The Effects of Anemia and Anemia Treatment on the Quality of Life of People With Cancer

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Anemia, common in people with cancer, can be due to the disease itself or to the associated therapy. Fatigue, the most prevalent of all symptoms experienced by cancer patients, is the primary symptom of anemia. Caused by many factors, fatigue, regardless of etiology, has an adverse impact on health-related quality of life.

Anemia, typically characterized by hemoglobin levels below 12 g/dL, is a common occurrence in oncology practice, particularly in patients receiving myelosuppressive chemotherapy.[1] Mild to moderate anemia, with hemoglobin levels between 8 and 12 g/dL, results in symptoms of fatigue, lethargy, dizziness, headache, and difficulty breathing and rapid or irregular heartbeat after exercise. More severe anemia, when hemoglobin levels are below 8 g/dL, results in markedly reduced exercise capacity, difficulty breathing at rest, rapid or irregular heartbeat at rest, and an increased risk of angina pectoris, myocardial infarction, or transient ischemic events.[1-3] Anemia can adversely affect the schedule and tolerability of cancer therapy, which may in turn influence the efficacy of the treatment.

Anemia, Fatigue, and Quality of Life

Anemia has been shown to have an adverse impact on health-related quality of life (QOL).[2-7] Fatigue is the principal symptom of anemia, but other associated symptoms (eg, headache, depression, cognitive impairment) adversely affect patients’ quality of life as well.[3,6] Health-related quality of life is reduced through compromised functional ability (reduced exercise tolerance, ability to work, social interaction, pursuit of leisure activities) and decline in subjective sense of well-being.[8] Even mild anemia (10-12 g/dL) can substantially impair quality of life.[2,3,5,7,9-12] In one study of patients with hemoglobin levels below 12 g/dL, 25% were not able to work at all, compared with 8% of patients with hemoglobin levels above 12 g/dL.[2,3] In addition, cancer-related anemia may compromise patients’ tolerance of treatments, resulting in the need to reduce duration or intensity.[13,14] Anemia has also been associated with reduced local tumor control and decreased survival.[1,6,9]

Fatigue is highly prevalent in cancer patients, and is associated with impairments in physical, functional, and emotional well-being and quality of life.[2-8,15] A number of studies have demonstrated significant associations between anemia, fatigue, and quality of life in cancer patients.[5,7,9,10,16]

Figure 1 presents a model depicting the potential impact of anemia on quality of life. According to the model, anemia directly causes fatigue, which in turn mediates a cascade of other potential problems. Fatigue can be defined as decreased capacity for work and reduced energy reserve,[17] leading to less activity, lower productivity, cognitive difficulties, and a decline in the ability to function normally in daily activities. These factors then often combine to compromise one’s social relationships and social role, due to a lack of interest and energy. If fatigue becomes chronic, self-esteem may suffer as people are unable to fully participate in the regular activities and relationships that provide a sense of accomplishment and fulfillment.[5,17,18] Ultimately, some patients with chronic, unremitting fatigue may be at risk for withdrawal from daily life and major depression.

Fatigue, like anemia, is complex and has a host of interactive etiologic factors, including anemia, mood disturbance, anorexia/cachexia, infection, pain, sleep disturbance, tumor burden, and prolonged stress.[13,18-20] In addition to negatively affecting quality of life, fatigue also poses physical, psychological, and economic problems for patients[14,21] and their caregivers.[18]

In summary, the symptoms of anemia in cancer patients have rather far-reaching consequences for cancer patients and their families. If anemia can be corrected with therapy, it is likely to have
significant value to the patient’s quality of life. Assuming cost-effectiveness can be demonstrated, it will likely have value to society as well.

Treating Anemia in Cancer Patients

Prior to the development of recombinant human erythropoietin, red blood cell transfusion was the standard treatment for cancer-related anemia. This treatment had historically not been utilized until hemoglobin levels dropped well below 10 g/dL, often below 8 g/dL. Given what has been learned about the QOL correlates of mild to moderate anemia, this practice has compromised health status in large numbers of patients. The introduction of erythropoietic agents has added an earlier treatment option, at considerable cost, thus introducing the question of the cost-effectiveness of managing anemia in cancer patients.

