Fatigue is common in cancer patients treated with chemotherapy, and it has detrimental effects on their quality of life. Chemotherapy-induced anemia, however, is often under-recognized and under-treated. There is a clear association between hemoglobin (Hgb) levels and fatigue, with fatigue being greater in patients with lower Hgb levels. Managing fatigue requires that its causes be determined and corrected, and it is important that patients report their fatigue. Patients, however, are unlikely to mention such adverse events unless they are asked about them. In addition, busy practitioners generally have very little time to discuss anemia-related fatigue with their patients. Many studies have used the validated quality-of-life instrument Functional Assessment of Cancer Therapy-Fatigue (FACT-F) to assess fatigue and quality of life in patients treated with chemotherapy; these studies have shown a relationship between chemotherapy-induced anemia, fatigue, and quality of life. Studies of erythropoiesis-stimulating proteins to treat chemotherapy-induced anemia have shown increases in patients' hemoglobin levels, improvement in their FACT-F and FACT-General scores, and improvements in their quality of life.

Fatigue is common in patients treated with chemotherapy, and it has substantial adverse physical, psychosocial, and economic consequences. Cancer-related fatigue is generally under-recognized and under-treated. Fatigue occurs on at least a few days of each month in 76% of patients treated with chemotherapy,[1] and has been reported to occur daily in 32% of patients treated in the United States and in 24% of patients treated in Ireland.[1] Physicians in the United States either offered no treatment or prescribed bed rest in 77% of cases, as did physicians in Ireland in 87% of cases.[1,2] Patients and their physicians are now paying closer attention to fatigue and anemia. These and other adverse events are often managed in the context of maintaining the chemotherapy dose and schedule.

Discussions about fatigue and anemia generally lack the interactivity to distinguish the cause of the fatigue from other problems such as sleep disorders, poor nutrition, cancer, and depression. Patients are often reluctant to volunteer information about adverse events and will discuss them only if they are asked specifically about them.[1] The physician or nurse generally initiates these discussions: they are usually short—less than a minute—and often only one question about fatigue is asked.[3] In contrast, the most commonly used fatigue scale in this setting contains 13 items. Physicians do not generally use such instruments for assessing fatigue, or use only parts of them. In addition, 90% of the questions about adverse events are simple yes or no questions that cannot fully capture the patient's feelings and experiences. Furthermore, physicians often speak in words and terms that their patients cannot understand. In this article I discuss the use of erythropoiesis-stimulating proteins (ESPs) in patients with fatigue resulting from chemotherapy-induced anemia, and their effects on patients' quality of life (QOL).

Understanding Fatigue
Managing fatigue requires that it be properly assessed and its causes determined and treated. It is not linked solely to anemia or any other disease or cause, and it can also result from depression, pain, sleep disorders, and other conditions.[1,4] The symptoms of fatigue can be treated with pharmacologic and nonpharmacologic interventions, but many of the pharmacologic interventions, such as psychostimulants and low-dose corticosteroids, have not been thoroughly tested in the setting of fatigue.[4] Among the nonpharmacologic interventions for cancer-related fatigue are patient education, exercise, modification of activity and rest patterns, stress management, cognitive therapies, and dietary changes.[4]

The precise relationship between hemoglobin (Hgb) levels and fatigue is not known, but it is clear that there is a link, and fatigue is greater in persons with lower Hgb levels.[5,6] Even small increases in patients' Hgb levels can improve their fatigue and anemia-related symptoms. Instruments that measure QOL such as the Functional Assessment of Cancer Therapy-Anemia (FACT-An, consisting of...
the FACT-General [FACT-G] plus 13 fatigue items and 7 nonfatigue anemia-related items) can be used to discriminate patients on the basis of Hgb level and fatigue.[7] Gabrilove and colleagues conducted a trial of epoetin alfa (Procrit) given once a week in patients with nonmyeloid malignancies and showed that the scores on the FACT-An were significantly higher in those with an increase in Hgb levels of 2 g/dL or more than in those with smaller increases.[8] Cella and colleagues administered the FACT-G to patients with cancer and found that the scores on the FACT-G, as well as on the items for fatigue and nonfatigue, physical well-being, and functional well-being, were significantly better in those with Hgb levels of 12 g/dL or higher than in those with lower levels (P ≤ .02) (Table 1).[7] These findings were confirmed in a large community trial in patients with anemia who were treated with chemotherapy and epoetin alfa, in whom the improvements in QOL measures correlated significantly with Hgb levels (r = .235; P < .001), independent of the response to chemotherapy.[9] Cella and colleagues also administered the FACT-Fatigue (FACT-F, consisting of the FACT-G plus 13 fatigue items) (Table 2) to 375 patients with cancer and to a sample of 1,400 persons in the general population, and, as expected, fatigue was more severe and more common in the patients with cancer.[10]

**Decreasing Fatigue and Improving Quality of Life**

Erythropoiesis-stimulating proteins are indicated for the treatment of chemotherapy-induced anemia, and they have been shown in clinical trials to correct or prevent anemia and to decrease the need for red blood cell transfusions.[9] In an analysis by Cella and colleagues of pooled data from five clinical trials in patients with cancer who were treated with the long-acting ESP darbepoetin alfa (Aranesp), there was a significant correlation between increases in Hgb level and reductions in fatigue.[6] Similarly, multivariate regression analysis of data from a randomized double-blind placebo-controlled study showed significantly greater benefits in QOL in patients treated with epoetin alfa than in those treated with placebo (Table 3).[11]

