

# Control of cancer-related anemia with erythropoietic agents: a review of evidence for improved quality of life and clinical outcomes

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**Background:** Anemia occurs frequently in patients with cancer and is associated with impaired health-related quality of life (HRQOL). Treatment of anemia results in significant improvements in energy, activity and overall HRQOL, particularly among patients with mild-to-moderate anemia. Importantly, studies have indicated that anemia may have a negative impact on the success of radiotherapy, reducing survival and locoregional control. Recent preclinical and preliminary clinical data have also suggested that anemia may be associated with poorer outcomes following chemotherapy or surgery.

**Materials and methods:** Data for review were identified and selected from searches of the literature published from January 1990 through to October 2002 using Medline<sup>®</sup>, and searches of proceedings from key international oncology and hematology meetings.

**Results:** A wealth of data indicate that treatment of anemia improves HRQOL in patients with cancer. Prospective studies exploring survival and/or treatment outcomes in anemic cancer patients are currently in their early stages, preventing any firm conclusions from being drawn, although they do indicate a benefit in treating anemia.

**Conclusions:** Recent studies support the use of erythropoietic agents in anemic cancer patients as a means of raising their hemoglobin levels and consequently improving their HRQOL. Randomized, controlled trials are needed to determine whether treating anemia with erythropoietic agents will improve other outcomes following therapy.

**Key words:** anemia, cancer, darbepoetin  $\alpha$ , health-related quality of life, recombinant human erythropoietin, survival

## Introduction

Anemia is a common occurrence in patients with cancer, particularly among those receiving myelosuppressive chemotherapy, in whom anemia can occur in up to 100% of patients, depending on the chemotherapy regimen used [1]. The incidence of anemia varies depending upon the type of underlying malignancy, the stage and duration of disease, the regimen and intensity of tumor therapy, and possibly the occurrence of intercurrent infections or surgery [2].

A number of factors may contribute to the development of anemia, which is defined by the World Health Organization as a hemoglobin level of  $\leq 12$  g/dl. Metastases within the bone marrow may displace and destroy stem cells and progenitor cells, which can damage the bone marrow microenvironment, impair production of hematopoietic growth factors or induce production

of cytokines that inhibit erythropoiesis [2]. These cytokines may shorten red cell survival, induce a hypoproliferative state that prevents the marrow from responding to hematopoietic demand or cause a defect in iron re-utilization [2]. Where bone marrow infiltration is not apparent, malignancy may induce anemia through decreased production of erythropoietin [3]. Tumor bleeding, nutritional deficiencies and infections may also contribute to the multifactorial etiology of anemia [4]. In addition, chemotherapy and radiotherapy may both contribute to the development of anemia in patients with cancer [1, 2, 4–7]. This may be due to the direct myelosuppressive effects of these therapies on the bone marrow, or, in the case of platinum-containing agents, it may be due to damage to erythropoietin-producing renal tubule cells.

Anemia may adversely affect patients with cancer in several ways. This article critically reviews selected evidence demonstrating that correction of anemia with erythropoietic agents improves health-related quality of life (HRQOL), and considers specific data indicating that raising hemoglobin levels may improve survival following cancer therapy. A better understanding of the way in which anemia affects patients with cancer

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should facilitate informed decisions regarding the appropriate management of anemia.

## Materials and methods

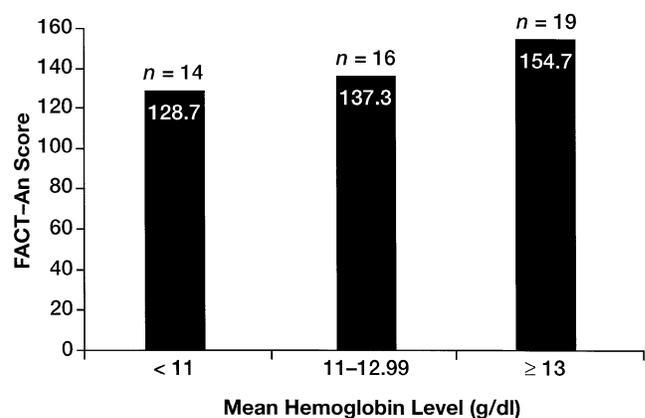
Potential data for review were identified from searches of the published literature using Medline® and proceedings from international oncology and hematology meetings (American Society of Hematology/American Society of Clinical Oncology/European Cancer Conference). The searches were limited to abstracts/articles in English, involving human adult subjects and published from January 1990 to October 2002. The text words ‘cancer, anemia, and quality of life’ were used in the title, abstracts or keyword list search for evidence relating to HRQOL. For data relating to anemia and cancer therapy outcomes the following text words were used in the search: ‘cancer, hemoglobin, local control, impact, and chemoradiation’. Key references, which reported original study results of direct relevance to the topic discussed, were then selected for review. Only prospective studies analyzing HRQOL were selected, while retrospective analysis on anemia and cancer therapy outcomes were also reviewed, due to the low number of prospective trials on this subject. The majority of studies selected for review were also found to be industry supported. It should be noted that in such studies, there is the potential for some bias in the selection of endpoints.

