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EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- Understand the basic mechanisms of cancer-related fatigue pathophysiology
- Determine the readily reversible causes of fatigue in the cancer patient
- Describe a treatment plan for a patient who needs intervention to manage cancer-related fatigue

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Cancer-related fatigue: Elusive causes challenge treatment

Donald R. Fleming, MD

STATEMENT OF NEED/PROGRAM OVERVIEW

Successful management of cancer-related fatigue can influence whether a patient continues with therapy. Fatigue is one of the most common complaints of patients with cancer. Some causes are reversible and can be remedied, while others may be more difficult to resolve. Understanding of the need for patient education, early intervention, and symptom management can ease the path the patient must take with their treatment.

CE INFORMATION

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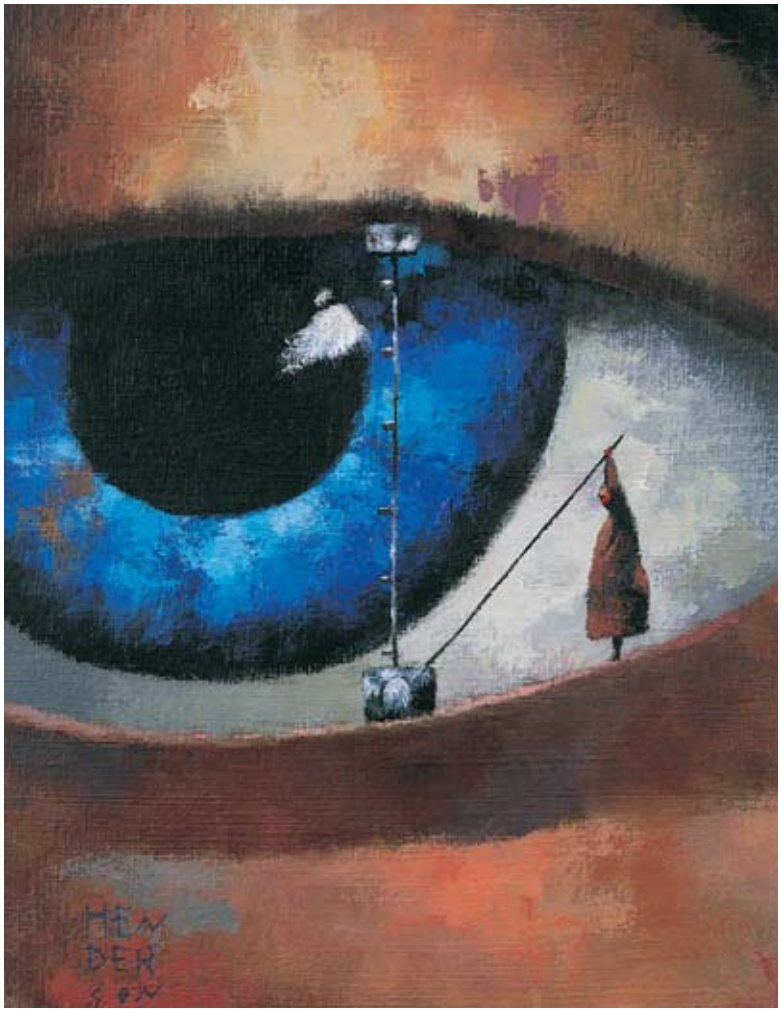
Cancer-related fatigue: Elusive causes challenge treatment

Effective management of this nonspecific and varied symptom of cancer and cancer treatment is based on the underlying mechanisms of action.



DONALD R. FLEMING, MD

Fatigue is a symptom of many diseases, and it is one of the most common complaints of patients with cancer. Due to the magnitude of the cancer diagnosis, however, the symptom is given the unique distinction of cancer-related fatigue (CRF) when it manifests in patients with cancer. Although CRF is difficult to define as it varies among cancer patients, the National Comprehensive Cancer Network (NCCN) guidelines define cancer-related fatigue as "a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning."[1] Cancer-related fatigue, whatever its cause, is the focus of many supportive care interventions that address patient needs associated with cancer.[2,3]

MECHANISMS OF FATIGUE

CRF varies among patients with cancer, and its causes are also extremely diverse. The etiology of fatigue is categorized as central or peripheral. Central fatigue refers to central nervous system (CNS)–associated mechanisms; peripheral fatigue, however, does not necessarily refer to the peripheral nervous system but to peripheral muscle activity as being the fatigue mechanism.[3,4]

Central fatigue involves pathophysiology within the cerebral hemispheres or the cerebrum of the brain. This is not to imply that the fatigue is psychological but that various contributors—chemotherapy, poor nutrition, and possibly, the cancer itself—affect the neurons in the central nervous system.[5] Chemotherapy agents affect the CNS and cause fatigue based on the agent's penetration through the blood-brain barrier. Nutritional deficiencies such as inadequate protein intake can also affect neurologic function. Many cancers affect higher-level neurologic function directly via metastasis or indirectly by way of paraneoplastic processes.[2,4] Changes in motor neuron activity in patients with cancer are similar to changes in motor neuron activity seen in patients with noncancer illnesses that manifest with symptoms of fatigue.

