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Management of Cancer-Related Fatigue

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Abstract

Guidelines for the management of cancer-related fatigue (CRF) emphasize evidence-based strategies for reducing this common symptom. The largest body of data exists for the benefits of exercise for reducing CRF. Patient education and counseling are also considered integral to effective management of CRF. Additional interventions can be nonpharmacologic or pharmacologic, although a combination of approaches may be employed. Several factors known to be associated with CRF may be particularly amenable to treatment.

Introduction

Guidelines for the management of cancer-related fatigue (CRF) are available from both the National Comprehensive Cancer Network (NCCN)¹ and the Oncology Nursing Society (ONS).² Current NCCN recommendations describe 4 categories of consensus regarding evidence for management of CRF, while ONS guidelines use 5 categories of evidence for approaches to symptom management (Table 1).^{1,2} This analysis will focus primarily on ONS guidelines for management of CRF, although NCCN guidelines may be referred to where appropriate.

A cancer patient's clinical status (ie, currently receiving active treatment, during long-term follow-up, or at the end of life) will influence CRF management strategies. As described in the earlier article in this supplement by Dr. Piper, the initial fatigue evaluation is used to identify whether any of the following known etiologic factors are present: pain, emotional distress, anemia, insomnia, deconditioning, nutritional problems, or comorbidities. These factors, if present, will guide the management of moderate or severe CRF.¹ The current ONS fatigue guidelines rate screening for and managing etiologic factors as "likely to be effective" fatigue management strategies.³ Additional interventions can be nonpharmacologic or pharmacologic, although in many cases a combination of approaches is employed.

Nonpharmacologic Interventions for CRF

Exercise

Strong evidence supports the benefit of exercise for management of CRF. Numerous randomized, controlled, clinical trials have evaluated exercise during and after treatment in patients with various malignancies and these data have been the subject of several comprehensive meta-analyses and review articles.⁴⁻¹⁰

Exercise can effectively reduce CRF in various settings. For example, during palliative care low-intensity exercise matched to patients' comfort levels was associated with quality of life (QOL) improvements.^{11,12} For patients receiving marrow or stem cell transplants, positive studies have been conducted using aerobic interval training with appropriate monitoring.¹³

During chemotherapy and radiation therapy, home-based exercise programs have proven beneficial.^{14,15} Strength resistance exercise has been effectively used for men with prostate cancer undergoing androgen deprivation therapy.^{4,16}

It is important to carefully consider which types of exercise may be beneficial. The current NCCN recommendation is to begin with low intensity and duration of exercise and then to progress slowly and modify the exercise plan as conditions change.¹ Timing, at least initially, might be 20 to 30 minute sessions, 3 to 5 times per week. One study showed that cancer patients who exercised more than 60 minutes per day reported an increase in fatigue.¹⁷ The appropriate intensity of exercise will vary depending on individual patient circumstances. Exercise should be used cautiously in the presence of bone metastases, neutropenia, low platelet counts, anemia, and fever, weighing risks and benefits. In some cases, a modified exercise regimen can be recommended; for example, the neutropenic patient should avoid environments with high risk for infection (such as gyms and swimming pools).¹⁰

Exercise is the only strategy that ONS guidelines for CRF classify as “recommended for clinical practice.” However, additional research is still needed regarding both safety and customization of exercise regimens (eg, type, intensity, frequency, duration) in different cancer patient populations.²

Education

Education and counseling should be used for all cancer patients, but are particularly beneficial for those beginning fatigue-inducing treatments. Data from several studies support the role of educational interventions (providing physical sensory information, anticipatory guidance, coping skills training, and coaching) in assisting patient self-management of CRF to reduce fatigue levels.¹⁸⁻²¹ Consultation regarding nutritional deficiencies that may result from anorexia, diarrhea, nausea, and vomiting associated with cancer or its treatment may be useful.²²

Strategies that can be taught for coping with fatigue include energy conservation and activity management. Energy conservation is the deliberate and planned management of one’s activities and personal energy resources. The goal is to balance rest and activity so valued activities can be maintained. Initiatives include planning, delegating, prioritizing activities, pacing, and resting. Randomized clinical trials have shown that cancer patients benefited from learning energy conservation.²³ The ONS guidelines describe energy conservation as “likely to be effective.”

Cognitive-Behavioral Interventions

Distress can result in fatigue. According to the NCCN guidelines, “distress” represents a complex, multifactorial experience that may include anxiety and depression.^{1,24} Complicating matters, distress can interfere with sleep which can worsen fatigue.

For moderate to severe distress, NCCN guidelines for distress management recommend referral to a specialist. If distress is mild, the oncology team can provide supportive care.^{1,24}

Stress reduction and the management of depression and anxiety can be useful in reducing fatigue.²⁵ Randomized trials have shown that cognitive-behavioral strategies such as progressive muscle relaxation or relaxation breathing may improve fatigue in cancer patients receiving radiation therapy or hematopoietic stem cell transplantation.^{26,27} Use of these strategies to improve sleep could also be effective in relieving fatigue; these strategies are classified by the ONS guidelines as “likely to be effective” in reducing fatigue.³

Studies support the role of a cognitive-behavioral approach to improve sleep quality in order to reduce fatigue.^{28,30} An important component of the cognitive-behavioral approach is having the patient set and maintain a schedule of regular sleep and wake times. Patients should also place themselves in an environment that is conducive to sleep and not stay in bed any longer than they intend to sleep. Caffeine, nicotine, and alcohol should be avoided, particularly in the evening or within several hours before intended sleep.³

