

Managing Anemia in the Cancer Patient: Old Problems, Future Solutions

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Key Words. Anemia · Cancer · Survival · Quality of life · Recombinant human erythropoietin · Darbepoetin alfa

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify potential benefits for EPO therapy beyond those of transfusions.
2. Recognize the impact of EPO therapy on aspects of health-related quality of life.
3. Appreciate recent advances in the field of hematopoietic growth factor support as it relates to anemia management.

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ABSTRACT

Anemia and associated symptoms commonly manifest in cancer patients and may have a considerable impact on outcomes. Preliminary studies suggest that overall survival and locoregional control following radiation therapy may be compromised by anemia, and recent preliminary data also suggest that anemia may be related to poorer outcomes following chemotherapy. Health-related quality of life of cancer patients is also significantly reduced by anemia. Treatment of anemia with recombinant human erythropoietin can improve these health-related quality-of-life outcomes. However, despite this knowledge, anemia remains under-recognized and under-treated in the cancer patient population.

A number of issues may be determinants of this suboptimal management of anemia. These include limitations of current therapies for anemia, varying practice strategies, and the lack of guidelines on how to treat anemia. Additionally, clinicians may underestimate the importance of health-related quality of life for their patients. It is vital that these issues are addressed, which, together with the development of novel erythropoietic agents, a review of the guidelines for anemia management, and consideration of further outcomes such as survival and cognitive function, may help to ensure that the cancer patient receives the best possible course of supportive care. *The Oncologist* 2002;7:331-341

INTRODUCTION

The optimal management of cancer patients is a complex and sensitive issue. In recent times, emphasis has been placed on the appropriate treatment of cancer-related symptoms and the impact this can have on patient quality of life and thera-

peutic outcomes. Anemia is a common complication of malignancy, occurring in over 50% of patients [1]. It is defined as an inadequate circulating level of hemoglobin or RBCs, and may arise as a result of the underlying disease, chemotherapy, or radiation therapy [2]. Anemia is associated

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with its own set of debilitating signs and symptoms and can have a significant effect on morbidity and mortality, as well as on the level of care that patients require. Despite this knowledge, anemia may not be optimally managed in the cancer patient population.

The underlying issues that contribute to this suboptimal care may be related to the failure of many clinicians to recognize the impact that anemia has on the lives of their patients and the inadequacies of current treatment options. However, the continuing development of novel erythropoietic agents [3], progress in defining parameters to better predict a patient's response to anemia treatment [4, 5], along with emerging data that consider the effect of anemia on end points such as survival and cognitive function [6, 7], may help to overcome these issues. Such initiatives suggest a promising future for the optimal management of anemia in the cancer patient.

The impact of anemia on cancer patients, its pathophysiology in cancer, and strategies for anemia treatment are reviewed in this article, with the aim of raising awareness about current knowledge and practice. Future approaches for research and management of anemia in cancer patients are also discussed to encourage understanding of how these activities can be improved and the implications this may have for patient and clinician alike.

IMPACT OF ANEMIA ON THE CANCER PATIENT

Treatment and Clinical Outcomes

As will be discussed later in this article, it is well established that patients with anemia may experience reduced health-related quality of life (HRQOL) as a result of the often debilitating symptoms of anemia, and that raising hemoglobin with erythropoietic proteins can improve HRQOL [8-11]. However, recent studies suggest that there

may be additional consequences of anemia, which if proven, may necessitate revision of the way patients with cancer are managed. Results from both prospective and retrospective studies in patients with head and neck cancer undergoing radiation therapy or combined modality therapy have indicated that anemia may be associated with decreased overall survival and reduced locoregional control [12-19]. For example, in a large study of 451 patients with stage III or IV squamous cell carcinoma of the head and neck who were undergoing concurrent radiation therapy with or without etanidazole treatment, 162 patients were considered to have a normal hemoglobin level (≥ 14.5 g/dl for men and ≥ 13.0 g/dl for women) and 289 patients were classified as anemic [12]. As shown in Figure 1, which illustrates rates of survival and locoregional failure over time in patients with normal and low hemoglobin levels, respectively, the estimated 5-year survival rates were 35.7% and 21.7%, respectively ($p = 0.0016$), and estimated 5-year locoregional failure rates were 51.6% versus 67.8% ($p = 0.00028$).

It has also been suggested that anemia may be an independent prognostic factor in cancer patients undergoing radiation therapy [12, 14, 15]. *Dubray et al.* presented data from multivariate analyses that indicated that a pretreatment hemoglobin level of < 13.5 g/dl in men and < 12 g/dl in women was one of several factors that were independently predictive of an increased relative risk of 2-year locoregional failure and death (relative risk of locoregional failure and death for anemic patients: 1.6 [$p = 0.06$] and 1.7 [$p = 0.04$], respectively) [14]. Similarly, *Warde et al.*, in a retrospective analysis, found evidence that pretreatment hemoglobin level was one of several independent prognostic factors for local failure after radiation therapy [15]. For example, the hazard ratio for a hemoglobin level of 12 g/dl versus a hemoglobin level of 15 g/dl was 1.8 (95% confidence interval 1.2-2.5).

