The Oncologist®

Symptom Management and Supportive Care

Management of Cancer-Related Anemia with Erythropoietic Agents: Doubts, Certainties, and Concerns

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Abstract

The management of cancer-related anemia with erythropoietic agents presents many unresolved issues. We reviewed the literature relating to epoetin alfa (Eprex®/Epypo®; Ortho Biotech/Janssen-Cilag, High Wycombe, United Kingdom, http://www.orthobiotech.co.uk; Procrit®; Ortho Biotech Products, L.P., Bridgewater, NJ, http://www.orthobiotech.com), epoetin beta (NeoRecormon®; Hoffman-La Roche, Basel, Switzerland, http://www.roche.com), and darbepoetin alfa (Aranesp®; Amgen Inc., Thousand Oaks, CA, http://www.amgen.com) highlighting the results of published clinical trials, safety, and cost-effectiveness. Studies were identified through MEDLINE and the bibliographies of relevant articles. Epoetin alfa, epoetin beta, and darbepoetin alfa have differing pharmacokinetic and pharmacodynamic profiles. They are all effective at reducing transfusion requirements and improving health-related quality-of-life parameters, irrespective of tumor response. A direct comparison between epoetin alfa and darbepoetin alfa is based on limited evidence, which does not allow definitive conclusions about relative efficacy and cost-effectiveness. No predictive factors for response to erythropoietic agents have been validated in prospective trials. The most consistent adverse events are thrombotic and may occur irrespective of an increase in hemoglobin. Recent research indicates that the erythropoietin receptor is expressed in several cancer cell lines, raising the concern of possible stimulation of tumor cell growth by these drugs. Studies on the cost-effectiveness of erythropoietins, particularly compared with transfusion therapy, have been challenging to conduct and analyze and have generated ambiguous results. The use of erythropoietins needs to be optimized in terms of cost-effectiveness, and issues surrounding safety need to be clarified. A stronger methodology for clinical studies and the design of new, randomized, clinical trials is a major priority. *The Oncologist* 2005;10:539–554

Introduction

Anemia is a common side effect of cancer and cancer therapy. Its prevalence varies with tumor type, stage, and therapy used [1–3]. The negative impact of anemia symptoms, such as fatigue, on patient quality of life (QoL) is substantial [4]. In addition, anemia may compromise patients'

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tolerance of treatments, resulting in the need to reduce the duration or intensity of those treatments [4–6]. Prior to 1993, when recombinant human erythropoietin (rHuEPO) was approved by the U.S. Food and Drug Administration (FDA), RBC transfusion was the sole option for the treatment of anemia in cancer. The availability of a therapeutic option with an apparently superior risk-benefit ratio has changed clinical practice and resulted in increased understanding of the impact of anemia treatment on the lives of cancer patients. Three erythropoietic agents are currently licensed for the treatment of chemotherapy-induced anemia: epoetin alfa (Eprex®/Epypo®; Ortho Biotech/Janssen-Cilag, High Wycombe, United Kingdom, http://www.orthobiotech.co.uk; Procrit®; Ortho Biotech Products, L.P., Bridgewater, NJ, http://www.orthobiotech.com), epoetin beta (NeoRecormon®; Hoffman-La Roche, Basel, Switzerland, http://www.roche.com; not marketed in the U.S.), and the longer-acting darbepoetin alfa (Aranesp®; Amgen Inc., Thousand Oaks, CA, http://www.amgen.com). The differences in the pharmacologic properties of these molecules have been detailed elsewhere [7]. Because of current levels of concern raised by recent reports [8], we reviewed the literature highlighting the results of clinical trials, safety, and cost-effectiveness, as well as unresolved issues on these drugs.

Materials and Methods

Data for review were identified using PubMed to search the MEDLINE database, limiting the search to abstracts/articles in English without date constraints. The key words erythropoietic agents, erythropoietin, epoetin, darbepoetin, novel erythropoiesis-stimulating protein, NESP, cancer, anemia, quality of life, fatigue, adverse events, cost, and cost-effectiveness were variously combined in the title, abstract, and key word search list.

Clinical Trials

Hematologic and Transfusion Outcomes

Epoetin Alfa and Epoetin Beta

rHuEPO was initially studied in anemic cancer patients receiving chemotherapy based on the observation that endogenous EPO concentrations were inadequate to account for the observed degree of anemia [9]. The first randomized, placebo-controlled clinical trial analyzed 413 patients with baseline hemoglobin levels <10.5 g/dl receiving either no chemotherapy ($n = 124$), cyclic chemotherapy not containing cisplatin (Platinol®; Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com) ($n = 157$), or cyclic cisplatin-containing chemotherapy ($n = 132$) [10]. In all three groups, the mean weekly hematocrit levels remained stable among the placebo-treated patients but increased progressively in those receiving epoetin alfa. Also, the mean proportion of patients transfused and the mean number of RBC units transfused were lower for all three rHuEPO treatment groups compared with placebo. However, the design of the trial involved a relatively low dose of rHuEPO and a treatment period of only 8 weeks, which was insufficient to demonstrate a statistically significant impact on the risk of transfusion for patients not receiving chemotherapy. Accordingly, the FDA limited the approval of rHuEPO to patients with nonmyeloid malignancies whose anemia was caused by the effects of chemotherapy.

A large number of additional controlled clinical trials in various settings have been performed and were reviewed in a meta-analysis [11]. With regard to anemia due primarily to cancer therapy, 22 controlled trials were analyzed [12–33]. Those studies employed different erythropoietic agents, used varied inclusion criteria for hemoglobin level, and included different patient populations (Table 1). Epoetin therapy decreased the percentage of patients transfused by 9%–45% in patients with mean baseline hemoglobin concentrations of ≤10 g/dl ($n = 1080$), by 7%–47% in patients with hemoglobin levels >10 g/dl <12 g/dl ($n = 431$), and by 7%–39% in patients with baseline hemoglobin levels >12 g/dl ($n = 308$). The combined odds ratio for transfusion in rHuEPO-treated patients compared with controls was 0.45 (95% confidence interval [CI], 0.33–0.62) in higher quality studies and 0.14 (95% CI, 0.06–0.31) in lower-quality studies. The general consensus reached by this meta-analysis was that rHuEPO reduced the odds of transfusion in patients receiving chemotherapy or radiotherapy. Nevertheless, several methodological limitations in the design and reporting of the studies evaluated leave some doubts about the final results of this meta-analysis. In fact, some studies (5 of 22) did not report the number or percentage of patients transfused, half of them (11 of 22) did not report the percentage of hematologic responses, just over half (12 of 22) reported the number of RBC units transfused per patient, criteria of response were not uniform, and no trial reported the effects of erythropoietin use on symptoms of anemia other than fatigue (Table 1). A number of confounding factors should also be considered. Among these are major differences in patient characteristics and trial entry criteria, the lack of clear references to the criteria for administering RBC transfusions (i.e., the hemoglobin concentration above which patients did not receive RBC transfusions and below which transfusions were always given), the lack of data to demonstrate that the mean or median hemoglobin concentrations at transfusion were comparable for all study arms, the lack of any reference to the control of the

