Symptom Control in Palliative Care—Part II: Cachexia/Anorexia and Fatigue

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INTRODUCTION

In the first part we addressed general symptom assessment, constipation, and chronic nausea. This part discusses cachexia/anorexia and fatigue, and once again most of the available research is cancer-related.

CACHEXIA/ANOREXIA

Cachexia may occur in up to 80% of patients with advanced cancer. This complex metabolic syndrome, characterized by profound loss of lean body mass, is the main cause of death in 20% of patients. Cachexia (involuntary loss of more than 10% of premorbid weight) is a marker for poor prognosis and is associated with anorexia (loss of appetite), asthenia and changes in body image. Cancer cachexia tends to occur in patients with solid tumors, in children, and in elderly patients. Cachexia is also common in acquired immune deficiency syndrome (AIDS), chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF) and other chronic illnesses, such as dementia, tuberculosis, malaria, chronic kidney disease, liver disease, and rheumatoid arthritis.

MECHANISMS

Cachexia is caused by a complex interaction between tumor by-products (proteolysis inducing factor, lipid mobilizing factor) and host cytokines (including interleukin [IL]-1, IL-6, tumor necrosis factor, interferon). Cachexia in experimental animal models can be relieved by specific cytokine antagonists, such as monoclonal antibodies to IL-6. The metabolic abnormalities are characterized by synthesis of acute phase proteins in the liver at the expense of muscle protein, proteolysis, lipolysis, insulin resistance, decreased lipogenesis, elevated triglycerides and decreased high density lipoproteins (Fig. 1). Neuroendocrine abnormalities and the production of anorexigenic compounds may further contribute to the development of cachexia. Nutritional supplementation and appetite stimulation alone cannot overcome the block in accretion of muscle mass. Similar mechanisms for cachexia in CHF, chronic kidney disease, COPD, and rheumatoid arthritis have been described.

ASSESSMENT

The patient’s subjective loss of appetite can be assessed with a numerical rating scale such as the Edmonton Symptom Assessment System (ESAS), or one of the other tools previously described. The clinical assessment includes a careful history that is focused on nutritional issues and a physical examination. Body weight is the only test commonly used outside the research setting. Measuring mid upper arm circumference may have prognostic value. Whole-body impedance and electroconductivity is based on the principle that lean tissue conducts electricity better than fat. This has the potential for more widespread clinical use as the equipment becomes more easily
available. For research and for follow-up, the effect of any intervention on related symptoms, such as fatigue and dyspnea, would be useful, as well as quality of life and functional assessments.

**MANAGEMENT**

The management of major contributors to this syndrome, such as chronic nausea, constipation, early satiety, taste alteration, dyspnea, deconditioning, and depression may result in significant improvement. Established pharmacologic treatment currently comprises either megestrol or corticosteroids, which predominantly stimulate appetite, however will not reverse cachexia in most patients. Weight gain may be necessary to alleviate distress associated with changes in body image. The other therapies described below may delay or reverse the cachexia component, or alleviate the symptom burden without major effects on body composition.

**Pharmacologic treatment**

**Progestational agents.** Megestrol acetate has demonstrated dose dependent improvements (starting at 160 mg/d) in appetite, fatigue, and general well-being in more than 60% of patients.\(^{15-17}\) Approximately 480–800 mg/d is optimal for weight gain, but it is prudent to start at a lower dose and titrate upward, since adverse effects\(^{18}\) and expense are dose-related. Symptomatic improvement in appetite occurs in less than 1 week; however, weight gain may take several weeks and it happens in less than one quarter of treated patients. In a comparison study, megestrol acetate (MA; 800 mg/d) was found to have fewer side effects than dexamethasone (0.75 mg four times daily [qid]), with a trend toward better weight gain.\(^{19}\) The authors concluded that for planned long-term use (weeks to months) it might be preferable to choose megestrol acetate. Consideration should also be given to cost (up to 20 times more expensive) and the higher risk for deep vein thrombosis (DVI).