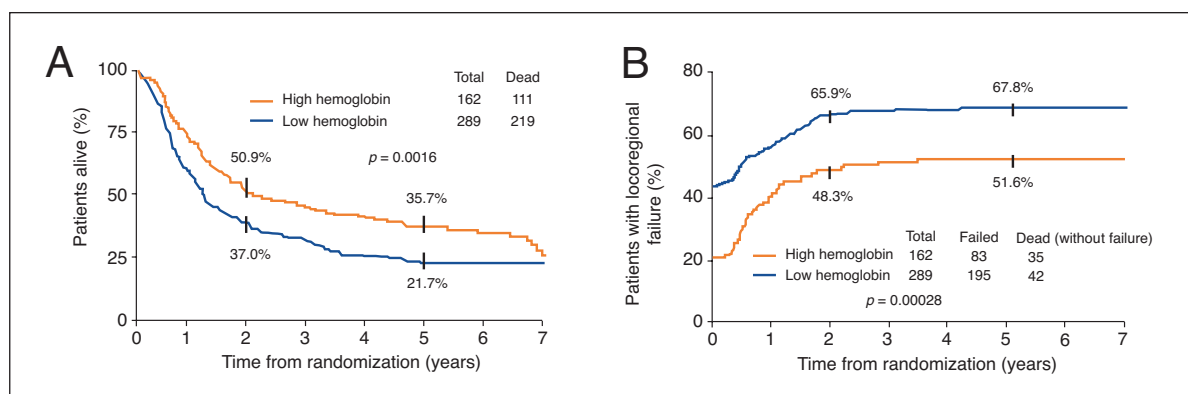


Figure 1. Overall survival (A) and locoregional failure (B) according to hemoglobin level in a prospective study of 451 patients with advanced head and neck cancer treated with radiation therapy. Reprinted with the permission of Elsevier Science from Lee et al. [12].

Although the most extensive pool of results on the effect of anemia on treatment and clinical outcomes exists for patients with head and neck cancer, data for other tumor types are available. One study in rectal cancer patients has recently indicated that anemia (hemoglobin <11 g/dl) may reduce overall survival after combined therapy [20]. A retrospective study in ovarian cancer patients indicated that a pretreatment hemoglobin value <12 g/dl was an independent prognostic factor for patients with stage I and II disease, but the association did not reach statistical significance in patients with stage III and IV disease [21]. A study of patients with cancer of the cervix has additionally suggested that an average weekly nadir hemoglobin level of <12 g/dl may be associated with inferior radiation therapy outcomes compared with a hemoglobin level ≥ 12 g/dl [22].

The underlying mechanism by which anemia affects treatment and clinical outcomes may be related to the degree of tumor oxygenation, since studies have indicated that hypoxia may have an adverse effect on the radiosensitivity of cells [18, 23]. However, while anemia can be an underlying cause of decreased tumor oxygenation, tumor hypoxia is a multifactorial process, and compensatory mechanisms may reduce the effect of anemia. For example, in a study of 63 head and neck cancer patients, tumor hypoxia was shown to adversely influence prognosis, and while there was a weak association between anemia and poorly oxygenated tumors, many nonanemic patients had hypoxic tumors [24].

Although evidence is beginning to accumulate suggesting that hemoglobin level may influence local control and survival following radiotherapy, other factors that may be related to anemia and which may affect outcomes need further investigation. Tumor size, for example, is known to play a significant role in the prognosis of cancer. A study in cervical cancer patients has indicated that those with bulky hypoxic tumors had a significantly lower chance of disease-free survival (12% at 2 years) than those with either bulky oxygenated or nonbulky oxygenated/hypoxic tumors (65%, $p = 0.0001$) [25]. Hemoglobin levels before and during treatment have been strongly correlated with tumor size, and it has been suggested that this may explain the impact of anemia on prognosis in earlier studies that did not record tumor bulk [23]. In addition, it is possible that, in patients who have a worse prognosis and who are less likely to respond to therapy, anemia simply occurs more often and is only a marker of poorer outcome rather than a cause. Furthermore, it is not yet clear at which time point hemoglobin level may have predictive value for outcomes. In three separate studies carried out in patients with head and neck cancer receiving radiation therapy, pretreatment and end-of-treatment hemoglobin levels have been reported to be of clinical significance [16, 17, 19].

It is apparent that a complex relationship exists among anemia, hypoxia, and treatment/clinical outcomes, however, we are still a long way from understanding this relationship [23]. Further investigation of anemia as an independent prognostic factor is required, along with randomized trials to determine the effect of anemia correction on clinical outcomes. These studies will help to conclusively determine whether there is an association among inadequate hemoglobin level, locoregional control, and survival.