Strategies for Pharmacologic Management of CRF Based on Associated Factors

Anemia

Published data suggests that the use of recombinant erythropoietic agents (epoetin or darbopoetin) to increase hemoglobin (Hgb) levels in cancer patients with disease- or treatment-related anemia (Hgb < 10 g/dL) may improve vigor, fatigue, and other QOL outcomes.³¹⁻³⁴

However, several major concerns recently have been raised regarding potential risks associated with the use of recombinant erythropoietins, including increased risk of death, thrombotic events, red cell aplasia (due to anti-erythropoietin antibodies), and growth stimulation of certain tumor types.³⁵⁻³⁸ Current ONS guidelines for management of fatigue emphasize that both clinicians and patients should carefully evaluate potential benefits and harmful effects of recombinant erythropoietins for individual patients.³

Pain

Pain can also be a contributing factor to fatigue. According to the ONS guidelines, management of pain is “likely to be effective” in reducing a cancer patient’s fatigue. NCCN guidelines for pain in adult cancer patients have been developed by experts from comprehensive cancer centers across the United States. These guidelines recommend universal screening to quantify pain intensity and to describe the quality and anatomical location(s). If pain is reported, a more comprehensive pain assessment is indicated.³⁹

NCCN guidelines for management of pain recommend an NSAID or acetaminophen (without an opioid), or a short-acting opioid for patients with low pain levels (pain score of 1 to 3). For moderate (pain score of 4 to 6) or severe pain (pain score of 7 to 10) an opioid may be prescribed with a co-analgesic as needed. Reassessment is recommended every 24 hours for patients with severe pain and every 1 to 3 days for patients with moderate or mild pain.¹

Sleep Disturbances/Insomnia

ONS guidelines for pharmacologic management of sleep-wake disturbances specify that clinician and patients need to carefully “weigh the benefits and potential harmful effects” of pharmacologic sleep interventions.⁴⁰ In general, there is little research on sleep drugs in cancer patients and a systematic assessment is needed regarding efficacy, safety, and possible drug interactions. Pharmacologic agents used for inducing sleep and improving sleep maintenance include benzodiazepines and nonbenzodiazepines. Other drugs prescribed for management of sleep disturbances are the tricyclic antidepressants and some of the newer antidepressants (such as bupropion SR). Antihistamines, chlorohydrates, and chlorpromazine have also been used. The general recommendation for sleep drugs is that they not be used for more than 7 to 10 days.⁴⁰ Many cancer patients also use herbal supplements to help with side effects related to their treatment or to induce sleep. However, there is currently minimal evidence to support the effectiveness of herbal supplements and concern exists regarding potential drug interactions with these agents.^{41,42}

Emotional Distress (Depression)

When depression has been identified as a contributing factor to fatigue, pharmacologic management of depression may be effective in controlling CRF.¹⁰ Patients may benefit from a combination of medication and counseling. Medications for depression include: selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants, and monoamine oxidase [MAO] inhibitors). Counseling methods include behavior therapy, counseling, education, and preparatory information. This strategy primarily has been used when fatigue was observed in association with depression, but many issues surrounding the relationship between these 2 symptoms as well as potential treatment options have not been extensively addressed in clinical studies and require further investigation. However, it is worth noting that two recent studies using the SSRI paroxetine in cancer patients have shown no significant effect on fatigue in the absence of depressed mood.^{43,44}

Future Options for Management of CRF

Several other agents have been used or are being evaluated for the management of CRF (Table 2). However, the efficacy (and safety) of these agents for this indication have not been established.³ According to NCCN guidelines, the use of psychostimulants can be considered for moderate or severe CRF but more data are necessary to recommend their use.¹ Investigational agents for management of CRF are the subject of the article in this supplement authored by Drs. Breitbart and Alici-Evcimen.

Summary

Management strategies for CRF have been described in clinical practice guidelines. Education and counseling are essential for helping cancer patients anticipate and cope with fatigue that may be associated with their disease or related to their cancer treatments. Effective strategies for coping with fatigue include energy conservation, activity management, optimizing restful sleep, and use of relaxation techniques. The most convincing data exist for the benefits of physical exercise in reducing CRF, although patient limitations must be considered. Management of some of the etiologic factors known to be associated with CRF, including pain, insomnia, and distress may also be effective in helping to reduce these symptoms in selected patients. Effective management of CRF may result in improved QOL for patients.

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Table 1ONS Categories of Evidence for Management of CRF²

Recommended for practice	Strong evidence from rigorously designed studies or reviews
Likely to be effective	Evidence less well established
Effectiveness not established	Insufficient data or data of inadequate quality
Effectiveness unlikely	Some evidence of ineffectiveness
Not recommended for practice	Clear evidence of ineffectiveness or harmfulness; cost/burden exceeds benefit

Table 2Potential Pharmacologic Options for CRF³

Agent	Drug Class	Approved Indication
Methylphenidate	CNS stimulant	Attention deficit disorder
Donepezil	Cholinesterase inhibitor	Alzheimer's disease
Modafinil	CNS stimulant	Daytime sleepiness associated with narcolepsy
Bupropion SR	Antidepressant	Smoking cessation
Levocarnitine	Amino acid supplement	
Adenosine 5'-triphosphate	Nutraceutical	