Table 1. Main features of the controlled trials analyzed in the meta-analysis of Seidenfeld et al. [11]

No. of controlled trials		
Randomized		18
	Placebo-controlled	7
Nonrandomized		4
	Concurrent controls	2
	Historical controls	2
No. of patients		
	Total	1,927
	Evaluable	1,838
Erythropoietic agent used in the trials		
	Epoetin alfa	17
	Epoetin beta	5
Tumor type		
	Mixed solid and nonmyeloid hematologic tumors	7
	Multiple solid tumors	5
	Gynecologic malignancies	5
	Sarcomas	2
	Breast cancer	1
	Small-cell lung cancer	1
	Multiple myeloma	1
Type of cancer therapy		
	Platinum chemotherapy	8
	Nonplatinum chemotherapy	4
	Platinum and nonplatinum chemotherapy	6
	Radiotherapy	4
Baseline Hb, No. of trials (No. of patients)		
	Adults: mean baseline Hb ≤10 g/dl	7 (1,080)
	Children: mean baseline Hb ≤10 g/dl	3 (108)
	Adults: mean baseline Hb ≤10 g/dl but <12 g/dl	7 (431)
	Adults: mean baseline Hb ≥12 g/dl	5 (308)
Range of Hb change between rHuEPO and control arms (g/dl)		
	Adults: mean baseline Hb ≤10 g/dl	1.6–3.08
	Children: mean baseline Hb ≤10 g/dl	1.78–2.5
	Adults: mean baseline Hb ≤10 g/dl but <12 g/dl	1.0–3.7
	Adults: mean baseline Hb ≥12 g/dl	0.1–2.4
Outcomes reported (No. of studies/No. of patients/% of patients)		
	Initial and final (or change in) Hb by study arm	16/1,407/73
	Percentage of hematologic responses by defined criteria	11/1,361/71
	No. or percentage of patients transfused	17/1,703/88
	RBC units transfused per patient	12/1,093/57
	Symptoms of anemia	0/0/0
	Reported QoL outcomes	9/851/44

Abbreviations: Hb, hemoglobin; Qol, quality life; rHuEPO, recombinant human erythropoietin.

adequacy of iron status during the course of the study and its implications for study outcomes, and the use of different doses of and methods for administering erythropoietin. Other theoretical confounding factors include distinguishing between hemoglobin response and the impact of other variables, such as disease progression, tumor response, and other comorbidities, on QoL measures, and the possible effects of patients' knowledge of hemoglobin values on QoL assessment.

Since high-quality studies have not enrolled patients with an average hemoglobin level >10 g/dl (and often not even >9 g/dl), it has not been clear whether patients with less severe anemia would also respond to therapy. However, the findings of the Littlewood et al. [34] trial (Table 2) suggest that rHuEPO therapy is effective for both patients with mild anemia and those with severe anemia [34]. The data from that study were recently analyzed using an intent-to-treat population, an efficacy population, and a per-protocol group (paper submitted for publication). The results were the same. In addition, when the hemoglobin values obtained within 28 days of a transfusion were censored (i.e., counted as missing), there was no difference in the outcome of the study.

Three additional randomized, double-blinded, placebo-controlled trials for patients with both hematologic and solid malignancies receiving chemotherapy have been published since that meta-analysis [35–37], showing similar results (Table 3). Dammacco et al. [35] evaluated the effects of epoetin alfa on transfusions, hemoglobin concentration, and QoL in 145 patients with multiple myeloma and anemia (hemoglobin <11 g/dl). Patients completing the 12-week, double-blind phase could enter the subsequent optional 12-week phase of open-label epoetin alfa treatment. During double-blinded treatment, epoetin alfa resulted in a significantly lower incidence of transfusion than placebo (28% versus 47%; $p = .017$), regardless of patients' transfusion history, and higher mean hemoglobin level (1.8 g/dl versus 0.0 g/dl; $p < .001$). However, the dropout rate was significantly higher in the placebo arm than in the rHuEPO arm (19.7% versus 7.2%; $p = .032$).

A high dropout rate was reported in the study by Witzig et al. [37] (30% in the placebo group and 28% in the rHuEPO group), who investigated the effects of weekly epoetin alfa (40,000 U, increased to 60,000 U after 1 month in nonresponders) in 334 patients with advanced cancer and with anemia after receiving myelosuppressive chemotherapy. The results indicate significant improvements in hemoglobin concentrations and lower transfusion needs in epoetin-treated patients ($p < .001$, Table 3). However, no mention was made of the criteria for the administration of RBC transfusions, which were prescribed at the discretion of the treating physician.

In the study by Österborg et al. [36], 349 transfusion-dependent patients with nonmyeloid hematologic malignancies and inadequately low endogenous serum erythropoietin concentrations received epoetin beta or placebo for 16 weeks. The response rates were 67% and 27% in the epoetin beta and placebo groups, respectively ($p < .0001$). However, the percentage of patients who had to double the rHuEPO dose was not reported.

Further evidence of the efficacy of rHuEPO in chemotherapy-related anemia stems from three large, open-label, nonrandomized studies carried out through the 1990s (Table 4) [38–40]. Despite the differences in rHuEPO dosing among the three trials, the outcomes were quite similar, with all studies achieving a mean hemoglobin change of 1.8–2.0 g/dl from baseline to the final value, a reduction in transfusion requirements, and improvements in QoL parameters.

Table 2. Response to rHuEPO therapy by tumor type and Hb level from the Littlewood et al. [34] trial

	rHuEPO therapy ($n = 244$)	Placebo ($n = 115$)
Tumor type[a]		
Solid	87/131 (66.4%)	13/61 (21.3%)
Hematologic	85/113 (75.2%)	9/54 (16.7%)
Hb level[a]		
≤10.5 g/dl	139/203 (68.5%)	22/100 (22%)
>10.5 g/dl	33/41 (80.5%)	0/15 (0%)

The results of this trial indicate that the response rates are similar between patients with solid tumors and those with hematologic tumors, and between patients with baseline Hb levels >10.5 g/dl and those with Hb levels ≤10.5 g/dl.
[a]*p* values not significant.
Adapted from 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. Adapted from [34], with permission.
Abbreviations: Hb, hemoglobin; rHuEPO, recombinant human erythropoietin.