Whether anemia may have an impact on cancer patients receiving chemotherapy alone is another largely unaddressed issue. A retrospective analysis conducted as part of a recently reported multicenter study has presented preliminary evidence that treatment of anemia may improve survival, although the results must be interpreted with caution, as the trial was not designed or powered to measure this end point [6]. Three hundred seventy-five patients with solid tumors or nonmyeloid hematologic malignancies receiving nonplatinum-based chemotherapy were assessed. Median survival time for patients who received three-times-weekly recombinant human erythropoietin (rHuEPO) was 17 months compared with 11 months for those who received placebo. Kaplan-Meier 12-month estimates of survival were 60% for patients receiving rHuEPO and 49% for those on placebo, suggesting a possible favorable trend in overall survival for rHuEPO, although the difference was not statistically significant ($p = 0.13$). Cox regression analysis, to control for factors such as age, tumor type, and baseline hemoglobin and neutrophil levels, also favored survival in the rHuEPO-treated group, although the difference was again not statistically significant ($p = 0.052$). While these results may appear promising, it should be noted that this study was not powered with respect to survival and, therefore, did not measure or stratify by variables that can influence survival, such as disease stage, bone marrow involvement, intensity of chemotherapy, and disease progression. Nevertheless, the possibility that correction of anemia can convey a survival benefit in cancer patients receiving chemotherapy deserves further investigation.

HRQOL Outcomes

Quality of life is a subjective and multidimensional concept that includes functional ability and emotional and social well-being, as influenced by disease, its symptoms, and treatment side effects [8]. Cancer-related anemia is associated with a whole host of symptoms that include dyspnea, tachycardia, fatigue, dizziness, depressive moods, menstrual problems, loss of libido, anorexia, nausea, and sleeping disorders [1, 26]. The occurrence and severity of symptoms in individual patients can vary considerably and may be influenced by the degree of anemia and how rapidly it develops,

the underlying malignancy, pulmonary and cardiovascular function, as well as nutritional status.

The negative impact of anemia and related manifestations on the HRQOL of cancer patients is now well documented, and a number of studies have highlighted the potential benefit of treating anemia on HRQOL [6, 9-11, 27]. The development of specialized tools to measure the effect of anemia and associated symptoms on HRQOL has also greatly aided this research.

The Functional Assessment of Cancer Therapy-Anemia (FACT-An) and FACT-Fatigue (FACT-F) tools were designed and validated to assess the impact of anemia, fatigue, and other associated symptoms on the cancer patient [8, 28]. These patient questionnaires were developed from the FACT-General scale but contain additional assessment items. Table 1 shows the FACT-An subscale items, with the separate fatigue and nonfatigue components of the questionnaire. Analysis of scores for physical and functional well-being, as well as for the fatigue and nonfatigue components of the FACT-An subscale, has clearly differentiated between patients with low and high hemoglobin levels [8, 29]. Those with lower hemoglobin levels (≤ 12 g/dl) had lower scores and, therefore, reduced HRQOL compared with patients who had hemoglobin levels >12 g/dl, which is shown in Figure 2 for the physical and functional well-being subscales and the fatigue and nonfatigue items. The ability to work has also been correlated with hemoglobin levels; in a survey of 50 patients, one in four with hemoglobin levels ≤ 12 g/dl reported that they could not work at all [29].

Fatigue, often described by patients as a feeling of tiredness, weakness, or lack of energy, has been suggested

Table 1. The FACT-An subscale items

Fatigue component

- I feel fatigued.
- I feel weak all over.
- I feel listless (“washed out”).
- I feel tired.
- I have trouble starting things because I am tired.
- I have trouble finishing things because I am tired.
- I have energy.
- I am able to do my usual activities.
- I need to sleep during the day.
- I am too tired to eat.
- I need help doing my usual activities.
- I am frustrated by being too tired to do the things I want to do.
- I have to limit my social activity because I am tired.

Nonfatigue component

- I have trouble walking.
- I feel lightheaded (dizzy).
- I get headaches.
- I have been short of breath.
- I have pain in my chest.
- I am interested in sex.
- I am motivated to do my usual activities.

Questions were answered based on a five-point scale: 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much.

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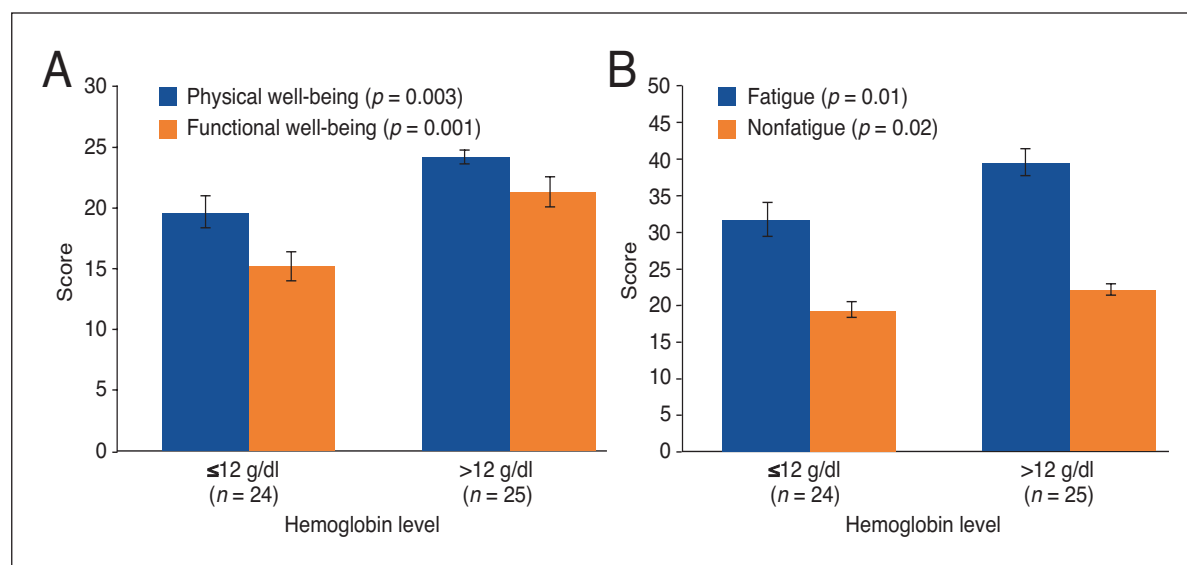


