

Cancer-Related Fatigue: Guidelines for Evaluation and Management

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Key Words. *Fatigue · Cancer · Quality of life · Anemia · Erythropoietin (EPO) · Epoetin alfa · Asthenia*

ABSTRACT

Fatigue is a highly prevalent condition among cancer patients. Although most cancer patients report that fatigue is a major obstacle to maintaining normal daily activities and quality of life, it is seldom assessed and treated in clinical practice. Few studies have explored its epidemiology, possible etiologies, or management. Cancer-related fatigue, which recently was accepted as a diagnosis in the International Classification of Diseases 10th Revision-Clinical Modification, reduces physical, psychological, and social functioning and results in significant distress for patients and caregivers. Adequate evaluation of fatigue must do more than simply assess severity. The assessment should clarify other characteristics, determine the degree to which fatigue interferes with the activities of daily living, and identify potential causes, including the underlying disease, disease treatments, intercurrent systemic disorders, psychological disorders, and other

conditions. Possible primary therapies include modification of the patient's drug regimen, correction of metabolic abnormalities, and pharmacologic treatments for anemia (e.g., epoetin alfa), depression, or insomnia. Other symptomatic interventions include specific drug treatments, exercise, modification of activity and rest patterns, cognitive therapies, sleep hygiene approaches, and nutritional support. Pharmacologic approaches, which are supported by limited studies and growing clinical experience, include psychostimulant drugs, corticosteroids, and possibly other therapies. Although additional research is needed to further identify the causes and corresponding treatment of fatigue, practitioners should routinely assess and treat patients who may benefit from currently identified interventions, because fatigue can profoundly undermine the quality of life of patients with cancer. *The Oncologist* 1999;4:1-10

INTRODUCTION

Fatigue has been identified by patients with cancer as a major obstacle to normal functioning and a good quality of life [1]. It is a nearly universal symptom in patients undergoing primary antineoplastic therapy or treatment with biologic response modifiers and is extremely common in populations with persistent or advanced disease [1-12].

Given the prevalence and impact of cancer-related fatigue, there have been remarkably few studies of the phenomenon. Its epidemiology has been poorly defined, and the variety of clinical presentations remains anecdotal. The existence of discrete fatigue syndromes linked with predisposing factors or potential etiologies has not been confirmed, and clinical trials to evaluate putative therapies for specific types of cancer-related fatigue are almost entirely lacking.

It is important to begin to characterize the phenomenon of cancer-related fatigue and offer guidelines for management.

Increased awareness will encourage better assessment and consideration of available therapeutic options. Management will improve as new research clarifies the prevalence and nature of the problem, yields validated assessment tools, and evaluates specific treatment strategies. This review discusses the clinical aspects of cancer-related fatigue and offers strategies to assist in the management of this undertreated condition.

DEFINITION, PREVALENCE, AND CAUSES OF FATIGUE

Patients and practitioners can generally differentiate "normal" fatigue experienced by the general population from clinical fatigue associated with cancer or its treatment. The term "asthenia" has been used to describe fatigue in oncology patients but has no specific meaning apart from the more common term. Fatigue is an inherently subjective and multi-dimensional condition. It may be described in terms of a variety of characteristics (e.g., severity, distress, temporal

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Accepted for publication January 19, 1999. ©AlphaMed Press 1083-7159/99/\$5.00/0

features) and specific impairments (e.g., lack of energy, weakness, somnolence, difficulty concentrating). Criteria have been needed to define this clinically relevant syndrome. Recently, cancer-related fatigue was accepted as a diagnosis in the International Classification of Diseases 10th Revision-Clinical Modification. Fatigue may be characterized as a multidimensional phenomenon that develops over time, diminishing energy, mental capacity, and the psychologic condition of cancer patients (Table 1) [13]. Fatigue is also linked with lethargy, malaise, and asthenia in the revised National Cancer Institute (NCI) Common Toxicity Criteria (CTC). These classifications may enhance awareness of fatigue and improve reporting of the condition.

Cancer-related fatigue is extremely prevalent. A recent population-based survey of 419 randomly selected patients observed that 78% experienced fatigue, which was defined as debilitating tiredness or loss of energy at least once each week; the majority of these patients reported that fatigue had either significantly (31%) or somewhat (39%) affected their daily routine [1]. In a cross-sectional survey of 151 ovarian cancer patients, the prevalence of fatigue was 69%, and approximately half of affected patients described the condition as highly distressing [11]. Other surveys of patients with metastatic disease suggest that the prevalence in this setting exceeds 75% [11, 14-18].

Numerous surveys have associated the occurrence of fatigue with specific treatments [3-6, 19-23]. These surveys suggest that fatigue commonly occurs after surgery, chemotherapy, radiotherapy, or immunotherapy. Prevalence rates

of fatigue as high as 96% have been reported in conjunction with chemotherapy and radiotherapy [5], and severe fatigue is almost universal with the use of biologic response modifiers, including α -interferon and the interleukins [19, 23, 24].

When fatigue is primarily related to a treatment, there is generally a clear temporal relationship between the condition and the intervention [21, 25-27]. In patients receiving cyclic chemotherapy, for example, fatigue often peaks within a few days and declines until the next treatment cycle. During a course of fractionated radiotherapy, fatigue is often cumulative and may peak after a period of weeks. Occasionally, fatigue persists for a prolonged period beyond the end of chemotherapy or radiotherapy.