Darbepoetin Alfa

Recently, darbepoetin alfa was investigated in cancer patients receiving chemotherapy (Table 5). In a phase III multicenter, double-blinded study [41], 320 patients with small-cell or non-small cell lung cancer who were scheduled to receive at least 12 more weeks of cisplatin-containing chemotherapy were randomized to receive either placebo or once-weekly s.c. injections of darbepoetin alfa at a dose of 2.25 μg/kg for 12 weeks. Hematopoietic response was defined as a 2-g/dl rise in hemoglobin, or the achieve-

Table 3. Main characteristics of high-quality trials of rHuEPO in anemia due primarily to cancer therapy published after the systematic meta-analysis by Seidenfeld et al. [11]

Study	Dammacco et al. [35]	Österborg et al. [36]	Witzig et al. [37]
Tumor type	Multiple myeloma	Lymphoproliferative malignancies	Advanced incurable cancer
Study description	Randomized; double-blinded; concurrent controls; placebo	Randomized; double-blinded; concurrent controls; placebo	Randomized; double-blinded; concurrent controls; placebo
Hb criteria at start of trial	<11 g/dl	<10 g/dl	Males <11.5 g/dl; females <10.5 g/dl
rHuEPO regimen	Epoetin alfa escalating: 150 U/kg s.c. 3 × wk × 12 wks; 300 U/kg final dose	Epoetin beta 150 U/kg s.c. 3 × wk × 16 wks	Epoetin alfa escalating: 40,000 U s.c. 1 × wk × 16 wks; 60,000 U final dose
Treatment	Nonplatinum CT plus rHuEPO Nonplatinum CT plus placebo	Nonplatinum CT plus rHuEPO Nonplatinum CT plus placebo	CT plus rHuEPO CT plus placebo
No. of patients[a]	66 66	146 147	164 166
Mean baseline Hb (g/dl) ± standard deviation (range)	9.3 ± 1.27 9.6 ± 0.95	9.2 ± 1.1 9.3 ± 1.0	9.5 9.4
No. of patients transfused (%)	27% 45%	34% 53%	25% 40%
Mean Hb change (g/dl)	1.8 ± 2.05 0 ± 1.18	1.7 0.5	2.8 0.9
Adverse events in the rHuEPO group	No notable differences between rHuEPO and placebo groups	No notable differences in serious adverse events between rHuEPO and placebo groups	No notable differences between rHuEPO and placebo groups

[a]Number of assessable patients.
Abbreviations: CT, chemotherapy; Hb, hemoglobin; rHuEPO, recombinant human erythropoietin; wk, week.

ment of a hemoglobin level of 12 g/dl. Responses occurred more frequently in the treated patients (66% versus 24%; mean difference, 42%; 95% CI, 31%–53%; $p < .001$). However, since the hemoglobin levels were not detailed for either the treatment or placebo group, any improvement in hemoglobin concentration cannot be adequately determined.

In a similar study, Hedenus et al. [42] investigated the efficacy of darbepoetin alfa in 349 anemic patients with lymphoproliferative malignancies. All patients were receiving multicycle therapy before enrolment and had hemoglobin concentrations of ≤11.0 g/dl. A hemoglobin response of 2.0 g/dl or greater from baseline with no RBC transfusions was seen in 60% of the treated group and in 18% of placebo patients ($p < .001$). Darbepoetin alfa was associated with a higher mean change in hemoglobin level (1.80 g/dl) relative to placebo (0.19 g/dl). Thirty-one percent of patients treated with darbepoetin alfa received RBC transfusions, versus 48% of patients in the placebo group ($p < .001$). However, the authors did not indicate how many patients had to double the darbepoetin alfa dose to achieve a response.

Changes in Health-Related QoL Parameters

In recent years, improvements in cancer care have allowed oncologists and patients to focus on QoL as a central issue. The aforementioned community studies [38–40] evaluated the relationship between hemoglobin level and QoL parameters in cancer chemotherapy patients. All those trials documented significant improvements in energy, activity, and overall QoL, associated with a significant increase in hemoglobin level. An incremental analysis of the data from the reports of Demetri et al. [39] and Glaspy et al. [38] showed a statistically significant, nonlinear relationship ($p < .01$) between hemoglobin level and QoL score [43]. An increase in hemoglobin consequent to treatment was associated with an improvement in QoL score for the range of 8–14 g/dl. The most substantial improvements in QoL scores, for every 1-g/dl increment in the level of hemoglobin, occurred when the hemoglobin concentration increased from 11 g/dl to 12 g/dl (range, 11–13 g/dl; Fig. 1). Of interest to clinicians, a hemoglobin level between 7 g/dl and 10 g/dl correlated with only a slight

Table 4. Main features of community-based studies of rHuEPO therapy for cancer-related anemia

Study	Glaspy et al. [38] (*n* = 2,342)	Demetri et al. [39] (*n* = 2,370)	Gabrilove et al. [40] (*n* = 2,964)
Inclusion criteria	Anemia	Hb ≤11.0 g/dl	Hb ≤11.0 g/dl
Tumor type	Nonmyeloid malignancies	Nonmyeloid malignancies	Nonmyeloid malignancies
Cancer treatment	Chemotherapy	Chemotherapy	Chemotherapy
rHuEPO dose	150 U/kg s.c. tiw; increase to 300 U/kg s.c. tiw if inadequate response at week 8	10,000 U s.c. tiw; increase to 20,000 U/kg s.c. tiw if Hb rise <1 g/dl at week 4	40,000 U s.c. qw; increase to 60,000 U/kg s.c. qw if Hb rise <1 g/dl at week 4
Tumor response analysis	Retrospective	Prospective	Prospective
Baseline Hb level	9.5 g/dl	9.3 g/dl	9.5 g/dl
Mean Hb change from baseline	1.8 g/dl[a]	2.0 g/dl[a]	1.8 g/dl[a]
Transfusion requirements baseline/end of study (%)	21.9/10.3[b]	28.5/5.3[b]	14.2/4.9
Mean change in linear analog score relative to baseline			
Energy	14.9 mm[a]	11.5 mm[a]	11.9 mm[a]
Activity	13.1 mm[a]	11.2 mm[a]	10.8 mm[a]
Overall quality of life	11.0 mm[a]	9.8 mm[a]	9.3 mm[a]

[a]Significantly greater ($p < .01$) than baseline.
[b]Statistically significant ($p < .001$).
Abbreviations: Hb, hemoglobin; rHuEPO, recombinant human erythropoietin; qw, weekly; tiw, three times per week.