Figure 2. FACT-An subscale physical and functional well-being scores (A) and FACT-An subscale fatigue and nonfatigue scores (B) according to low (≤ 12 g/dl) and high (≥ 12 g/dl) hemoglobin levels in cancer patients. A higher score represents higher well-being in A and lower levels of fatigue in B. Reprinted with the permission of W.B. Saunders & Company from Cella *et al.* [8].

to be one of the most common symptoms of cancer and cancer therapy. It can be a distressing condition and can have serious adverse effects on HRQOL [30]. *Curt et al.* have reported that, in a survey of 379 cancer patients, 91% of subjects stated that fatigue prevented them from having a "normal life" [31]. Anemia often contributes to fatigue; in a group of patients split by hemoglobin level, those with hemoglobin >12 g/dl reported significantly less fatigue [8]. However, it should be noted that a recent study by *Cella et al.* indicated that a significantly lower percentage of patients (17%) may have experienced cancer-related fatigue, as opposed to general fatigue due to overexertion or lack of sleep, than previously estimated (60%-90%) [32]. It is worth noting, however, that in the group of patients reporting cancer-related fatigue (17%), the majority had completed treatment more than a year previously, and fatigue in this group was assessed using a set of stringent, formal diagnostic criteria. This is in contrast to the studies estimating a 60%-90% prevalence, which were not necessarily based on formal diagnostic criteria and usually estimated the prevalence of any fatigue at any time, usually during treatment.

As anemia, fatigue, and other related symptoms can have such a profound effect on patients' HRQOL, numerous studies have been conducted to address how treatment of anemia with rHuEPO impacts on HRQOL [6, 10, 11, 27]. Evidence from three large community-based trials has provided data indicating that patients' HRQOL can significantly improve following treatment of anemia [10, 11, 27].

Glaspay et al. and *Demetri et al.*, in their respective studies, analyzed over 4,000 patients with malignancies undergoing chemotherapy and receiving rHuEPO three times per week [10, 11]. As measured by the Linear Analog Scale Assessment (LASA), a significant correlation was demonstrated between improvements in HRQOL and increases in hemoglobin levels from baseline. Energy, activity level, and overall quality of life scores all improved, and transfusion use was shown to decrease. Importantly, it was shown that HRQOL improved regardless of whether patients exhibited a complete or partial tumor response or had stable disease. *Glaspay et al.* even reported a significant improvement in energy levels in patients who had progressive disease.

In the study by *Demetri et al.*, HRQOL assessment using the FACT-An subscale was also performed [11]. Similar to results using the LASA, their findings showed that HRQOL improved in correlation with hemoglobin and that those who achieved a mean increase in hemoglobin of 2 g/dl or greater had the largest increase in HRQOL. Interestingly, patients who experienced a hemoglobin change of <2 g/dl also had a significant increase in

FACT-An total score when tumor response was complete, partial, or stable, as shown in Figure 3. A separate analysis of the data from the *Glaspay et al.* [10] and *Demetri et al.* [11] studies noted that the largest incremental gains in HRQOL occurred when hemoglobin increased from 11 to 12 g/dl [33], which highlights the potential importance of detecting and treating even mild anemia.

In the third, large, community-based study, *Gabrilove et al.* prospectively evaluated the effectiveness and clinical benefits of once-weekly rHuEPO [27]. Improvements in HRQOL were shown to correlate significantly ($p < 0.001$) with increased hemoglobin levels, and transfusion requirements were decreased with this less frequent dosing regimen. *Littlewood et al.* have additionally studied HRQOL and hemoglobin levels in a placebo-controlled trial of patients with solid or nonmyeloid hematologic malignancies undergoing chemotherapy and receiving rHuEPO three times per week [6]. Changes in energy level, ability to do daily activities, and fatigue were all associated with an elevation in hemoglobin level. In a recent analysis of data from two clinical trials of patients with solid tumors undergoing chemotherapy and receiving a novel erythropoiesis-stimulating protein, darbepoetin alfa, a positive, although small, correlation was demonstrated between fatigue score on the FACT-F subscale and change in hemoglobin ($r = 0.19$; $p = 0.002$) [34]. An increase in hemoglobin of ≥ 2 g/dl resulted in a mean improvement in FACT-F score of 4.0 points. While these latter results suggest that increased hemoglobin level may correlate with improvement in patient-reported fatigue, other factors may also cause changes in fatigue levels, such as the disease itself, anticancer therapy, depression, anxiety, or even sleep deprivation [31].

