

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

## Fatigue in Cancer Patients



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### **H&O** How common is fatigue in cancer patients?

**SY** Fatigue is a ubiquitous symptom in cancer patients, occurring in approximately 60–90%.<sup>1</sup> Fatigue is more frequent in patients receiving chemotherapy, radiation therapy, or hormonal therapy. Additional treatments are associated with increased fatigue, as seen in patients with breast cancer. The fatigue usually improves over a period of time after the treatment ends.

### **H&O** Why is fatigue common in patients with cancer?

**SY** The exact mechanisms of cancer-related fatigue are unknown. Multiple factors may contribute. The current hypothesis attributes fatigue to a dysregulation of the inflammatory pathways as a result of the cancer and its treatment. In cancer patients, the disturbed regulation of inflammatory cytokines leads to a proinflammatory state that affects the brain and other systems, resulting in fatigue.

The mechanism of how cancer therapies cause fatigue is also unclear. Studies have shown that treatments often affect the inflammatory process by stimulating the immune mechanisms. Other factors that may be involved include dysregulation of the hypothalamic regulatory axis and dysregulation of the serotonin-tryptophan pathways. Some studies have shown that fatigue is associated with cancer-related symptoms, the most important being anxiety and depression. Other contributing factors include pain, anorexia, shortness of breath, and weight loss.

### **H&O** How does fatigue affect the patient's quality of life and course of management?

**SY** Recent studies have shown that approximately one-third to one-fourth of the reduction in quality of life seen in cancer patients may be due to worsening of fatigue. Fatigue affects not only physical aspects of the patient's daily activities, but also psychologic and economic aspects. Caregivers may also be affected by the patient's fatigue, which they may associate with a worsening disease state. Fatigue has a direct correlation with performance status, and therefore clinicians may be less willing to intensify treatment in patients with fatigue. Studies have shown that worsening performance status is directly correlated to decreased survival. Alleviation of fatigue may improve the patient's performance status and ability to tolerate treatment.

### **H&O** What are the traditional approaches to management of fatigue?

**SY** Previously, quality of life issues such as pain and nausea have received more attention than fatigue. Recently, however, there has been an increased focus on the management of fatigue. It is important to inform patients of what they can expect; physicians should educate patients regarding the trajectory of fatigue when they discuss the cancer diagnosis, symptoms, and prognosis. If patients understand that fatigue increases in the first week of chemotherapy or in the latter half of radiation therapy, they can prepare for it.

**Table 1.** Patient Characteristics in a Study of Fatigue in Cancer

Characteristics		Number	%
Age (years)	Mean (SD)	58 (13)	
	Median	59	
	Range	15–90	
Sex	Male	918	52
Race	White	1,213	68
Cancer Type	Lung or head and neck	473	27
	Gastrointestinal	301	17
	Genitourinary	176	10
	Sarcoma	68	4
	Gynecologic	120	7
	Breast	128	7
	Other*	512	28
Severity of Baseline Fatigue	Mild	293	16
	Moderate	909	51
	Severe	580	33
	Moderate or severe	1,489	84

\*Leukemias, lymphomas, cancer of unknown primary, melanoma.

SD=standard deviation.

Data from Yennu S et al. *BMC Palliat Care*. 2012;11:16. doi: 10.1186/1472-684X-11-16.

For all patients (including those with early cancer or advanced cancer) and cancer survivors, exercise therapy has the best evidence.<sup>2</sup> A recent Cochrane review confirmed the beneficial effects of exercise in the management of cancer-related fatigue. In a meta-analysis of 56 studies that included 1,461 participants who received an exercise intervention and 1,187 control participants, exercise was reported to be statistically more effective than control interventions in reducing fatigue (standardized mean difference, -0.27; 95% confidence interval, -0.37 to -0.17).<sup>3</sup> Both aerobic and resistance exercises, such as brisk walking, cycling, swimming, and weight lifting, are helpful; at least one 15–20-minute episode per day (100–150 minutes per week) has been shown to reduce fatigue levels. Maintaining a high level of cardiorespiratory fitness throughout treatment will help prevent muscle loss and other symptoms that may contribute to fatigue, including anxiety and depression. Frail and terminally ill patients are often unable to exercise. With these patients, it is important to discuss energy conservation and the use of assistive devices, such as orthotics, so that they can use their available energy on the most beneficial activities on a given day.