A recent review of the literature on MA\(^{20}\) showed that this drug was safe and effective in patients with cancer and AIDS. Megestrol has also been used in other noncancer conditions. A randomized double-blinded placebo controlled 8 week trial\(^{21}\) of either megestrol 800 mg daily or placebo in underweight patients with COPD demonstrated significant weight gain (mostly fat mass) in the megestrol group. Ventilation was stimulated (PaCO\(_2\) decreased), but there was no change in the 6-minute walk test. Side effects of megestrol include edema, hyperglycemia, and elevated liver enzymes.

Medroxyprogesterone\(^{22}\) at doses of 1000 mg/d (equivalent to megestrol 160 mg/d) has demonstrated significant improvements in appetite and body weight.

Corticosteroids may stimulate appetite and decrease nausea as well.\(^{23,24}\) Randomized clinical trials have demonstrated that compared to placebo, corticosteroids can improve appetite and food intake.\(^{25}\) The effects of corticosteroids on ap-
petite and food intake are usually limited to a couple of weeks, and the side effects of these drugs increase dramatically over time. Therefore, corticosteroids should be considered most useful for patients with a life expectancy of less than 6 weeks. Most authors have used prednisone doses ranging from 20–40 mg, or dexamethasone at an equivalent dosage.

**Cannabinoids.** Dronabinol, a synthetic cannabinoid, is Food and Drug Administration (FDA) approved for anorexia related to AIDS and chemotherapy-induced nausea and emesis. In a study of patients with AIDS-related cachexia, dronabinol showed significant improvement in nausea, appetite, and mood but no weight gain.26 Although some studies found beneficial effects of dronabinol on appetite in patients with advanced cancer,27,28 the effects of dronabinol on cachexia appear to be limited. In a more recent study comparing dronabinol with megesterol acetate, the latter drug was found to be more beneficial as an orexigenic agent.29 A combination of both drugs was not better than MA alone. The use of dronabinol is also limited by undesirable central nervous side effects, such as sedation, confusion, and perceptual disturbances.30

Thalidomide has immunomodulatory and antineoplastic effects and its use is being explored in a variety of conditions.31 Recent trials in patients with advanced cancer have been encouraging. Thalidomide was found to improve appetite, nausea and well-being after 10 days of treatment (100 mg daily) in patients with advanced cancer. A recent randomized placebo controlled trial33 of 50 patients with pancreatic cancer demonstrated that a dose of 200 mg daily for 24 weeks was well-tolerated and effective at attenuating loss of weight and lean body mass. There was no significant difference in appetite symptom scores between thalidomide and placebo. Two patients developed peripheral neuropathy that resolved on cessation of the drug. Another open-label trial of thalidomide for 2 weeks in patients with esophageal cancer appeared to reverse loss of lean body mass, and although sedation was experienced by all patients, daytime somnolence was transitory and disappeared after 2 or 3 days.

Thalidomide also appears to benefit patients without cancer with cachexia. Patients with human immunodeficiency virus (HIV) with aph-thous ulcers have demonstrated weight gain on doses of 200 mg daily.35 Low-dose (100 mg) thalidomide36 for 8 weeks in AIDS-associated cachexia was also associated with significant weight gain, half of which was fat-free mass. A trial of thalidomide in patients with active pulmonary tuberculosis was well tolerated and resulted in significant weight gain and reduction of tumor necrosis factor (TNF)-α.

Testosterone and its derivatives, such as oxandrolone,38 have been studied in patients with AIDS, neuromuscular disorders, and alcoholic cirrhosis. A recent review of oxandrolone concluded that improvements in body composition and muscle strength are significant in the majority of well-designed trials. Long-term safety (> 1 year) and dosage titration still need to be determined. A prospective open-label study demonstrated a preferential increase of lean body mass in patients with COPD after 2 months of oxandrolone. There was an increase in 6 minute walking distance of more than 65 m in the majority of patients. Eighteen percent of patients withdrew because of side effects. Nandrolone has shown similar benefits in patients with COPD and AIDS, however, it can only be given parenterally and this limits its use.

Other hormones, such as growth hormone, have demonstrated increases in lean body mass in patients with AIDS,41 and may have future applications in the syndrome of frailty in the elderly, but the cost is prohibitive. Ghrelin, a novel growth hormone-releasing peptide isolated from the stomach, may have future therapeutic potential for cachexia of different causes (cardiac or cancer).