The relationships between fatigue and demographic characteristics, physiologic factors, and psychosocial factors are not well defined. The specific mechanisms that precipitate or

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Table 1. Proposed criteria for cancer-related fatigue [13]

The following symptoms have been present every day or nearly every day during the same 2-week period in the past month:

▲ Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level

Plus five (or more) of the following:

▲ Complaints of generalized weakness or limb heaviness

▲ Diminished concentration or attention

▲ Decreased motivation or interest in engaging in usual activities

▲ Insomnia or hypersomnia

▲ Experience of sleep as unrefreshing or nonrestorative

▲ Perceived need to struggle to overcome inactivity

▲ Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued

▲ Difficulty completing daily tasks attributed to feeling fatigued

▲ Perceived problems with short-term memory

▲ Post-exertional malaise lasting several hours

The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer-related therapy.

The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium.

sustain the syndrome are unknown. Fatigue may represent a final common pathway to which many predisposing or etiologic factors contribute (Table 2) [29-35]. The pathophysiology in any individual may be multifactorial. Proposed mechanisms

include abnormalities in energy metabolism related to increased requirements (e.g., due to tumor growth, infection, fever, or surgery); decreased availability of metabolic substrate (e.g., due to anemia, hypoxemia, or poor nutrition); or the abnormal production of substances that impair metabolism or normal functioning of muscles (e.g., cytokines or antibodies). Other proposed mechanisms link fatigue to the pathophysiology of sleep disorders and major depression. There is no clear evidence in support of any of these mechanisms, and further research is needed.

EVALUATION OF FATIGUE

Assessment of Fatigue Characteristics

A detailed characterization of fatigue, coupled with an understanding of the most likely etiologic factors, is necessary

Table 2. Potential predisposing factors or etiologies of cancer-related fatigue [28]**Physiologic**

- Underlying disease
- Treatment for the disease
 - Chemotherapy
 - Radiotherapy
 - Surgery
 - Biologic response modifiers
- Intercurrent systemic disorders
 - Anemia
 - Infection
 - Pulmonary disorders
 - Hepatic failure
 - Heart failure
 - Renal insufficiency
 - Malnutrition
 - Neuromuscular disorders
 - Dehydration or electrolyte disturbances
- Sleep disorders
- Immobility and lack of exercise
- Chronic pain
- Use of centrally acting drugs (e.g., opioids)

Psychosocial

- Anxiety disorders
- Depressive disorders
 - Stress-related
 - Environmental reinforcers

Table 3. Evaluation of cancer-related fatigue**Assessment of fatigue characteristics and manifestations**

- ▲ Severity, temporal features (onset, course, duration, daily pattern), exacerbating and palliative factors, associated distress, impact
- ▲ Lack of energy, muscle weakness, somnolence, dysphoric mood, or impaired cognitive function

Evaluation of potential etiologies and comorbid conditions**Evaluation of broader constructs**

- ▲ QOL, symptom distress, goals of care

QOL = quality of life.

to develop a therapeutic strategy (Table 3). A comprehensive assessment includes a description of fatigue-related phenomena, a physical examination, and a review of laboratory and imaging studies. These data may allow plausible hypotheses concerning pathogenesis, which in turn may suggest appropriate treatment strategies.

Patients may describe fatigue in terms of decreased vitality or lack of energy, muscular weakness, dysphoric mood, somnolence, impaired cognitive functioning, or some combination of these disturbances. Although this variability

suggests the existence of fatigue subtypes, this has not yet been empirically confirmed. Regardless, the patient's history should clarify the spectrum of complaints and attempt to characterize features associated with each component. This information may suggest specific etiologies (e.g., depression) and influence the choice of therapy. Neurologic and psychologic evaluations also may help further clarify potential etiologies of fatigue in some patients.

Other characteristics are similarly important. Onset and duration, for example, distinguish acute and chronic fatigue. Acute fatigue has a recent onset and is anticipated to end in the near future. Chronic fatigue has persisted for a prolonged period (weeks to months, or longer) and is not expected to remit soon. Patients perceived to have chronic fatigue typically require a more intensive evaluation, as well as a management approach focused on both short- and long-term goals. Other important descriptors of fatigue include its severity, daily pattern, course over time, exacerbating and palliative factors, and associated distress.

To measure fatigue severity, consistent use of a simple unidimensional scale, such as a verbal rating scale (none, mild, moderate, severe) or a numeric scale (for example, a 0-10 scale, where "0" equals no fatigue and "10" equals the worst fatigue imaginable, or a 0-4 scale, as applied in the NCI CTC) are useful for monitoring changes over time [36]. Other unidimensional scales include the fatigue subscale of the Profile of Mood States [37], linear analog scales (linear analog scale assessment [LASA]) [38], and single items incorporated into symptom checklists [39-41].