Table 5. Main characteristics of the randomized trials of darbepoetin alfa in cancer-related anemia

Study	Vansteenkiste et al. [41]	Hedenus et al. [42]
Tumor type	Small-cell and non-small cell lung cancer	Lymphoproliferative malignancies
Study description	Randomized; double-blinded; concurrent controls; placebo	Randomized; double-blinded; concurrent controls; placebo
Hb criteria at start of trial	Hb ≤11.0 g/dl	Hb ≤11.0 g/dl
Darbepoetin alfa regimen	Escalating: 2.25 μg/kg s.c. once per wk × 12 wks; 4.5 μg/kg final dose	Escalating: 2.25 μg/kg s.c. once per wk × 12 wks; 4.5 μg/kg final dose
Treatment	Platinum CT plus darbepoetin Platinum CT plus placebo	Nonplatinum CT plus darbepoetin Nonplatinum CT plus placebo
No. of patients[a]	149 149	147 146
Mean Baseline Hb (g/dl) ± standard deviation (range)	10.4 (7.4–13.6) 10.15 (6.6-12.3)	9.59 ± 1.22 9.50 ± 1.21
Patients transfused (%)	27% 52%	31% 48%
Mean Hb change (g/dl)	NR NR	1.80 0.19
Adverse events in the darbepoetin alfa group	Hypertension in nine patients (6%), thrombotic events in seven patients (5%)	No notable differences between the darbepoetin alfa and placebo groups; all adverse events associated with death were judged by the investigators as unlikely to be related to study treatment

[a]Number of assessable patients.
Abbreviations: CT, chemotherapy; Hb, hemoglobin; NR, not reported; wk, week.

improvement in QoL. This was the range for management of patients' anemia receiving transfusions before the advent of rHuEPO therapy. Since hemoglobin level was seldom improved to >10 g/dl, it is not surprising that physicians and patients did not note significant differences in QoL. In contrast, with an incremental improvement in hemoglobin level between 11 g/dl and 13 g/dl, substantial changes were noted in the overall QoL assessment.

However, given the methodological limitations inherent in community-based studies, these findings should be interpreted only as an additional support to the results of randomized clinical trials, which are the gold standard of evidence-based medicine. In this regard, benefits to health-related QoL following treatment of cancer-related anemia with rHuEPO have been demonstrated more convincingly in recent reports. Littlewood et al. [34] prospectively evaluated QoL using a placebo control [34]. The cancer-specific measures of QoL included the Functional Assessment of Cancer Therapy–General (FACT-G Total) scale, the Functional Assessment of Cancer Therapy–Anemia (FACT-An) fatigue subscale (FACT-An Fatigue), and the Cancer Linear Analogue Scales measuring energy, ability to do daily activities, and overall QoL. The analysis indicated major improvements in QoL parameters in patients who received epoetin alfa. These improvements were restricted to patients who experienced hemoglobin elevations. While in the Littlewood et al. [34] report only a univariate analysis was performed, the results of a multiple linear regression analysis of QoL data on the same patients were published by Fallowfield et al. [44]. The multiple linear regression analysis, which accounted for the effects of disease progression and other possible confounding variables on QoL, showed a significant advantage for rHuEPO over placebo for the five scales (all, $p < .05$), and confirmed the results of the univariate analysis (Fig. 2). Other recent studies with rHuEPO have confirmed and expanded on these findings [36, 37, 45–47].

Regarding the darbepoetin alfa trials, Vansteenkiste et al. [41] showed a nonsignificantly higher FACT-An Fatigue subscale score in the darbepoetin alfa group (56%; 95% CI, 47%–65%) relative to the placebo group (44%; 95% CI, 35%–52%). However, 32% (95% CI, 23%–40%) of patients in the darbepoetin alfa group showed at least a 25% improvement, whereas only 19% (95% CI, 12%–26%) of patients in the placebo group showed at least a 25% improvement ($p = .019$). On the other hand, Hedenus et al. [42] demonstrated that patients treated with darbepoetin alfa had a greater improvement in their FACT-An Fatigue subscale score than those given placebo regardless of their level of fatigue at baseline. Those patients with the lowest baseline FACT-An Fatigue subscale scores reported the largest improvements in FACT-An Fatigue subscale score at the end of treatment. After adjusting for the effect of baseline score, increases in FACT-An Fatigue subscale scores with darbepoetin alfa treatment were significantly greater than those observed with placebo ($p = .032$). In addition, a statistically significant ($p < .001$) relationship between change in hemoglobin and change in FACT-An Fatigue subscale score over the treatment period was found. For every 1-g/dl increase in hemoglobin, the estimated mean increase in FACT-An Fatigue subscale score was 1.39 (95% CI, 0.83–1.94).

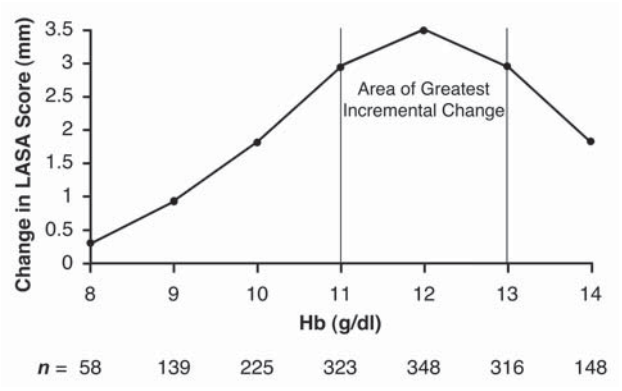

Figure 1. Incremental changes in LASA overall quality-of-life scores and Hb levels, based on a longitudinal analysis of the Demetri et al. [39] trial. Data collected at baseline, week 8, and week 16 were included in the analyses. Adapted from [43], with permission. Abbreviations: Hb, hemoglobin; LASA, Linear Analog Scale Assessment .

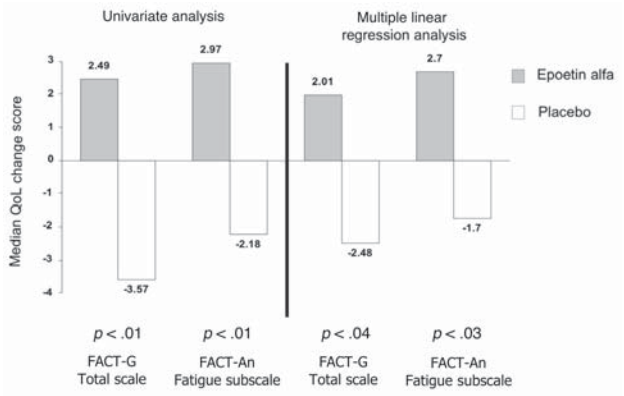

Figure 2. Quality of life mean change scores by treatment group in the Littlewood et al. [34] trial: results of univariate and multiple linear regression analyses using the FACT-G Total scale and FACT-An Fatigue subscale. Adapted from [44], with permission. Abbreviations: FACT-An, Functional Assessment of Cancer Therapy–Anemia Fatigue subscale; FACT-G, Functional Assessment of Cancer Therapy–General Total scale.