## Impact of anemia on HRQOL

Decreased oxygen delivery to tissues can result from anemia, which may adversely affect virtually all organs [8]. Anemia is a multi-symptom syndrome, with fatigue being the primary symptom. Other manifestations include exertional dyspnea, cardiovascular complications, dizziness, headache, chest pain, decreased motivation and depression, impaired cognitive function, anorexia, nausea, indigestion, sleeping disorders, menstrual problems and loss of libido [9]. Symptom severity depends on the degree of anemia, as well as the rapidity of its onset, and the patient’s pulmonary and cardiovascular function. Obviously, these symptoms also impact on HRQOL, and several studies have documented the effects of anemia on the lives of patients with cancer [10–13].

Although care should be taken when making clinical interpretations from results generated by any HRQOL assessment, a number of tools to measure HRQOL in patients with cancer have become widely used and accepted. One of these, the Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale, was developed specifically to assess the impact of anemia on patients [10]. Other tools frequently used include the Linear Analog Scale Assessment (LASA) and the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) scale. These tools provide a useful measure of energy levels and ability to perform daily tasks as well as physical, social and emotional well-being in patients with cancer.

Health-related quality of life has been shown to correlate directly with the degree of anemia in patients with cancer [10, 11]. Figure 1 shows the relationship between HRQOL (measured using the FACT-An scale) and hemoglobin levels [10]. The patient’s ability to work is also associated with hemoglobin levels. In one study, 25% of patients with hemoglobin levels  $\leq 12$  g/dl reported that they were unable to work, compared with only 8% of patients with hemoglobin levels  $>12$  g/dl [11]. Overall,



**Figure 1.** The association between health-related quality of life [as measured by the Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale] and hemoglobin level in cancer patients with anemia [10].

patients with hemoglobin levels  $>12$  g/dl have reported significantly less fatigue and other symptoms of anemia, better physical and functional well-being, and higher general HRQOL [11].

## Anemia and fatigue

Fatigue can be defined as the subjective sensation of having reduced energy, loss of strength or becoming easily tired [14]. Several researchers have assessed the prevalence, consequences and perceptions of fatigue in patients with cancer, caregivers and oncologists [15–17]. They found that more than three-quarters of patients with cancer experienced fatigue, defined for the purposes of these studies as debilitating tiredness during the course of their disease and treatment [15]. Of the patients reporting fatigue in a study by Curt et al. [16], 91% said that it prevented them from leading a ‘normal’ life and 88% indicated that fatigue altered their daily routine.

Fatigue is often attributed to low hemoglobin levels [9]. However, anemia is not the only cause of fatigue and the precise relationship between hemoglobin level and fatigue is not well understood [14]. Nevertheless, hemoglobin levels should be evaluated when patients present with fatigue, as therapy for anemia is available.

## Treating anemia associated with cancer

Anemia in patients with cancer is primarily treated with red blood cell transfusions, or administration of erythropoietic proteins. Blood transfusions provide rapid relief from anemia but are associated with many real and perceived risks, such as infections and hemolytic reactions [18]. Furthermore, patients often prefer to avoid these procedures [18].

Epoetin ( $\alpha/\beta$ ) effectively raises hemoglobin levels and decreases transfusion requirements in 50–60% of patients with anemia of cancer [19–21]. Increased hemoglobin levels and decreased transfusions have also been reported following treatment with darbepoetin  $\alpha$ , a novel erythropoiesis stimulating protein with a longer serum half-life than epoetin [22–25]. However,