Multidimensional fatigue assessment, which captures multiple characteristics and manifestations of fatigue and its impact on function, is more informative than the measurement of severity alone. In the practice setting, when time for evaluation is limited, the routine use of three simple questions may help assess fatigue severity and impact over time [36]:

- ▲ Are you experiencing any fatigue?
- ▲ If yes, how severe has it been, on average, during the past week, using a 0-10 scale?
- ▲ How is the fatigue interfering with your ability to function?

Validated multidimensional questionnaires provide a more sophisticated alternative for practice, or, more commonly, for use in research settings [12, 22, 36, 42-47].

Multidimensional Assessment Tools

The first validated multidimensional instrument was the Piper Fatigue Self-Report Scale. This scale addresses the severity, distress, and impact of fatigue using a 41-item

questionnaire administered as either a series of LASA or numeric scales [36]. It was developed to assess fatigue in patients receiving radiotherapy. It is both reliable and valid in this population and may also be used to assess cancer patients who are not receiving radiotherapy. Efforts continue to further refine it [48].

A 20-item scale that evaluates well-being associated with fatigue and anemia has been developed as a module of a general quality of life instrument known as the Functional Assessment of Cancer Therapy (FACT) [12, 42, 43]. The fatigue, or fatigue and anemia, subscales of this module can be used alone as brief, reliable, and valid assessments. Using this questionnaire, an association between fatigue and anemia was demonstrated in a large survey of cancer patients in community settings. Patients with hemoglobin values >12 g/dL reported significantly less fatigue, fewer nonfatigue anemia symptoms, better physical and functional well-being, and a higher overall quality of life than those with hemoglobin values ≤ 12 g/dL [49].

Other validated multidimensional instruments are available [9, 44-47]. The Fatigue Symptom Inventory, for example, has been used in a series of studies that evaluated the severity and impact of treatment-related fatigue [44]. Investigators or clinicians who seek a detailed assessment of fatigue should review the items in these questionnaires and select the instrument that captures the fatigue-related phenomena of greatest interest.

Assessment of Related Constructs

An assessment of cancer-related fatigue also should include consideration of broader concerns, including global quality of life, symptom distress, and the goals of care. Fatigue may be only one of numerous factors that influence quality of life. Among these factors are progressive physical decline, psychological disorders, social isolation, financial concerns, and spiritual distress. Optimal care of the cancer patient includes a broad assessment of these factors and should be directed toward maintaining or enhancing quality of life.

The concept of global symptom distress is useful in characterizing patients who often have multiple symptoms concurrently [39-41]. Fatigue, pain, and psychological distress are the most prevalent symptoms across varied cancer populations [41]. Patients who report fatigue should be queried about the presence of other symptoms and the degree to which fatigue predominates as a cause of distress.

The goals of care guide all therapeutic decision making. Specific treatments may or may not be appropriate depending on the degree to which the preeminent goals relate to prolonging life, improving function, or providing comfort alone.

MANAGEMENT STRATEGIES

A successful strategy should ameliorate fatigue within a broader approach to patient care. Education of the patient regarding the nature of fatigue, options for therapy, and anticipated outcomes is an essential aspect of the therapy. Unfortunately, results of a recent survey indicate that fatigue is seldom discussed by patients and their oncologists [1].

Treatment of Underlying Causes

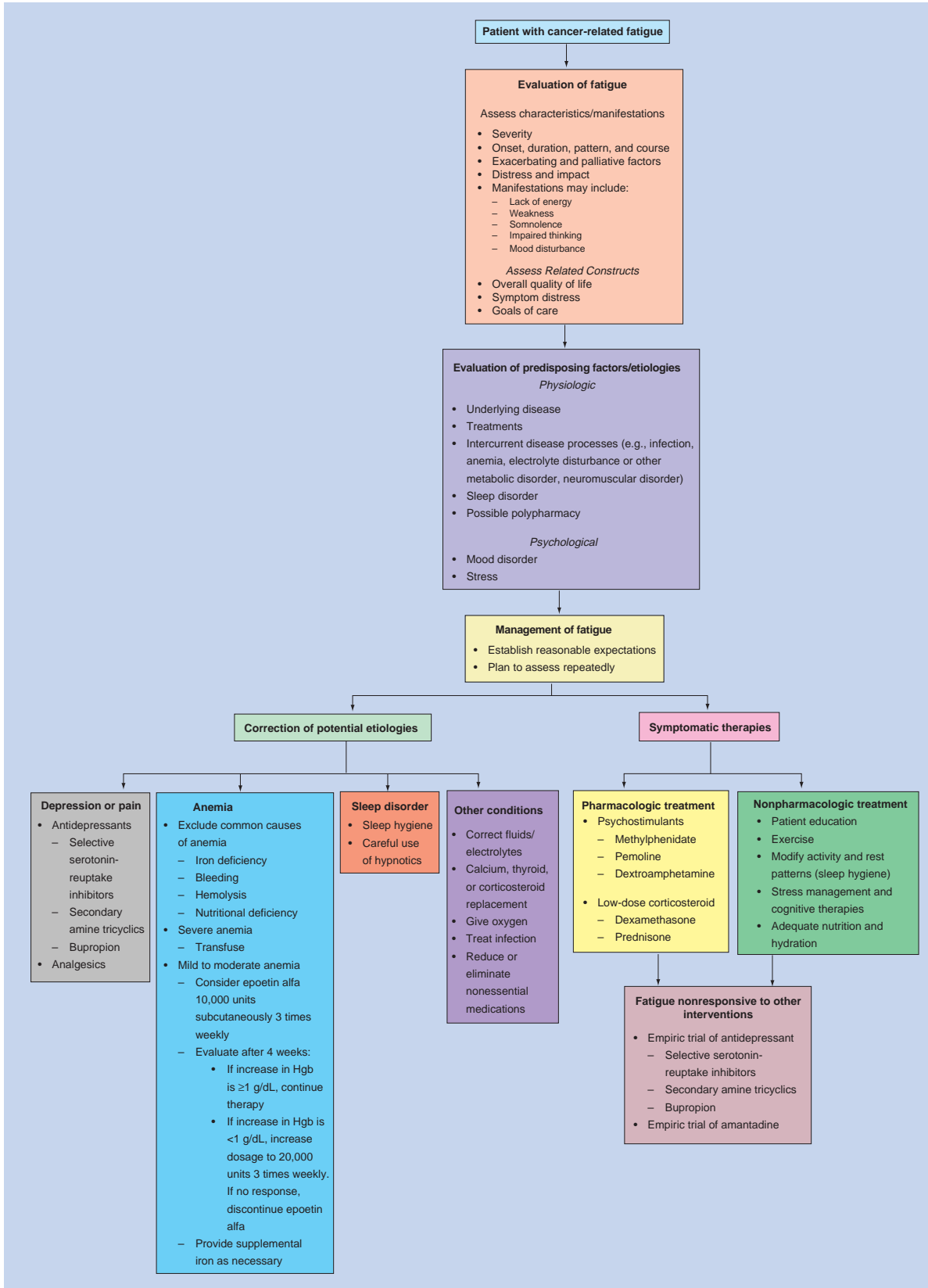
As an initial approach to cancer-related fatigue, efforts should be made to correct potential etiologies, if possible and appropriate (Fig. 1). This may include elimination of nonessential centrally acting drugs, treatment of a sleep disorder, reversal of anemia or metabolic