PATHOPHYSIOLOGY OF ANEMIA IN CANCER

It is clear from the presented evidence that anemia is a common occurrence in cancer patients and has a significant impact on clinical and HRQOL outcomes. It is, therefore, important to understand the underlying etiology of anemia in cancer in order to provide the correct and most effective treatment for individual patients.

Factors including the type and stage of malignancy, duration of tumor growth, regimen and intensity of chemotherapy or radiation therapy, and complications of treatment, such as infection or sepsis, may contribute to the development of anemia [1, 35]. A high incidence of anemia (50%-60%) occurs in patients with lymphomas, multiple myeloma, lung tumors, and gynecologic or genitourinary tumors, and while the occurrence of anemia in patients with solid tumors is less than that observed for hematological malignancies, incidence of mild-to-moderate anemia can be

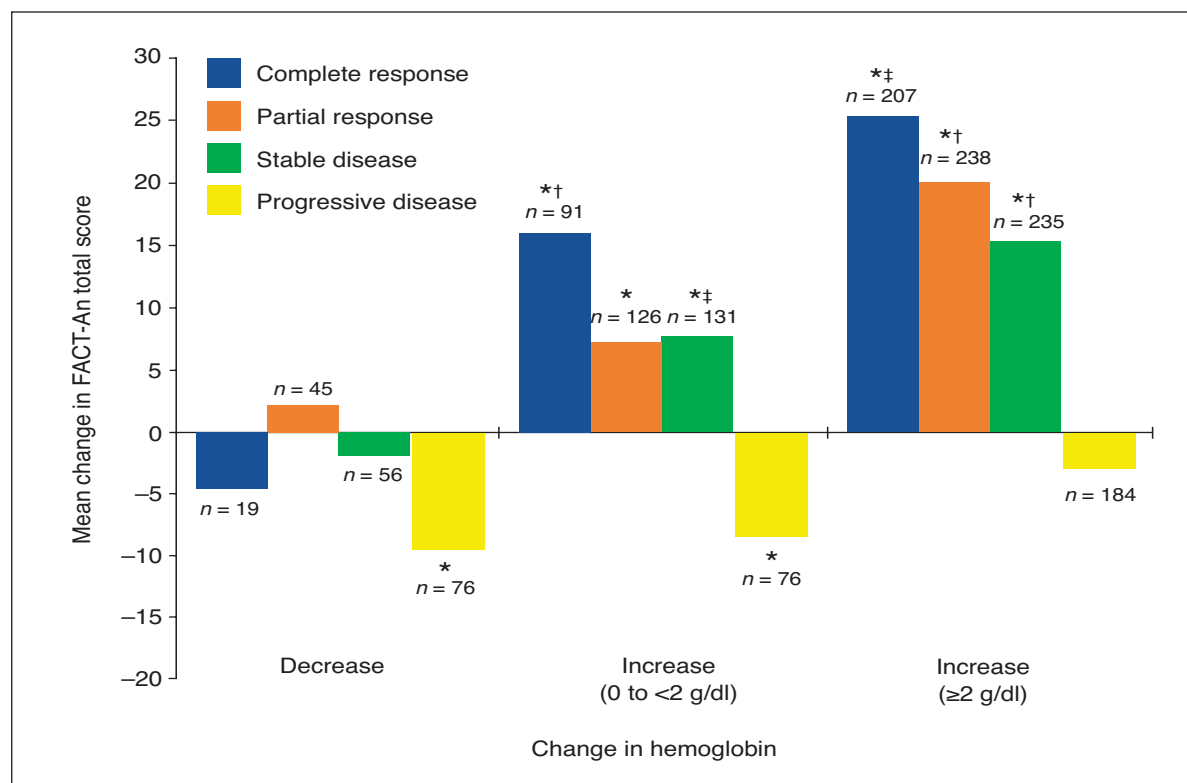


Figure 3. Analysis of HRQOL parameters (assessed by FACT-An) based on changes in hemoglobin levels and tumor response from baseline to final assessment, in a study of 2,289 patients with nonmyeloid malignancies receiving chemotherapy and rHuEPO treatment. *Significantly different from baseline ($p < 0.01$); †significantly different from adjacent hemoglobin change group ($p < 0.01$); ‡significantly different from adjacent hemoglobin change group ($p < 0.05$). Reprinted with the permission of Lippincott, Williams & Wilkins from Demetri et al. [11].

high [1, 26, 35]. Platinum-based therapies are also known to be associated with a high incidence of anemia, which may help to explain the frequency of anemia in lung and ovarian cancer patients who regularly receive such treatment.

Multiple underlying mechanisms can contribute to the development of anemia in the cancer patient. Bone marrow replacement may be a direct effect of cancer. Metastases within the bone marrow can lead to displacement and destruction of progenitor cells, disrupting the microenvironment as well as the production of mature erythroid-lineage cells [1, 36]. Anemia associated with chronic disease is also an extremely common manifestation in cancer patients [1]. Current thinking suggests this is a largely cytokine-mediated disorder, and that tumor interaction with the immune system leads to overproduction of inflammatory cytokines such as interleukin-1 and tumor necrosis factor- α . These cytokines can impair erythroid colony formation in response to erythropoietin (EPO), decrease the life span of erythrocytes, impede EPO production, and prevent the normal utilization of iron [37, 38].