the cost-effectiveness of these erythropoietic proteins has not yet been demonstrated. Published studies have differed significantly in their design and perspective, inclusion of indirect costs (such as patient travel time), their choice of a primary outcome variable and their treatment of HRQOL effects. Comparison across studies is therefore difficult. Cost-effectiveness studies, conducted from a healthcare system perspective, found that epoetin therapy was not cost-effective relative to the use of transfusions [26, 27]. Transfusion therapy was found to be cost-saving relative to epoetin in the study by Sheffield et al. [26], while in a study by Barosi et al. [27] the marginal cost of epoetin therapy relative to standard care was estimated to be US \$189 652 per quality-adjusted life year, an amount generally not considered to be cost-effective [27]. A further study by Ortega et al. [28] demonstrated that patients in Canada were willing to pay far less on average than the incremental cost of erythropoietin (including both direct medical costs plus patient travel time for the purpose of receiving a transfusion), resulting in a net incremental treatment cost of at least US \$2943. However, other research has suggested that the use of epoetin therapy may be cost-effective relative to standard care. A modeling study conducted from the provider perspective by Cremieux et al. [29] drew direct medical cost and effectiveness assumptions from a literature review and three US clinical trials involving more than 4500 patients with cancer. Using cumulative change in hemoglobin levels for a 16-week treatment period, the study showed that the effectiveness from US \$1 spent on standard care could be achieved with US \$0.81 using epoetin therapy. The estimated cost-effectiveness of epoetin therapy relative to transfusion is dependent on multiple study design issues, and is in need of further evaluation. Reduced administration costs and improved targeting of epoetin therapy to those most likely to benefit from the treatment could improve the cost-effectiveness of its use.

Research conducted in 3472 cancer patients from 1996 to 2000 suggests that as few as 30% of patients in the USA receive epoetin treatment for anemia despite the high incidence of anemia in patients with cancer and the known benefits of therapy [30]. Furthermore, a recent survey of physicians in the USA showed that anemia remains under-treated across all hemoglobin levels, with only 35% and 15% of patients with hemoglobin levels of <10 g/dl and 10–12 g/dl, respectively, receiving epoetin therapy [31]. European physicians are much less likely than their US counterparts to support epoetin use [32].

Some limitations of epoetin may contribute to this apparent under utilization. For example, the requirement for once, twice or three times a week injections necessitate frequent patient visits to oncology clinics, which may not coincide with routine cancer treatment visits. Furthermore, 40–50% of patients do not respond to epoetin when given at recommended dosages, and currently there are no reliable means of predicting whether a patient will respond. Studies demonstrating less frequent dosing and a robust dose–response curve with darbepoetin  $\alpha$  may help to address these issues [23, 33]. Finally, the relatively long time it takes some patients to exhibit a response (up to 12 weeks) remains an issue [34], although studies addressing this matter with higher initial doses of epoetin or darbepoetin  $\alpha$  are in progress [35, 36].

These studies utilize a high-dose loading phase with the aim of inducing an initial rapid hematological response, followed by a lower-dose maintenance phase to sustain the response.

## Treating anemia with erythropoietic agents improves HRQOL

Numerous placebo-controlled and open-label studies have demonstrated that measurable improvements in HRQOL can be achieved through the treatment of anemia with erythropoiesis stimulating proteins in patients with cancer [12, 13, 19–22, 37–39]. The US Cancer Pain Relief Committee recently analyzed five randomized, placebo-controlled trials and two large, open-label trials, published between 1990 and 2001, to confirm the beneficial effects of epoetin on HRQOL in anemic cancer patients. From this analysis, evidence-based guidelines have been proposed that recommend epoetin as a safe and effective treatment that should be used in patients for whom symptoms of anemia are sufficient to impair functional capacity or HRQOL, where the anemia is sufficient to necessitate blood transfusion, or if blood transfusion is not an acceptable treatment option [40]. Similarly, the evidence-based review commissioned by the Agency for Healthcare Research and Quality recommends that epoetin is effective in reducing transfusion risk among anemic (hemoglobin declining to near 10 g/dl) cancer patients receiving chemotherapy. This report also concluded that available quality of life data from adequately powered, methodologically rigorous studies were not yet sufficient to support the quality of life benefits from epoetin therapy in this setting [41]. However, since this analysis, which considered data published up until the end of 1999, data from prospective trials assessing HRQOL by validated questionnaires in patients with cancer receiving erythropoietic agents have been published. These more recent trials, which were considered in the US Cancer Pain Relief Committee analysis, demonstrate significant improvements in HRQOL following treatment of anemia with an erythropoietic protein [38, 39, 42]. Most recently, another placebo-controlled trial of epoetin  $\alpha$  therapy during cancer chemotherapy has been reported, demonstrating a greater improvement in FACT-F score in the treatment group [43]. We believe that these additional studies, published since the meta-analysis by the Agency for Healthcare Research and Quality, demonstrate the HRQOL benefits of anemia therapy in patients with cancer.