abnormalities, or management of major depression. Many of these initial interventions are relatively simple and pose minimal burdens to the patient, healthcare provider, and caregiver.

In patients with fatigue-associated major depression, treatment with an antidepressant is strongly indicated. As many as 25% of cancer patients develop major depression at some point during the illness; patients at greatest risk are those with advanced disease, uncontrolled physical symptoms (e.g., pain), or previous history of psychiatric disorder [50]. Although the relationship between depression and fatigue is not understood, they often occur together, and both adversely affect quality of life [51, 52]. Despite the high prevalence in the cancer population, depression is often underdiagnosed, and, consequently, undertreated [53, 54]. A trial with an antidepressant usually is warranted in a patient with fatigue associated with any significant degree of depressed mood, particularly if concurrent anxiety or pain exists.

Anemia may be a major factor in the development of cancer-related fatigue. Anecdotally, transfusion therapy for severe anemia often has been associated with substantial improvement in fatigue. Until the early 1980s, red blood cell transfusions were administered empirically when hemoglobin concentrations fell below 10 g/dL [55, 56] and were the primary treatment for cancer-related and chemotherapy-induced anemia. At that time, concern about the safety of the blood supply related to potential transmission of the human

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immunodeficiency virus prompted clinicians to alter their treatment approach [56, 57]. Without an alternative to transfusion, treatment of mild or moderate anemia was generally avoided until hemoglobin concentrations declined to more severe levels (7-8 g/dL) or the patient experienced signs and symptoms of severe anemia [55, 58]. As reticence to treat anemia increased, it was less often reported as an adverse sequela in published chemotherapy trials and received less attention in the medical literature overall.

New data demonstrate an association between chemotherapy-induced mild-to-moderate anemia and both fatigue and quality-of-life impairment. For example, combined data from 413 patients in three randomized, placebo-controlled trials of epoetin alfa, the recombinant form of human erythropoietin, reveal that treated patients experienced a significant increase in hematocrit, a reduced need for transfusion, and a significant improvement in overall quality of life. Those patients with an increase in hematocrit of >6% also demonstrated significant improvement in energy level and daily activities [59]. Additional studies in patients treated with chemotherapy and radiation therapy for a variety of hematologic and solid tumors confirm that epoetin alfa has positive effects on hemoglobin levels [60-63].

Two large, prospective, nonrandomized, multicenter community trials evaluated the effectiveness of epoetin alfa in anemia associated with cancer chemotherapy [64, 65]. In the more recent trial, *Demetri et al.* assessed the effectiveness of epoetin alfa as an adjunct to chemotherapy in more than 2,000 cancer patients undergoing cytotoxic chemotherapy [64]. Patients received epoetin alfa 10,000 units three times weekly for a maximum of 16 weeks. If the increase in hemoglobin level was <1.0 g/dL at four weeks, the dose was increased to 20,000 units three times weekly. Quality-of-life parameters were assessed with LASA and the FACT-Anemia instruments. Over time, patients experienced significant improvements in energy level, activity level, functional status, and overall quality of life; these improvements were independent of antitumor response and were significantly correlated with hemoglobin levels. These results were similar to the findings in the previous large, community-based study by *Glaspy et al.* [65].

