetin	12	10	450	900
Mean/median baseline Hb > 10 and < 12 g/dL; adult patients							
Markman, 1993	*8.0*	*11.1‡*	*Control*	*46*	*40*	*0*	
		11.5‡	*Epoetin*	*17*	*16*	*350*	
Dusenbery, 1994	*9.5*	*11.1‡*	*Control*	*61*	*61*	*0*	
		10.3‡	*Epoetin*	*15*	*15*	*1,000*	*500*
Lavey, 1993	*NA*	*11.8*	*Control*	*20*	*20*	*0*	
		11.9	*Epoetin*	*20*	*20*	*900*	*450*
Wurnig, 1996	**8.5**	**10.5**	**Control**	**14**	**14**	**0**	
		11	**Epoetin**	**16**	**15**	**1,200**	
Henke, 1999	NA	12.3	Control	11	11	0	
		10.9	Epoetin 1	19	19	450	
		11.4	Epoetin 2	14	14	900	
Quirt, 1996 (abstract)	NA	10.7‖	Control	28	27	0	
		10.9‖	Epoetin	28	27	450	900
ten Bokkel Huinink, 1998	9.7	11.8‡	Control	34	33	0	
		12.0‡	Epoetin 1	46	45	450	225
		11.6‡	Epoetin 2	42	42	900	450
Mean/median baseline Hb ≥ 12 g/dL; adult patients							
Gamucci, 1993	NA	12.7	Control	17	17	0	
		12.2	Epoetin	21	21	450	
Sweeney, 1998	NA	10.7	Control	24	24	0	
		12.1	Epoetin	24	22	1,000	500
Del Mastro, 1997	8.0	13.1	Control	31	31	0	
		13	Epoetin	31	31	450	
Thatcher, 1999	8.5	13.4‡	Control	44	44	0	
	8.6	13.7‡	Epoetin 1	42	42	450	225
	8.0	13.6‡	Epoetin 2	44	44	900	450
Welch, 1995	8.5	12.8	Control	15	15	0	
	8.3	13	Epoetin	15	15	900	450

mendations regarding the appropriate starting threshold for epoetin and to account for different population/sex norms. Seven trials (five placebo-controlled) enrolled adult patients with baseline hemoglobin ≤ 10 g/dL (Table 3).[9-16] The difference in the percentage of patients who responded favorably to epoetin compared with controls (epoetin − control) ranged from 28% to 80%, with an absolute difference in change of mean hemoglobin level ranging between 1.6 to 3.1 g/dL. In five of these seven trials, the difference in hematologic outcomes achieved statistical significance.[9,10,12,13,15,16]

Table 3. (Cont'd)

First Author/Year	Response (%)	*P*	Difference in % Response (epo-control)	Hb Change (± SD)	*P*	Difference in Hb Change (epo-control)
Mean/median baseline Hb ≤ 10 g/dL; adult patients						
Silvestris, 1995	0.0					
	77.8		*77.8*			
Oberhoff, 1998	6.8					
	34.7	.0001	27.9			
Case, 1993	**13.5**			**0.33**		
	58.2		**44.7**	**2.3**	**.0001**	**1.97**
Henry, 1995	**6.6**			**0.4§ ± 1.7**		
	48.4	**< .0001**	**41.8**	**2.0§ ± 2.3**	**< .0001**	**1.60**
Cascinu, 1994	**2.0**			**−0.6**		
	82.0		**80.0**	**1.9**		**2.5**
Kurz, 1997	**0.0**			**0.22**		
	56.5	**.001**	**56.5**	**3.3**		**3.08**
Littlewood, 1999 (abstract/slides)	**19.1**			**0.9**		
	70.5	**.001**	**51.4**	**2.5**		**1.60**
Mean/median baseline Hb ≤ 10 g/dL; pediatric patients						
Varan, 1999				−0.07		
				1.71		1.78
Leon, 1998				*0.1*		
	72.0			*2.6*	*< .001*	*2.5*
Porter, 1996						
Mean/median baseline Hb > 10 and < 12 g/dL; adult patients						
Markman, 1993	*40.0*					
	87.5	*< .005*	*47.5*			
Dusenbery, 1994				*−0.8*		
				2.9	*.001*	*3.70*
Lavey, 1993	*5.0*			*0.0 ± 0.7*		
	80.0	*< .001*	*75.0*	*3.2 ± 1.78*	*< .001*	*3.2*
Wurnig, 1996						
					NS	
Henke, 1999				0.6 ± 1.4		
				3.2 ± 1.6	< .0001	2.6
				3.5 ± 1.2		2.9
Quirt, 1996 (abstract)				0.6		
				1.6		1.0
ten Bokkel Huinink, 1998						
Mean/median baseline Hb ≥ 12 g/dL; adult patients						
Gamucci, 1993				−1.5 ± 1.67		
				0.9 ± 1.32	< .005	2.4
Sweeney, 1998	0.0			0.29		
	45.5		45.5	1.55	.0012	1.26
Del Mastro, 1997				−3.1 ± 1		
				−0.8 ± 1.4	< .005	2.3
Thatcher, 1999	34.1			−3.4		
	52.4	< .05	18.3	−3.2		0.2
		.005	27.3	−3.3		0.1
Welch, 1995				−2.1		
				−1.3		0.8

NOTE. "Higher quality" trials in bold font; nonrandomized studies in italics. Source: Seidenfeld J, Aronson N, Piper M, et al: Uses of Epoetin for Anemia in Oncology: Evidence Report/Technology Assessment No. 30 (AHRQ Publication No. 01-E009). Rockville, MD, Agency for Healthcare Research and Quality, June 2001, p 91, Table 15.

Abbreviation: NS, not statistically significant.

*Single entry = transfusion trigger; multiple entries = mean hemoglobin levels at transfusion.

†Mean/median hemoglobin level at baseline not specified, but enrollment limited to patients with hemoglobin ≤ 10 g/dL.

‡The report provided only a median value, not a mean.

§Change in hemoglobin level calculated as change in hematocrit divided by 3.

‖Did not specify whether reported value is mean or median.

Table 4. Transfusion Outcomes for Studies Grouped by Baseline Hemoglobin Levels

First Author/Year	Transf Trigger or Mn Hb at Transf*	Baseline Hb	Study Arm	No. Enrolled	No. Assessable	EPO Dose (U/kg/week) Start	EPO Dose (U/kg/week) Final
Mean/median baseline Hb ≤ 10 g/dL; adult patients							
Silvestris, 1995	NA	–†	Control	24	22	0	
	–†		Epoetin	30	27	450	900
Oberhoff, 1998	NA	10.3‡	Control	110	88	0	
		9.6‡	Epoetin	117	101	~450	
Case, 1993	**8.2**	**9.8**	**Control**	**76**	**74**	**0**	
	8.2	**9.5**	**Epoetin**	**81**	**79**	**450**	
Henry, 1995	**8.5**	**9.5**	**Control**	**65**	**61**	**0**	
	8.2	**9.8**	**Epoetin**	**67**	**64**	**450**	
Cascinu, 1994	**8.0**	**8.7**	**Control**	**50**	**49**	**0**	
		8.6	**Epoetin**	**50**	**50**	**300**	
Kurz, 1997	**8.0**	**9.85**	**Control**	**12**	**12**	**0**	
		9.88	**Epoetin**	**23**	**23**	**450**	**900**
Littlewood, 1999 (abstract/slides)	**NA**	**9.7**	**Control**	**124**	**115**	**0**	
		9.9	**Epoetin**	**251**	**244**	**450**	**900**
Mean/median baseline Hb ≤ 10 g/dL; pediatric patients							
Varan, 1999	6.0	8.48	Control	17	17	0	
		8.5	Epoetin	17	17	450	
Leon, 1998	*6.0*	*9.5*	*Control*	*25*	*25*	*0*	
		9.8	*Epoetin*	*25*	*25*	*450*	
Porter, 1996	8.0	9.4‡	Control	12	10	0	
		9.7‡	Epoetin	12	10	450	900
Mean/median baseline Hb > 10 and < 12 g/dL; adult patients							
Markman, 1993	*8.0*	*11.1‡*	*Control*	*46*	*40*	*0*	
		11.5‡	*Epoetin*	*17*	*16*	*350*	
Dusenbery, 1994	*9.5*	*11.1‡*	*Control*	*61*	*61*	*0*	
		10.3‡	*Epoetin*	*15*	*15*	*1,000*	*500*
Mean/median baseline Hb > 10 and < 12 g/dL; adult patients							
Lavey, 1993	*NA*	*11.8*	*Control*	*20*	*20*	*0*	
		11.9	*Epoetin*	*20*	*20*	*900*	*450*
Wurnig, 1996	**8.5**	**10.5**	**Control**	**14**	**14**	**0**	
		11	**Epoetin**	**16**	**15**	**1,200**	
Henke, 1999	NA	12.3	Control	11	11	0	
		10.9	Epoetin 1	19	19	450	
		11.4	Epoetin 2	14	14	900	
Quirt, 1996 (abstract)	NA	10.7#	Control	28	27	0	
		10.9#	Epoetin	28	27	450	900
ten Bokkel Huinink, 1998	9.7	11.8‡	Control	34	33	0	
		12.0‡	Epoetin 1	46	45	450	225
		11.6‡	Epoetin 2	42	42	900	450
Mean/median baseline Hb ≥ 12; adult patients							
Gamucci, 1993	NA	12.7	Control	17	17	0	
		12.2	Epoetin	21	21	450	
Sweeney, 1998	NA	10.7	Control	24	24	0	
		12.1	Epoetin	24	22	1,000	500
Del Mastro, 1997	8.0	13.1	Control	31	31	0	
		13	Epoetin	31	31	450	
Thatcher, 1999	8.5	13.4‡	Control	44	14	0	
	8.6	13.7‡	Epoetin 1	42	42	450	225
	8.0	13.6‡	Epoetin 2	44	44	900	450
	8.5	12.8	Control	15	15	0	
Welch, 1995	8.3	13	Epoetin	15	15	900	450

Transfusion requirements: The difference in the percentage of adult patients requiring any transfusions between epoetin and control arms in the various trials ranged from 9% to 45% in favor of epoetin (Table 4). In four trials, the difference was reported as statistically significant[10,13,14,16]; however, many of these trials did not use intention-to-treat analysis. Some trials reported that patients receiving epoetin required fewer units of transfused RBCs compared with the control group; adults in the control groups of the trials required 0.6 to two units of RBCs per 4-week period, compared with 0.1 to two units for those randomized to epoetin, representing an absolute difference

Table 4. (Cont'd)