Peripheral fatigue involves peripheral muscle activity or a lack thereof. Neuromuscular physiology studies have demonstrated electroactivity and chemical changes in patients with illness-related fatigue. Both the loss of electrical stimuli and calcium synaptic activity correlates with increased fatigue. Although magnetic resonance spectrometry has been used to document altered peripheral muscle activity in patients with noncancer illnesses, its effectiveness in measuring the extent of peripheral fatigue in cancer patients with CRF has yet to be studied. These two basic mechanisms of fatigue typically do not manifest exclusively; instead both play a varying role in each case of cancer-related fatigue.[6,7]

MECHANISMS SPECIFIC TO CANCER

In addition to these mechanisms, causes of fatigue that are specific to patients with cancer need to be elucidated. Precipitating maladies that can cause cancer-related fatigue include cachexia, anemia, hypogonadism, hypothyroidism, infection, chemo- or radiotherapy, dehydration, pain, and psychological distress.[8,9]

Cachexia, defined as a 5% or greater loss of lean body weight, is often precipitated by both the cancer and its treatment and results in altered muscle physiology and dysfunction. Anemia, for obvious reasons, results in decreased tissue oxygenation and expectant fatigue. An often overlooked cause of CRF is hypogonadism, as gonadal dysfunction, and decreased or altered hormone levels often explain the mechanism of fatigue. Pain control and hydration status can be assessed with an adequate history and a complete physical examination, and correction improves CRF. Mental fatigue is associated with depression and often overlooked as a cause of CRF. Psychological and pharmacologic interventions are used to manage mental fatigue.[8,9]

TREATMENT-RELATED MECHANISMS

Radiation therapy can cause cancer-related fatigue in some patients. Cancer-related fatigue can occur in patients who receive radiation therapy to the brain; however, evidence indicates that CRF also occurs when the radiation is focused on areas outside of the cerebrum, often referred to as an *abscopal effect*. Recently, the event was studied in more detail in women undergoing pelvic radiotherapy for anal or uterine cancer.

Radiation therapy-related CRF has multiple causes, including the release of inflammatory mediators such as various cytokines in the gastrointestinal (GI) tract. A clinical investigation demonstrated an inverse relationship between serum citrulline (an amino acid produced by GI epithelial cell glutamine degradation) levels and fatigue scores.[10] Reduced plasma citrulline levels also correlated with reduced epithelial cell mass. In addition, a reduction in citrulline level was proposed to be a biomarker for CRF in patients receiving pelvic radiation.[11,12]

CRF symptoms can persist in many cancer patients. Pharmacologic intervention to mask the effects of the syndrome may be necessary.

Targeted therapy is a novel approach to cancer treatment. One targeted approach uses small molecule inhibitors to disrupt tyrosine kinase signaling, which initiates the molecular cascade for cell growth in malignant, as well as normal, tissues.[13] Asthenia and/or chronic fatiguelike side effects are associated with small molecule inhibitors. An important note to remember, CRF may be due to thyroid hormone suppression in some patients.

APPROACHES TO TREATMENT

Once cancer-related fatigue is diagnosed in a patient, easily reversed causes should be addressed immediately. **Figure 1** illustrates an algorithm for diagnosis and treatment of CRF. Anemia should be corrected with transfusions or recombinant erythropoietin-type agents, when appropriate. Nutritional counseling and support, especially if mechanical issues are the result of poor nutrition, should also be provided. Rehydration should be achieved in patients with clinically evident dehydration. Hormonal insufficiencies determined through androgen, estrogen, and thyroid level measurements can often be corrected easily. However, this may be

contraindicated in patients with hormone-dependent tumors such as prostate and breast cancer. Identifying and treating infectious disease processes is based on clinical as well as objective parameters using various culturing techniques. Pharmacologic agents and both individual and group therapy can be instituted to address depression and other psychological issues related to CRF.[2,8,9]

Exercise CRF symptoms may persist despite treatment of causative factors and if no easily resolved mechanisms of fatigue are found. Recent studies have evaluated exercise as a resolution for CRF symptoms. While seemingly counterintuitive, some evidence suggests that patients with cancer lack strength despite having adequate muscle mass. Muscle weakness in these patients can be improved with physical activity. While this implies that exercise has a role in reversing peripheral mechanisms of CRF, its impact on cancer patients' central mechanisms of fatigue is less clear. Exercise programs recommended for patients with CRF are not rigorous workouts but are more moderate with a gradual increase in anaerobic and strength-enhancing activities. Support groups are often successful in encouraging patients to participate in these activities on a regular basis.[2,5,8]