**Table 3**

| Changes in FACT Scores After Treatment With Epoetin Alfa |
|---------------------|---------------------|---------------------|---------------------|
| **Mean Change in Score** | **Epoetin Alfa** | **Placebo** | **P Value** |
| FACT-G (n = 200) | +2.42 | −3.31 | < .05 |
| (n = 192) | | | |
| FACT-F | +2.97 | −2.18 | < .01 |
| FACT-An | +4.02 | −2.64 | < .05 |

**FACT-G** = Functional Assessment of Cancer Therapy–General; **FACT-F** = Fatigue; **FACT-An** = Anemia.

Data from Fallowfield et al.[4]

In summary, studies have shown:
- Significant correlations between pretreatment Hgb levels and QOL
- Significant correlations between changes in Hgb levels and changes in QOL
- Meaningful improvements in measures of fatigue in patients treated with darbepoetin alfa
- Associations of improvements in fatigue with improvements in physical, functional, emotional, and overall well-being.

Another randomized double-blind placebo-controlled clinical trial, by Littlewood and colleagues, also showed greater improvements from the pretreatment FACT-F scores in patients treated with epoetin alfa than in those treated with placebo, with significant correlations between the changes in Hgb levels and the changes in QOL scores (P = .03 to < .001).[12]

**The FACT-F Instrument**

The FACT-F is a validated health-related QOL instrument that has been used in clinical studies of darbepoetin alfa and other agents. The FACT-F was used in a phase I/II trial of 429 patients with solid tumors with anemia who were treated with darbepoetin alfa or epoetin alfa[13]; in a phase III
placebo-controlled trial of darbepoetin alfa in 320 patients with lung cancer[14]; in a study of 2,289 patients with cancer and anemia treated with epoetin alfa[9]; and in a survey of 1,400 persons in the general population.[10] Fatigue at baseline was greatest in the patients with cancer and anemia and was least in the members of the general population (Figure 1).

Quality of life was assessed by using the FACT-F in a double-blind trial conducted by Witzig and colleagues in patients with solid tumors, most with advanced disease, who were randomized to epoetin alfa once a week or to placebo.[15] All patients received oral iron. Hemoglobin levels were assessed weekly and QOL was evaluated monthly. Fewer transfusions were required and the Hgb response rate was higher among patients treated with epoetin alfa. The pretreatment scores in the FACT-F were similar in both groups. After treatment, the mean FACT-F score was 5.1 points higher in patients with an Hgb response and 2.1 points lower in those without a response. Although not significantly different in the intent-to-treat analysis, there was a +0.6 change in fatigue score among patients treated with placebo vs a +3.0 fatigue change score among patients treated with epoetin alfa. The QOL differences between groups were not significant. The modest overall improvement in FACT-F score among patients treated with epoetin alfa may have been blunted by the severity of the disease and the fairly large number of patients in the study, relative to other studies in the field, with respect to tumor progression while on study. Median survival of patients was 11 months.

The Canadian Prevention Trial, by Chang and colleagues, randomized 354 patients with breast cancer (79% of whom were being treated with adjuvant chemotherapy) to epoetin alfa once a week, to maintain the Hgb levels at 12 to 14 g/dL, or to standard of care.[16] The mean pretreatment score on the FACT-F was about 7 points (twice the difference considered minimally important) higher in these patients than in patients in the trial by Witzig and colleagues.[15] Responses were assessed at week 12, and Hgb levels of 12 g/dL or higher were more common in patients treated with epoetin alfa than in those treated with standard of care (52% vs 5%), as were increases of 2 g/dL or more in the Hgb levels (66% vs 6%). The FACT-F score at week 12 was 1.8 points higher than the pretreatment score in patients treated with epoetin alfa and 3.6 points lower in those treated with standard of care. Quality of life was greater and the need for red blood cell transfusions was lower in the patients whose Hgb levels were maintained with epoetin alfa given once a week.
The two trials previously mentioned supported the efficacy of weekly epoetin alfa in maintaining Hgb levels and decreasing the need for transfusions.[17] There was QOL discordance between the studies (Figure 2), which may be explained by the open-label design of the trial by Chang and colleagues and differences in the patient populations between studies: the patient population was homogeneous in the trial by Chang and colleagues and heterogeneous in the trial by Witzig and colleagues. The timing of treatment initiation must also be considered, given that it can take several weeks for an effect to be observed. Treatment was initiated earlier in the trial by Chang and colleagues, which may have lessened the time during which patients had symptoms of anemia.[17] The trial by Chang and colleagues did not have a control group, however, and its open-label design could introduce bias, particularly with a subjective end point. The previously mentioned trial by Littlewood and colleagues[12] had a blinded control group and a heterogeneous population similar to that in the trial by Witzig and colleagues, suggesting that the differences in outcomes in the trial by Chang and colleagues could be a result of its design.

**Conclusions**

Fatigue related to cancer or chemotherapy is under-recognized and under-treated. Patients have some responsibility to report their fatigue to their providers. Providers, however, play a major role in helping to set treatment priorities with the patient, and placing fatigue in the hierarchy of concerns to address requires discussion about patient values and treatment goals. Patients and their physicians are becoming more aware of anemia and fatigue, but discussions about these side effects are generally short and are inadequate to pinpoint the cause of the fatigue. There are many causes and manifestations of cancer-related fatigue. Optimal management flows from proper diagnosis and discussion with the patient.

**Disclosures:**

Dr. Cella serves as a consultant for Amgen and Ortho Biotech.

**References:**


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