First Author/Year	% Transfused	*P*	Difference in % Transfused (control-epo)	RBC Units per Patient ± SD	*P*	RBC Units per Patient per 4 Weeks	Difference in RBC Units per Patient per 4 Weeks (control-epo)
Mean/median baseline Hb ≤ 10 gdL; adult patients							
Silvestris, 1995							
Oberhoff, 1998	40.9			0.6		0.6	
	25.7	–§	15.2	0.5	.044	0.5	0.1
Case, 1993	**36.8‖**			**1.6 ± 0.3**		**0.8**	
	28.6‖	**NS¶**	**8.5‖**	**0.9 ± 0.3**	**NS**	**0.5**	**0.3**
Henry, 1995	**68.9**			**4.0 ± 0.8**		**2.0**	
	53.1	**NS**	**15.8**	**4.0 ± 0.9**	**NS**	**2.0**	**0**
Cascinu, 1994	**57.1**			**1.8**		**0.8**	
	20.0	**.01**	**37.1**	**0.3**	**.01**	**0.1**	**0.7**
Kurz, 1997	**66.7**			**3.6**		**1.2**	
	21.7	**.009**	**45.0**	**1.4**		**0.5**	**0.7**
Littlewood, 1999 (abstract/slides)	**35.7‖**						
	23‖	**.0168**	**12.7‖**				
Mean/median baseline Hb ≤ 10 g/dL; pediatric patients							
Varan, 1999	47.1						
	5.9	.008	41.2				
Leon, 1998	*96*			*3.6*		*1.2*	
	16	*< .001*	*80.0*	*0.3*	*< .001*	*0.1*	*1.1*
Porter, 1996	100			13.0‡		3.3	
	90	NS	10.0	4.5‡	.01	1.1	2.2
Mean/median baseline Hb > 10 and < 12 g/dL; adult patients							
Markman, 1993	*22.5*						
	6.3	*NS*	*16.2*				
Dusenbery, 1994	*6.6*						
	0.0		*6.6*				
Mean/median baseline Hb > 10 and < 12 g/dL; adult patients							
Lavey, 1993							
Wurnig, 1996	**100**			**8.4**		**1.7**	
	53.3	**NS**	**46.7**	**2.1**	**< .01**	**0.4**	**1.3**
Henke, 1999							
Quirt, 1996 (abstract)	29.6			0.7			
	14.8	NS¶	14.8	0.2			
ten Bokkel Huinink, 1998	39.4			1.2		0.2	
	4.4	–§	35.0	0.3		0.1	0.1
	14.3		25.1	0.4		0.1	0.1
Mean/median baseline Hb ≥ 12; adult patients							
Gamucci, 1993							
Sweeney, 1998							
Del Mastro, 1997	6.5						
	0	NS¶	6.5				
Thatcher, 1999	59.1			6.1		0.9	
	45.2	< .05	13.9	3.8	< .01	0.6	0.3
	20.5	< .001	38.6	2.1	< .001	0.3	0.6
	53.3			5.4			
Welch, 1995	26.7	NS	26.6	4.0	NS		

NOTE. "Higher quality" trials in bold font; nonrandomized studies in italics. Source: Seidenfeld J, Aronson N, Piper M, et al: Uses of Epoetin for Anemia in Oncology: Evidence Report/Technology Assessment No. 30 (AHRQ Publication No. 01-E009). Rockville, MD, Agency for Healthcare Research and Quality, June 2001, p 97, Table 16.

Abbreviation: NS, not statistically significant.

*Single entry = transfusion trigger; multiple entries = mean Hb levels at transfusion.

†Mean/median hemoglobin level at baseline not specified, but enrollment limited to patients with hemoglobin ≤ 10 g/dL.

‡The report provided only a median value, not a mean.

§Calculated odds ratio for transfusion suggests a significant difference, as upper limit of 95% confidence interval is < 1.0 (see Meta-Analysis).

‖Measured from day 28 to end of study.

¶Calculated odds ratio for transfusion suggests no significant difference, as upper limit of 95% confidence interval is < 1.0 (see Meta-Analysis).

#Did not specify whether reported value is mean or median.

Table 5. Quality-of-Life Outcomes for Studies Grouped by Baseline Hemoglobin Levels: Comparisons Between Control and Epoetin-Treated Study Arms

				Overall QoL		Energy Level		Daily Activities			Other QoL	
Study	Treatment Arm	No. Assessable for Transfusion	No. Assessable for QoL	% Change	*P*	% Change	*P*	% Change	*P*	Other QoL Measure*	% Change	*P*
Mean/median baseline Hb < 10 g/dL												
Kurz, 1997	**Control**	**12**	**12**					**!14.5**		**Well-being**	**4.0**	
	Epoetin	**23**	**23**					**!6.5**	**NS**	**Well-being**	**!0.1**	**NS**
	Control	**12**	**12**							**Physical ability**	**8.0**	
	Epoetin	**23**	**23**							**Physical ability**	**8.3**	**NS**
	Control	**12**	**12**							**Social activities**	**12.8**	
	Epoetin	**23**	**23**							**Social activities**	**1.0**	**NS**
Henry, 1995	**Control**	**61**	**40**	**0.2**		**6.2**		**0.7**				
	Epoetin	**64**	**46**	**11.0**	**.013**	**8.8**	**NS**	**8.2**	**NS**			
Littlewood, 1999	**Control**	**115**	**108**	**NA**		**!5.8**		**!6.0**				
	Epoetin	**244**	**227**	**NA**	**< .01**	**7.8**	**< .001**	**7.3**	**< .01**			
	Control	**115**	**90**							**FACT-An: Anemia**	**!9.4**	
	Epoetin	**244**	**200**							**FACT-An: Anemia**	**14.4**	**< .01**
	Control	**115**	**90**							**FACT-An: Fatigue**	**!4.2**	
	Epoetin	**244**	**200**							**FACT-An: Fatigue**	**5.7**	**< .01**
	Control	**115**	**?**							**SF-36**	**NA**	
	Epoetin	**244**	**?**							**SF-36**	**NA**	**NS**
Leon, 1998	*Control*	*25*	*25*							*Kamofsky PS*	*1.4*	
	Epoetin	*25*	*25*							*Kamofsky PS*	*8.6*	*< .05*
Mean/median baseline Hb > 12 g/dL												
Sweeney, 1998	Control	24	24	6.3								
	Epoetin	22	22	19.1	.15, NS							
Welch, 1995	Control	15	?15	NA		NA		NA				
	Epoetin	15	?15	NA	NS	NA	NS	NA	NS			
Del Mastro, 1997	Control	31	26							PDI score	2.3	
	Epoetin	31	27							PDI score	6.0	NS

NOTE. "Higher quality" trials in bold font; nonrandomized studies in italics. Source: Seidenfeld J, Aronson N, Piper M, et al: Uses of Epoetin for Anemia in Oncology: Evidence Report/Technology Assessment No. 30 (AHRQ Publication No. 01-E009). Rockville, MD, Agency for Healthcare Research and Quality, June 2001, p 109, Table 22.

Abbreviations: QoL, quality of life; FACT-An, Functional Assessment of Cancer Therapy–Anemia; SF-36, Short Form 36; PS, performance scale; PDI, Psychological Distress Inventory.

*In order to accommodate several "other" QoL instruments or different statistical testing results, study control and treatment arms may be listed more than once.

range of zero to 0.7 units of RBCs. The differences in transfused units were statistically significant in two trials.[10,14]

Meta-analysis confirmed a reduction in the relative odds of transfusion for those randomized to epoetin. The meta-analysis conducted by the TEC (see Appendix B), when applied to those randomized controlled studies that used subcutaneous epoetin and reported numbers of patients transfused, yielded a cumulative odds ratio of 0.38 (95% confidence interval [CI], 0.28 to 0.51), suggesting that use of epoetin decreases the relative odds of receiving a RBC transfusion by an average of 62% (Table 7). When the meta-analysis was restricted to data from studies meeting TEC criteria for higher quality, the odds ratio remained significant at 0.45 (95% CI, 0.33 to 0.62).

The *relative* odds of requiring transfusion can be translated into an *absolute* risk reduction, where this also depends on the baseline probability that the patient will require a transfusion. The TEC estimated the baseline risk of transfusion by using the control arms of trials that reported the proportion of patients transfused by 12 weeks of follow-up; this was applied to the relative risk reductions to determine absolute benefit. Using this approach, the TEC calculated an absolute benefit that corresponded to a number-needed-to-treat of 4.4 (95% CI, 3.6 to 6.1) in order to benefit one patient. (The number-needed-to-treat is the reciprocal of the absolute risk difference.) The estimated number-needed-to-treat, derived only from studies meeting TEC criteria for higher quality, was 5.2 (95% CI, 3.8 to 8.4). That number would be higher if the risk of requiring a transfusion were lower than that assumed by the TEC.

Symptomatic improvement: Whether improvement in hemoglobin and reduction in transfusions with epoetin therapy translate into clinically meaningful symptomatic improvement requires further study. Some studies that have examined functional status or overall quality of life have pro-

Table 6. Levels of Evidence and Grade of Recommendations

Level	Type of Evidence
I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and low false-negative errors (high power)
II	Evidence obtained from at least one well-designed experimental study; randomized trials with high false-positive and/or -negative errors (low power)
III	Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled single-group, pre-post, cohort, time, or matched case-control series
IV	Evidence from well-designed, nonexperimental studies such as comparative and correlational descriptive and case studies
V	Evidence from case reports and clinical examples
Grade	**Grade of Recommendations**
A	There is evidence of type I or consistent findings from multiple studies of type II, III, or IV
B	There is evidence of type II, III, or IV and findings are generally consistent
C	There is evidence of type II, III, or IV but findings are inconsistent
D	There is little or no systematic empirical evidence

duced inconsistent results or rely on data of variable methodologic quality (Table 5). Threats to validity of these trials include higher than usual dropout rates; among the trials that include quality of life as an outcome, 10% to 40% of the patients were not assessable at the end of the study. Quality-of-life studies can be difficult to conduct and, unlike transfusion or hemoglobin outcomes, depend on respondents completing surveys at distant time points. Therefore, missing data in quality-of-life studies does not necessarily represent neglect on the part of investigators. The largest randomized trial to date (total N = 375), though supporting a significant improvement in quality of life in the epoetin arm, does suffer from the problem of missing data, thus threatening the validity of the inferences that can be made.[16] It is unclear whether this missing data had any significant effect on the distribution of quality-of-life outcomes between the treatment arms.[17] Ideally, randomized studies of quality of life would be analyzed using intention-to-treat principles; however, research to identify proper methods for handling nonrandom missing data in quality-of-life studies is ongoing.[17] Many studies used quality-of-life instruments that have only recently been introduced.[18] Since the experience with these instruments is limited, research defining minimum clinically meaningful changes in quality-of-life scores is ongoing. In particular, psychometric research is underway to quantify the clinical impact associated with changes in the quality of life measured by one popular instrument, the Functional Assessment of Cancer Therapy–General questionnaire.[19] Because the trials on which these conclusions are based are only of fair quality regarding quality-of-life outcomes (due to limitations in reporting and conduct of the investigations), the probability of false-positive and false-negative results cannot be assumed to be low (level II evidence, see Table 6). In making recommendations for use of epoetin, the evidence for improvements in hemoglobin and transfusions outcomes was considerably stronger then that for quality-of-life outcomes. Replication of quality-of-life improvements that are demonstrated to be clinically meaningful in other well-designed clinical trials would improve the strength of evidence and further support this recommendation.