Evaluations of the efficacy of erythropoietic agents have relied on one or more of three criteria: change in hemoglobin, reduced transfusion requirements, or subjective benefits that fall under a general heading of patient-reported outcomes. These criteria are summarized in Table 1. Absolute or relative change in hemoglobin or hematocrit is the most direct indicator of drug effect, with a two-point increase from baseline hemoglobin most typically considered to be indicative of significant improvement. Anemia correction, or bringing the patient above 12 g/dL, has been another proposed approach to expressing the benefit of therapy to hemoglobin level.

A second indicator is the number of units of transfused blood, or the proportion of patients who require a transfusion during the period of study. Erythropoietin trials have consistently shown that these end points are achieved, with response rates in the vicinity of 50% to 60% and relative risk of transfusion reduced by 30% to 50%.[9,11,12,16,22-31a] Among the patient-reported outcomes, fatigue and quality of life are the two that are utilized most frequently in erythropoietin studies.

QOL Instruments Used in Efficacy Studies

Quality of life is now a widely accepted patient-reported health outcome measure for clinical trials among patients with chronic illnesses, particularly cancer. Most of the early trials of recombinant erythropoietin used a set of three linear analog self-assessment (LASA) scales.[24,32] The LASA scale is a 100-mm line on which the respondent is instructed to make a mark indicating the degree of endorsement. The content of the three scales included perceived energy level, ability to perform daily activities, and overall quality of life. Scores range from 0, indicating "as low as could be," to 100, indicating "as high as could be."

The Functional Assessment of Cancer Therapy-General (FACT-G)[33] is a cancer-specific QOL instrument that measures physical, emotional, social/family, and functional well-being. The FACT-G can be supplemented with condition-specific subscales, including a 20-item anemia subscale that includes a 13-item fatigue component.[2,3] The general instrument plus the condition-specific subscale is then referred to as the Functional Assessment of Chronic Illness Therapy (FACT)-Anemia or FACT-Fatigue, respectively.[2,3](See Appendix for all scales.) There is now a new subscale for the FACT measurement system that assesses the cognitive complaints experienced by cancer patients undergoing chemotherapy (www.facit.org). Some cognitive complaints during chemotherapy may be influenced by anemia. This question is now being studied.

In most trials initiated after 1996, the Functional Assessment of Cancer Therapy-Anemia (FACT-An) or the Fatigue Subscale has been included with or replaced the LASA scales. In the FACT-An, fatigue and other symptoms of anemia (eg, dizziness, joint aches, etc) are measured using an anemia-specific symptom scale that assesses self-report of the cognitive, physical, and emotional manifestations of anemia. In one pivotal study, the generic SF-36 instrument (see Appendix) was also used in combination with the LASA and FACT-An.[9] In that trial of erythropoietic therapy vs placebo, the FACT-An and LASA scales (but not the SF-36) scores improved significantly in the erythropoietin-treated patients compared to the placebo-treated patients.[9]

Some studies have used the European Organization for Research and Treatment of Cancer (EORTC) core QOL questionnaire (see Appendix), including its three-item fatigue subscale, to assess efficacy of erythropoietin.[34,35a] Studies that have employed the EORTC core questionnaire have not supported evidence for a benefit of erythropoietic therapy on an intent-to treat basis. It is not clear whether this is due to the true absence of a difference in these studies at doses employed, relative imprecision in the measurement of fatigue, or relatively low sample sizes.

Phase III/IV Studies of Erythropoietic Agents: QOL End Points
A number of clinical trials have demonstrated that erythropoietic therapy increases hemoglobin levels and reduces transfusion requirements in anemic cancer patients.[8-11,16] There is a growing body of literature demonstrating that such therapy is not only associated with improvements in hematologic parameters but patient well-being and quality of life as well.[35b-35d] However, two systematic literature reviews, using strict criteria for inclusion and interpretation of evidence, have concluded that whereas erythropoietin therapy undoubtedly increases hemoglobin and decreases transfusion requirements, benefits to quality of life remain to be demonstrated in a convincing manner.[36,37] One of these reviews concluded that at the time of this writing, there were significant methodologic limitations in the existing studies of anemia and health-related quality of life.[37]

However, it is noteworthy that several well-controlled trials, including random assignment and placebo treatment, have been published since these reviews. Early placebo-controlled studies examined the effect of thrice-weekly dosing of recombinant erythropoietin in anemic cancer patients.[24,32] A decrease in the number of transfused units of blood and improvements in hematocrit were observed. Quality-of-life results were mixed. For example, Abels et al showed LASA differences in overall quality of life in favor of such therapy, but no significant difference in energy level or activities of daily living.[24]

Two more recent, placebo-controlled, double-blind phase III studies of erythropoietic agents more emphatically supported the QOL benefits of treating anemia.[9,38] These trials are particularly significant for two reasons: First, the use of rigorous, random-controlled trial methodology addresses concerns about reliance on positive findings from poorly controlled studies; and second, eligibility criteria in both trials specified that subjects must meet criteria for anemia, thus addressing methodologic critiques of previous studies that included nonanemic subjects who were unlikely, therefore, to benefit from the drug.