Cancer Therapy Outcomes

Anemia has been reported as an independent prognostic factor in a variety of cancer types and treatments. A systematic review of 60 articles reporting the survival of cancer patients in relation to anemia and hemoglobin concentration found a 65% higher relative risk of death for anemic patients than for nonanemic patients (Fig. 3) [48]. The study by Littlewood et al. [34] also collected data on survival and found that the median survival duration was 17 months for patients treated with epoetin alfa compared with 11 months for patients treated with placebo. However, that trial was neither designed nor powered for a survival end point, and no definitive studies have been conducted.

The body of evidence suggesting a possible benefit has been recently challenged by the publication of two negative studies [49, 50].

The Breast Cancer Eprex Survival Study (INT-76), which enrolled 939 patients with metastatic breast cancer who were receiving first-line chemotherapy, was terminated early because of a higher mortality in the epoetin alfa treatment arm than in the placebo arm at 12 months [49]. These findings were primarily attributed to the observation of a greater incidence of breast cancer progression in rHuEPO-treated patients than in placebo recipients (6% versus 3%), and to a higher incidence of fatal thrombotic and vascular events in the rHuEPO arm (1% versus 0.2%). Most of these deaths occurred in the first 4 months of the trial (Fig. 4), and the authors stated that they were unlikely to be the result of rHuEPO administration. The authors also reported limitations of the study with regard to design, conduct, and post-trial analyses.

In a multicenter European trial (MF4449), Henke et al. [50] investigated the effects of anemia correction with epoetin beta on the outcome of curative radiotherapy among patients with head and neck cancer. Three hundred fifty-one anemic patients (hemoglobin level <12 g/dl in women or <13 g/dl in men) undergoing radiotherapy were assigned to receive either s.c. placebo ($n = 171$) or 300 U/kg epoetin beta ($n = 180$) three times weekly, from 10–14 days before and continuing throughout radiotherapy. Whereas epoetin beta treatment was shown to correct anemia, locoregional progression-free survival was poorer with epoetin beta than with placebo (adjusted relative risk, 1.62; 95% CI, 1.22–2.14; $p = .0008$). For locoregional progression, the relative risk was 1.69 (95% CI, 1.16–2.47; $p = .007$), and for survival it was 1.39 (95% CI, 1.05–1.84, $p = .02$). In that study, vascular disorders including hypertension, hemorrhage, venous thrombosis, pulmonary embolism, and cerebrovascular events were observed in 11% of participants in the rHuEPO group and in 5% of patients in the placebo group. However, more than 30% of patients did not receive radiotherapy per protocol, and a further 8% had major protocol violations. In addition, no statistically significant differences in disease progression or survival end points were seen when the data were analyzed for the group of patients who did receive radiotherapy per protocol. Finally, the investigators noted that, in a subgroup of patients with cancer of the hypopharynx, more rHuEPO-treated patients than placebo-treated patients had certain unfavorable characteristics.

Dosing Regimens

Despite uncertainties regarding the optimal regimen, the doses of rHuEPO taken forward into phase III studies became the current standard. Following the meta-analysis report, the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) jointly published guidelines that recommended rHuEPO as a treatment option for patients having chemotherapy-associated

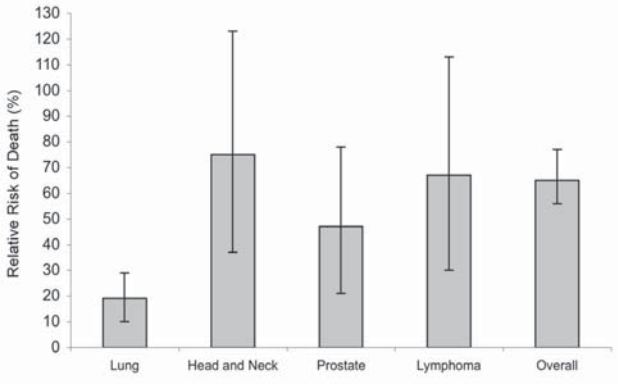

Figure 3. Impact of anemia on relative risk of death. Vertical bars represent 95% confidence intervals. Adapted from [48], with permission.

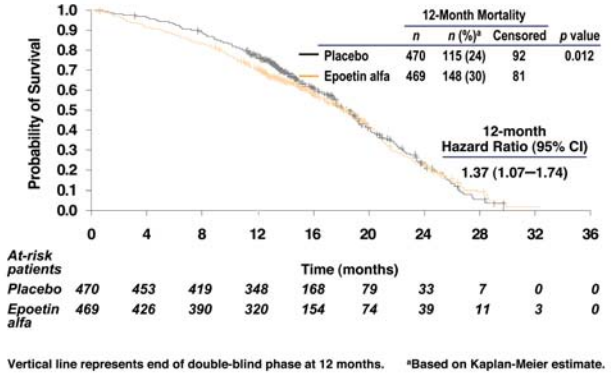

Figure 4. Survival estimates from the INT-76 trial (see text for details). Data available at http://www.fda.gov/ohrms/dockets/ac/04/slides/4037s2.htm. Abbreviation: CI, confidence interval.

anemia (hemoglobin level <10 g/dl), advising s.c. administration at a starting dose of 150 IU/kg three times weekly [51, 52]. If an adequate hematologic response is not seen at week 4, the dose may be doubled. An alternative weekly dosing regimen (40,000 IU/week; 60,000 IU/week in nonresponders), also cited in the guidelines of the National Comprehensive Cancer Network (NCCN) [53], was based on results of the Gabrilove et al. [40] trial. Although this approach has not been compared with placebo or with three-times-weekly dosing in randomized trials, and this dosing schedule therefore does not appear on the label, it is used in clinical practice in the U.S. and in many European countries for chemotherapy patients.