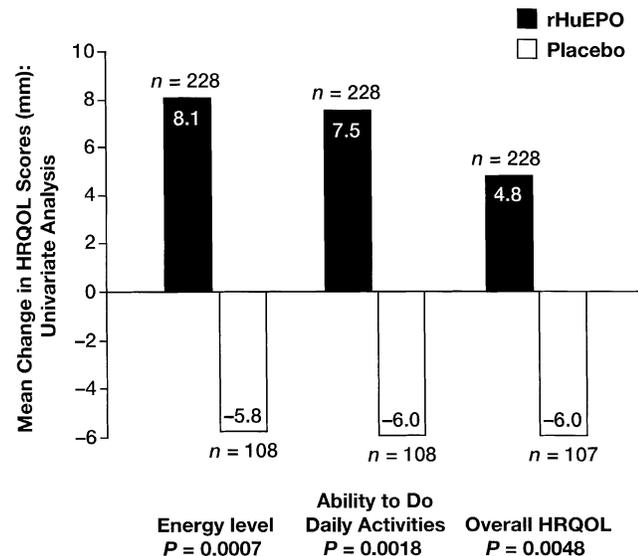
In a recent, double-blind, placebo-controlled trial involving 375 patients with non-myeloid malignancies, administration of 150–300 U/kg epoetin  $\alpha$  three times a week for 12–24 weeks resulted in a significant decrease in red blood cell transfusion requirements. Twenty-five per cent of patients receiving epoetin  $\alpha$  required a transfusion after day 28, compared with 40% of placebo patients ( $P = 0.0057$ ). Patients receiving epoetin  $\alpha$  also experienced a significant increase in hemoglobin compared with patients receiving placebo (2.2 versus 0.5 g/dl;  $P < 0.001$ ). In addition, compared with placebo-treated patients, patients receiving epoetin  $\alpha$  reported significant increases in energy levels (epoetin  $\alpha$  +8.1; placebo –5.8;  $P = 0.007$ ), ability to carry out daily activities (epoetin  $\alpha$  +7.5; placebo –6.0;  $P = 0.0018$ ) and

overall HRQOL (epoetin  $\alpha$  +4.8; placebo -6.0;  $P = 0.0048$ ), as assessed using a linear analog scale (Figure 2) [38].

Three large, open-label, community-based trials studying the effect of epoetin on HRQOL in the setting of clinical oncology practice, where prescribing practice is less controlled, have provided further compelling evidence for the benefits of treating anemia in patients undergoing chemotherapy [12, 39, 44].

Demetri et al. [12] demonstrated that raising hemoglobin levels with epoetin  $\alpha$  significantly improved HRQOL. When patients were divided into subgroups according to their response to therapy, the improvement in quality of life parameters (measured by the FACT-An scale and LASA) was shown to be independent of tumor response. In other words, patients who achieved a complete or partial response, or who had stable disease but no meaningful increase in hemoglobin levels did not have a meaningful or significant increase in quality of life. Small and significant correlations between the change in hemoglobin levels and change in overall quality of life for complete response ( $r = 0.242$ ;  $P < 0.001$ ), partial response ( $r = 0.275$ ;  $P < 0.001$ ) and stable disease ( $r = 0.253$ ;  $P < 0.001$ ) were shown, but not for progressive disease ( $r = 0.084$ ).

An open-label study by Gabrilove et al. [39] reported similar findings; however, in this study, patients received epoetin  $\alpha$  at a dose of 40000 U/week for a maximum of 16 weeks. The dose could be increased to 60000 U/week after 4 weeks if hemoglobin response was inadequate. As Figure 3 shows, a small, positive and significant ( $r = 0.173$ ;  $P < 0.001$ ) correlation was demonstrated between the increase in overall HRQOL and the increase in hemoglobin levels from baseline. Functional status and

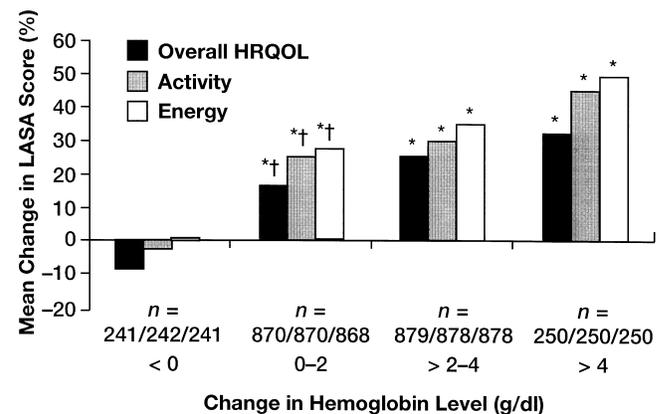


**Figure 2.** Comparison of health-related quality of life (HRQOL) mean change scores (measured using a linear analog scale comprising energy level, ability to carry out daily activities and overall quality of life) for patients receiving epoetin  $\alpha$  (rHuEPO) or placebo (HRQOL population). All  $P$  values, which correspond to primary measures, are adjusted for multiple comparisons (sequentially rejective Bonferroni procedure). Reprinted with permission from the American Society of Clinical Oncology, from Littlewood et al. [38].