Dose and dose schedule of epoetin: Please refer to discussion below regarding optimal dose and dose schedule for administering epoetin.

Recommendation: **For patients with declining hemoglobin levels but less severe anemia (those with hemo-**

Table 7. Summary: Meta-Analysis of the Effect of Epoetin on Transfusion

Analysis of:	Odds Ratio*	95% CI	No. Needed to Treat	95% CI
All randomized studies, subcutaneous epoetin delivery	0.380	0.282-0.513	4.4	3.6-6.1
All randomized studies, subcutaneous epoetin delivery, higher quality (300-450 weekly dose)	0.453	0.330-0.621	5.2	3.8-8.4
All randomized studies, subcutaneous epoetin delivery, lower quality (300-450 weekly dose)	0.137	0.060-0.313	2.6	2.1-3.8

NOTE. Source: Seidenfeld J, Aronson N, Piper M, et al: Uses of Epoetin for Anemia in Oncology: Evidence Report/Technology Assessment No. 30 (AHRQ Publication No. 01-E009). Rockville, MD, Agency for Healthcare Research and Quality, June 2001, p 107, Table 21.

*Odds of transfusion for epoetin-treated patients relative to the odds of transfusion for control patients. The odds of transfusion for the combined control study arms (from those studies with a known followup duration) was estimated using a logistic normal model and the point estimate for a 12-week follow-up duration (Hasselblad, 1998). For the number needed to treat for all randomized studies that delivered epoetin subcutaneously, the estimate was 0.99, corresponding to a probability of 0.498 (odds=probability of transfusion/(1–probability of transfusion)). From this and the summary odds ratio, the odds of transfusion for the combined epoetin-treated study arms was calculated as 0.380*0.99 or 0.376, corresponding to a probability of 0.273. Number needed to treat is equal to the reciprocal of the absolute risk reduction (Laupacis et al, 1988) or 1/(0.498 to 0.273) = 4.44. The 95% confidence limits are 1/(0.498 to 0.216) = 3.55 to 1/(0.498 to 0.335) = 6.13.

globin concentration < 12 g/dL, but who never have fallen below 10 g/dL), the decision of whether to use epoetin immediately or to wait until hemoglobin levels fall closer to 10 g/dL should be determined by clinical circumstances. RBC transfusion is also a therapeutic option when warranted by severe clinical conditions.

Level of evidence (status of evidence): II (several small [N < 100], randomized and nonrandomized, mostly nonblinded studies consistently favoring epoetin but with inconsistent statistical significance for reported outcomes across the studies).

Grade of recommendation: C.

Rationale: Improvement in Hemoglobin concentration: Among trials that enrolled patients with this concentration of hemoglobin at baseline, there is mixed evidence that epoetin achieves a statistically significant improvement in hemoglobin concentrations (Table 3). Seven trials[20-26] involving patients with a starting hemoglobin level of 10 to 12 g/dL reported that the difference in the percentage of patients achieving a designated hematologic response to epoetin versus control ranged from 48% to 75%, with a mean difference in changes in hemoglobin of 1.0 to 3.7 g/dL. The difference in response rate, or change in mean hemoglobin, all favoring epoetin, was statistically significant in four out of seven trials.[20-23] None of these four trials met the TEC criteria for higher quality (see Appendix B). In the only trial meeting these criteria,[24] there was no statistically significant difference reported for change in hemoglobin level.

Transfusion requirements: Of the five trials that used as an outcome the percentage of patients requiring transfusion,[21,22,24-26] the range of the difference in percent transfused was from 7% to 47%, all favoring epoetin (Table 4). The difference in the proportion of patients requiring transfusion was statistically significant in one of the five trials.[25] Of the three studies that reported the number of units transfused, the differences between epoetin and control groups over a 4-week period ranged between 0.1 and 1.3 units per patient, all favoring epoetin. One trial[24] reported that the reduction in transfused units was statistically significant, but the other two did not discuss statistical significance.[25,26] In this trial,[24] the dose of epoetin was among the highest used, 1,200 U/kg/wk.

The meta-analysis performed by the TEC, which pooled randomized trials for patients with all levels of hemoglobin at entry, did show a reduction in the relative odds of receiving a transfusion for those treated with epoetin. However, because study quality may confound the effect of baseline hemoglobin on the odds of transfusion, and because all of the studies considered to be of "higher quality" by the TEC enrolled patients with baseline hemoglobin ≤ 10 g/dL, the meta-analysis was unable to test for a specific effect of baseline hemoglobin on the odds of transfusion.

Symptomatic improvement: No trials reported data to evaluate whether epoetin improves symptoms or quality of life specifically among patients with baseline hemoglobin levels of 10 to 12 g/dL (Table 5). Although one randomized trial reporting significant quality-of-life improvement with epoetin included patients with baseline hemoglobin levels of 10 to 12 g/dL, this group represented only 16% of all patients studied and outcomes were not presented for quality of life stratified by hemoglobin level.[16]

The panel's ability to support a definitive recommendation is limited by the heterogeneity of the statistical significance of response outcomes. This heterogeneity may, in fact, be due to the small size of these trials. It is noteworthy, however, that the *relative* improvement in outcomes observed in these studies, although often not statistically significant, is consistent with the *relative* rates seen for patients with more severe anemia (baseline hemoglobin < 10 g/dL), and in all studies, including those that were placebo-controlled, the direction of the effect always favored epoetin. Unfortunately, the meta-analysis accounts for small sample sizes by pooling the data from many trials, but it could not be used to isolate the effect of epoetin on transfusion outcomes for specific baseline hemoglobin levels. The lower *absolute* risk for transfusions among patients with a baseline hemoglobin level of 10 to 12 g/dL limits the absolute probability of benefit (and the statistical power of published trials to demonstrate such a benefit) in this population.

The recommendation for use of epoetin in patients with baseline hemoglobin levels of 10 to 12 g/dL based on clinical judgment is premised on the assumption that patients with specific comorbid conditions face a higher absolute probability of anemia or a higher risk of adverse events related to this degree of anemia than do other patients with this hemoglobin concentration. Examples of patients at this higher degree of absolute risk, who may be considered reasonable candidates for this agent, based on clinical judgment, include but are not limited to elderly individuals with limited cardiopulmonary reserve or patients with underlying coronary artery disease and symptomatic angina.

Recommendation: **The recommendations are based on evidence from trials in which epoetin was administered subcutaneously thrice weekly. The recommended starting dose is 150 U/kg thrice weekly for a minimum of 4 weeks, with consideration given for dose escalation to 300 U/kg thrice weekly for an additional 4 to 8 weeks in those who do not respond to the initial dose. Although supported by less strong evidence, an alternative weekly dosing regimen (40,000 U/wk), based on common clinical**

practice, can be considered (see discussion below). Dose escalation of weekly regimens should be under similar circumstances to thrice weekly regimens.

Level of evidence (status of evidence): II (19 comparative, controlled trials involving a total of 1,618 patients, of which 15 trials were randomized and six were either blinded or placebo-controlled; epoetin was administered three times weekly in the treatment arm for all controlled trials reviewed except one, where it was administered daily).

Grade of recommendation: B.

Rationale: Dosing interval: Most trials were parallel group designs comparing subcutaneous epoetin with transfusion alone. Two nonblinded, randomized trials used three-arm designs to compare two different doses of subcutaneous epoetin to transfusion alone. Three studies used intravenous epoetin.[10,13,23] Of the 17 two-arm subcutaneous epoetin trials, 13 were randomized and six were either blinded or placebo-controlled. In studies using subcutaneous epoetin, the most common initial dose was 150 U/kg administered three times weekly (the most common higher starting dose was 300 U/kg three times weekly). The dose range was 300 to 450 U/kg/wk in 12 trials and 700 to 1,000 U/kg/wk in five trials. The two three-arm trials compared initial doses of 450 and 900 U/kg/wk with controls.[25,27] Four of the six trials designated as higher quality by the TEC used 450 U/kg/wk as the starting dose of epoetin. All of these trials administered epoetin three times weekly. One study administered 5,000 units daily, regardless of weight or body size.[14]

Because the multiple-arm studies detecting improvements in hemoglobin and transfusion outcomes favoring epoetin have based dosing on a three times weekly regimen, the most compelling evidence for use of epoetin supports a thrice-weekly regimen. However, for convenience of patients, common clinical practice has evolved to once-weekly dosing. Pharmacokinetic studies suggest that once-weekly dosing intervals with higher doses of epoetin achieves similar rises in reticulocyte counts when compared with three-times-weekly intervals.[28,29] Though both are randomized controlled trials, they are small ($<$ 40 persons), involve normal volunteers, and are descriptive in nature (not powered to detect statistical significance). A large, nonrandomized, community-based study using once-weekly dosing has reported improvements in hemoglobin and quality of life similar to those with thrice-weekly dosing.[30] In addition to lacking a concurrent control comparison, the study has been criticized because of lack of adjustment for potential baseline confounding variables and for its handling of the relatively large dropout rate.[31] No randomized controlled trials have yet been reported to substantiate or contradict the outcome of once-weekly epoetin versus thrice-weekly treatment. A randomized trial comparing once-weekly epoetin dosing with a placebo control arm has completed accrual and was presented as an abstract in May 2002.[32] The preliminary results suggest that weekly epoetin increases hemoglobin concentrations and decreases transfusion rates compared with placebo among patients receiving chemotherapy.

Another pharmaceutical erythropoiesis-stimulating protein that requires less frequent dosing (darbepoetin alfa) is also being tested in randomized trials to confirm the data from dose-finding studies,[33] which suggest it can be administered effectively as infrequently as once per chemotherapy cycle. Comparative studies are in progress to evaluate darbepoetin in patients with cancer. Table 8 lists the ongoing studies and preliminary reports available to the panel at the time of this writing regarding darbepoetin.[34-38]

The preliminary results for the effectiveness of darbepoetin alfa from these studies are sufficiently promising to justify ongoing assessment by the panel. Preliminary results not yet reported as published peer-reviewed studies can be a useful complement to fully published studies when making a clinical recommendation. However, because preliminary results are the only data available in this case, and reasonable alternative therapy already exists, the panel chose the prudent course of waiting until such studies are published before committing to a clinical recommendation about darbepoetin. The panel will add to the current recommendations in a timely manner once such data become available.