Melatonin may inhibit cancer cell growth, improve survival and decrease chemotherapy induced side effects. In two studies with a large number of patients (total = 1640), the frequency of cachexia, asthenia, and thrombocytopenia was significantly lower in patients treated with 20 mg of melatonin at night.44 A randomized pilot trial in patients with cancer of fish oil, melatonin, or their combination did not induce major biochemical changes suggestive of a strong antica cachetic effect, but may have produced a weight-stabilizing effect.45 This well-tolerated drug deserves further placebo-controlled trials.

ω-3 fish oil has few adverse effects and several benefits, including an immunomodulatory action and an antidepressant effect. Despite its
promise, there was no nutritional or symptomatic benefit in two randomized double-blinded controlled trials of advanced cancer patients. \(^47,48\)

- **β-Antagonists and agonists.** The possible role of the sympathetic nervous system in cardiac cachexia was illustrated by a study\(^49\) that measured body weight, plasma norepinephrine, leptin, and insulin in both cachectic and noncachectic chronic heart failure patients. After 6 months of \(β\)-blocker therapy, patients with baseline cachexia demonstrated significantly greater weight gain, increase in leptin levels, and decrease in norepinephrine levels compared to noncachectic patients. The \(β\)-agonist Clenbuterol has an anabolic effect in normal and wasted muscles of animals. A single double-blinded placebo controlled trial\(^50\) of healthy postoperative orthopedic patients demonstrated increased muscle strength in the group treated with clenbuterol.

- **Immunologic.** A review\(^51\) of six clinical trials of various monoclonal antibodies to IL-6 in the treatment of cancer showed that the therapy was well tolerated and decreased the cancer-related symptoms of cachexia, pain, and fever. In most patients C-reactive protein levels decreased below detectable limits. A recent trial\(^52\) of a low-cost oral therapeutic HIV vaccine (V1) in patients with AIDS prolonged survival and increased body mass.

- **Psychotropics.** Antidepressants, such as mirtazapine, and atypical antipsychotics, such as olanzapine, may be useful for the management of anorexia, nausea, and other symptoms in patients with cancer.\(^53\) Tricyclics, such as amitriptylline, may improve appetite but unfortunately have side effects, especially in the elderly.

- **Nonpharmacologic treatment**

  - **Nutritional support and counseling.** Those patients with a predominant starvation component resulting from obstructive gastrointestinal tumors or painful mucositis as a result of head and neck cancer treatment may benefit from nutritional interventions.

    Artificial nutrition via the enteral or parenteral routes is inappropriate for most patients with advanced cancer and may hinder the transition to hospice. A meta-analysis\(^54\) of total parenteral nutrition (TPN) in patients with cancer undergoing chemotherapy showed decreased survival and increased susceptibility to infection. A review of 70 prospective randomized trials of enteral and parenteral nutrition in cancer patients\(^55\) concluded that if there is any therapeutic benefit it is small and confined to a small subset of patients. In rare cases, home TPN can be associated with long-term survival. A retrospective single institution study of home TPN\(^56\) identified 16 patients with cancer over a 20-year period who survived a year or longer. Most of the tumors were carcinoid and quality of life data were not assessed. One recent randomized prospective study\(^57\) of patients with primarily gastrointestinal tumors suggested a trend toward increased survival in patients who received TPN.

- **Counseling.** Compassionate communication is required to address the benefits and burdens of nutrition and to reframe the condition from that of “starving to death” to the more complex one of irreversible (usually) metabolic abnormalities. The psychological component is also important to consider, because eating meals together is important for social integration. Families of patients who are able to eat should be advised that frequent small meals may be more tolerable than three large meals daily. Nutritional counseling has been reported to improve nutritional intake in patients undergoing chemotherapy but not to influence symptom distress or survival.\(^58\) In patients with advanced cancer, this increased nutritional intake may last for only a few weeks.\(^59\) Unfortunately, there has been only limited research on the value of nutritional counseling in palliative care.