**The Littlewood Trial**

In one of these studies, Littlewood et al[9] evaluated this question in patients who were receiving non-platinum-based chemotherapy for solid tumors or nonmyeloid hematologic malignancies. Eligibility criteria required that subjects have a baseline hemoglobin of 10.5 g/dL or a baseline level of between 10.5 and 12 g/dL that represented at least a 1.5 g/dL hemoglobin decrease after starting chemotherapy. Over the 12 to 24 weeks of thrice-weekly drug administration, the primary end point—proportion of patients transfused—was significantly lower in the treatment arm (24.7% vs 39.5%). Hemoglobin levels, anemia-specific QOL concerns, and cancer-related quality of life improved significantly in the erythropoietic therapy group, but not in the placebo group. General health status, as measured by the SF-36, showed a trend in the same direction. Finally, the correlations between hemoglobin change and QOL change were significant.

**The Osterborg Trial**

A second well-controlled trial evaluated the use of erythropoietin in 349 severely anemic, transfusion-dependent patients with a hematologic malignancy.[38] The treatment arm received erythropoietin three times per week, and a significant increase in overall quality of life, as measured by the FACT-An and FACIT-Fatigue scales, was observed in the last 4 weeks of the trial (weeks 12 through 16). These improvements were observed in social/family well-being and emotional well-being after 12 weeks and physical well-being and social/family well-being after 16 weeks. Interestingly, the groups did not differ on the QOL subscales that measured specific anemia- or fatigue-related concerns. When QOL reports between responders and nonresponders to the erythropoietic therapy were compared, statistically significant differences were observed for most QOL subscales, including the fatigue- and anemia-specific subscales.

**Other Trials**

Initial placebo-controlled registration studies in anemic cancer patients showed that three-times-weekly dosing of recombinant erythropoietin was associated with significant increases in hematocrit, decreases in units transfused, and improvements in energy level and daily activities that contributed to improvement in overall quality of life.[12,24] Further evidence stems from two prospective, multicenter, community-based, open-label, nonrandomized studies of three-times-weekly dosing of erythropoietin, each involving more than 2,000 patients.[10,16] Both studies assessed quality of life with the LASA, and Demetri et al[16] also used the FACT-An questionnaire. Both studies demonstrated a relationship between increased hemoglobin levels and improvement in quality of life. Increases in FACT-An scores reflected significant increases in QOL scores from baseline and a significant relationship between higher hemoglobin levels and higher scores for physical and functional well-being subscales of the FACT-An. In addition, the salutary effect of hemoglobin increase on quality of life was independent of tumor response to...
An analysis of the ratio of change in QOL scores (LASA and FACT) to change in hemoglobin level showed that women experienced a significantly greater improvement in quality of life on average, with twice the increase in QOL score for every 1 g change in hemoglobin level compared with men. This enhanced QOL response among women has been confirmed by others.[22,39a,39b] Several more recent studies have confirmed and expanded on these findings. Gabrilove et al[22] used a once-weekly dosing schedule for erythropoietin in a multicenter, open-label, nonrandomized trial of over 3,000 patients receiving chemotherapy. This study used the LASA and the 20-item anemia subscale of the FACT-An and similarly found a significant increase in hemoglobin levels, reduced transfusion requirements, and improvements in QOL.

Once-weekly dosing of recombinant erythropoietin was similarly shown to be effective in increasing hemoglobin levels and improving patient-assessed energy and activity levels and overall quality of life (assessed via LASA) in both lung cancer[40] and breast cancer[41] patients receiving concomitant or sequential chemoradiation.