Dose escalation and duration: In studies using subcutaneous epoetin, the most common initial dose was 150 U/kg administered three times weekly. The most common higher starting dose was 300 U/kg three times weekly. Among studies using subcutaneous epoetin at these lower dose ranges (300 to 450 U/kg/wk), four trials increased the dose for nonresponders after a fixed period of time, four decreased the dose for responders, and four used a fixed and continuous dose throughout treatment. The criteria for dose escalation were typically a combination of failure to achieve at least a 1 g/dL rise over baseline hemoglobin and a reticulocyte count less than 40,000/μL by the fourth week of treatment. Treatment duration was more than 20 weeks in six trials, 12 to 16 weeks in eight trials, and $\leq$ 10 weeks in five trials. Heterogeneity of dosing limits comparability among trials.

Weight-based versus uniform dosing: Most trials reviewed by the TEC utilized weight-based epoetin dosing regimens (Table 2). Recently, some single-arm studies have shifted to uniform dosing (10,000 units three times weekly, 40,000 units once weekly).[30,39] No randomized trials have

Table 8. Summary of Preliminary Data From Randomized Trials of Darbepoetin

First Author/Year	Treatment Arm	Blinding	No. of Patients	Outcomes Assessed*
Kotasek, 2000	Placebo	Double	24	a,c
	NESP 1		32	
	NESP 2		17	
	NESP 3		46	
Pirker, 2001	Placebo	Double	158	a,b,c,d
	NESP 1		156	
Hedenus, 2001	Placebo	Unknown	11	a,c
	NESP 1		11	
	NESP 2		22	
	NESP 3		22	
Glaspy, 2001	Epoetin (tiw)	Unknown	53	a,c,d
	NESP (weekly) 5 doses		216	
	Epoetin (weekly)		32	
	NESP (q 2 week) 4 doses		126	
Kotasek, 2002	Placebo (q 3 week)	Double	51	a,b,c
	NESP (q 3 week) 6 doses		198	
	Placebo (q 4 week)		31	
	NESP (q 4 week) 4 doses		125	

*Outcomes assessed: a, change in hemoglobin; b, transfusion requirements (number of units); c, proportion of patients transfused; d, quality of life.

directly compared weight-based dosing with uniform dosing.

Subcutaneous versus intravenous administration: Virtually all studies evaluating the effectiveness of epoetin have used subcutaneous administration. Intravenous administration has been used in only three studies (98 patients),[23,24,40] limiting the ability to make a specific recommendation. No study included in this report compared intravenous with subcutaneous administration. Evidence from hemodialysis patients suggests that subcutaneous administration is 30% to 50% more efficient than the intravenous route.[41,42]

Recommendation: **Continuing epoetin treatment beyond 6 to 8 weeks in the absence of response (eg, < 1 to 2 g/dL rise in hemoglobin), assuming appropriate dose increase has been attempted in nonresponders, does not appear to be beneficial. Patients who do not respond should be investigated for underlying tumor progression or iron deficiency. As with other failed individual therapeutic trials, consideration should be given to discontinuing the medication.**

Level of evidence (status of evidence): Not applicable (N/A) (expert opinion based on indirect evidence and biologic inference).

Grade of recommendation: Panel consensus.

Rationale: A number of weeks may be required to observe a response to treatment with epoetin, but available studies suggest a low probability of response if hemoglobin/hematocrit concentrations have not risen significantly by 6 to 8 weeks. In the best trials that have consistently reported hemoglobin response criteria, response has been defined as a rise in hemoglobin of at least 2 g/dL at study end. It is reasonable to suggest that responders would achieve a hemoglobin improvement of at least 1 g/dL by 8 weeks from initiation of epoetin. For patients not responding, it is advisable to investigate for tumor progression. In patients with myelodysplasia, it is reasonable to repeat the bone marrow analysis if patients respond initially to epoetin and then develop worsening anemia to ensure that the myelodysplasia is not evolving toward a more malignant state. Likewise, the clinician should consider iron deficiency, intercurrent infection, blood loss, and hemolysis as other causes of anemia. Similarly, a recent report suggests that antibodies directed against erythropoietin causing pure RBC aplasia can develop in patients with anemia of chronic renal failure treated with epoetin.[43] Whether this phenomenon will be observed in cancer patients receiving chemotherapy or in patients with hematologic malignancies receiving epoetin for shorter duration is not known. There is no empirical evidence to support these suggestions, but it can be reasoned that obtaining this information would be useful in recognizing the need to discontinue epoetin therapy and to revise the patient's treatment plan.

Recommendation: **Hemoglobin levels can be raised to (or near) a concentration of 12 g/dL, at which time the dosage of epoetin should be titrated to maintain that level or restarted when the level falls to near 10 g/dL. Insufficient evidence to date supports the "normalization" of hemoglobin levels to above 12 g/dL.**

Level of evidence (status of evidence): N/A (expert opinion based on indirect evidence and biologic inferences).

Grade of recommendation: Panel consensus.

Rationale: All of the trials conducted to date have focused on raising the hemoglobin level to a maximum of 12 g/dL. Clinical trials have generally mandated that the dosing of epoetin be suspended until the hemoglobin has fallen to a level indicative of the need to restart therapy. While there are some observational data to suggest that the benefits of epoetin continue to improve with rising hemoglobin levels,[39,44] no randomized controlled studies in cancer have been conducted to validate the additional benefit of routinely improving hemoglobin above the level of 12 g/dL.

It should also be considered that in a large (N = 1,233) prospective clinical trial of patients with chronic renal failure and concurrent cardiac disease treated with epoetin, patients randomized to achieve a target hematocrit of 42% were shown to have higher mortality than those randomized to a target of 30%.[45] The trial was designed with 90% power to detect a 20% difference (two-sided) in survival or time to first nonfatal myocardial infarction between the two groups using intention-to-treat analysis. It was discontinued at its third interim analysis when patients in the normal hematocrit group were found to have a higher event rate (relative risk, 1.3; 95% CI, 0.9 to 1.8) than patients in the low-hematocrit target group. Although this result was not statistically significant, the study monitors believed that it was very unlikely that continued accrual to the study would reveal a benefit for the normal hematocrit group. As well, in posthoc analysis it was shown that those in the normal hematocrit group had less adequate dialysis and greater iron chelation therapy than the control group, which may have contributed to the higher mortality rates.

A substantial proportion of patients who receive epoetin report adverse events. Of the 10 studies reporting any adverse event among the 1,155 patients, the rate was 46% among the controls and 56% among the epoetin-treated groups.[3] These complications, however, are often reasonably ascribable to concurrent treatments or to the underlying disease. Most of the trials examined for this guideline evaluated relatively few patients. Trials powered to detect specified differences in main outcomes may not have sufficient power to detect adverse events that are less frequent. With relatively few patients in each study arm, differences in adverse events in these trials are unlikely to achieve statistical significance.

Recommendation: **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.**

Level of evidence (status of evidence): N/A (expert opinion based on indirect evidence and biologic inferences).

Grade of recommendation: Panel consensus.

Rationale: Clinical experience and informal reports suggest that correcting iron deficiency can obviate the need for epoetin, enhance its effectiveness, and explain the emergence of nonresponse over time. These assumptions have not been tested in controlled trials, nor have studies formally tested which monitoring protocols maximize sensitivity, specificity, and cost-effectiveness. No data exist to support the use of endogenous erythropoietin levels to guide therapy outside of myelodysplastic syndrome.

Myelodysplasia, Multiple Myeloma, Non-Hodgkin's Lymphoma, and Chronic Lymphocytic Leukemia (anemia primarily related to hematologic malignancy)

Recommendation: **There is evidence from one well-designed, placebo-controlled, randomized trial that supports the use of epoetin in patients with anemia associated with low-risk myelodysplasia, but there are no published high-quality studies to support its use in anemic myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients in the absence of chemotherapy. Treatment with epoetin for myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anemia should follow the recommendations outlined in the previous section.**

Level of evidence (status of evidence): II (one placebo-controlled, randomized trial in myelodysplasia involving 87 patients and using a credible clinical outcome measure; five randomized trials with important design or reporting flaws for patients with lymphatic malignancy and/or myeloma not necessarily receiving chemotherapy at enrollment).

Grade of recommendation: B.

Rationale: In order to provide a recommendation for patients who would be anemic whether or not they were receiving chemotherapy for their malignancy, the TEC reviewed six trials that reported patients with hematologic malignancies enrolled regardless of whether or not chemotherapy was given. Trials of epoetin for patients with these diseases requiring treatment with chemotherapy at enrollment were reviewed in the sections pertaining to chemotherapy-associated anemia. Two additional randomized, double-blinded, placebo-controlled trials for patients with multiple myeloma and/or hematologic malignancies receiving chemotherapy have been published since the TEC review.[46,47] These trials appear to show similar results to

those reviewed by the TEC for chemotherapy-associated anemia. Of the six trials in patients with hematologic malignancies where chemotherapy was not required for enrollment, only the trial for patients with myelodysplastic syndrome[48] restricted enrollment to patients to whom no chemotherapy was given. The other five trials for patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia all include patients receiving concurrent or recent chemotherapy for their disease.[49-53] Three of these trials specify that between 79% and 88% of the patients received concurrent chemotherapy.[50,51,53] No trials have been reported for patients with anemia related to these diseases in the absence of chemotherapy. Patients with myeloid malignancies have typically been excluded from epoetin trials; consequently, no evidence is available to make a recommendation in this area.

Myelodysplasia: The effectiveness of epoetin has been examined in one randomized, double-blind, placebo-controlled trial involving 87 patients with myelodysplasia.[48] Significantly more patients who were treated with epoetin achieved a hematologic response compared with placebo controls (37% *v* 11%; $P = .007$). Patients received a fixed epoetin dose of 1,050 U/kg/wk. Nearly 50% of patients in both groups had refractory anemia. In a subgroup analysis, 50% of the patients with refractory anemia in the epoetin group experienced a response, whereas only 6% of patients with refractory anemia in the control group responded ($P = .007$). A partial response was defined as a 1- to 2-g/dL rise in hemoglobin. Surprisingly, for patients with refractory anemia with ringed sideroblasts in the respective arms, the response rates were 38% versus 18% ($P = .6$), and for patients with refractory anemia with excess blasts they were 17% versus 11% ($P = 1.0$). Neither transfusion requirements nor quality-of-life outcomes were reported. Baseline serum erythropoietin levels greater than 200 mU/L predicted for nonresponse. The results of this study are limited in terms of generalizability because the study included patients with low-risk myelodysplasia (mostly refractory anemia) and the definition of hematologic response was not standard. In addition, there was inadequate information on baseline vitamin B12, iron status, or use of iron supplements, which may be more important in this disease than cancer chemotherapy. On the basis of the evidence, a reasonable approach in low-risk myelodysplasia (refractory anemia) patients with a low endogenous erythropoietin level (eg, < 200 mU/L) involves an 8-week trial of epoetin. No randomized trials have evaluated alternate dosing regimens of epoetin for patients with myelodysplasia.

