

EPECTM-O

Education In Palliative And End-Of-Life Care For Oncology

Self-Study Module 3k:

Fatigue

Module 3k: Fatigue

Abstract	3
Introduction	3
Case	4
Pathophysiology	4
Assessment.....	5
Management	7
Summary	9
Key Take-Home Points	9
References	11

Abstract

Many symptoms and syndromes are commonly encountered in patients with cancer. This module first presents general approaches to symptom management, followed by management of the specific symptoms and syndromes, including: anorexia/cachexia, anxiety, constipation, depression, diarrhea, fatigue, insomnia, menopausal symptoms and sexual health, mucositis, nausea and vomiting, and skin problems.

Any symptom can be debilitating and prevent the patient and family from achieving goals that are important to them. As with other aspects of medicine, tailored management is based on the underlying etiology and pathophysiology. When several symptoms occur together, they can be interrelated and management can be complex.

Introduction

Cancer-related fatigue is a persistent sense of tiredness, which may be secondary to cancer or its treatment and interferes with usual functioning. It is unrelieved by rest and may affect both physical and mental capacity. (Ref. 1)

Prevalence

Fatigue is one of the most common symptoms in patients with cancer. Its prevalence is estimated to range from 80 to 96%. (Ref. 2) (Ref. 3) (Ref. 4) Fatigue is the symptom with the greatest impact on everyday life. (Ref. 5) Among cancer outpatients, 58% report that fatigue affects them “somewhat” or “very much.” This symptom is more common than pain (22%) or nausea and vomiting (18%).

The experience of fatigue varies with the type and stage of cancer. It is experienced by 50% of patients with nonsmall-cell lung cancer and 15% of those with breast cancer. Nearly 80% of patients with advanced disease experience fatigue. (Ref. 5) In contrast, the prevalence of fatigue in the general population is only 6%.

Cancer-related fatigue is associated with specific treatments. It occurs after surgery, chemotherapy, radiation therapy, and treatment with biologic response modifiers, such as alpha interferon and interleukin-2. (Ref. 6) (Ref. 7)

Patterns of fatigue vary. Treatment with cyclic chemotherapy results in peak fatigue scores a few days after treatment, with improvement over the cycle duration. (Ref. 8) (Ref. 9) By contrast, a course of fractionated radiotherapy is more likely to cause

cumulative fatigue, with onset 7 to 10 days into therapy and peak severity at the conclusion of treatment. (Ref. 10)

Cancer-related fatigue may persist for a prolonged period of time, even years. Up to 30% of cancer survivors report persistent fatigue for years after completion of antineoplastic therapy. (Ref. 11)

Prognosis

Fatigue is a debilitating clinical symptom. The presence of fatigue, or its severity, has not been demonstrated to provide independent prognostic information. However, from a patient perspective, progressive fatigue is feared, not only as a symptom, but as a harbinger of progressive disease.

Case

Review the case below, and keep it in mind as you progress through the module. How would you approach the assessment of this patient? What interventions might be appropriate?

L.M. is an 88-year-old woman with a long history of chronic obstructive pulmonary disease. Four months ago she developed hemoptysis and sought evaluation. Chest x-ray demonstrated a large right lower lobe lung mass. Computed tomography scan of the chest revealed a 6-cm right lower lobe lung mass with bulky mediastinal adenopathy. Fine needle aspiration of the lung mass confirmed a diagnosis of nonsmall-cell lung cancer, probably squamous. The patient declined further evaluation or treatment because she felt well overall. She returns today for follow-up. Her only complaint is fatigue.

“Doctor, I can't understand it. I'm tired all the time. I don't have the energy to do any of my usual activities. It's so frustrating to me. Can't something be done about this?”