Chemotherapy can cause or exacerbate anemia in cancer patients by reducing EPO production or sensitivity to

this hormone and damaging or destroying progenitor and mature hematopoietic cells, while radiation therapy causes bone marrow damage. Blood loss and nutritional deficiencies may additionally contribute to anemia in cancer patients [1].

MANAGING ANEMIA

Although there is a large body of data describing the negative outcomes of anemia in cancer patients, and information on the etiology of anemia is accumulating, the question remains as to how to optimally treat anemia, and management of this condition remains a controversial subject. For example, at a debate on the use of rHuEPO held at the annual meeting of the European Society for Medical Oncology in October 2000, 40% of the audience, comprising largely Europeans, indicated that they did not use rHuEPO to treat anemia at all [39]. In a U.S. community practice study, Lawless et al. have also reported that 52%-70% of cancer patients, with a range of tumor types, were not administered rHuEPO therapy despite being anemic [40].

As discussed, limitations in current therapies for anemia, which include RBC transfusions, iron supplementa-

tion, and rHuEPO, lack of global guidelines for treatment, and an underappreciation of the impact of anemia may contribute to this situation. It is critical that these factors be addressed and that emerging and future approaches are incorporated into clinical practice to maximize the future treatment of anemia in the cancer patient.

RBC Transfusions

RBC transfusions provide immediate correction of anemia, which is of particular value in patients with life-threatening anemia. However, transfusions have been associated with a number of risks, and although the introduction of stringent screening programs has greatly increased their safety, some hazards still remain. These include immunosuppression, which may enhance tumor growth, adverse hemolytic reactions, infection, and alloimmunization [2, 26]. Additionally, some patients may be reluctant to undergo transfusions on personal, religious, or logistical grounds.

Despite these drawbacks, RBC transfusions will still find application for cancer patients who are anemic due to bone marrow infiltration or damage to hematopoietic precursor cells, or who are unresponsive to rHuEPO therapy. Definitive studies investigating any potential benefits of transfusions on HRQOL are also required.

Recombinant Human Erythropoietin

The introduction of rHuEPO as a treatment option represented a significant advance in the treatment of anemia. rHuEPO can increase erythrocyte and hemoglobin levels, and therefore, alleviate the symptoms of anemia while reducing patients' requirements for blood transfusions [10, 11, 41-43]. It also has been shown to be safe and well tolerated and is associated with very few side effects in cancer patients with a range of tumor types receiving varying chemotherapy/radiation therapy regimens.

A study by *Abels* analyzed 413 patients receiving either no chemotherapy ($n = 124$), cyclic noncisplatin chemotherapy ($n = 157$), or cyclic cisplatin-containing chemotherapy ($n = 132$) [42]. Those in the 'no chemotherapy' group received 100 U/kg rHuEPO three times per week for 8 weeks, while those in the latter two groups received 150 U/kg rHuEPO three times per week for 12 weeks. In all three groups, mean weekly hematocrit levels remained stable among the placebo-treated patients but increased progressively in those receiving rHuEPO, as shown in Figure 4. The mean proportion of patients transfused and mean number of RBC units transfused decreased for all three rHuEPO treatment groups compared with placebo.

However, rHuEPO therapy has been associated with moderate response rates (50%-60%) and slow time to

response. In addition, it is difficult to predict which patients will respond. It has been shown, in one cohort of patients, that median time to response was approximately 4 weeks, but it can take up to 12 weeks to determine responsiveness [44]. Such long-term treatment and monitoring of patients can be expensive and represents a burden, especially if the patient ultimately fails to respond to treatment, as happens in 40%-50% of cases. The inconvenience of three-times-weekly dosing schedules may also be a consideration for some patients and clinicians [44], although the study by *Gabrilove et al.* in the U.S. recently has shown that once-weekly dosing of rHuEPO is safe and effective [27].

Data on useful predictive parameters for response are emerging. For example, studies have indicated that patients with relatively high levels of EPO before treatment are less likely to respond to rHuEPO [45, 46]. The combination of baseline EPO level and the increase in hemoglobin or transferrin receptor after 2 weeks of therapy with rHuEPO has also been suggested as a good predictor of response [4]. Ultimately, whichever parameters prove to be the most accurate and useful, it is extremely important that predictive algorithms are developed that utilize easily measurable factors [47].