Myeloma, lymphoma, and chronic lymphocytic leukemia: The TEC review identified two randomized controlled trials that examined the use of epoetin in myeloma only,[49,50] a randomized study of patients with chronic lymphocytic leukemia that is available only as an abstract,[51] and two randomized trials involving myeloma and non-Hodgkin's lymphoma/chronic lymphocytic leukemia.[52,53] The combination of diverse disease groups in the latter trials complicates interpretations. Several publications from an additional randomized controlled trial[54-56] were excluded from detailed TEC analysis because of incomplete reporting by the investigators.

In the five trials reviewed by the TEC, all patients were adults with mean or median hemoglobin levels ≤ 10 g/dL, and sample sizes were generally small (ranging from 24 to 221). Two trials were placebo-controlled and blinded; however, neither provided information regarding number of patients receiving concurrent treatment.[49,51] Epoetin was administered subcutaneously in all trials. Three trials used a dose of 150 U/kg three times per week, one in a continuous fixed-dose regimen[51] and two with an increasing-dose regimen where 300 U/kg was the final dose.[49,50] Two trials[52,53] were multiarm trials that compared outcomes for different regimens of epoetin administration. A five-arm trial of 8 weeks' duration compared fixed and continuous epoetin doses ranging from 100 to 1,000 U/kg/wk (administered to achieve specified hemoglobin targets) to a control group managed by transfusion alone.[52] A three-arm trial of 24 weeks' duration compared a start/stop regimen (to achieve a target hemoglobin level not requiring transfusion) starting at 1,000 U/kg/wk, an increasing-dose regimen starting at 200 U/kg/wk, and a control group managed by transfusion alone.[53]

All five trials reported the percentage of patients who had a hematologic response. More patients randomized to epoetin responded (31% to 75% for those given ≥ 200 U/kg/wk) compared with control (7% to 23%).[3] Of the three trials that reported the magnitude of change in hemoglobin levels, however, a difference was reported as statistically significant only in the study published as an abstract.[51] A second trial reported a statistically significant ($P = .02$) difference in hemoglobin favoring the epoetin group, but it did not report the magnitude of hemoglobin change for either arm.[49] The five-arm trial, which reported median hemoglobin increases per week by dosage level, reported small but statistically significant differences for all but the 100-U/kg/wk dose.[52] A meta-analysis of these five trials was not performed.

Transfusion outcomes were reported in only the two multiarm trials.[52,53] One trial reported significantly fewer patients transfused in the epoetin arms than in the control group (58% to 64% *v* 82%) but no significant reduction in the number of units of RBCs transfused.[53] The other trial reported fewer patients transfused (15% to 19% *v* 27%) and

fewer units transfused (0.2 to 0.5 *v* 0.9) in the arms given ≥ 500 U/kg/wk of epoetin, but a test of statistical significance was not reported for either outcome.[52] Both trials were nonblinded and enrolled patients with multiple myeloma and non-Hodgkin's lymphoma. Neither had a specified transfusion trigger, and there were significant discrepancies between the trials in baseline hemoglobin levels, transfusion dependency at entry, and duration of treatment.

With one exception,[51] no studies reported outcomes with respect to quality of life, symptoms of anemia, number of days in hospital, or changes in performance status. The study of patients with chronic lymphocytic leukemia reported significantly improved energy levels in the epoetin-treated group but did not describe the quality-of-life instrument or other methodologic details for evaluating the validity of the data.[51] The abstract reported that epoetin-treated patients who achieved a hematocrit of 38% showed significant improvements in energy, self-rated health, physical function, role function/physical, role function/emotional, social function, and mental health. There is inadequate detail in the abstract to evaluate whether results were confounded by or adjusted for tumor response, rise in neutrophil count, or the administration of iron, B12, or folic acid supplements.

Methodologic and reporting weaknesses exist for all of the studies involving anemia directly related to myeloma, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia and not induced or complicated by chemotherapy, limiting the strength of the evidence supporting these recommendations.

Recommendation: **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 a rise in hemoglobin is not observed after chemotherapy, epoetin should be used in accordance with the criteria outlined above for chemotherapy-associated anemia if clinically indicated. Blood transfusion is also a therapeutic option.**

Level of evidence (status of evidence): IV (indirect evidence generalized from studies involving other patient populations).

Grade of recommendation: C.

Rationale: Although there is no direct evidence for this recommendation, it is reasonable to extrapolate from the evidence cited above for chemotherapy-induced anemia as a basis for guiding therapy in this patient population.

RESEARCH AGENDA

Future research priorities for epoetin include not only the need to answer specific questions about the effectiveness, indications, and optimal treatment protocols for using the drug and to explore similar questions for newer erythropoiesis stimulants, but also the need to incorporate specific design features to address the limitations of prior trials. For example, it is important for studies to have adequate sample size to achieve sufficient statistical power to demonstrate a significant effect on outcomes, including secondary outcomes such as quality of life. Prospective plans for handling dropouts/missing data for outcomes anticipated to be problematic (quality of life, adverse reactions) should be incorporated.

Past trials have sometimes been deficient in defining and documenting critical information about the study population and its baseline health status and clinical history, details of treatment protocols for each study group, especially concomitant chemotherapy, and specification and validation of outcome measures relied on to infer an effect. Even some randomized trials have not been attentive to using (or documenting) proper methods of randomization, concealment of allocation, and blinding. Documentation of dropouts and other sources of attrition, including the reasons for withdrawal and the number of cases, has also been inadequate. Trials examining the effect of epoetin on quality of life have used recently developed instruments whose validity is still being established, sometimes with incomplete documentation of their content, performance characteristics, or clinical relevance. Statistical analyses have often disregarded intention-to-treat analysis or have engaged in excessive posthoc data analysis, which for statistical reasons tends to increase the identification of significant associations by chance.

Unanswered questions remain as to whether increases in hemoglobin to levels above 12 g/dL are of clinical benefit. One complicating factor in defining the optimal target hemoglobin level is the recognition that the normal ranges for hemoglobin levels in men and women are different and, hence, that sex-specific norms are needed. Ideally, studies would define entry criteria based on these norms and report outcomes based on hemoglobin level at study entry. Uncontrolled cohort studies suggest that rises in hemoglobin above the 12-g/dL point are associated with a continued, though attenuated, improvement in quality-of-life parameters.[39,44] Randomized controlled trials evaluating the optimal hemoglobin target will be required to answer this question. Additional studies should also be initiated to define better the appropriate hemoglobin level at which to begin epoetin therapy based

on sex-specific norms mentioned above. One trial design which may address this would be a direct randomized comparison of one group for which treatment begins as soon as they go below hemoglobin of 12 g/dL versus another group for which treatment does not begin until they get close to 10 g/dL (definitely below 10.5 g/dL).

Further research regarding the effectiveness of once-weekly dosing regimens is necessary. While shown to be effective in a large, single-arm, nonrandomized study,[30] once-weekly regimens have not been compared in a randomized study with appropriate three-times-weekly regimens or placebo. Optimally, epoetin or other erythropoiesis-stimulating pharmaceuticals intended to be given weekly or less frequently will be directly compared with three-times-weekly administration programs for effectiveness in randomized trials. Such phase III randomized trials appear to be underway for both epoetin and darbepoetin.

The proper role for iron supplementation in epoetin-treated patients is unknown. Aside from monitoring iron levels, more recent clinical experience has suggested that rises in hypochromic RBCs and high levels of soluble serum transferrin receptor may indicate the early need for iron supplementation. The optimal form of iron is unsettled as well. When iron supplementation was reported in the clinical trials reviewed, oral supplementation was most common. Oral iron is associated with gastrointestinal side effects, whereas hypersensitivity reactions limit parenteral use. Newer forms of parenteral iron, associated with significantly fewer anaphylactic reactions, are now being used to treat patients with severe iron deficiency. With this in mind, the optimal schedule for iron repletion is unclear, with some clinicians favoring complete replacement at baseline and others advocating weekly infusions to enhance the amount of available circulating iron.

It has been hypothesized that anemia may have some physiologic effects that should be evaluated as "harder" end points of potential clinical benefit. These end points include effects on respiratory function as demonstrated by measurements of $\dot{V}O_2$ max and the potential effects on cognitive function. The latter may be impacted either directly by the degree of anemia or indirectly by the degree of fatigue associated with anemia. Prospective clinical trials focused on these end points may produce results that support the use of epoetin for purposes other than preventing the need for RBC transfusions.

No trial to date has adequately defined the baseline prognostic factors that predict response to epoetin. Parameters such as circulating cytokine levels (eg, tumor necrosis factor-alpha) have been hypothesized as potentially limiting the response to epoetin,[57-59] but this has not been evaluated in a controlled trial. Prospective evaluation of baseline erythropoietin levels as predictors for response to epoetin should be undertaken. There is little firm evidence to support the contention that transfusion-dependent patients respond less dramatically to epoetin. Further work is needed to expand the outcomes of interest in evaluations of epoetin beyond transfusion parameters, such as validating improved measures of quality of life, and clinical surrogates such as cognitive function and respiratory function ($\dot{V}O_2$ max). Further research is needed, and some is underway, to define minimally important differences and clinically meaningful improvements in quality of life for this group of patients.

One trial suggests a survival advantage for patients treated with epoetin, but the study was not adequately powered to test this hypothesis.[16] Further research is needed to determine whether higher hemoglobin levels improve survival or whether, in some manner, epoetin potentiates the antitumor effects of chemotherapy.

Children are relatively underrepresented in the studies reported to date that evaluate the effectiveness of erythropoietin. Only three studies reviewed by the TEC involved treatment-related anemia in children.[40,60,61] Whether this can be attributed to a belief that children tolerate symptoms and side effects better or experience them less often is not known. Certainly future investigation could focus more attention on the clinical effectiveness and quality-of-life changes that children may experience with epoetin.

No available studies have evaluated the costs of administering epoetin, an analysis complicated by the need to incorporate the indirect costs of transfusions. A series of ongoing and recently completed trials are expected to provide relevant economic data. Ultimately, cost-effectiveness/cost utility analyses should be pursued.