Recently, Cazzola et al. [54] conducted a prospective, randomized trial to compare the relative efficacy of two schedules of epoetin beta. Two hundred forty-one anemic patients with various lymphoproliferative diseases were randomized to receive epoetin beta either once weekly (119 patients; 30,000 IU fixed dose) or three times weekly (122 patients; 10,000 IU fixed dose) over 16 weeks. The analysis of the hemoglobin area under the concentration-versus-time curve (Hb-AUC) showed that the once-weekly regimen was clinically comparable with the thrice-weekly regimen (difference = –.20 g/dl; 90% confidence interval –0.52–0.11). Therapeutic response rates were high and similar in both groups (72% in the once-weekly regimen and 75% in the thrice-weekly regimen). It should be noted that inclusion criteria required a baseline serum EPO level of <100 mU/l; this may have contributed to the high response rates. Although that study requires confirmation, it has obvious cost implications. In fact, if rHuEPO given once weekly at a dose of 30,000 U produces results indistinguishable from those of a dose of 10,000 U × 3/week, then the current level of patient benefit may be achieved with 25% less cost.

The dose-response relationships for darbepoetin alfa administered every 1–2 weeks were analyzed in a large phase II study in cancer patients receiving chemotherapy [55, 56]. A clear relationship was evident between the dose and the magnitude of mean increase in hemoglobin in each cohort until a dose of 4.5 μg/kg per week or 9 μg/kg every 2 weeks was reached. That trial also included a control group treated with epoetin alfa administered at starting doses of either 150 U/kg three times weekly or 40,000 U/wk, with dose increases permitted for nonresponding patients. Results suggest that darbepoetin alfa at a dose of 3 μg/kg every 2 weeks was comparable with epoetin alfa at a dose of 40,000 U/wk [56]. In addition, results of a large community-based study of darbepoetin alfa (3 μg/kg every 2 weeks) were comparable with results of community-based studies of epoetin alfa [57]. The comparability of darbepoetin alfa at a dose of 3 μg/kg every 2 weeks and a 200-μg fixed dose every 2 weeks was suggested by pharmacokinetic and pharmacodynamic modeling and clinical trial simulation [58]. Although this approach has not been compared with placebo in a randomized clinical trial and is not the labeled dose and schedule, it is the darbepoetin regimen currently used in the U.S. in chemotherapy patients. Recommended guidelines were then developed to assist pharmacists and physicians with the therapeutic substitution [59]. A once-every-3-weeks regimen was explored recently. A placebo-controlled trial of 249 cancer patients receiving chemotherapy showed hemoglobin responses in >50% of patients receiving 4.5–15.0 μg/kg of darbepoetin every 3 weeks and an overall reduction in transfusion needs in those receiving active drug [60]. Finally, the concept of "front-loading," that is, higher doses of darbepoetin alfa administered early in therapy to achieve an earlier response in a higher proportion of patients, has been tested recently. Pilot data from a study of 127 patients receiving chemotherapy support the effectiveness of this schedule in cancer patients [61].

Comparisons Between Erythropoietic Agents

To date, just one large, head-to-head trial of erythropoietic agents in cancer-related anemia has been published. Schwartzberg et al. [62] recently reported the results of a randomized comparison of darbepoetin alfa (200 μg s.c. every 2 weeks) and epoetin alfa (40,000 U s.c. once a week) in 312 patients with breast cancer, non-small cell lung cancer, or gynecological cancer receiving concurrent chemotherapy. Three identical but separate protocols were used, one for each tumor type, with a combined analysis of all data from each trial prespecified in each protocol. Doses were increased to 300 μg every 2 weeks for darbepoetin alfa or 60,000 U weekly for epoetin alfa if, after 4 weeks of treatment, hemoglobin levels did not increase by 1 g/dl from baseline. Furthermore, doses for either drug were withheld if hemoglobin levels were >13 g/dl and were restarted at the previous dose once hemoglobin levels were ≤13 g/dl. The results were analyzed based upon the achievement and maintenance of a target hemoglobin threshold (≥11 g/dl) and range (11–13 g/dl).

More than 80% of patients in both arms of the study achieved target hemoglobin levels. Transfusions were similar in the two treatment groups, at 16% for the darbepoetin alfa group and 17% for the epoetin alfa group. After achievement of a hemoglobin level >11 g/dl, the mean hemoglobin level was maintained at approximately 12 g/dl for the remainder of the trials in both treatment groups. Eighty-one percent of patients in the darbepoetin alfa group remained in the target range, versus 75% in the epoetin alfa group. No differences in the percentages of patients who had to increase the dose, the median times to achieve the target hemoglobin level, or the incidences of adverse events were observed.

These results should be interpreted cautiously because efficacy and safety of the two agents were secondary objectives of the trials, and the sample size was not formally powered to test noninferiority. In fact, the study's primary end point was validation of the Patient Satisfaction Questionnaire for Anemia Treatment (PSQ-An), which assessed the impact of receiving anemia treatment. More definitive evidence should be provided by the results of a National Cancer Institute–sponsored randomized trial, including approximately 1,200 patients and specifically designed to compare the efficacy and safety of darbepoetin alfa and epoetin alfa.

Prediction of Response to Erythropoietic Agents

Although reduced endogenous erythropoietin production was the rationale for the use of rHuEPO in anemic cancer patients, baseline levels of serum EPO have been inconsistently associated with response. Several analyses have been performed to identify factors predicting a response to rHuEPO treatment in patients with anemia, and their results are reported in Table 6. However, these algorithms have not been validated prospectively in larger trials [63]. A recent publication on the use of darbepoetin alfa supports the contention that there are no valid predictive factors for response to erythropoiesis-stimulating therapy [42].

Iron Supplementation and Response to Erythropoietic Agents

The pathogenesis of cancer-related anemia is complex and multifactorial but is known to involve absolute or functional iron deficiency, with access to iron stores inadequate to support the increased demand associated with erythropoiesis-stimulating therapy [64]. The most accurate method for detecting functional iron deficiency in cancer patients is the measurement of the percentage of hypochromic RBCs or reticulocyte hemoglobin content [65]. Such measurements, however, require specialized instrumentation that is not widely available. An alternative method for evaluating available iron stores is transferrin saturation. A transferrin saturation of 20%–30% is thought to indicate sufficient iron stores to support erythropoiesis in rHuEPO-treated patients, whereas lower levels may reflect functional iron deficiency [66]. A randomized trial of iron supplementation was conducted recently in patients with chemotherapy-related anemia (hemoglobin ≤105 g/l, serum ferritin ≤450 pmol/l or ≤675 pmol/l with transferrin saturation ≤19%) receiving epoetin alfa. The results suggest that the erythropoietic response is greater when parenteral iron is given in addition to rHuEPO than when patients receive oral iron or no iron support [67]. Although additional trials are needed, i.v. iron supplementation is reasonable in anemic patients with iron deficiency, whether or not they are receiving an erythropoietic agent.