Symptomatic Approaches

Pharmacologic Treatments

The pharmacologic therapies for fatigue associated with medical illness have not been rigorously evaluated in

controlled trials. Nonetheless, there is evidence to support the use of several drug classes. Psychostimulants, such as methylphenidate, pemoline, and dextroamphetamine, have been well studied for the treatment of opioid-related somnolence and cognitive impairment [66], and depression in the elderly and medically ill [67-69]. There are no controlled studies of these drugs for cancer-related fatigue, but empiric administration may yield favorable results in some patients.

Clinical response to one drug does not necessarily predict response to the others, and sequential trials may be needed to identify the most beneficial therapy. Methylphenidate has been more extensively evaluated in the cancer population than other stimulant drugs and often is the first drug administered.

Pemoline has less sympathomimetic activity than other psychostimulants but has a low risk of severe hepatotoxicity compared with similar agents [70]. It is available in a chewable formulation that can be absorbed through the buc-

cal mucosa for patients who are unable to swallow or take oral medications.

Adverse effects associated with the psychostimulants include anorexia, insomnia, tremulousness, anxiety, delirium, and tachycardia. To ensure safety, slow and careful dose escalation should be undertaken to minimize potential adverse effects. A regimen of methylphenidate, for example, usually begins with a dose of 5-10 mg once or twice daily (morning and, if needed, midday). If tolerated, the dose is increased. Most patients appear to require less than 60 mg per day, but some require much higher doses.

Extensive anecdotal observations and very limited data from controlled trials [71, 72] support the use of low-dose corticosteroids in fatigued patients with advanced disease and multiple symptoms. Dexamethasone and prednisone are most commonly used. There have been no comparative trials.

The selective serotonin-reuptake inhibitors, secondary amine tricyclics (e.g., nortriptyline and desipramine), or bupropion are sometimes associated with the experience of increased energy that appears disproportionate to any change in mood. For this reason, these agents also have been tried empirically in nondepressed patients with fatigue. Given the limited experience in the use of these drugs for this indication, an empiric trial should be considered only in severe and refractory cases.

Amantadine has been used to treat fatigue in patients with multiple sclerosis, but it has not been studied in other

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patient populations. This drug is usually well tolerated, and an empiric trial may be warranted in selected patients with severe refractory cancer-related fatigue.

Nonpharmacologic Interventions

Nonpharmacologic approaches for the management of cancer-related fatigue are largely supported by favorable anecdotal experience (Table 4). Patient preferences should be considered in the selection of one or more of these approaches.

Education about fatigue greatly benefits some patients [73-77]. There are large individual differences in patients' preferences for information, however, and efforts to educate should be directed at the patients' educational level and readiness to learn. The use of a patient diary may help the clinician and patient discern a pattern to the fatigue or identify specific activities that are associated with increased levels. This information may be useful in developing a management plan that modifies specific activities and incorporates appropriate periods of rest [27]. For example, some patients identify a pattern that suggests the utility of scheduled brief rest periods during the day.

Some patients benefit from education about sleep hygiene. Sleep hygiene principles should be tailored to the individual patient and might include the establishment of a specific bedtime and wake time, and routine procedures prior to sleep [78]. Patients also should be instructed to avoid stimulants and central nervous system depressants prior to sleep [78]. Regular exercise performed at least 6 h before bedtime may improve sleep, whereas napping in the late afternoon or evening may worsen it.

Exercise may be beneficial in relieving fatigue [25, 77, 79-81].

This may be counterintuitive to patients, and considerable education may be needed to foster cooperation with an exercise program. There are no data that clarify the most appropriate exercise program for cancer patients with fatigue. In general, exercise should be individualized, considering such factors as the patient's age and medical condition. Anecdotally, the type of exercise that appears to be most beneficial involves rhythmic and repetitive movement of large muscle groups such as walking, cycling, or swimming. The exercise program should be initiated gradually and should include a light-to-moderate workout several days a week.

Anxiety, difficulties in coping with cancer or its treatment, or sleep disturbances may contribute to fatigue and may be ameliorated using stress reduction techniques or cognitive therapies, such as relaxation therapy, hypnosis,

Table 4. Nonpharmacologic interventions for the management of cancer-related fatigue

Patient education

- ▲ Consider the patient's preferences, education level, and readiness to learn
- ▲ Use of a patient diary

Exercise

- ▲ Individualize exercise program
- ▲ Use of rhythmic and repetitive types of exercise
- ▲ Initiate gradually

Modification of activity and rest patterns

- ▲ Assess sleep hygiene
- ▲ Establish routine sleep patterns
- ▲ Avoid use of stimulants prior to sleep
- ▲ Regular exercise

Stress management and cognitive therapies

- ▲ Use of stress reduction techniques or cognitive therapies
- ▲ Use of relaxation therapy, hypnosis, or distraction

Adequate nutrition and hydration

- ▲ Proper diet
- ▲ Monitor weight and hydration status regularly
- ▲ Referral to a dietician

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guided imagery, or distraction. Some patients find distraction (e.g., listening to music) or other cognitive techniques to be particularly effective when the symptom is associated with attention deficits [82, 83]. Referral

to a psychologist for counseling and training in stress management techniques or cognitive therapies may be warranted in some patients.

