The Management of Fatigue in Cancer Patients

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Fatigue, the most common symptom reported by people with cancer, is associated with functional impairments and decrements in quality of life. As Drs. Lipman and Lawrence have pointed out, research on the etiology of cancer-related fatigue is scant. Morrow et al[1] conducted a detailed review of the evidence to support four hypotheses for cancer-related fatigue and highlighted independent findings that implicate cytokines, 5-HT, and the hypothalamic-pituitary axis in the development of cancer-related fatigue. Additional research is needed in this area to articulate the pathophysiology of fatigue and the associated clinical implications.

Assessment of Cancer-Related Fatigue

A comprehensive assessment of patients with cancer-related fatigue is required given the multifactorial nature of the etiology and manifestation of fatigue. Because of the subjective nature of fatigue, it is important to use standardized instruments that have been validated in oncology samples. For a review of instruments available to assess cancer-related fatigue, see Wagner and Cella.[2] Drs. Lipman and Lawrence believe that while most instruments being used to assess fatigue within the context of research are psychometrically valid and reliable, their clinical significance remains obscure. We disagree with that evaluation and highlight three publications on the clinical significance of fatigue scores obtained from two standardized questionnaires: the Functional Assessment of Chronic Illness Therapy-Fatigue subscale (FACIT-F) and the Brief Fatigue Inventory (BFI).

Clinical Significance of Fatigue Scores

Cella et al[3] examined FACIT-F data from three samples: anemic cancer patients (n = 2,369), nonanemic cancer patients (n = 113), and the general US population (n = 1,010). Each sample demonstrated a distinct distribution of FACIT-F scores. Based on a discriminant analysis approach, the investigators were able to distinguish between cancer patients with anemia, cancer patients without anemia, and respondents from the general US population with high sensitivity and reasonable specificity. These findings also indicated that cancer-related fatigue appears to be significantly more disruptive to daily functioning than everyday fatigue. The following example illustrates the clinical applicability of these results. A patient who obtains a raw score of 22 on the 13-item FACIT-F has performed just below the mean for anemic cancer patients and has more fatigue than 95% of the general population. Mendoza et al[4] examined fatigue severity ratings on the BFI in relationship to the extent to which fatigue interfered with functional domains. Based on these results, the authors recommended using a cut-off of ≥ 7 to differentiate severe from nonsevere cases of fatigue. Clinically significant changes on the FACIT-F have been established in a series of coordinated research projects. Cella et al[5] examined data from three oncology samples (n = 50, 131, and 2,402 patients). Using anchor- and distribution-based methods, minimally clinically important differences were calculated for the FACIT-F subscale (3.0 points), the Trial Outcome Index-Fatigue (5.0 points), and the Functional Assessment of Cancer Therapy- General (4.0 points). One can comfortably conclude that when compared to usual care, an intervention that increases FACIT-F scores by 3 or more points overall can be considered to have yielded a meaningful therapeutic effect.

Diagnostic Criteria for Cancer-Related Fatigue

Drs. Lipman and Lawrence correctly point out that diagnostic criteria for cancer-related fatigue set forth by the Fatigue Coalition have not been widely adopted. Given the problems the authors cite as impeding research progress on cancer-related fatigue, such as variability in the definitions of fatigue and the grading of fatigue severity, we advocate the use of these diagnostic criteria. The use of diagnostic criteria would standardize the case definition for cancer-related fatigue, thus...
standardizing eligibility criteria for research and developing a common language for understanding the phenomenology of fatigue in cancer patients. We recently reviewed nonpharmacologic and pharmacologic interventions for cancer-related fatigue,[6] with priority given to the most methodologically sound clinical trials. Few randomized clinical trials for the treatment of cancer-related fatigue have been conducted; however, research to date has identified a few potentially efficacious management approaches. **Nonpharmacologic Interventions**