Safety and Tolerability

Early comparative studies reported similar adverse-event profiles for rHuEPO and placebo except for shortness of breath, which was twice as frequent in patients receiving placebo [10]. Five per cent of rHuEPO-treated patients experienced hypertension, compared with 3.5% of placebo-treated patients. Although the difference was not significant, it is recognized that erythropoietin-treated patients may occasionally experience hypertension. In patients with solid tumors, the adverse event profiles were similar in the rHuEPO and placebo groups, though a few more cases of deep vein thrombosis occurred in the rHuEPO group. In six trials in patients with anemia due to an underlying hematologic malignancy [68–73], there was a statistically significant higher rate of hypertension (10% versus 1%; $p = .011$) and a nonsignificantly higher rate of thromboembolic events (3% versus 0%; $p = .55$) among rHuEPO-treated patients [11]. The incidences of adverse events were similar in three community-based, open-label trials [38–40] and generally lower than those reported in the comparative trials.

Bohlius, Langensiepen, Schwarzer et al. recently performed a systematic meta-analysis based on 1,738 participants in 12 trials published up to 2001 [74]. Overall, the data evaluated in that review did not provide conclusive evidence that rHuEPO treatment increased the risk for hypertension and thromboembolic events or related complications in cancer patients. However, the safety of rHuEPO needs to be reconsidered in light of recent reports. We have already described the high rate of thrombotic and vascular events in the rHuEPO groups of the INT-76 and MF4449 trials [49, 50]. A retrospective study of 147 consecutive patients with localized carcinoma of the uterine cervix or vagina treated with chemotherapy and radiation evaluated women who received rHuEPO ($n = 75$) and women who did not ($n = 72$) [75]. Patients who received rHuEPO had an odds ratio of developing thrombosis of 10.3 (95% CI, 2.3–46.2). Multiple logistic regression revealed that only the use of rHuEPO was associated with an increased risk of thrombosis (odds ratio, 15.3; 95% CI, 3.1–76.7). No association was found between the mean or peak hemoglobin level and the risk of thrombosis. In this regard, it is noteworthy that multiple doses of rHuEPO can produce potential adverse rheologic effects, regardless of the degree of red cell mass increase. Furthermore, rHuEPO is known to possess procoagulant activities that predispose to thrombosis. [76, 77]

Another safety issue concerns the potential support and extension of tumor growth by rHuEPO. In fact, expression of EPO and its receptor has been demonstrated in several tumor cell lines [78–81], and there is increasing evidence that tumor cells can use the erythropoietin system for growth and angiogenesis [81, 82]. Given the major vari-

Table 6. Factors reported to predict a response to erythropoietin in cancer-related anemia

Study	No. of patients	Predictive factors identified: Before treatment	After 2 weeks treatment	After 4 weeks treatment
Hematologic malignancies and solid tumors with or without chemotherapy				
Ludwig et al. [92]	40		Serum erythropoietin <100 U/l; Hb ↑≥0.5 g/dl; serum ferritin <400 ng/ml	
Cazzola et al. [93]	48	Serum erythropoietin <100 U/l	Serum soluble transferrin receptor ↑≥25%	Hb ↑≥1 g/dl; reticulocyte count ↑≥40,000/μl
Solid tumors with or without chemotherapy				
Henry et al. [94]	206			Hb ↑≥1 g/dl; reticulocyte count ↑≥40,000/μl
Gonzalez-Baron et al. [95]	117			Hb ↑≥0.5 g/dl
Witzig et al. [37]	164			Serum erythropoietin <100 U/l; Hb ↑≥0.5 g/dl
Multiple myeloma and non-Hodgkin lymphoma with or without chemotherapy				
Cazzola et al. [73]	57	Serum erythropoietin ≤50 U/l	Hb ↑≥0.3 g/dl	
Österborg et al. [71]	82	Serum erythropoietin <50 U/l; platelet count >100 × 10^9/l		
Österborg et al. [36][a]	170	Platelet count >100 × 10^9/l; Hb ≥9 g/dl; pretreatment transfusion requirement <2 units in 3 months		
Cazzola et al. [54][b]	241	Serum erythropoietin ≤41 U/l		
Myelodysplastic syndromes				
Hellstrom-Lindberg [96]	179	Serum erythropoietin ≤200 U/l; no transfusions; no refractory anemia with ringed sideroblasts		
Hellstrom-Lindberg et al. [97] (erythropoietin plus G-CSF)	98	Serum erythropoietin <100 U/l; <2 transfusions/month		
Italian Cooperative Study Group [68]	44	Serum erythropoietin ≤200 U/l		

[a]All patients in this study were required to have an inadequately low endogenous serum erythropoietin concentration, defined as a serum erythropoietin level ≤100 IU/l (if Hb level was >9 to <10 g/dl), ≤180 IU/l (if Hb level was >8 to ≤9 g/dl), or ≤300 IU/l (if Hb level was ≤8 g/dl).
[b]All patients in this study had baseline serum erythropoietin levels ≤100 U/l.
↑ indicates increase.
Abbreviation: Hb, hemoglobin.

ability of the data reported in the literature thus far, the negative results of the INT-76 and MF4449 trials cannot be considered conclusive. Furthermore, as an additional note, the principal investigator of one of those studies urged that caution should be used in interpreting these results because of concerns with study design [49].

Finally, in spite of the extensive use of this drug in oncology, there is no report of pure red-cell aplasia (PRCA) associated with use of rHuEPO in cancer patients [83]. Patients with cancer are probably less likely to develop PRCA than patients with chronic renal disease because of a decrease in immune competence, other therapies, and reduced time of exposure to the drug.

Most of the data on darbepoetin alfa are provided by the registrative trial of Vansteenkiste et al. [41]. Hypertension was reported as an adverse event in nine patients (6%) in the darbepoetin alfa group and in six patients (4%) in the placebo group. Thrombotic events occurred in seven patients (5%) in the dar-

bepoetin alfa group and in five patients (3%) in the placebo group. Similar proportions of patients from both groups withdrew because of an adverse event (other than death). No deaths were considered by the investigators to be related to the study drug, and most of the deaths (61% in the darbepoetin alfa group and 58% in the placebo group) were attributed to disease progression. In the Hedenus et al. [42] trial, the safety profiles of darbepoetin alfa and placebo were consistent with those generally associated with malignant disease and the toxic effects of chemotherapy. The incidence of withdrawal from the study as the result of an adverse event (other than death) was similar for the darbepoetin alfa (3%) and placebo (4%) groups. Ten patients (6%) in the darbepoetin alfa group and four patients (2%) in the placebo group died during the study or within 30 days after the last dose of study drug. Most deaths were attributed to progressive disease, and none was considered to be related to the study drug by the investigators. An initial analysis of long-term data on disease status and survival was conducted after a median follow-up period of approximately 11 months. During the combined study period and follow-up period, the incidences of disease progression or death (i.e., progression-free survival) were similar in the darbepoetin alfa group (82 patients, 47%) and the placebo group (76 patients, 45%).