fatigue, assessed using LASA, improved, with patients reporting increased energy levels, ability to perform daily tasks and overall HRQOL. The fact that the correlations between hemoglobin level and HRQOL in both studies were significant but small, confirm that fatigue is multifactorial in nature.

A recent study by Johansson et al. [45] evaluated the benefits of epoetin  $\beta$  therapy in advanced hormone-refractory prostate cancer, an area where only limited data are available. In this multi-center study, 180 patients were randomized to receive either epoetin  $\beta$  5000 U or 1000 U three times a week for 12 weeks. They found that hemoglobin levels were significantly higher in the high-dose group compared with the low-dose group ( $P < 0.001$ ) after 8 and 12 weeks of therapy, and 43% and 25% of patients, respectively, achieved a hemoglobin increase  $\geq 2$  g/dl after 12 weeks of therapy. Additionally, significantly fewer patients in the high-dose group compared with the low-dose group required blood transfusions (40% versus 54%, respectively;  $P < 0.005$ ). Using a cancer-specific HRQOL questionnaire, patients who responded with a hemoglobin increase  $\geq 2$  g/dl reported improved physical functioning (mean values 62 versus 43;  $P < 0.01$ ), improved overall HRQOL (58 versus 44;  $P < 0.01$ ) and decreased fatigue (42 versus 58;  $P < 0.05$ ) after 12 weeks of therapy compared with patients who did not respond. There were, however, no differences between the high- and low-dose groups in terms of overall HRQOL and fatigue. This trial showed that epoetin  $\beta$  therapy is effective in the treatment of anemia and resulted in improved HRQOL.

Another open-label study recently examined the efficacy of epoetin  $\alpha$  in 401 patients with non-myeloid malignancies who were or were not receiving chemotherapy. Results showed that there was a significant increase in mean hemoglobin levels for both chemotherapy ( $n = 218$ ) and non-chemotherapy patients ( $n = 183$ ) of 2.8 and 2.5 g/dl, respectively ( $P < 0.002$ ). Additionally, a significant improvement in HRQOL scores was observed for both patient cohorts ( $P = 0.001$ ) using LASA and FACT-An



**Figure 3.** Percentage change in Linear Analog Scale Assessment (LASA) scores by hemoglobin level change from baseline in anemic cancer patients receiving epoetin  $\alpha$ . \*Statistically significant difference ( $P < 0.002$ ) from baseline to final assessment; †statistically significant difference ( $P < 0.002$ ) from the previous category. Reprinted with permission from the American Society of Clinical Oncology, from Gabrilove et al. [39]. HRQOL, health-related quality of life.

scales (Figure 4). This study demonstrated that patients with cancer-related anemia can benefit from epoetin  $\alpha$  therapy whether or not they are receiving chemotherapy [42].

A recent trial examined the efficacy of epoetin  $\alpha$  in 145 patients who were receiving chemotherapy for multiple myeloma. In this double-blind, placebo-controlled trial administration of epoetin  $\alpha$  150 U/kg three times a week for 12 weeks resulted in a significant decrease in the incidence of blood transfusions compared with placebo (28% versus 47%;  $P = 0.017$ ) and an increase in mean hemoglobin level (1.8 versus 0.0 g/dl;  $P < 0.001$ ). Additionally, although multivariate analysis did not show any significant differences between the two treatments, univariate analysis showed significant ( $P \leq 0.05$ ) improvement in more HRQOL measures with epoetin  $\alpha$  than with placebo. In addition, significantly more patients receiving epoetin  $\alpha$  had improved performance scores compared with those receiving placebo ( $P = 0.038$ ) [46].