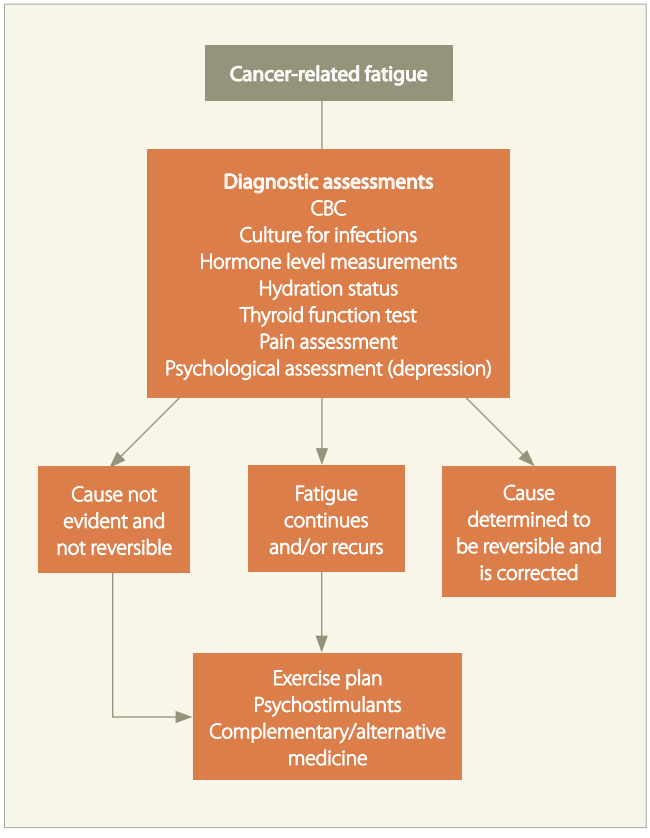


FIGURE 1. Diagnostic algorithm

Pharmacologic intervention Despite medical intervention and/or exercise for easily reversible forms of fatigue, CRF symptoms persist for many cancer patients. At this juncture, pharmacologic intervention to mask the effects of CRF may be necessary. A variety of agents may be employed for symptom control; essentially, these agents are either psychostimulants or other drugs such as corticosteroids and progestational agents (often megestrol [Megace]). Megestrol is proven to enhance appetite and improve fatigue and general well-being.

Methylphenidate (Ritalin) and modafinil (Provigil) are often used to reverse the perceived affects of cancer-related fatigue.[14] As one would expect, masking the effects of CRF always has drawbacks, especially when using psychostimulants. These drugs, as well as corticosteroids, often cause insomnia and possibly heightened degrees of anxiety. Donepezil (Aricept), which is used to treat Alzheimer disease, also reverses some of the symptoms attributed to CRF syndrome, especially when narcotic or opioid pain medication is a contributory factor.[15,16] In addition, thalidomide (Thalomid) and omega-3 fish oils have been utilized to reverse CRF symptoms.[2,17]

Complementary/alternative medicine (CAM) As in other areas of cancer management, some patients experiment with CAM practices. In one study, American ginseng (*Panax quinquefolius*) demonstrated activity over placebo in resolving CRF symptoms.[18] Another CAM therapeutic intervention for fatigue involves the use of noni (*Morinda citrifolia*), an evergreen plant indigenous to Southeast Asia, Australia, Hawaii, and the Polynesian islands. The plant is available as a juice or in tablet, capsule, or powder forms. Although clinical evidence is lacking, anecdotal evidence of immunostimulatory and antimicrobial effects of the noni plant have been reported. The plant has only testimonial support for its use in treating CRF, and caution is advised based on reports of hyperkalemia and liver damage when ingested in large quantities.[19-21]

CONCLUSION

Cancer-related fatigue can manifest differently in each cancer patient who experiences its symptoms. Mechanisms of cancer-related fatigue can be elucidated through pathophysiologic evaluation, and cancer patients should be assessed for easily reversible causes of central and peripheral fatigue. Treatment is based on the patient's presenting symptoms and diagnosis and may include exercise and/or pharmacologic intervention. Complementary/alternative medicine therapies may relieve CRF symptoms in some patients. For those patients in whom these interventions are not effective,

pharmacologically masking the effects of cancer-related fatigue may provide an improved quality of life. ■

Donald Fleming is an oncologist at the Cancer Care Center, Davis Memorial Hospital, Elkins, West Virginia, and a member of the *Oncology Nurse Advisor* editorial board.

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