Pharmacoeconomic Considerations

Studies of rHuEPO cost-effectiveness have been challenging to conduct and analyze. The costs of some outcomes, such as QoL indicators or the impact of anemia on an individual patient's productivity, have been difficult to quantify. Also, a proper evaluation of the affordability of rHuEPO should include a comparison of both the costs of administration and the costs of the consequences of transfusion. Recent economic analyses of erythropoietin for chemotherapy-induced anemia have reported varying results depending upon the methodology used to determine costs or cost-effectiveness.

In Europe, the cost of the prophylactic use of rHuEPO for four cycles of chemotherapy at the recommended dose (150 U/kg three times a week) was estimated to be US$4,400 per patient; transfusion for the same patients was US$206 [84]. Moreover, rHuEPO was effective at abolishing transfusional needs in only half the patients, and a cost-effectiveness analysis that considered all the risks and benefits of the two treatment strategies resulted in an incremental cost-effectiveness ratio of US$189,652/quality-adjusted life year [84]. In patients treated with cisplatin chemotherapy, rHuEPO added US$190,142/quality-adjusted life year [84]. In general, this is considered to be a high figure relative to other commonly used healthcare interventions in other settings. However, it has been argued that cost per quality-adjusted life year gained may not be the most appropriate measure to use in economic evaluations when comparing two supportive care measures with no difference in survival [85].

A U.S. study used changes in hemoglobin level and QoL as measures of effectiveness of rHuEPO [85]. The study drew cost and effectiveness assumptions from a literature review and three clinical trials involving more than 4,500 patients. Treatment with rHuEPO, which gave a 9.3-point increase in QoL over 16 weeks, gave costs per quality-adjusted life year ranging from US$110,769 to US$214,391 [85].

These results suggest that the cost-effectiveness of rHuEPO therapy relative to transfusion is mostly dependent on the cost of the drug. Inability to predict response to rHuEPO therapy can add to its perceived expense [86]. Therefore, strategies to improve the cost-effectiveness ratio include both a better tailoring of its use in patients with a high probability of response and reducing the market cost of the drug.

Finally, it has been shown that changes in dosing and pricing over time can have profound effects on the cost per quality-adjusted life year ratios. For example, the cost per quality-adjusted life year of rHuEPO in chronic renal failure was more than 100,000 British pounds in 1992, [87] but has recently been estimated at 17,000 British pounds [88], and it may well be that estimates produced by more recent cost-effectiveness studies of rHuEPO in cancer-related anemia are nearer the threshold of acceptability.

Conclusions

Despite the abundance of data, the role of erythropoietic agents in the treatment of anemia in cancer still presents many unresolved issues. Most patients eligible for epoetin or darbepoetin therapy on the basis of having hemoglobin levels <10 g/dl during chemotherapy do not receive treatment [4, 89], mainly because of financial considerations [90]. Several randomized trials and large open-label studies support the use of these agents for the treatment of anemia related to cancer therapy, since they can reduce the need for transfusions and improve hemoglobin levels. But these trials do not indicate whether such drugs are the best treatment option both in terms of effects on the patients and economics. The ideal starting time for initiation of erythropoietin therapy is also controversial [51–53]. If individuals are allowed to develop symptomatic anemia with hemoglobin levels of 8.0–9.0 g/dl, it takes 3–4 weeks before their hemoglobin levels begin to rise, resulting in a long interval during which their QoL deteriorates. Retrospective studies show that a fall in hemoglobin level of 1.5 g/dl or more during the first 6–8 weeks of chemotherapy predicts a high rate of

anemia (70%–85%) and transfusion (30%–50%) [91]. Therefore, a reasonable strategy would be to institute erythropoietin when a fall in hemoglobin of 1.5 g/dl is documented on two consecutive occasions.

Although erythropoietins are well tolerated, they are slow to exert an effect, and ineffective in a substantial proportion of patients. On the other hand, transfusion of RBCs is associated with a small risk of infection and other complications. However, no study has produced comparative results of toxicity between erythropoietins and transfusions in cancer patients, and the purported superior risk-benefit ratio of erythropoietic agents remains to be fully demonstrated. Blood transfusion is reliable, with a prompt hemoglobin increase in most patients treated. Another important consideration is that, in many patients with cancer, anemia is a feature of advanced disease. Therefore, a substantial proportion of these patients will not live long enough to experience the long-term hazards of blood transfusion. In others, anemia is a transient problem caused or aggravated by cancer therapy. These patients require few, if any, blood transfusions, and their risk of incurring lasting damage is small. Indeed, treatment with erythropoietins is attractive in patients with a long life expectancy and chronic transfusion dependency, such as patients with low-risk myelodysplastic syndromes. Unfortunately and ironically, only a minority of these patients are likely to respond.

An issue that might tilt the balance in favor of erythropoietin therapy would be a positive impact on cancer treatment outcome. To date, a possible survival trend favoring rHuEPO has not been confirmed in recent reports, which have raised concern about thromboembolic risks and the potential stimulation of tumor cell growth by the study drug. However, we underline the fact that the two recent trials with negative outcomes involved attempts to maintain hemoglobin concentrations in a range higher than those currently approved for the use of erythropoietic agents [49, 50]. The use of either rHuEPO or darbepoetin alfa in this setting should continue to be considered only in the context of well-designed, clinical investigations with appropriate safeguards for patients.

Cost-effectiveness issues are also of major importance, and the number of patients needed to be treated with erythropoietins to avoid one transfusion has been estimated at 4.4 (95% CI, 3.6–6.1) [11]. In addition, the impact of these drugs on survival, life years, and quality-adjusted life years gained needs to be available in order for a detailed appraisal to be undertaken. At present there is insufficient evidence on which to assess the cost-effectiveness of erythropoietins in the treatment of cancer-related anemia.

Currently, the strongest arguments to support the use of erythropoietic agents in cancer patients seem to be the effects on health-related QoL parameters. All studies that have specifically assessed QoL have produced convincing data indicating an improvement in this end point.

In conclusion, erythropoietic agents are a class of drug with an enormous potential for the treatment of cancer-related anemia and its consequences. However, their use needs to be optimized in terms of cost-effectiveness, indications need to be redefined, and issues regarding safety need to be clarified. To resolve these issues, the design of new randomized clinical trials with a stronger methodology is a major priority.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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