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APPENDIX A
ASCO/ASH Epoetin Expert Panel

Investigator	Institution/Specialty	Conflict of Interest Disclosure Statement
Michael S. Gordon, MD ASCO Co-Chair TEC Panel Member	University of Arizona HSC Phoenix, AZ Medical Oncology/Hematology	Consultant within the last 2 years for Amgen; received research funding from Amgen; received honoraria directly in excess of $2,000 per year or $5,000 over a 3-year period from Amgen; member on the board of directors or advisory committee of Amgen
Alan E. Lichtin, MD ASH Co-Chair TEC Panel Member	Cleveland Clinic Foundation Cleveland, OH Medical Oncology/Hematology	No conflicts noted
Charles L. Bennett, MD, PhD TEC Panel Member	VA Chicago Health Care System Chicago, IL Medical Oncology/Hematology	Consultant within the last 2 years for OrthoBiotech and Amgen; received research funding from OrthoBiotech and Amgen
David Cella, PhD	Evanston Northwestern Healthcare Evanston, IL Quality of Life	Consultant within the last 2 years for Amgen and OrthoBiotech; received research funding from Amgen and OrthoBiotech; received honoraria directly in excess of $2,000 per year or $5,000 over a 3-year period from Amgen and OrthoBiotech
Benjamin Djulbegovic, MD, PhD	H. Lee Moffitt Cancer Center, University of South Florida Tampa, FL Medical Oncology/Hematology	No conflicts noted
Matthew J. Goode	Mesa, AZ Patient representative	No conflicts noted
Ann A. Jakubowski, MD, PhD	Memorial Sloan-Kettering Cancer Center New York, NY Medical Oncology/Hematology	No conflicts noted
Stephanie J. Lee, MD, MPH	Dana-Farber Cancer Institute Boston, MA Medical Oncology/Hematology	No conflicts noted
Carole B. Miller, MD	St Agnes Hospital Baltimore, MD Medical Oncology	Received research funding from OrthoBiotech and Amgen; received honoraria directly in excess of $2,000 per year or $5,000 over a 3-year period from Amgen
Mark U. Rarick, MD	NW Kaiser Permanente Portland, OR Hematology	No conflicts noted
David H. Regan, MD	Northwest Cancer Specialists Portland, OR Hematology	No conflicts noted
Steven H. Woolf, MD, MPH	Virginia Commonwealth University Fairfax, VA Internal Medicine/Methodological Consultant	No conflicts noted
Ex Officio		
J. Douglas Rizzo, MD	Medical College of Wisconsin IBMTR/ABMTR Milwaukee, WI Medical Oncology/Hematology	No conflicts noted
George P. Browman, MD	Hamilton Regional Cancer Center Hamilton, Ontario, Canada Medical Oncology	No conflicts noted
Jerome Seidenfeld, PhD TEC Co-Principal Investigator	Blue Cross and Blue Shield Association Technology Evaluation Center Chicago, IL	No conflicts noted

APPENDIX B
Detailed Summary of Evidence Incorporated in Guideline Development

The details of the evidence reviewed by the TEC are available in its full report and reviewed in a journal article.[3,4] The important highlights are summarized here as they relate to the recommendations provided in the guideline.

CHEMOTHERAPY-INDUCED ANEMIA

The TEC review identified 22 controlled trials with a total enrollment of 1,927 patients with chemotherapy-induced anemia meeting the study selection criteria.[9-16,20-27,40,60-65] Common to each study was a comparison of outcomes of managing anemia with epoetin (plus transfusion if necessary) to those achieved with RBC transfusion alone in patients undergoing therapy for malignancy. All but four trials[20-22,62] with 1,698 patients were randomized, and seven randomized trials[9,10,12,13,15,16,24,40] with a total of 853 patients were placebo-controlled and double-blinded. Most trials involved patients with solid organ and tissue malignancies and two trials were restricted to hematologic malignancies. In many studies, the specific cancer types were not reported. Some publications pooled results from multiple studies but gave few details about the component projects. Three small trials (108 enrolled patients) were restricted to pediatric patients.[40,60,61]

Quality of Evidence

In general, the quality of the design, conduct, and reporting of this body of evidence was not ideal. In some ways this reflects the difficulties of clinical research. The TEC reviewers were able to use only three criteria to label a trial as "higher quality": (1) a randomized controlled design, (2) double blinding, and (3) low attrition (eg, $< 10\%$ of subjects within each study arm excluded from the analysis or intention-to-treat analysis). They could not incorporate other important features that are typically considered important to ensure internal validity[66] and to limit the probability of false-negative and false-positive results because the authors of the studies did not report them. Thus, although the TEC report gave certain trials a designation of "higher quality" for purposes of sensitivity analysis, such studies often failed to document concealment of allocation, an important determinant of trial quality,[67] nor did they present reasons for postrandomization exclusion of subjects, explicit criteria for decisions to transfuse, reporting of or adjustment for cofactors that influence anemia and its related symptoms, intention-to-treat analysis of data, or blinding of patients to their hemoglobin values when conducting quality-of-life assessments. Other design limitations for this body of evidence relate to the following:

Adequacy of randomization (comparability of groups). The methods used for randomization, and whether allocation was concealed, were not described for some trials. Allocation concealment aims to prevent foreknowledge of the treatment assignment. Tests of statistical significance for differences in outcomes between epoetin and control arms were not consistently reported across the publications. For six randomized controlled trials, the TEC could not find sufficient data to assess the comparability of the study arms.[3] They judged the remaining 16 to have comparable study arms, but this determination was based on "estimated equivalence from the raw numbers or percentages reported" for some of these studies. Many trials have unexplained discrepancies in the number of enrolled and assessable patients and used vague or arguable criteria for postrandomization exclusions and censorship of patients.

Heterogeneity/ambiguity of cancer treatment regimens. The 22 trials included three studies in which treatment consisted only of radiotherapy. Of the remaining 19 trials that involved chemotherapy, two did not provide information on the specific regimen, 12 trials used various combinations of platinum-based chemotherapy (which were not always explicitly identified), and five trials used nonplatinum chemotherapy. Radiotherapy was combined with chemotherapy in three trials involving platinum-based chemotherapy and in two trials involving nonplatinum chemotherapy. Seven trials did not provide information on the use of radiation therapy. In most studies, the chemotherapy regimens used were not protocol-specified.[3] While this heterogeneity of treatment regimens does not compromise the quality of the evidence, per se, it may limit the internal validity for a given study and limit the comparability among studies.

Heterogeneity/ambiguity of confounders. Most trials did not provide information on the previous transfusion history of enrolled patients. Only three trials ($n = 204$) reported outcomes for groups in which 20% or fewer patients had previously been transfused and only one study ($n = 50$) reported on patients of whom $\geq 80\%$ were previously transfused. Iron supplementation occurred in both arms in nine trials ($n = 449$), the epoetin arm only in three trials ($n = 194$), and in neither arm in three trials; in

seven trials there was no documentation regarding iron supplementation.[3]

Heterogeneity/ambiguity of epoetin treatment. Seventeen trials used two-arm designs to compare subcutaneous epoetin with transfusion alone, two trials used three-arm designs to compare two different doses of subcutaneous epoetin to transfusion alone, and three studies used intravenous epoetin.[3] In studies using subcutaneous epoetin, the most common initial dose was 150 U/kg administered three times weekly (the most common higher starting dose was 300 U/kg three times weekly). Of the 17 two-arm trials, the dose range was 300 to 450 U/kg/wk in 12 trials and 700 to 1,000 U/kg/wk in five trials. The two three-arm trials (n = 252) compared initial doses of 450 to 900 U/kg/wk.[25,27] One study[14] administered 5,000 units daily, regardless of weight or body size. Among studies using subcutaneous epoetin at the lower-dose range, four trials (n = 520) increased the dose for nonresponders after a fixed period of time, four (n = 451) decreased the dose for responders, and four (n = 362) used a fixed and continuous dose throughout treatment. Treatment duration was more than 20 weeks in six trials, 12 to 16 weeks in eight trials, and ≤ 10 weeks in five trials. Assuming the dosing of epoetin was constant within a given trial, this would not necessarily compromise the validity of results for that trial, but it may limit the comparability among trials.

Heterogeneity/ambiguity of RBC transfusion policies. All studies managed anemia in the control arm with RBC transfusions. Although 10 trials prospectively specified a transfusion trigger, only four reported the mean hemoglobin level at transfusion for each arm, and in some studies the transfusion trigger was ignored. RBC transfusion was initiated when the patient's hemoglobin level fell below a defined threshold (range of 6.0 to 9.7 g/dL across the studies) or, in three studies,[9,12,27] at the discretion of the investigator or treating physician. Transfusion may have been at the discretion of the physician in the remaining studies. Only six studies[10,13,27,62,63,66] mentioned symptomatic anemia as an indication for transfusion. Only one study[24] reported a protocol specifying the number of units of RBCs transfused for each event.

Limitations in outcome measures. Only five trials reported all four hematologic and transfusion outcomes of interest to the TEC reviewers. Specifically, 16 trials (n = 1,407) reported the change in hemoglobin levels, 11 trials (n = 1,361) reported the proportion of patients that achieved a defined treatment target, 17 trials (n = 1,703) reported the proportion of patients transfused, 12 trials (n = 1,093) reported the number of units transfused, and nine trials (n = 981) measured symptomatology (eg, energy level, quality of life).[3] For any given category of outcomes, the specific definitions of treatment responses varied across trials, creating difficult inequivalencies in pooling data. The TEC reviewers raised concerns about reporting bias, noting for example that studies with patients at lower baseline risk of transfusion (hemoglobin > 10 g/dL) were less likely to report the percentage of patients transfused than did studies with more anemic patients.

No trial reported on symptoms of anemia (eg, dyspnea, angina) or number of days in hospital. The only trial that reported changes in performance status used the Karnofsky scale.[60] Of the nine studies that measured quality of life or the components (eg, energy level) that are associated with quality of life, only seven compared pre- and posttreatment scores between epoetin and control arms, and five met the TEC criteria for higher quality. Two studies[9,27] made before-and-after comparisons of quality-of-life measures within treatment arms but did not compare results between arms. None of the studies reported the features considered important for minimizing bias in measuring quality of life (eg, procedures to minimize the impact of other factors on response to quality-of-life instruments, handling of missing data). No study prospectively defined the minimum differences in quality-of-life scores that would be considered clinically significant, which may limit the ability to interpret the implications of any statistically significant differences that were observed. It should be noted that for some quality-of-life instruments, active research is ongoing to define *minimum* clinically meaningful differences.[19] In many studies, as many as 10% to 40% of randomized patients were excluded from quality-of-life outcomes because of missing data, and intention-to-treat analysis was not performed. The potential bias introduced by this attrition is that the subset of treatment and control patients, no longer consisting of the originally randomized groups, may differ in characteristics other than epoetin treatment that could influence answers to quality-of-life questions. Unfortunately, this problem is not unique to epoetin. Quality-of-life studies may be more difficult for patients to complete, often causing dropout rates for quality-of-life outcomes in clinical trials to be higher than for other outcome measures.