Pathophysiology

The etiology of fatigue is multifactorial and is a result of both physiologic and psychosocial factors. Proposed mechanisms for fatigue include abnormalities in energy metabolism related to increased need, decreased availability of metabolic substrate, or the production of abnormal substances that impair metabolism or the normal function of muscle. (Ref. 11) An alternate proposed mechanism is the increased production of cytokines; particularly interleukin-6. (Ref. 12) (Ref. 13) Depression, sleep disorders, and neuromuscular dysfunction are all potential contributors in the development of fatigue.

To date, there is no clear evidence to support any of these mechanisms, and further research is needed.

Assessment

Fatigue is a subjective experience and, like the assessment of pain, is best evaluated by the report of the patient. The National Comprehensive Cancer Network (NCCN) recommends the following algorithm:

- Screen each patient for the presence and severity of fatigue.
- Rate the severity of fatigue on a 0-10 scale, with 0 being “no fatigue” and 10 “the worst fatigue imaginable.” If fatigue is moderate (4-6 on a 0-10 scale) or worse, initiate a thorough history and physical examination.
- Include the disease status and treatment.
- Rule out recurrent or progressive disease.
- Review current medications and recent changes.
- Pursue an in-depth assessment of the fatigue, including:
 - Onset, pattern, duration, and change over time
 - Associated or alleviating factors
 - Interference with function.
- Evaluate the patient for the presence of:
 - Treatable, contributing factors (e.g., pain, depression, insomnia, anemia, or malnutrition)
 - Deconditioning and comorbidities (e.g., infection or cardiac, pulmonary, renal, hepatic, neurologic, or endocrine dysfunction) (Ref. 14) (Table 1).

Table 1. Potential Predisposing Etiologies of Cancer-Related Fatigue

Psychosocial factors	Anxiety disorders Depressive disorders Stress-related Environmental
Physiologic factors	Treatment-related Chemotherapy Radiation therapy Surgery Biologic response modifiers
Malignancies	
Intercurrent System Disorders	Anemia Infection Pulmonary disorders Hepatic failure Cardiac failure Renal failure Malnutrition Neuromuscular disease Dehydration or electrolyte imbalance Endocrine dysfunction
Alterations in activity level	Deconditioning
Sleep disorders	
Pain	
Medications	Use of centrally acting medications Opioids Antiemetics Hypnotics Anxiolytics Antihistamines

Management

Intervention for patients with cancer-related fatigue, particularly for those on active treatment, begins with education about the known patterns of fatigue during and following treatment. Reassure the patient that treatment-related fatigue is not necessarily an indicator of progressive disease. (Ref. 15)

Treat reversible causes and contributing factors. Review medications and discontinue centrally active agents. Correct sleep disorders or metabolic abnormalities. Depression does not appear to be a major factor in most patients' cancer-related fatigue, but should be treated if present. (Ref. 16) Treat pain, if present. Pain can be successfully controlled in more than 90% of patients and is frequently associated with fatigue. Less common, reversible etiologies of fatigue include hypothyroidism and hypogonadism.

Anemia

Anemia is the most common cause of reversible fatigue and occurs in about half of all cancer patients undergoing treatment. Multiple, randomized, controlled trials have demonstrated clinically significant improvement in overall quality of life in association with an increase in hematocrit. (Ref. 17) (Ref. 18) (Ref. 19) (Ref. 20) Increases in quality of life are greatest when the hemoglobin is in the range of 11-13 gm/dl. (Ref. 20)

Erythropoietin alpha administered to prevent significant anemia can sustain quality of life, energy level, and the ability to perform daily activities. Its use can prevent the need for transfusions. (Ref. 21) This may signal a shift in the paradigm for when to initiate erythropoietic agents. Dosing options include:

- **Erythropoietin alpha**, 40,000 IU SC once q week.
- **Darbepoetin alfa**, 200 mcg SC, once q 2 weeks. (Ref. 22) (Ref. 23) Weekly dosing (i.e., front loading), results in more rapid improvements in quality of life than q 2 week therapy. (Ref. 24)

Non-pharmacologic therapies

A variety of non-pharmacologic therapies have been evaluated and utilized for the treatment of fatigue.