A double-blind, placebo-controlled trial by Osterborg et al. [47] studied the effect of the use of epoetin  $\beta$  on anemia, transfusion need and HRQOL. Severely anemic patients ( $n = 349$ ) with non-Hodgkin's lymphoma, chronic lymphocytic leukemia

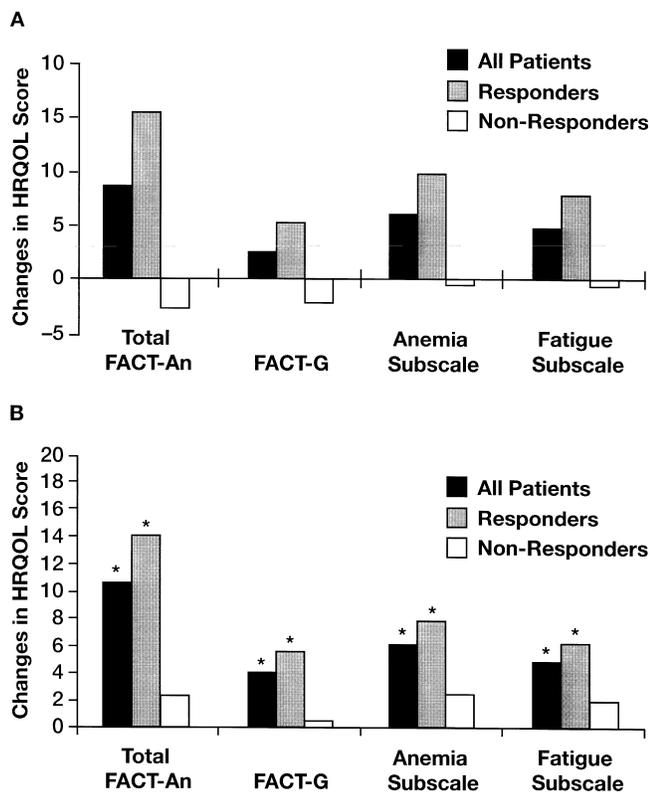
or multiple myeloma were evaluated. Patients in the epoetin  $\beta$  arm received epoetin  $\beta$  150 IU/kg three times a week for 16 weeks, with increases in dose if no response was observed within 4 weeks. HRQOL, measured using the total FACT-General (FACT-G) and FACT-An scores, was significantly greater for patients in the epoetin  $\beta$  arm compared with placebo ( $P < 0.05$ ). No statistically significant differences were found between the two groups on the FACT-An and FACT-F subscales. Transfusion-free, and transfusion- and anemia-free survival were significantly greater for patients who received epoetin  $\beta$  compared with those who received placebo ( $P < 0.01$ ).

One recent analysis compared FACT-An data from two studies. Results from a randomized, double-blind trial of epoetin  $\alpha$  versus standard care in cancer patients with anemia were compared with data from an internet survey of a representative healthy population [48]. HRQOL was assessed using a scale of 0–100, on which higher scores correlated with better HRQOL. In 1080 healthy people surveyed, the mean scores for general HRQOL, fatigue and the anemia subscale were 74.2, 77.06 and 77.6, respectively. In comparison, baseline FACT-An scores for patients about to receive epoetin  $\alpha$  in the clinical trial were lower. In this group, the deficits in score for general HRQOL, fatigue and anemia subscale were 5.8, 19.96 and 17.1, respectively. Following treatment with epoetin  $\alpha$ , significant improvements in HRQOL were observed ( $P$  value not supplied), and nearly the entire deficit in score for general HRQOL and anemia subscale were corrected, while the deficit in fatigue score was halved.

Furthermore, a double-blind, placebo-controlled trial of darbepoetin  $\alpha$  has recently demonstrated an improvement in FACT-F scores following treatment [22]. Three hundred and twenty patients with lung cancer and receiving chemotherapy were randomized to once weekly darbepoetin  $\alpha$  (2.25  $\mu\text{g}/\text{kg}$ ) or placebo for 12 weeks. More of the patients receiving darbepoetin  $\alpha$  experienced an increase in hemoglobin level to  $\geq 12.0$  or of  $\geq 2.0$  g/dl from baseline (66% versus 24%;  $P < 0.001$ ) and fewer required transfusions (27% versus 52%;  $P < 0.001$ ), compared with patients receiving placebo. In addition, 56% of patients in the darbepoetin  $\alpha$  group had an improvement in FACT-F scale score compared with 44% of patients in the placebo group ( $P = 0.052$ ). An improvement in FACT-F score of at least 25% was observed in 32% of patients in the darbepoetin  $\alpha$  group compared with only 19% of patients in the placebo group ( $P = 0.019$ ).

While it may seem logical that raising hemoglobin levels from a low level will have the greatest effect on HRQOL, analysis of two large, community-based studies of epoetin [12, 44] noted that the largest incremental gains in HRQOL occurred when hemoglobin levels were increased from 11 to 12 g/dl [49]. That is, not when patients were severely anemic, but when they were experiencing mild-to-moderate anemia, highlighting the potential benefits of identifying and treating mild anemia.