Statistical methods. Most trials had small sample sizes and therefore may lack statistical power to detect a difference between study arms. Two trials described an effort to calculate the necessary sample size and inherent assumptions about expected reductions in transfusion requirements.[40,64] The TEC calculated that detection of a 50% reduction in the percentage of patients transfused at 80% power would require 58 patients per study arm.[3] Four trials (n = 891) enrolled more than 100 patients (range, 132 to 375 patients) and had ≥ 50 patients in each study arm.[9,12,14-16] The mean number of patients in the remaining

18 trials was 26.5 (range, 12 to 50 patients). Studies were inconsistent in reporting the statistical significance of *P* values for differences in outcomes, with seven studies doing so for only selected outcomes and three studies[11,25,26] not reporting *P* values for any outcome of interest. Most studies that did not report *P* values also omitted sufficient data to enable the TEC analysts to calculate *P* values. However, despite not reporting a *P* value, in one instance meta-analysis found a significant result.[25] Failure to report a *P* value does not necessarily indicate that a result was not statistically significant. Meta-analysis was performed by the TEC for transfusion outcomes in order to overcome the small sample sizes of some individual studies.

Summary of Results

The TEC reviewers classified the 22 trials into three categories based on the study patients' mean or median hemoglobin level at enrollment: $\leq$ 10 g/dL, greater than 10 and less than 12 g/dL, and $\geq$ 12 g/dL. The largest body of evidence is from trials enrolling patients with mean or median hemoglobin concentrations of $\leq$ 10 g/dL at study entry. Of 1,927 patients enrolled in the 22 trials analyzed in the TEC report, 1,188 (62%) were in the most anemic category, 431 (22%) were in the intermediate category (hemoglobin $>$ 10 and $<$ 12 g/dL), and 308 (16%) were in the latter category. The results of the trials for chemotherapy-induced anemia are summarized in Tables 2 through 5.

Community Studies

The hypothesis that epoetin improves quality of life finds support in the results of large phase IV community studies (sample sizes of approximately 2,300 to 3,000 patients).[30,39,44] These single-arm cohort studies of cancer patients with chemotherapy-related anemia demonstrated a statistically significant association between increases in hemoglobin levels and quality-of-life scores on the Functional Assessment of Cancer Therapy–Anemia and other instruments. However, the absence of an internal control group in these studies and methodologic questions about the statistical methods used for adjustment for covariables and dropouts raise questions about the degree to which these salutary findings can be attributed with confidence to epoetin therapy.[3] These studies were therefore excluded from detailed analysis in the TEC review.

Meta-Analysis

The meta-analysis conducted by the TEC, when applied to those randomized controlled studies that used subcutaneous epoetin and reported numbers of patients transfused, yielded a cumulative odds ratio of 0.38 (95% CI, 0.28 to 0.51), suggesting that use of epoetin decreases the relative odds of receiving a RBC transfusion by an average of 62% (Table 7). When the meta-analysis was restricted to data from studies meeting TEC criteria for higher quality, the odds ratio remained significant at 0.45 (95% CI, 0.33 to 0.62).

The *relative* odds of requiring transfusion can be translated into an *absolute* risk reduction, where this also depends on the baseline probability that the patient will require a transfusion. The TEC estimated the baseline risk of transfusion from using the control arms of trials that reported the proportion of patients transfused by 12 weeks of follow-up; this was applied to the relative risk reductions to determine absolute benefit. Using this approach, the TEC calculated an absolute benefit that corresponded to a number-needed-to-treat of 4.4 (95% CI, 3.6 to 6.1) in order to benefit one patient. (The number-needed-to-treat is the reciprocal of the absolute risk difference.) The estimated number-needed-to-treat, derived only from studies meeting TEC criteria for higher quality, was 5.2 (95% CI, 3.8 to 8.4). That number would be higher if the risk of requiring a transfusion were lower than that assumed by the TEC.

ANEMIA DUE PRIMARILY TO MALIGNANT DISESASE (myelodysplasia, myeloma, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia)

The TEC literature search identified six controlled trials, all randomized (n = 693), that enrolled patients regardless of whether they were receiving concurrent cancer therapy. Three trials were placebo-controlled and double-blind (n = 332), and four were multicenter (n = 448). Each study compared the outcomes of epoetin treatment (n = 448) supplemented with transfusions when required and with transfusion alone (n = 245) for patients with anemia primarily due to malignant disease (hematologic malignancies).

The TEC review identified two randomized controlled trials examining the use of epoetin in myeloma only,[49,50] a randomized study of patients with chronic lymphocytic leukemia that is available only as an abstract,[51] and two randomized trials involving myeloma and non-Hodgkin's lymphoma/chronic lymphocytic leukemia.[52,53] Each of these studies included patients receiving concurrent therapy for their malignancy. One randomized controlled trial reports on results of epoetin therapy in patients with myelodysplastic syndrome; none of these patients received concurrent therapy.[48] The combination of diverse disease groups in the former trials complicates interpretations. Several publications from an additional randomized controlled trial[54-56] were excluded from detailed TEC analysis because of incomplete reporting by the investigators and will not be discussed here. In the six trials reviewed by the TEC, all patients were adults with mean or median hemo-

globin levels ≤ 10 g/dL, and sample sizes were generally small (ranging from 24 to 221 patients).

Transfusion history differed across studies. Three studies reported on patient groups who had received prior transfusions (n = 222) and in three studies 0% to 20% of patients had received previous transfusions. Three studies used iron supplementation (n = 304), and three studies did not specify whether patients were supplemented. Since the failure to rule out other causes of anemia, including iron deficiency, might lead to underestimating the effects of epoetin, the TEC used stringent criteria to assess verification of iron status. Four trials met these criteria.[48,50,52,53]

Quality of Evidence

The methods used in the six trials are, in general, not well described and limit the quality of the evidence. None met the TEC criteria for higher quality. In several studies,[49,51,52] randomization methods were not detailed, and treatment and control arms had unexplained differences in size, baseline clinical characteristics, or comorbid conditions.[50,52,53] No studies reported a statistical comparison of patient characteristics by study arm. Two trials[49,51] provided no data on the percentage of patients receiving concurrent treatments, such as chemotherapy or corticosteroids, or on the specific regimen. The inclusion criteria for one study[50] required resistance to conventional chemotherapy. Studies had high attrition rates[50] or excluded patients after randomization for factors that might have independent associations with outcomes (eg, need for autologous stem-cell transplantation).[49]

Three trials[48,50,53] specified the threshold for administering RBC transfusions (7 to 10 g/dL), but in the other three trials,[49,51,52] the trigger was unspecified and left to the discretion of the treating physician. Ambiguities in the extent to which the various study arms received transfusions make it unclear to what extent observed outcomes were ascribable to epoetin. Finally, comparing hematologic treatment responses across trials is difficult because investigators used inconsistent definitions for "complete response."

REFERENCES

1. Agency for Health Care Policy and Research (AHCPR): AHCPR Requests Topic Nominations for Evidence Reports and Technology Assessments: Media advisory. November 28, 1997. Http://www.ahcpr.gov/news/press/epcnompr.htm, accessed October 27, 2000

2. Agency for Health Care Policy and Research (AHCPR): AHCPR Announces New Evidence Report Topics: Press release. October 29, 1998. Http://www.ahcpr.gov/news/press/epctopic.htm, accessed October 27, 2000

3. Seidenfeld J, Aronson N, Piper MA, et al: Use of erythropoietin for anemia in oncology: Evidence Report/Technology Assessment No 30 (AHRQ Publ No. 01–E009). Prepared by the Blue Cross and Blue Shield Association Evidence-based Practice Center under Contract No. 290-97–0015. Rockville, MD, Agency for Healthcare Research and Quality, June 2001

4. Seidenfeld J, Piper M, Flamm C, et al: Epoetin treatment for anemia of cancer therapy: A systematic review and meta-analysis of controlled clinical trials. J Natl Cancer Inst 93:1204-1214, 2001

5. Http://oncology.medscape.com/Home/Topics/oncology/oncology.html

6. Cook DL, Guyatt GH, Laupacis A, et al: Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 102:305S-311S, 1992 (suppl 4)

7. Sackett DL: Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 95:2S-4S, 1989

8. American Society of Clinical Oncology: Outcomes of cancer treatment for technology assessment and cancer treatment guidelines. J Clin Oncol 14:671-679, 1996

9. Case DC Jr, Bukowski RM, Carey RW, et al: Recombinant human erythropoietin therapy for anemic cancer patients on combination chemotherapy. J Natl Cancer Inst 85:801-806, 1993

10. Cascinu S, Fedeli A, Del Ferro E, et al: Recombinant human erythropoietin treatment in cisplatin-associated anemia: A randomized, double-blind trial with placebo. J Clin Oncol 12:1058-1062, 1994

11. Silvestris F, Romito A, Fanelli P, et al: Long-term therapy with recombinant human erythropoietin (rHu-EPO) in progressing multiple myeloma. Ann Hematol 70:313-318, 1995

12. Henry DH, Brooks BJ Jr, Case DC Jr, et al: Recombinant human erythropoietin therapy for anemic cancer patients receiving cisplatin chemotherapy. Cancer J Sci Am 1:252, 1995

13. Kurz C, Marth C, Windbichler G, et al: Erythropoietin treatment under polychemotherapy in patients with gynecologic malignancies: A prospective, randomized, double-blind placebo-controlled multicenter study. Gynecol Oncol 65:461-466, 1997

14. Oberhoff C, Neri B, Amadori D, et al: Recombinant human erythropoietin in the treatment of chemotherapy-induced anemia and prevention of transfusion requirement associated with solid tumors: A randomized, controlled study. Ann Oncol 9:255-260, 1998

15. Littlewood TJ, Bajetta E, Cella D, et al: Efficacy and quality of life outcomes of epoetin alfa in a double-blind, placebo-controlled multicenter study of cancer patients receiving non-platinum containing chemotherapy. Proc Am Soc Clin Oncol 18:574a, 1999 (abstr 2217)

16. Littlewood TJ, Bajetta E, Nortier JW, et al: Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: Results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol 19:2865-2874, 2001

17. Fairclough DL, Gagnon D: The significance of missing data in clinical trials. Presented at the International Society for Quality of Life Research conference, October 2000 (abstr 1697)