Erythropoietic Agents and Survival in Cancer Patients

Results from an international, randomized, double-blind, placebo-controlled clinical trial of 375 patients receiving nonplatinum chemotherapy were consistent with previous trials in showing increased hemoglobin levels, reduced transfusion requirements, and significant improvements in all cancer- and anemia-specific QOL domains for the erythropoietin-treated group compared to placebo.[9] Additionally, although not powered for survival as an end point, the results were suggestive of a survival advantage for patients treated with erythropoietin compared with placebo. These results must be interpreted with caution, however, as other variables potentially influencing survival (eg, stage, bone marrow involvement, chemotherapy intensity, disease progression) were not controlled for or stratified. This is currently being investigated in properly powered and designed trials.

Erythropoietic Therapy for Nonchemotherapy Patients

Quirt et al[23] expanded on previous investigations that included cancer patients likely to experience anemia, but not receiving chemotherapy. He treated this cohort of patients with a higher dose (150 vs 100 U/kg) and for a longer duration (12 vs 8 weeks) than a previous placebo-controlled study.[24] They also collected prospective disease response data and measured quality of life with the FACT-An questionnaire in addition to the LASA. Results from this recent study[23] revealed that nonchemotherapy patients experienced significant increases in hemoglobin levels that were correlated with significantly improved QOL scores and change in Eastern Cooperative Oncology Group (ECOG) performance status scores. These changes were comparable with the results reported for patients receiving chemotherapy in the two large open-label studies,[16,25] and suggest that anemic cancer patients may benefit from erythropoietic therapy whether or not they are receiving chemotherapy.

Erythropoietin and Quality of Life in Multiple Myeloma

Demonstration of the benefits of erythropoietic therapy was extended to patients with multiple myeloma with the results of a multicenter, randomized trial that included a 12-week double-blind, placebo-controlled treatment phase and a 12-week open-label extension phase.[26] Erythropoietin-treated patients experienced significantly reduced transfusion requirements compared with placebo, an increase in hemoglobin levels of at least 2 g/dL in significantly more patients than placebo, and significantly improved ECOG performance status. Although univariate analyses revealed significant improvements in various QOL domains, multivariate analyses failed to reveal group differences. Significantly, however, the hematologic benefits of erythropoietic therapy were observed in patients with progressive multiple myeloma considered resistant or refractory to chemotherapy. The stability of quality of life and performance status scores in patients treated with erythropoietin during the open-label phase led the authors to suggest that erythropoietin might be useful in both improving and maintaining quality of life in multiple myeloma patients.

QOL Benefits of Erythropoietic Therapy

As noted above, a number of randomized trials and supporting open-label studies suggest that
erythropoietic agents improve quality of life, probably through an indirect pathway resulting from increases in hemoglobin and associated oxygen transport. However, these significant results are often expressed as numbers that change over the course of erythropoietic therapy, or that change after hemoglobin is normalized. By themselves, these numbers communicate little. Therefore, efforts to provide meaning to these numbers are important to the clinical, regulatory, and/or paying communities.

A recently completed study compared FACT-An scores of a nationally representative sample of healthy individuals to those of a sample of 375 anemic cancer patients from a randomized, double-blind, clinical trial evaluating erythropoietin vs standard care.[27] Cancer patients’ responses reflected QOL deficits for general quality of life and the 13-item fatigue subscale of the FACT-An. By the end of the trial, the erythropoietin-treated group had nearly erased deficits from the general quality of life and anemia subscale and halved the deficit from the fatigue subscale, providing an example of the magnitude of impact from erythropoietin treatment for cancer-related anemia.[27]

In an effort to aid in the interpretation of the same clinical trial described above,[9] changes in QOL scores were mapped onto changes in hemoglobin concentrations.[28] This study had confirmed results from many previous studies in finding lower transfusion requirements, improved hemoglobin levels, and improved quality of life in erythropoietin-treated patients. Additionally, comparison of patients with improved (≥ 1 g/dL) and stable hemoglobin levels (< 1g/dL) indicated that a ≥ 1g/dL hemoglobin increase was associated with improved quality of life, and that the QOL improvements in the erythropoietin-treated group are clinically significant. This was done by positioning the change in FACT-G and LASA QOL scores to hemoglobin change score, in such a way that allowed one to estimate a unit change in quality of life that could be compared to a unit change in hemoglobin.[28] Fatigue is a serious symptom in the cancer population; however, it is also a common problem in the general population. This observation allowed us to establish "normative data" in the general United States population, so that the fatigue of cancer patients can be compared on the same measure.[21] We compared the level of fatigue in anemic cancer patients with nonanemic cancer patients and the general United States population over time using a standardized set of 13 questions from the FACIT measurement system. Results showed that fatigue scores were significantly worse in the anemic cancer patients. Additionally, the study highlighted the impact of hemoglobin levels on the level of fatigue in cancer patients (see Figure 2). While all study participants were able to relate to fatigue, the impact of fatigue in the cancer population, in particular the anemic subgroup, was decidedly worse.