The studies described above demonstrate that treating anemia significantly improves HRQOL in patients with cancer. Apart from the obvious benefits to patients' quality of life, a subjective improvement in the sense of well-being may motivate patients to adhere to rigorous chemotherapy and treatment regimens [44], thus potentially improving outcomes. However, when con-



**Figure 4.** Mean change from baseline in health-related quality of life (HRQOL) scores for (A) non-chemotherapy patients and (B) chemotherapy patients; both patient groups received epoetin  $\alpha$  treatment. HRQOL was measured using the Functional Assessment of Cancer Therapy (FACT) questionnaire [results from the FACT-Anemia (FACT-An) scale, FACT-General (FACT-G), anemia and FACT-Fatigue subscales are shown here]. \* $P < 0.001$  compared with baseline. Reprinted with permission from the American Society of Clinical Oncology, from Quirt et al. [42].

sidering HRQOL data, it should be noted that there is potential for methodological problems with the various HRQOL assessments applied [50, 51]. Data may be skewed by missing values, shifts in patients' responses over time or differential interpretation of results. Therefore, HRQOL data, even from seemingly well-designed studies, should be interpreted with some caution. Use of different assessments can also limit comparison between trials.

## Anemia may be associated with negative therapy outcomes

### Effect on treatment outcome

As the efficacy of curative radiotherapy may be reduced if the tumor site is inadequately oxygenated [52, 53], it is possible that anemia may contribute to poorer locoregional control and survival in patients undergoing either radiotherapy alone or concurrent chemoradiotherapy. A number of studies, mostly retrospective analyses, have noted that radiotherapy was less successful at lower hemoglobin levels, or that hemoglobin level was an independent prognostic factor for local control and/or survival [54–64]. The most dramatic and consistent effect of anemia on treatment outcome has been noted in patients with head and neck cancer [55–61], but other studies have also reported that anemia influences outcome in carcinomas of the cervix [54], lung [62, 63] and rectum [64].

Glaser et al. [65] retrospectively reviewed the association between hemoglobin level, tumor control and survival in 191 patients with oral squamous cell carcinoma who were treated with neoadjuvant chemoradiotherapy and surgery. Patients were divided into three groups for the purpose of multivariate analysis: those with a pretreatment hemoglobin level of  $\geq 14.5$  g/dl who did not receive epoetin  $\alpha$  (group 1), those with a pretreatment hemoglobin level of  $< 14.5$  g/dl who did not receive epoetin  $\alpha$  (group 2) and those with a pretreatment hemoglobin level of  $< 14.5$  g/dl who were given epoetin  $\alpha$  at a dose of 10000 U/kg three to six times a week (group 3). Investigators found that group 2 had significantly lower locoregional control and overall survival rates than either group 1 ( $P < 0.05$ ) or group 3 ( $P \leq 0.001$ ). There was, however, no significant difference between groups 1 and 3 in either locoregional control ( $P = 0.3$ ) or overall survival ( $P = 0.4$ ). The potential for bias in this study was limited by the lack of differences in treatment and staging procedures over the analysis period, and the similarity in duration of patient follow-up across the study groups.

There is some preclinical evidence suggesting that anemia may have an adverse impact on survival in cancer patients undergoing chemotherapy [66]. Tumor hypoxia associated with anemia may have the same deleterious effect on chemotherapeutic efficacy that it has on radiotherapy [67, 68]. A recent placebo-controlled trial examining the effect of epoetin  $\alpha$  therapy on HRQOL in cancer patients receiving chemotherapy and with anemia, also assessed survival, 12 months after the end of the treatment period [38]. Median survival times were 17 months for patients receiving epoetin  $\alpha$  compared with 11 months for patients who received placebo. These interesting, but preliminary, data indicated a

potential survival benefit with epoetin  $\alpha$  treatment. However, this study was not powered to assess survival as an endpoint, nor designed to ensure that survival potential was balanced between the two groups at baseline. The results should be interpreted with caution and a survival advantage for chemotherapy patients treated for anemia has not been established. An additional trial of darbepoetin  $\alpha$  in patients receiving chemotherapy for lung cancer has, however, demonstrated a trend towards increased disease-free survival in small-cell lung cancer patients receiving therapy for anemia [22]. Further trials are currently underway to determine whether raising hemoglobin levels with erythropoietic proteins can improve therapeutic outcome following radiotherapy or chemotherapy [69, 70]. Preliminary data indicate promising results, although more extensive, prospective studies, designed and adequately powered to analyze the relationship between hemoglobin levels and survival, are needed before definitive conclusions can be made.

