EPEC-O

Education in **P**alliative and **E**nd-of-life **C**are - **O**ncology

Participant's Handbook

Module 3k:

Symptoms – Fatigue

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Case*

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 need aspiration of the lung mass confirmed a diagnosis of non-small cell lung cancer, probably squamous. The patient declined further evaluation or treatment because she, overall, felt well. 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?"

* This case is not on an EPEC-O Curriculum trigger tape.

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.[1]

Prevalence

Fatigue is one of the most common symptoms. Its prevalence is high, with estimates ranging from 80% to 96%.[2,3,4] It is also the symptom with the greatest impact on everyday life.[5] Among cancer outpatients, 58% report that fatigues affect them 'somewhat or very much.' This is more common than pain (22%) or nausea and vomiting (18%).

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

Fatigue is associated with specific cancer treatments. It occurs after surgery, chemotherapy, radiation therapy, and treatment with biologic response modifiers, such as alpha interferon and interleukin-2.[6,7]

Patterns of fatigue vary. Treatment with cyclic chemotherapy results in peak fatigue scores a few days after treatment, with improvement over the cycle duration.[8,9] By contrast, a course of fractionated radiotherapy is more likely to cause cumulative fatigue, with onset 7-10 days into therapy and peak severity at the conclusion of treatment.[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.[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.

Pathophysiology

The etiology of fatigue is multifactorial and a result of both physiologic and psychosocial factors. Proposed mechanisms for fatigue include abnormalities in energy metabolism related to increased need, decreased substrate, or the production of abnormal substances that impair metabolism or normal function of muscle.[11] An alternate proposed mechanism is the increased production of cytokines; particularly interleukin-6.[12,13] 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 patient report. 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; and pursue an in-depth assessment of fatigue, including its onset, pattern, duration, and change over time, associated or alleviating factors, and interference with function.
- Evaluate the patient for the presence of:
    - Treatable, contributing factors, eg, pain, depression, insomnia, anemia, malnutrition
    - Deconditioning and comorbidities, eg, infection, cardiac, pulmonary, renal, hepatic, neurologic, or endocrine dysfunction[14] (See 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.[15]

Treat reversible causes and contributing factors. Review medications and discontinue centrally active agents. Correct sleep disorders or metabolic abnormalities.

Treat depression, if present, as it is associated with fatigue but does not appear to be a major factor in most patients.[16] Treat pain, if present, as it 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.[17,18,19,20] Increases in quality of life are greatest when the hemoglobin is in the range of 11-13 gm/dl.[20]

Erythropoietin alfa administered to prevent significant anemia can sustain quality of life, energy level, ability to perform daily activities and prevent transfusions.[21] This may signal a shift in the paradigm for thinking about 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.[22,23] Weekly dosing, ie, 'front loading,' results in more rapid improvements in quality of life than q 2 week therapy.[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.[25] The beneficial effects of exercise have been observed in patients undergoing cancer treatment as well as in survivors who have already completed their therapy.[26,27,28,29,30,31,32] 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.[28,31,33] A simple, practical prescription for exercise might include walking 20 minutes a day, 10 minutes out and 10 minutes back.[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 the tasks that are most important to the patient first, scheduling activities at times of peak energy, postponing non-essential

activities, structuring a daily routine, and attending to one activity at a time. Consultation with an occupational therapist may be valuable for identifying the best strategies for an individual patient.

Pharmacologic therapies

Numerous pharmacologic therapies have been recommended for cancer-related fatigue but, to date, have not 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.[31,35] 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.[31] Significant improvement in fatigue, functional and physical well-being was reported by patients taking patient controlled analgesics. All of the patients took afternoon and evening doses and 93% took 3 or more doses daily. The dose can be increased every few days until the desired effect or toxicity is apparent. The risk of toxicity increases as the dose increases, with few patients requiring 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.[36,37] Dosing options include:

- Dexamethasone, 4 mg PO q AM
- Prednisone, 20 mg PO daily[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.[39] A standard dosing regimen is:

- Modafinil, start with 100 mg in the morning and at noon. Titrate to effect, up to the maximum does 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

Despite the high prevalence and altered quality of life associated with fatigue, there is little knowledge about pathogenesis or management. 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 every day life.
2. The pattern of the 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 people to exercise. Too much ‘rest’ increases fatigue.
3. If possible, recommend exercise along with adjuvant (or other) chemotherapy.
4. Anemia is the most common cause of reversible fatigue. Increases in quality of life appear greatest when the hemoglobin is in the range of 11-13 gm/dl.

Pitfalls

1. Doing nothing. Try something! This is a major debilitating symptom.
2. Too much rest may lead to progressive muscle wasting and further reduction of energy level.

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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 patient's 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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