Excessive rest contributes to cancer-related fatigue rather than lessening it. Structured exercise programs have been shown to improve fatigue as well as the patient's emotional and overall sense of well-being. (Ref. 25) The beneficial effects of exercise have been observed in patients undergoing cancer treatment and in survivors who have already completed therapy. (Ref. 26) (Ref. 27) (Ref. 28) (Ref. 29) (Ref. 30) (Ref. 31) (Ref. 32) Exercise programs are effective for patients undergoing chemotherapy, bone marrow transplantation, or radiation therapy. Additionally, whether the prescribed exercise is walking or bicycling or some combination, the outcomes are equivalent.

(Ref. 28) (Ref. 31) (Ref. 33) A simple, practical prescription for exercise might include walking 20 minutes a day, 10 minutes out and 10 minutes back. (Ref. 34) Additional benefits of exercise include potential improvements in appetite, weight, strength, self-image, and bowel habits.

If fatigue is severe, energy conservation strategies are often recommended. Such strategies include:

- Setting priorities to perform tasks that are most important to the patient first
- Scheduling activities at times of peak energy
- Postponing non-essential activities
- Structuring a daily routine
- Attending to one activity at a time

Consultation with an occupational therapist may be valuable in identifying the best strategies for an individual patient.

Pharmacologic therapies

Numerous pharmacologic therapies have been recommended for cancer-related fatigue but, to date, none have been rigorously evaluated in controlled trials.

Methylphenidate can improve cancer- and AIDS-related fatigue. A standard dosing regimen is:

- **Methylphenidate**, 5-30 mg PO daily.

Response rates up to 100% have been noted. (Ref. 31) (Ref. 35) Start with 2.5 to 5 mg every morning and noon. The recommendation for this fixed dose schedule is largely anecdotal, arising from concerns that treatment late in the day will cause insomnia. A recent preliminary report of patient-controlled methylphenidate for the management of cancer-related fatigue raises questions about this assumption. (Ref. 31) Significant improvement in fatigue and functional and physical well-being was reported by patients taking patient-controlled stimulant medications. All of the patients took afternoon and evening doses and 93% took three or more doses daily. The dose can be increased every few days until the desired effect is achieved or toxicity is apparent. The risk of toxicity increases as the dose increases. Few patients require greater than 60 mg/day for effect. Adverse effects include anorexia, insomnia, anxiety, confusion, tremor, other organic brain syndromes, and tachycardia. The beneficial effects of methylphenidate may decrease over time, and dose escalation may be needed to maintain benefit.

Corticosteroids may improve fatigue for patients with advanced disease and fatigue. (Ref. 36) (Ref. 37) Dosing options include:

- **Dexamethasone**, 4 mg PO q am
- **Prednisone**, 20 mg PO daily (Ref. 38)

Modafinil is a CNS stimulant approved for the treatment of narcolepsy in doses of 200 mg/day. This agent has been shown to improve fatigue in patients with multiple sclerosis. (Ref. 39) A standard dosing regimen is:

- **Modafinil**, start with 100 mg in the morning and at noon. Titrate to effect, up to the maximum dose of 400 mg/day.

Amantadine has been used to treat fatigue in patients with multiple sclerosis but has not been evaluated in the setting of cancer-related fatigue.

Summary

Although fatigue is the most common symptom reported by cancer patients and has serious adverse effects on quality of life, the pathogenesis and management of fatigue remain poorly understood. Treatment requires careful assessment of potentially reversible factors and utilization of both pharmacologic and non-pharmacologic interventions. Provide all patients with information about treatment-related fatigue and recommendations about the effect of exercise on fatigue. Anemia is an important, reversible cause of fatigue; treat it preventively. Fatigue is often not readily reversible. A trial of a pharmacologic stimulant, such as methylphenidate, is an option for treatment.