Although the research mentioned above suggests that anemia has a detrimental effect on survival, it is not yet known whether there is a point during therapy at which it is most critical to maintain patients' hemoglobin levels. Several analyses have noted that pretreatment anemia is significantly associated with poorer outcomes [55, 61]. However, another study found that the nadir hemoglobin level was the most predictive factor for treatment failure ( $P = 0.015$ ), whereas hemoglobin level at presentation was insignificant [71].

### Surgery

Recent data suggest that anemia may also adversely affect treatment outcome following surgery for carcinoma of the glottis [72]. A retrospective analysis by Lutterbach and Guttenberger [72] found that the presence of anemia in patients undergoing conventional surgery for glottic squamous cell carcinoma was associated with significantly worse 5-year locoregional control (60% versus 85%; log rank test  $P = 0.003$ ). Additionally, subgroup analyses suggested that hemoglobin levels might be predictive of survival even when within the normal range. The authors postulated that the poor prognosis of anemic patients could be owing to hypoxia-induced tumor cell migration beyond the resection margin.

Conversely, treatment of surgery-related anemia with blood transfusions has been shown to have a negative effect on survival. Perioperative blood transfusion has been correlated with poor prognosis following surgery in a number of cancer types, including colorectal, esophageal and hepatocellular tumors [73–75]. The apparent adverse effect associated with transfusion is thought to occur via an immunosuppressive process and may be related to the volume of blood transfused. Further research is needed to better explore the effect of anemia and its treatment in the surgical setting and to elucidate possible mechanisms.

### The future

As described earlier, certain limitations exist for the therapeutic use of epoetin and there continue to be a number of unmet needs in anemia management. Darbepoetin  $\alpha$ , a recent addition to the

family of erythropoietic proteins, may potentially meet some of these needs.

Darbepoetin  $\alpha$  contains two additional sialic acid-containing carbohydrate side chains compared with epoetin [76], and stimulates erythropoiesis in the same manner as endogenous erythropoietin and epoetin. Darbepoetin  $\alpha$  has a three-fold longer serum half-life and increased *in vivo* biological activity compared with epoetin [76, 77]. This permits darbepoetin  $\alpha$  to be administered at less frequent dosing intervals than epoetin, providing greater flexibility and improved convenience.

Completed and ongoing clinical trials in the oncology setting have demonstrated that darbepoetin  $\alpha$  is active and well tolerated in this patient population [22–25]. Furthermore, results from phase I, II and III trials, mainly involving patients with non-myeloid malignancies, show that administration of darbepoetin  $\alpha$  at a range of doses (including 1.5, 2.25 and 4.5  $\mu\text{g}/\text{kg}$ ) and dose intervals (once every 1, 2 or 3 weeks) alleviates anemia and reduces the need for transfusions in patients with cancer undergoing multicycle chemotherapy [22–25, 78].

The efficacy of darbepoetin  $\alpha$  has also been demonstrated in patients with chronic anemia of cancer who were not receiving concurrent chemoradiotherapy [24]. In a phase I/II dose escalation trial, 100% of patients achieved a hematopoietic response at the highest dose of darbepoetin  $\alpha$  (4.5  $\mu\text{g}/\text{kg}$ ) administered once weekly. A report by Hedenus et al. [79] has additionally shown that darbepoetin  $\alpha$  appeared to be as effective in raising hemoglobin levels in patients with lymphoproliferative malignancies as in those with solid tumors.

Darbepoetin  $\alpha$  was well tolerated in all trials, with patients reporting adverse events that were consistent with the population being studied. No evidence of drug accumulation or the development of anti-darbepoetin  $\alpha$  antibodies has been detected [23, 80, 81]. Trials are underway that will provide further insights into the future role of darbepoetin  $\alpha$  in managing anemia. Results from studies could also indicate ways in which the use of darbepoetin  $\alpha$  may be a cost-effective alternative to standard therapy.

## Conclusions

Anemia is associated with significant decreases in HRQOL and may have a negative impact on prognosis. It is clear that alleviating anemia with erythropoietic agents improves HRQOL; however, research suggests that anemia is under-recognized and under-treated [30–32]. This may be partly due to the limitations of current epoetin therapy, which includes a large percentage of patients who do not respond to this treatment, the need for frequent dosing, the relatively slow time to response and the cost of therapy. New treatments, such as darbepoetin  $\alpha$ , may offer an alternative therapy that can address some of these limitations.

Whether alleviating anemia can improve the traditional clinical outcomes of cancer therapy remains to be confirmed. Nevertheless, anemia should remain an important issue on the basis of its profound effect on quality of life.

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