18. Yellen SB, Cella DF, Webster K, et al: Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage 13:63-74, 1997

19. Cella D, Hahn EA, Dineen K: Meaningful change in cancer-specific quality of life scores: Differences between improvement and worsening. Qual Life Res 11:207-221, 2002

20. Markman M, Reichman B, Hakes T, et al: The use of recombinant human erythropoietin to prevent carboplatin-induced anemia. Gynecol Oncol 49:172-176, 1993

21. Lavey RS, Dempsey WH: Erythropoietin increases hemoglobin in cancer patients during radiation therapy. Int J Radiat Oncol Biol Phys 27:1147-1152, 1993

22. Dusenbery KE, McGuire WA, Holt PJ, et al: Erythropoietin increases hemoglobin during radiation therapy for cervical cancer. Int J Radiat Oncol Biol Phys 29:1079-1084, 1994

23. Henke M, Guttenberger R, Barke A, et al: Erythropoietin for patients undergoing radiotherapy: A pilot study. Radiother Oncol 50:185-190, 1999

24. Wurnig C, Windhager R, Schwameis E, et al: Prevention of chemotherapy-induced anemia by the use of erythropoietin in patients with primary malignant bone tumors (a double-blind, randomized, phase III study). Transfusion 36:155-159, 1996

25. ten Bokkel Huinink WW, de Swart CA, van Toorn DW, et al: Controlled multicentre study of the influence of subcutaneous recombinant human erythropoietin on anaemia and transfusion dependency in patients with ovarian carcinoma treated with platinum-based chemotherapy. Med Oncol 15:174-182, 1998

26. Quirt I, Coutere F, Pichette R, et al: The role of recombinant human erythropoietin (EPO) in reducing red blood cell transfusions and maintaining quality of life (QOL) in patients with lymphoma and solid tumors receiving cytotoxic chemotherapy: Results of a randomized, double-blind, placebo-controlled clinical trial. Blood 88:347a, 1996 (abstr 1378)

27. Thatcher N, De Campos ES, Bell DR, et al: Epoetin alpha prevents anaemia and reduces transfusion requirements in patients undergoing primarily platinum-based chemotherapy for small cell lung cancer. Br J Cancer 80:396-402, 1999

28. Cheung WK, Goon BL, Guilfoyle MC, et al: Pharmacokinetics and pharmacodynamics of recombinant human erythropoietin after single and multiple subcutaneous doses to healthy subjects. Clin Pharmacol Ther 64:412-423, 1998

29. Cheung W, Minton N, Gunawardena K: Pharmacokinetics and pharmacodynamics of epoetin alfa once weekly and three times weekly. Eur J Clin Pharmacol 57:411-418, 2001

30. Gabrilove JL, Cleeland CS, Livingston RB, et al: Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: Improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. J Clin Oncol 19:2875-2882, 2001

31. Nguyen TV, Trinh GN: Clinical evaluation of once-weekly and three-times-weekly dosings of epoetin alfa in chemotherapy patients: Problems of study design and interpretation. J Clin Oncol 20:878, 2002 (letter)

32. Silberstein PT, Witzig TE, Sloan JA, et al: Weekly erythropoietin for patients with chemotherapy induced anemia: A randomized, placebo-controlled trial in the North Central Cancer Treatment Group. Proc Am Soc Clin Oncol 21:356a, 2002 (abstr 1422)

33. Glaspy J, Jadeja JS, Justice G, et al: A dose-finding and safety study of novel erythropoiesis stimulating protein (NESP) for the treatment of anaemia in patients receiving multicycle chemotherapy. Br J Cancer 84:17-23, 2001 (suppl 1)

34. Kotasek D, Berg R, Poulsen E, et al: Randomized, double-blind, placebo controlled, phase I/II dose finding study of Aranesp administered once every three weeks in solid tumor patients. Blood 96:294a, 2000 (abstr)

35. Pirker R, Vansteenkiste J, Gateley J, et al: A phase 3, double-blind, placebo-controlled, randomized study of novel erythropoiesis stimulating protein (NESP) in patients undergoing platinum treatment for lung cancer: NESP 980297 Study Group. Proc Am Soc Clin Oncol 20:394a, 2001 (abstr 1572)

36. Hedenus M, Hansen S, Dewey C, et al: A randomized, blinded, placebo-controlled, phase II, dose-finding study of novel erythropoiesis stimulating protein (NESP) in patients with lymphoproliferative malignancies. Proc Am Soc Clin Oncol 20:393a, 2001 (abstr 1569)

37. Glaspy JA, Jadeja J, Justice G, et al: Randomized, active-controlled, phase 1/2, dose-escalation study of NESP administered weekly and every 2 weeks in patients with solid tumors. Proc Am Soc Clin Oncol 20:387a, 2001 (abstr 1546)

38. Kotasek D, Albertsson M, Mackey J, et al: Randomized, double-blind, placebo-controlled, dose-finding study of darbepoetin alfa administered once every 3 (Q3W) or 4 (Q4W) weeks in patients with solid tumors: Darbepoetin alfa 980291 Study Group. Proc Am Soc Clin Oncol 21:356a, 2002 (abstr 1421)

39. Demetri GD, Kris M, Wade J, et al: Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: Results from a prospective community oncology study—Procrit Study Group. J Clin Oncol 16:3412-3425, 1998

40. Porter JC, Leahey A, Polise K, et al: Recombinant human erythropoietin reduces the need for erythrocyte and platelet transfusions in pediatric patients with sarcoma: A randomized, double-blind, placebo-controlled trial. J Pediatr 129:656-660, 1996

41. Albitar S, Meulders Q, Hammoud H, et al: Subcutaneous versus intravenous administration of erythropoietin improves its efficiency for the treatment of anaemia in haemodialysis patients. Nephrol Dial Transplant 10:40-43, 1995 (suppl 6)

42. Kaufman JS, Reda DJ, Fye CL, et al: Subcutaneous compared with intravenous epoetin in patients receiving hemodialysis: Department of Veterans Affairs Cooperative Study Group on Erythropoietin in Hemodialysis Patients. N Engl J Med 339:578-583, 1998

43. Casadevall N, Nataf J, Viron B, et al: Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med 346:469-475, 2002

44. Glaspy J, Bukowski R, Steinberg D, et al: Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice: Procrit Study Group. J Clin Oncol 15:1218-1234, 1997

45. Besarab A, Bolton WK, Browne JK, et al: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 339:584-590, 1998

46. Dammacco F, Castoldi G, Rodjer S: Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma. Br J Haematol 113:172-179, 2001

47. Osterborg A, Brandberg Y, Molostova V, et al: Randomized, double-blind, placebo-controlled trial of recombinant human erythropoietin, epoetin beta, in hematologic malignancies. J Clin Oncol 20:2486-2494, 2002

48. Anonymous: A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes: Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes. Br J Haematol 103:1070-1074, 1998

49. Garton JP, Gertz MA, Witzig TE, et al: Epoetin alfa for the treatment of the anemia of multiple myeloma: A prospective, randomized, placebo-controlled, double-blind trial. Arch Intern Med 155:2069-2074, 1995

50. Dammacco F, Silvestris F, Castoldi GL, et al: The effectiveness and tolerability of epoetin alfa in patients with multiple myeloma refractory to chemotherapy. Int J Clin Lab Res 28:127-134, 1998

51. Rose E, Rai K, Revicki D, et al: Clinical and health status assessments in anemic chronic lymphocytic leukemia (CLL) patients treated with epoetin alfa (EPO). Blood 84:526a, 1994 (abstr)

52. Cazzola M, Messinger D, Battistel V, et al: Recombinant human erythropoietin in the anemia associated with multiple myeloma or non-Hodgkin's lymphoma: Dose finding and identification of predictors of response. Blood 86:4446-4453, 1995

53. Osterborg A, Boogaerts MA, Cimino R, et al: Recombinant human erythropoietin in transfusion-dependent anemic patients with multiple myeloma and non-Hodgkin's lymphoma: A randomized multicenter study—The European Study Group of Erythropoietin (Epoetin Beta) Treatment in Multiple Myeloma and Non-Hodgkin's Lymphoma. Blood 87:2675-2682, 1996

54. Abels R: Erythropoietin for anaemia in cancer patients. Eur J Cancer 29A:S2-S8, 1993 (suppl 2)

55. Abels RI, Larholt KM, Krantz KD, et al: Recombinant human erythropoietin (rHuEPO) for the treatment of the anemia of cancer. Oncologist 1:140-150, 1996

56. Henry DH, Abels RI: Recombinant human erythropoietin in the treatment of cancer and chemotherapy-induced anemia: Results of double-blind and open-label follow-up studies. Semin Oncol 21:21-28, 1994

57. Stasi R, Brunetti M, Bussa S, et al: Serum levels of tumour necrosis factor-alpha predict response to recombinant human erythropoietin in patients with myelodysplastic syndrome. Clin Lab Haematol 19:197-201, 1997

58. Kreuzer KA, Rockstroh JK, Jelkmann W, et al: Inadequate erythropoietin response to anaemia in HIV patients: Relationship to serum levels of tumour necrosis factor-alpha, interleukin-6 and their soluble receptors. Br J Haematol 96:235-239, 1997

59. Takemasa A, Yorioka N, Ueda C, et al: Stimulation of tumour necrosis factor-alpha production by recombinant human erythropoietin may contribute to failure of therapy. Scand J Urol Nephrol 34:131-135, 2000

60. Leon P, Jimenez M, Barona P, et al: Recombinant human erythropoietin for the treatment of anemia in children with solid malignant tumors. Med Pediatr Oncol 30:110-116, 1998

61. Varan A, Buyukpamukcu M, Kutluk T, et al: Recombinant human erythropoietin treatment for chemotherapy-related anemia in children. Pediatrics 103:E16, 1999

62. Sweeney PJ, Nicolae D, Ignacio L, et al: Effect of subcutaneous recombinant human erythropoietin in cancer patients receiving radiotherapy: Final report of a randomized, open-labelled, phase II trial. Br J Cancer 77:1996-2002, 1998

63. Gamucci T, Thorel MF, Frasca AM, et al: Erythropoietin for the prevention of anaemia in neoplastic patients treated with cisplatin. Eur J Cancer 29A:S13-S14, 1993 (suppl 2)

64. Del Mastro L, Venturini M, Lionetto R, et al: Randomized phase III trial evaluating the role of erythropoietin in the prevention of chemotherapy-induced anemia. J Clin Oncol 15:2715-2721, 1997

65. Welch RS, James RD, Wilkinson PM, et al: Recombinant human erythropoietin and platinum-based chemotherapy in advanced ovarian cancer. Cancer J Sci Am 1:261, 1995

66. Moher D, Pham B, Jones A, et al: Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 352:609-613, 1998

67. Schulz KF, Chalmers I, Hayes RJ, et al: Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 273:408-412, 1995