Key Take-Home Points

1. Fatigue is the symptom with the greatest impact on everyday life.
2. The pattern of treatment-related fatigue varies with the type of treatment.
3. Corticosteroids and psychostimulants may have a beneficial effect.
4. Anemia, though an important cause of fatigue, may not be the therapy-resistant etiology of fatigue in many patients with cancer.

Pearls

1. Peak fatigue after chemotherapy occurs a few days after treatment.
2. Encourage patients to exercise. Too much “rest” increases fatigue.

3. If possible, recommend exercise along with adjuvant chemotherapy.
4. Anemia is the most common cause of reversible fatigue. Increases in quality of life appear greatest when hemoglobin is in the range of 11-13 gm/dl.
5. Make a partnership with your patient and the family caregiver; draw them into the interdisciplinary team and foster their active participation in the care plan.
6. Additional material can be found in Module 3: Health Professional Resources and Module 3: Patient Resources.

Pitfalls

1. Doing nothing. Try something! Fatigue is a major debilitating symptom.
2. Recommending too much rest, which may lead to progressive muscle wasting and further reduction of energy.

References

Module 3k: Fatigue

- 1 Cella D, Peterman A, Passik S, et al. Progress toward guidelines for the management of fatigue. *Oncology*. 1998;12:369-377. PMID: 10028520.

This review focuses on the etiology of fatigue, its treatment, and impact on quality of life.

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Fatigue can be a prevalent and serious problem for the individual with cancer and can negatively impact the individual's quality of life. This study investigated the prevalence of clinical fatigue among patients with cancer and how the fatigue cancer patients experience compares with the fatigue people experience as a function of their normal daily activities.

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For cancer patients, fatigue is a disturbing symptom caused by many factors. Since fatigue is the most common adverse effect of localized radiation to the breast, this treatment provides a unique opportunity to follow patients prospectively as they develop one type of fatigue. This trial evaluated the effect of radiation treatment on fatigue in 15 women with Stage I or II node-negative breast cancer who were otherwise healthy.

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Although fatigue is the most common symptom reported by cancer patients and has serious adverse effects on quality of life, it remains poorly understood. Using a telephone survey of patients and their caregivers, the epidemiology of cancer-related fatigue from the perspectives of the patient, primary caregiver, and oncologist is characterized.

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- 7 Piper BF, Rieger PT, Brophy L, et al. Recent advances in the management of biotherapy-related adverse effects: Fatigue. *Oncol Nurs Forum.* 1989;16(6 Suppl):27-34. PMID:2480583.

This paper presents a comprehensive view of current knowledge on fatigue to guide present nursing practice with patients receiving biotherapy and provide direction for future nursing and clinical trial research.

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This study describes the patterns of cancer-related fatigue (CRF) and vigor in patients receiving chemotherapy or radiation therapy.

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This article describes a study that employed a daily diary with the aim of prospectively charting the onset, pattern, duration, intensity, and distress associated with fatigue in 109 patients receiving chemotherapy.

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To assess the prevalence, course, and prognosis of fatigue over the course of radiotherapy, 76 patients with breast cancer receiving external radiation therapy were followed longitudinally from the onset of treatment to 6 months posttreatment.

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The objectives of this study were to describe the quality of life of African American women with breast cancer and test a model of factors that might affect their quality of life.

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This randomized clinical trial tested whether paroxetine, a selective serotonin reuptake inhibitor antidepressant known to modulate brain serotonin, would reduce fatigue in cancer patients and whether any reduction was related to depression.

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This prospective, open-label study evaluated efficacy, safety, and quality-of-life (QOL) changes with epoetin alfa therapy for anemia in patients with nonmyeloid malignancies.

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This analysis presents the quality-of-life responses to darbepoetin alfa 3.0 mcg/kg administered to patients with fatigue who were undergoing chemotherapy.

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This study describes the patterns of daily fatigue in women with breast cancer who did and did not exercise while receiving the first three cycles of adjuvant chemotherapy.

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