Cancer and its treatment also can interfere with dietary intake. With aggressive approaches to management, patients' weight, hydration status, and electrolyte balance should be monitored and maintained to the extent possible [84]. Regular exercise may improve appetite and increase nutritional intake. Referral to a dietitian for nutritional guidance and suggestions for nutritional supplements may be useful.

SUMMARY

Despite the high prevalence and distress associated with fatigue, there have been few studies of this condition, and relatively little is known about its epidemiology, etiologies,

pathogenesis, and management. With growing interest in palliative care, however, there is recognition of fatigue as an important issue for research and treatment guideline development [13]. Oncologists, as well as the entire medical team, must become more aware of this problem, its impact

on patient quality of life, and the various strategies that may be helpful in its treatment. Although further research is needed, many patients could benefit from more comprehensive evaluation and greater use of available interventions for cancer-related fatigue.

REFERENCES

- 1 Vogelzang N, Breitbart W, Cella D et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. *Semin Hematol* 1997;34(suppl 2):4-12.
- 2 Cassileth BR, Lusk EJ, Bodenheimer BJ et al. Chemotherapeutic toxicity—the relationship between patients' pretreatment expectations and post-treatment results. *Am J Clin Oncol* 1985;8:419-425.
- 3 Greenberg DB, Sawicka J, Eisenthal S et al. Fatigue syndrome due to localized radiation. *J Pain Symptom Manage* 1992;7:38-45.
- 4 Haylock PJ, Hart LK. Fatigue in patients receiving localized radiation. *Cancer Nurs* 1979;2:461-467.
- 5 Irvine DM, Vincent L, Bubela N et al. A critical appraisal of the research literature investigating fatigue in the individual with cancer. *Cancer Nurs* 1991;14:188-199.
- 6 Irvine D, Vincent L, Graydon JE et al. The prevalence and correlates of fatigue in patients receiving treatment with chemotherapy and radiotherapy: a comparison with the fatigue experienced by healthy individuals. *Cancer Nurs* 1994;17:367-378.
- 7 King KB, Nail LM, Kreamer K et al. Patients' descriptions of the experience of receiving radiation therapy. *Oncol Nurs Forum* 1985;12:55-61.
- 8 Knobf MT. Physical and psychologic distress associated with adjuvant chemotherapy in women with breast cancer. *J Clin Oncol* 1986;4:678-684.
- 9 Kobashi-Schoot JAM, Hanewald GJFP, van Dam FSAM et al. Assessment of malaise in cancer treated with radiotherapy. *Cancer Nurs* 1985;8:306-314.
- 10 Meyerowitz BE, Sparks FC, Spears IK. Adjuvant chemotherapy for breast carcinoma: psychosocial implications. *Cancer* 1979;43:1613-1618.
- 11 Portenoy RK, Thaler HT, Kornblith AB et al. Pain in ovarian cancer: prevalence, characteristics, and associated symptoms. *Cancer* 1994;74:907-915.
- 12 Yellen SB, Cella DF, Webster MA et al. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage* 1997;13:63-74.
- 13 Cella D, Peterman A, Passik S et al. Progress toward guidelines for the management of fatigue. *Oncology* 1998;12:1-9.
- 14 Curtis EB, Kretch R, Walsh TD. Common symptoms in patients with advanced cancer. *J Palliat Care* 1991;7:25-29.
- 15 Dunphy KP, Amesbury BDW. A comparison of hospice and homecare patients: patterns of referral, patient characteristics and predictors of place of death. *Palliat Med* 1990;4:105-111.
- 16 Dunlop GM. A study of the relative frequency and importance of gastrointestinal symptoms and weakness in patients with far-advanced cancer: student paper. *Palliat Med* 1989;4:37-43.
- 17 Portenoy RK, Thaler HT, Kornblith AB et al. Symptom prevalence, characteristics, and distress in a cancer population. *Qual Life Res* 1994;3:183-189.
- 18 Ventafridda V, DeConno F, Ripamonti C et al. Quality of life assessment during a palliative care program. *Ann Oncol* 1990;1:415-420.
- 19 Dean GE, Spears L, Ferrell B et al. Fatigue in patients with cancer receiving interferon alpha. *Cancer Pract* 1995;3:164-171.
- 20 Fobair P, Hoppe RT, Bloom J et al. Psychosocial problems among survivors of Hodgkin's disease. *J Clin Oncol* 1986;4:805-814.
- 21 Pickard-Holley S. Fatigue in cancer patients: a descriptive study. *Cancer Nurs* 1991;14:13-19.
- 22 Piper BF, Lindsey AM, Dodd MJ et al. The development of an instrument to measure the subjective dimension of fatigue. In: Funk SG, Tornquist EM, Champagne MT et al, eds. *Key Aspects of Comfort. Management of Pain, Fatigue and Nausea*. New York: Springer Publishing Company, 1989:199-208.
- 23 Skalla K, Rieger P. Fatigue. In: Rieger PT, ed. *Biotherapy: Comprehensive Review*. Boston: Jones and Bartlett, 1995:221-242.
- 24 Piper BF, Rieger PT, Brophy L et al. Recent advances in the management of biotherapy-related side effects: fatigue. *Oncol Nurs Forum* 1989;16(suppl 6):27-34.
- 25 Berger AM. Patterns of fatigue and activity and rest during adjuvant breast cancer chemotherapy. *Oncol Nurs Forum* 1998;25:51-62.
- 26 Broeckel JA, Jacobsen PB, Horton J et al. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *J Clin Oncol* 1998;16:1689-1696.
- 27 Richardson A, Ream E, Wilson-Barnett J. Fatigue in patients receiving chemotherapy: patterns of change. *Cancer Nurs* 1998;21:17-30.
- 28 Portenoy RK, Miaskowski C. Assessment and management of cancer-related fatigue. In: Berger A, Portenoy RK, Weissman DE, eds. *Principles and Practice of Supportive Oncology*. Philadelphia: Lippincott-Raven, 1998:109-118.
- 29 Aistars J. Fatigue in the cancer patient: a conceptual approach to a clinical problem. *Oncol Nurs Forum* 1987;14:25-30.
- 30 Piper BF, Lindsey AM, Dodd MJ. Fatigue mechanisms in cancer patients: developing nursing theory. *Oncol Nurs Forum* 1987;14:17-23.