Darbepoetin alfa

Darbepoetin alfa (ARANESP™; Amgen Inc.; Thousand Oaks, CA) is a novel erythropoiesis-stimulating protein that is currently undergoing trials in cancer patients and may confer benefits in the treatment of anemia. Darbepoetin alfa

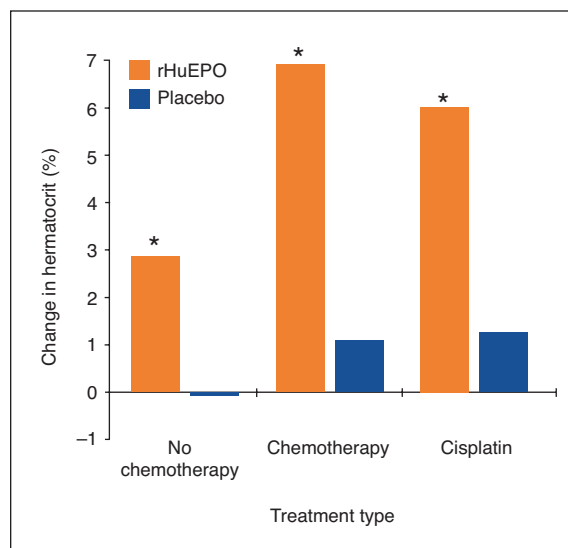


Figure 4. Change in hematocrit levels from baseline to last value in a study of cancer patients receiving rHuEPO with or without chemotherapy. *Significantly ($p < 0.004$) greater than placebo. Adapted from [42].

was developed to contain two additional sialic acid-containing carbohydrate side chains compared with rHuEPO [3]. It binds to the EPO receptor, stimulates erythropoiesis, and, in preclinical studies and trials involving patients with chronic kidney disease, it has been shown to have a two to three times longer serum half-life than rHuEPO [3, 48]. Darbepoetin alfa has undergone extensive testing in the renal disease setting and has recently been approved for use in chronic kidney disease in both the U.S. and Europe.

The half-life of subcutaneously administered darbepoetin alfa in cancer patients receiving chemotherapy is over 40 hours [49]. In phase I, II, and III clinical studies to date, over 1,000 cancer patients have received darbepoetin alfa, and it was effective and well tolerated, with an adverse event profile consistent with that for cancer patients and comparable with that observed for rHuEPO [50-53]. Administration of darbepoetin alfa at intervals of once every 1, 2, or 3 weeks increased hemoglobin levels and reduced the requirement for RBC transfusions in patients with lymphoproliferative malignancies or solid tumors undergoing multicycle chemotherapy [50-54]. Additionally, in patients with chronic anemia of cancer not receiving chemotherapy, once-weekly darbepoetin alfa at doses of 1.0, 2.25, and 4.5 $\mu\text{g}/\text{kg}$ demonstrated efficacy in eliciting a hemoglobin response (increase ≥ 2 g/dl) in 68%, 66%, and 92% of patients, respectively [55].

Darbepoetin alfa administered every 2 weeks also appears to be as effective as darbepoetin alfa administered weekly, according to results from a study in anemic (hemoglobin ≤ 11 g/dl) patients with solid tumors receiving multicycle chemotherapy [50]. The percentages of patients achieving a hematopoietic response (hemoglobin level ≥ 12 g/dl or a hemoglobin increase ≥ 2 g/dl) in the cohorts receiving darbepoetin alfa once weekly at 1.5 $\mu\text{g}/\text{kg}$ or 4.5 $\mu\text{g}/\text{kg}$ were 53% and 84%, respectively. Similarly, respective response rates of 66% and 84% were observed with darbepoetin alfa given once every 2 weeks at 3.0 $\mu\text{g}/\text{kg}$ or 9.0 $\mu\text{g}/\text{kg}$. Blood transfusion rates were also comparable between patients assigned once-weekly and once-every-2-weeks treatment. Additionally, in this and in separate trials, efficacy and rapidity of response appears to increase with higher doses of darbepoetin alfa [50-52].

Importantly, these data indicate that darbepoetin alfa has the potential to be dosed less frequently, which could simplify anemia management for patients and physicians alike and reduce the burden on health care resources. Furthermore, results from a phase III trial involving lung cancer patients receiving chemotherapy and once-weekly darbepoetin alfa suggest that median time to disease progression may be increased for small-cell lung cancer patients receiving darbepoetin alfa compared with placebo

(33 weeks versus 23 weeks, respectively) [54]; however, this relationship was not observed in non-small cell lung cancer patients. Darbepoetin alfa impacted positively on RBC transfusion requirements, with 26% of the darbepoetin alfa cohort and 60% of the placebo cohort receiving transfusions over the course of the study. Data from this study also suggested patients administered darbepoetin alfa spent fewer days in hospital compared with placebo (mean number of days hospitalized [standard deviation]: 10.3 [13.5] days versus 13.0 [17.7] days, respectively) and that significantly more darbepoetin alfa recipients had a $\geq 10\%$ increase in FACT-F scale score relative to placebo recipients (42% versus 28%, respectively, $p = 0.023$). Studies of darbepoetin alfa in the oncology setting are ongoing and should provide additional data on the potential advantages of this novel agent in the cancer patient population.

Complicating Factors

Potentially, a number of factors may complicate the treatment of anemia and outline the need for further research and the development of treatment guidelines. For example, functional iron deficiency, a suboptimal mobilization of iron despite the presence of adequate iron stores, is the most common cause of inadequate response to rHuEPO in chronic renal failure patients [56]. There is a real possibility that this underutilization of iron may also inhibit the response to rHuEPO therapy in cancer patients. Parameters that appropriately measure iron deficiency or predict the development of iron deficiency are not clearly defined, and the most appropriate method for iron supplementation is uncertain [47, 56]. However, increasing recognition of this problem and debate and further research into iron metabolism will aid in the definition of the best way to approach functional iron deficiency in cancer patients with anemia [57]. While iron may be delivered orally or intravenously, recent research suggests that the latter route provides a better source of iron in deficiency, as it can meet the required rate of iron delivery in rHuEPO-stimulated erythropoiesis [56]. Aggressive iron supplementation has led to substantial reductions in rHuEPO doses in hemodialysis patients [47], and this fact may have important cost implications if it holds true in the oncology setting.