There is some early evidence supporting the use of pharmacologic agents to improve fatigue in cancer patients. Corticosteroids and psychostimulants (eg, methylphenidate) have been studied.<sup>4</sup> It is important to note that corticosteroids should be used only in very advanced cancer patients for a short period of time because increased side effects have been reported when these agents are used for longer periods of time.

It is also important to identify any reversible causes of fatigue. In patients with anemia, for example, fatigue might improve with the use of a blood transfusion or erythropoiesis-stimulating agents. It should be noted that erythropoiesis-stimulating agents are indicated only in anemic cancer patients receiving chemotherapy. This is due to the increased risk of cardiovascular events and tumor progression in cancer patients receiving these agents.<sup>5</sup>

### **H&O** Are there any novel approaches to management of fatigue in cancer patients?

**SY** The most important approach consists of multimodal therapy that combines both pharmacologic and nonpharmacologic interventions. The rationale is that the primary

causes of fatigue are multidimensional, and it is important to target the different mechanisms. It may not be possible to use a single pharmacologic agent or nonpharmacologic therapy to mitigate fatigue. The use of a multimodal approach might help to target the multidimensional causes. Further research is needed in this area.

### **H&O** What are the particular challenges in the management of fatigue in cancer patients?

**SY** The key issue is the lack of definitive treatment, especially in advanced cancer patients. The primary reason is the multifactorial nature of fatigue, which prevents the targeting of a single causative mechanism. In addition, there is limited research in this area and no unified definition of what represents cancer-related fatigue.

### **H&O** Could you please describe your recent study of fatigue in cancer patients?

**SY** This retrospective study examined data from 1,778 patients who presented to the outpatient supportive care clinic at MD Anderson Cancer Center from 2003 to 2010. These patients were first seen in supportive care after referral by their primary oncologists at the center. The patients were managed by a supportive care team that included a physician, a nurse, a social worker, a pharmacist, a nutritionist, and a chaplain. These team members provided a standardized program of supportive or palliative care. They assessed the patient's fatigue, evaluated causes, and identified risk factors in a systematic manner to devise a standardized management plan. All patients completed the Edmonton Symptom Assessment System (ESAS) questionnaire at the initial visit and subsequent follow-up visits. The ESAS questionnaire assesses fatigue, pain, nausea, anorexia, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath.

In the analysis of these data, the most important finding was that most patients presented with moderate or severe

fatigue at their initial visit. The fatigue improved at the first follow-up visit. Another important finding was that the severity of fatigue at the time of the initial visit to the supportive care center was predicted by the occurrence of other cancer-related symptoms, such as pain, nausea, depression, appetite, drowsiness, shortness of breath, decreased feeling of well-being, and low albumin levels. It is highly likely that managing these other symptoms would help improve fatigue. The common treatments may include optimal pain management, counseling, and exercise prescription.

### **H&O** Is there any other promising research in this area?

**SY** There has been recent interest in complementary treatments for management of fatigue, including the traditional approaches used in Eastern countries, such as mindfulness, qigong, acupuncture, and yoga. These treatments seem to be associated with some initial responses in improvement of fatigue, but further research is needed. Another interesting idea is the use of pharmacologic agents/supplements such as ginseng or astragalus, which seem to have some impact on fatigue, although studies are very limited.

## References

1. Yennu S, Urbauer DL, Bruera E. Factors associated with the severity and improvement of fatigue in patients with advanced cancer presenting to an outpatient palliative care clinic. *BMC Palliat Care*. 2012;11:16. doi: 10.1186/1472-684X-11-16.
2. Segal R, Reid R, Courneya K, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol*. 2009;27:344-350.
3. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev*. 2012;11. Art. No.: CD006145. DOI: 10.1002/14651858.CD006145.pub3.
4. Yennurajalingam S, Bruera E. Palliative management of fatigue at the close of life. *JAMA*. 2007;297:295-304.
5. FDA.gov. Information for Healthcare Professionals: Erythropoiesis Stimulating Agents (ESA) [Aranesp (darbepoetin), Epogen (epoetin alfa), and Procrit (epoetin alfa)] (3/2007). <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm126485.htm>. Updated June 22, 2010.