- 31 Jacobs LA, Piper BF. The phenomenon of fatigue and the cancer patient. In: McCorkle R, Grant M, Frank-Stromberg M et al., eds. *Cancer Nursing: A Comprehensive Textbook*. Philadelphia: WB Saunders, 1996:1193-1210.
- 32 Nail LM, Winningham M. Fatigue. In: Groenwald SL, Frogge MH, Goodman M et al, eds. *Cancer Nursing: Principles and Practice*. Boston: Jones and Bartlett, 1993:608-619.
- 33 Piper BF. Alterations in comfort: fatigue. In: McNally JC, Somerville E, Miaskowski C et al, eds. *Guidelines for Oncology Nursing Practice*, 2nd ed. Philadelphia: WB Saunders, 1991:155-162.
- 34 Smets EMA, Garssen B, Schuster-Uitterhoeve ALJ et al. Fatigue in cancer patients. *Br J Cancer* 1993;68:220-224.
- 35 Winningham ML, Nail LM, Burke MB et al. Fatigue and the cancer experience: the state of the knowledge. *Oncol Nurs Forum* 1994;21:23-35.
- 36 Piper BF. The Groopman article reviewed. *Oncology* 1998;12:345-346.
- 37 Cella DF, Jacobsen PB, Orav EJ et al. A brief POMS measure of distress for cancer patients. *J Chronic Dis* 1987;40:939-942.
- 38 Bruera E, Chadwick S, Brenneis C et al. Methylphenidate associated with narcotics for the treatment of cancer pain. *Cancer Treat Rep* 1987;71:67-70.
- 39 de Haes JCJM, van Kippenberg FCE, Neijt JP. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. *Br J Cancer* 1990;62:1034-1038.
- 40 McCorkle R, Young K. Development of a symptom distress scale. *Cancer Nurs* 1978;1:373-378.
- 41 Portenoy RK, Thaler HT, Kornblith AB et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics, and distress. *Eur J Cancer* 1994;30A:1326-1336.
- 42 Cella DF, Tulskey DS, Gray G et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;11:570-579.
- 43 Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. *Semin Hematol* 1997;34(suppl 2):13-19.
- 44 Hann DM, Jacobsen PB, Azzarello LM et al. Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. *Qual Life Res* 1998;7:301-310.
- 45 Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. *Psychiatry Res* 1991;36:291-298.
- 46 Morant R, Stiefel F, Berchtold W et al. Preliminary results of a study assessing asthenia and related psychological and biological phenomena in patients with advanced cancer. *Support Care Cancer* 1993;1:101-107.
- 47 Cleeland CC. Brief Fatigue Inventory (BFI), URL: <http://www.qlmed.org/BFI/index.html>
- 48 Piper BF, Dibble SL, Dodd MJ et al. The revised Piper Fatigue Scale: psychometric evaluation in women in breast cancer. *Oncol Nurs Forum* 1998;25:677-684.
- 49 Cella D. Factors influencing quality of life in cancer patients: anemia and fatigue. *Semin Oncol* 1998;25:43-46.
- 50 Breitbart W. Identifying patients at risk for, and treatment of major psychiatric complications of cancer. *Support Care Cancer* 1995;3:45-60.
- 51 Visser MR, Smets EM. Fatigue, depression and quality of life in cancer patients: how are they related? *Support Care Cancer* 1998;6:101-108.
- 52 Dimeo F, Stieglitz RD, Novelli-Fischer U et al. Correlation between physical performance and fatigue in cancer patients. *Ann Oncol* 1997;8:1251-1255.
- 53 Hardman A, Maguire P, Crowther D et al. The recognition of psychiatric morbidity on a medical oncology ward. *J Psychosom Res* 1989;33:235-239.
- 54 Passik SD, Dugan W, McDonald MV et al. Oncologists' recognition of depression in their patients with cancer. *J Clin Oncol* 1998;16:1594-1600.
- 55 Consensus conference. Perioperative red cell transfusion. *JAMA* 1988;260:2700-2703.
- 56 Welch HG, Meehan KR, Goodnough LT. Prudent strategies for elective red blood cell transfusion. *Ann Intern Med* 1992;116:393-402.
- 57 Surgenor DM, Wallace EL, Hale SG et al. Changing patterns of blood transfusions in four sets of United States hospitals, 1980 to 1985. *Transfusion* 1988;28:513-518.
- 58 Silberstein LE, Kruskall MS, Stehling LC et al. Strategies for the review of transfusion practices. *JAMA* 1989;262:1993-1997.
- 59 Abels RI, Larholt KM, Drantz KD et al. Recombinant human erythropoietin (r-HuEPO) for the treatment of the anemia of cancer. In: Murphy MJ, ed. *Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology*. Dayton: AlphaMed Press, 1992:121-141.
- 60 Cascinu S, Fedeli A, Del Ferro E et al. Recombinant human erythropoietin treatment in cisplatin-associated anemia: a randomized, double-blind trial with placebo. *J Clin Oncol* 1994;12:1058-1062.
- 61 Ludwig H, Fritz E, Kotzmann H et al. Erythropoietin treatment of anemia associated with multiple myeloma. *N Engl J Med* 1990;322:1693-1699.
- 62 Oster W, Hermann F, Gamm H et al. Erythropoietin for the treatment of anemia of malignancy associated with neoplastic bone marrow infiltration. *J Clin Oncol* 1990;8:956-962.
- 63 Platanius LC, Miller CB, Mick R et al. Treatment of chemotherapy-induced anemia with recombinant human erythropoietin. *J Clin Oncol* 1991;9:2021-2026.
- 64 Demetri GD, Kris M, Wade J et al. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. *J Clin Oncol* 1998;16:3412-3425.
- 65 Glaspy J, Bukowski R, Steinberg D et al. The impact of therapy with epoetin alfa on clinical outcomes during cancer chemotherapy in community oncology practice. *J Clin Oncol* 1997;15:1218-1234.