The question of when to treat anemia also deserves consideration. Currently there are no universally accepted guidelines for managing anemia, and treatment practices may differ among hospitals, regions, and countries, adding to the confusion and ultimately leading to the suboptimal treatment of anemia. The appropriate hemoglobin levels at which to initiate therapy, stop treatment, or increase dose are also controversial, and gender differences are often ignored [1, 58]. Additionally, questions remain as to whether anemia-associated symptoms

and their severity should be considered in the diagnosis of the condition, whether patients are sufficiently monitored for anemia, and whether patients are considered on an individual basis [59]. Guideline development and specification of treatment criteria and end points are ongoing and should provide support for the future optimization of anemia management.

FUTURE APPROACHES TO ANEMIA MANAGEMENT

While many clinicians may be aware to some degree that anemia is associated with reduced HRQOL and possibly poorer treatment outcomes following radiation therapy, knowledge and understanding of recent and emerging data are also vital. Further end points and outcomes of anemia in cancer patients are currently being explored and, although data are currently only preliminary, these end points may prove to be significant in the management of anemia.

Possible Survival Benefit of Treating Anemia in Patients With Cancer

As previously described, preliminary evidence suggests that anemia may impact on radiation therapy outcomes. However, *Littlewood et al.* have very recently reported a possible survival benefit in patients treated with rHuEPO and chemotherapy, although as previously mentioned, these data are preliminary and require confirmation [6]. Similarly, preliminary data from trials of darbepoetin alfa in small-cell lung cancer patients receiving platinum-based chemotherapy suggest that median time to disease progression may be decreased with improvement of anemia [54]. However, further research into the survival benefit of treating anemia in cancer patients is required to support these data.

It has also been suggested that anemia may stimulate tumor-associated angiogenesis via hypoxia, as increased levels of vascular endothelial growth factor (VEGF), a factor contributing to increased angiogenesis and, thus, tumor growth, have been detected in the serum of anemic cancer patients [60]. Twenty-six patients with low hemoglobin levels (<13 g/dl) had raised serum VEGF compared with 28 patients with hemoglobin levels >13 g/dl (805 ± 656 pg/ml versus 438 ± 360 pg/ml, respectively; $p = 0.016$). Several other factors, including total tumor volume and platelet counts, were also found to correlate with elevated serum VEGF levels, suggesting that lowered hemoglobin levels may only partially explain the upregulation of VEGF expression detected in these anemic patients. Nevertheless, hemoglobin is a variable that can be corrected, suggesting that treating anemia in all cancer patients may be an important part of their care.

HRQOL and Cognitive Function Outcomes

The debilitating effects that anemia can have on HRQOL outcomes have been reviewed, and management of these

issues should be of high priority, as even small incremental increases in hemoglobin level can significantly improve a patient's HRQOL [10, 11]. While factors such as energy level, ability to work, and fatigue have been assessed, closer evaluation of other HRQOL end points, such as social interaction and depression, may also further delineate the impact of anemia on cancer patients.

Whether treating anemia can improve cognitive function in cancer patients may also deserve investigation. It has been suggested that increases in hematocrit levels following rHuEPO therapy may improve cognitive function in hemodialysis patients, as assessed by improved memory and ability to sustain attention [7, 61]. Additionally, in rat models, rHuEPO has recently been shown to cross the blood-brain barrier via specific capillary receptors and protect against hypoxia-induced neuronal death by preventing apoptosis [62, 63]. Potentially, rHuEPO could have a direct effect in the brain by binding to specific receptors, preventing brain injury and, therefore, sustaining cognitive function. However, whether the findings in animals and in hemodialysis patients translate to patients with cancer needs to be further investigated.

Hospitalization

It has been suggested that rHuEPO and darbepoetin alfa may decrease the number of days cancer patients with anemia spend in hospital [64, 65]. Hospitalization represents a significant burden on health care resources, as well as an inconvenience to the patient. Consideration of treatments that lighten this load is, therefore, important.

CONCLUSIONS

Accumulating evidence suggests anemia is a common complication in cancer patients and may impact on HRQOL, radiation therapy and chemotherapy efficacy, and survival. Management of anemia can improve these outcomes, but it is apparent that anemia may not be optimally managed in cancer patients at this time. However, new approaches and novel therapies that may shift the balance to a more promising future for cancer patients with anemia are on the horizon.

Furthermore, end points such as survival and cognitive function are beginning to be explored, and improved predictive algorithms developed. Continued research into anemia and discussion and understanding of the impact that even mild-to-moderate anemia can have on patient outcomes will ultimately contribute to the optimization of anemia management.

ACKNOWLEDGMENT

M.S.G. is a consultant for Amgen.

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