Among nonpharmacologic interventions for cancer-related fatigue, the effectiveness of exercise in reducing fatigue and functional impairments has received the most empirical support. Drs. Lipman and Lawrence point out the pronounced impact of exercise on fatigue severity and functional abilities. Effect sizes from recent studies range from 0.31 for a resistance training program among prostate cancer patients receiving androgen ablation therapy[7] to 0.72 for exercise group training (cycle ergometers) among postmenopausal breast cancer survivors.[8] Despite the methodologic limitations, the availability of empirical support for exercise in samples of patients with breast cancer as well as other cancer types suggests that tailored exercise programs, including home-based exercise programs, hold promise as a first-line treatment for the prevention or management of cancer-related fatigue. Seven randomized clinical trials have supported the efficacy of psychosocial interventions for the management of cancer-related fatigue.[6] The type of intervention evaluated and the mode of delivery (individual or group) has varied. Findings published by Jacobsen et al[9] on the efficacy of a stress management training program are particularly noteworthy given the sample size (N = 411), the random assignment of participants to treatment, and the potential ease of implementing their intervention in a clinical setting. Jacobsen et al[9] examined a sample of mixed cancer patients undergoing chemotherapy and reported increased vitality and mental health among patients who participated in the stress management training program. Participants who completed the self-administered stress management training (via audio- and videocassette) also experienced therapeutic benefit. The home-based nature of this intervention facilitates its ease of implementation in busy clinical settings with limited access to mental health service providers. **Pharmacologic Interventions**

Research on pharmacologic approaches to the management of cancer-related fatigue is limited, as few studies have been published and many have methodological shortcomings. Classes of potentially useful medications include erythropoietic agents (when anemia is present), psychostimulants, selective serotonin-reuptake inhibitors, and low-dose corticosteroids. For cancer-related fatigue not attributable to an underlying causative factor, psychostimulants have received the most empirical support.[6] **Erythropoietic Agents: Impact on Fatigue and Quality of Life**

As Drs. Lipman and Lawrence have stated, the efficacy of erythropoietic agents to stimulate erythropoiesis and increase hemoglobin, reducing the likelihood of red blood cell transfusion, has been clearly established. The authors assert that the association between treatment of anemia with erythropoietic agents and quality of life, including symptom burden, is unclear. This contention ignores supportive data from many recent randomized trials.[10-15] While the Agency for Healthcare Research and Quality technology report written by Blue Cross/Blue Shield questioned the handling of missing data and unclear clinical significance of differences, several new studies and clarifying analyses of the Littlewood trial[11] have addressed the concerns raised in the report. As a result, the principal author of that report has acknowledged Level 1 evidence in support of a quality-of-life benefit to epoetin alfa treatment of chemotherapy-receiving patients who begin with hemoglobin levels below 10 g/dL. Drs. Lipman and Lawrence focused on findings presented in Littlewood et al,[14] which included results from a univariate linear regression analysis of quality-of-life data. Further results from an a priori analysis of quality of life and fatigue data from the Littlewood et al[14] trial addressed the methodologic issues raised by Drs. Lipman and Lawrence and by the authors of the now-outdated technology evaluation report. Fallowfield and colleagues[11] presented baseline quality-of-life data, carefully articulated missing data issues, and conducted a multiple linear regression analysis to control for the effects of disease progression and many other potentially confounding variables (eg, age, sex, baseline hemoglobin) on quality of life and symptom burden. Findings provided solid evidence that increasing hemoglobin levels through epoetin alfa administration significantly improved cancer patients’ quality of life and reduced fatigue. These results appear to be equally applicable to darbepoetin alfa treatment, as summarized in a recent pooled analysis of five randomized clinical trials.[10] Clinically meaningful adjusted mean differences in FACT-Fatigue scores were observed between hemoglobin responders and nonresponders. Across all five trials, hemoglobin response was associated with reductions in fatigue, which was associated with improved physical, functional, emotional, and overall well-being. **Safety Issues**
Given the Oncologic Drugs Advisory Committee meeting in May 2004 on the safety of erythropoietic agents, Drs. Lipman and Lawrence provided a timely review of safety issues to consider—namely, the risk of thrombotic events when administering erythropoietic therapy. While methodologic shortcomings limit conclusions that can be drawn from the clinical trials that initiated these concerns, these safety concerns warrant further investigation. Drs. Lipman and Lawrence identified pure red cell aplasia as a potential adverse event of erythropoietic treatment. A recent report suggests that there have been no published reports of epoetin-associated pure red cell aplasia in patients with cancer, perhaps due to chemotherapy-associated immunosuppression.[16]

Conclusions
Cancer-related fatigue is a prevalent and clinically significant issue among oncology patients. We appreciate the excellent review of treatment strategies written by Drs. Lipman and Lawrence and highlight empirical support that exists for nonpharmacologic interventions, namely exercise and psychosocial interventions. Updated evidence supports a role for erythropoietic agents in relieving fatigue associated with anemia. Recently identified risks of erythropoietic therapy warrant further investigation.

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