Using these normative data, Kallich et al[31] portrayed clinical trial results against the backdrop of these normative scores, and scores from baseline assessment in the Demetri et al[16] erythropoietin community-based trial. This is illustrated in Figure 3, allowing one to note that after erythropoietic therapy patients achieve improvements in fatigue that lie between the normative levels of fatigue in the general population and the baseline scores of patients with anemia prior to starting erythropoietic therapy.

**Novel Erythropoiesis-Stimulating Protein**

Recent studies have evaluated a novel erythropoiesis-stimulating protein (NESP), darbepoetin alfa (Aranesp), which has a 2- to 3-fold longer serum half-life than erythropoietin and may therefore require less-frequent administration.[10,29-31] (Figures 4 and 5) Preliminary results suggest that, in addition to favorable hematologic responses, an increase in hemoglobin levels from baseline may be associated with a positive impact on quality of life, as measured by FACT-Fatigue scale scores, in patients with nonmyeloid malignancies.[29] solid tumors,[10] and lung cancer.[30] Kallich et al[31] reported that darbepoetin alfa improved patients’ fatigue (as measured by the FACT-Fatigue scale) over placebo an average of 35% when hemoglobin levels increased by ≥ 2 g/dL. This group also found a differential impact of darbepoetin alfa on FACT-Fatigue scores, with women’s scores increasing more than men’s by increment of hemoglobin change from baseline.

**Undertreatment of Anemia and Possible Explanations**

It has been conclusively demonstrated that cancer-related anemia can be treated successfully in most patients. A recent estimate suggests that only 15% to 35% of anemic cancer patients receive a trial of an erythropoietic agent.[42,43] There are several factors that contribute to this undertreatment. One factor is the under-recognition of the problem on the part of both providers and patients.[15,18] A second factor is the inconvenience of current therapy, which requires injection typically one to three times per week, depending upon local practice and reimbursement regulations. If a patient must come to a clinic for injections, this is very inconvenient. A third factor is the fact
that nearly 50% of patients will not respond to the therapy. Given there is no reliable way to predict responders, this can lead to lack of conviction regarding its value, given that most chemotherapy patients will eventually recover on their own.

Finally, hanging over all of these considerations is the very high cost of the therapy. Because the charges for all currently approved erythropoietic agents are based upon considerably lower dose requirements seen in nephrology, the cost of treating a cancer patient is often seen as unacceptable. Drawing on data from one of the community studies, Barosi et al[44] modeled the cost-effectiveness of erythropoietin therapy relative to standard care as a preventive measure, and reported marginal cost-effectiveness to be $189,652 per quality-adjusted life year. Similarly, Ortega et al[45] reported that patients were unwilling to pay the net incremental treatment cost of $2,943 realized if erythropoietin were added to care. However, Cremieux and colleagues,[46] drawing assumptions from the literature and three US-based clinical trials, showed that the effectiveness from $1 spent on standard care could be achieved with $0.81 if erythropoietin were added. The area of cost-effectiveness remains controversial, as none of these reports are based on a prospectively designed and implemented randomized clinical trial. Further study of this important issue may help achieve a fair and rational basis for pricing this helpful therapy.

**Conclusion**

For patients with cancer, anemia and its primary symptom—fatigue—represent prevalent problems that profoundly impact functional status, sense of well-being, and quality of life. Clinical trials have suggested a benefit to fatigue and quality of life of erythropoietin therapy for anemia in a number of cancer populations, as have recent studies exploring more convenient dosing schedules and new longer-acting drugs. Future trials designed to correct the methodologic limitations of earlier studies are likely to make significant contributions to the growing body of literature on the QOL effects of erythropoietin as well as novel pharmacotherapies for anemia. These studies will hopefully also help to further delineate the nature of the QOL benefit, its clinical significance, the best way to identify responding patients early in treatment, and a cost-effective management strategy that allows more people with cancer-related anemia access to this therapy.

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