- 66 Bruera E, Brenneis C, Paterson AH et al. Use of methylphenidate as an adjuvant to narcotic analgesics in patients with advanced cancer. *J Pain Symptom Manage* 1989;4:3-6.
- 67 Breitbart W, Mermelstein H. An alternative psychostimulant for the management of depressive disorders in cancer patients. *Psychosomatics* 1992;33:352-356.
- 68 Fernandez F, Adams F, Levy JK. Cognitive impairment due to AIDS-related complex and its response to psychostimulants. *Psychosomatics* 1988;29:38-46.
- 69 Katon W, Raskind M. Treatment of depression in the medically ill elderly with methylphenidate. *Am J Psychiatry* 1980;137:963-965.
- 70 Berkovitch M, Pope E, Phillips J et al. Pemoline-associated fulminant liver failure: testing the evidence for causation. *Clin Pharm Ther* 1995;57:696-698.
- 71 Bruera E, Roca E, Cedaro L et al. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. *Cancer Treat Rep* 1985;69:751-754.
- 72 Tannock I, Gospodarowicz M, Meakin W et al. Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *J Clin Oncol* 1989;7:590-597.
- 73 Egbert LD, Battit GE, Welch CE et al. Reduction of postoperative pain by encouragement and instruction of patients. *N Engl J Med* 1964;207:825-827.
- 74 Fortin F, Kirouac S. A randomized controlled trial of preoperative patient education. *Int J Nurs Stud* 1976;13:11-24.
- 75 Johnson J, Fuller S, Endress MP et al. Altering patients' responses to surgery: an extension and replication. *Res Nurs Health* 1978;1:111-121.
- 76 Johnson J, Rice V, Fuller S et al. Sensory information, instruction in a coping strategy, and recovery from surgery. *Res Nurs Health* 1978;1:4-17.
- 77 Winningham ML. Fatigue. In: Groenwald SL, Frogge MH, Goodman M et al, eds. *Cancer Symptom Management*. Boston: Jones and Bartlett, 1996:42-58.
- 78 Yellen SB, Dyonzak JV. Sleep disturbances. In: Groenwald SL, Frogge MH, Goodman M et al, eds. *Cancer Symptom Management*. Boston: Jones and Bartlett, 1996:151-168.
- 79 Dimeo F, Rumberger BG, Keul J. Aerobic exercise as therapy for cancer fatigue. *Med Sci Sports Exercise* 1998;30:475-478.
- 80 MacVicar SB, Winningham ML. Promoting functional capacity of cancer patients. *Cancer Bull* 1986;38:235-239.
- 81 Schwartz AL. Patterns of exercise and fatigue in physically active cancer survivors. *Oncol Nurs Forum* 1998;25:485-491.
- 82 Cimprich B. Attentional fatigue following breast cancer surgery. *Res Nurs Health* 1992;15:199-207.
- 83 Cimprich B. Developing an intervention to restore attention in cancer patients. *Cancer Nurs* 1993;16:83-92.
- 84 Dalakas MC, Mock V, Hawkins MJ. Fatigue: definitions, mechanisms, and paradigms for study. *Semin Oncol* 1998;25(suppl 1):48-53.

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Oncologist 1999;4;1-10

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