**FATIGUE**

Fatigue is one of the most common symptoms encountered in palliative care patients.\(^60,61\) It has been ranked as the longest lasting and most disruptive of symptoms,\(^62\) having the greatest impact on quality-of-life parameters.\(^63\) Fatigue, similar to other symptoms, is a subjective sensation, which manifests with varying dimensions of impaired physical, cognitive, and affective functioning.\(^64\) The physical dimension is usually described as a perception of muscle weakness or decreased energy. The cognitive and affective dimensions include difficulty in concentrating or maintaining attention and lack of motivation or interest in activities.
Frequency rates as high as 96% for fatigue have been reported in association with chemotherapy and radiotherapy, and severe fatigue is almost universal in patients receiving biological response modifiers, such as interferon-α and IL-2. In cancer survivors, fatigue has also been reported as a disruptive symptom months or years after cancer treatment ends. A qualitative study of patients with severe heart failure revealed difficulties with walking and extreme fatigue similar to that of patients living with advanced cancer. In a study of 427 ambulatory patients with AIDS, fatigue was found to be present in 54%, and its presence correlated strongly with the number of AIDS-related physical symptoms, anemia and pain. The patients with fatigue were also observed to have relatively poorer physical functioning and quality of life and greater psychological distress than those with no fatigue.

**MECHANISMS**

Multiple etiological factors may coexist and be interrelated. The common contributors to fatigue in advanced cancer include the tumor, the treatments and the proinflammatory cytokines produced (interleukin-1, IL-6, and TNF-α). Cytokines are the likely mediators of anemia, fever, pain, cachexia, and depression. Comorbidities such as congestive heart failure, kidney, and liver failure exacerbate fatigue as do electrolyte endocrine and mood disorders. These factors are shown in Figure 2.

**ASSESSMENT**

Fatigue is assessed much like any other symptom, namely by characterizing the severity, temporal features (onset, course, duration, and daily pattern), exacerbating and relieving factors, associated distress, and impact on daily life, while searching for contributing factors. Additional information is obtained from the history and physical examination and laboratory data. In palliative care practice, patients present with multiple symptoms, which can be simultaneously assessed by the ESAS. The presence of other symptoms such as pain, sleep, depression, and anxiety, are strongly correlated with fatigue.

A more rigorous method, used for research purposes and validated for internal consistency, Functional Assessment of Cancer Therapy-Fatigue Subscale (FACT-F). The Brief Fatigue Inventory (BFI) has also been used and validated as a measure of fatigue in patients with cancer, as has the Memorial Symptom Assessment Scale-Short Form (MSAS-SF). A study of patient re-
responses to BFI, FACT-F, and the lack of energy item yielded similar information for assessing fatigue.\textsuperscript{77}

**MANAGEMENT**

Figure 3 shows an approach to management of fatigue and is discussed below.

*Specific measures*

Anemia is frequent in patients with cancer and may be secondary to bleeding, treatment-related myelosuppression, chronic disease, and malnutrition. Severe anemia (hemoglobin < 8 g/dL) is known to cause profound fatigue; however, a higher hemoglobin may also be associated with fatigue. Using a hemoglobin value of 12 g/dL or less to define anemia, anemic cancer patients requiring chemotherapy were found to have significantly higher levels of fatigue and impaired physical and functional well-being.\textsuperscript{78} There is a clear relationship between anemia and fatigue in patients with cancer receiving chemotherapy,\textsuperscript{79} and treatment of these patients with red blood cell transfusion and/or erythropoetin alpha\textsuperscript{80} has shown to im-

![Fatigue management diagram](image-url)
prove quality of life and energy. Although therapy with erythropoietic agents is relatively safe, the disadvantages include the cost and the delay of 4–8 weeks before an increase of 1–2 g/dL and symptom improvement occurs. Recent data suggest that erythropoietin leads to an increase risk of deep venous thrombosis and may, in certain populations, increase mortality. Moreover, data supporting erythropoetin’s usefulness in patients not on chemotherapy are less clear. In a recent retrospective study of 147 patients with cancer receiving palliative care, anemia was not found to be independently associated with fatigue. Because the number and severity of other comorbid conditions increase with advancement of disease, the relative contribution of anemia to fatigue likely decreases progressively.

**Infection.** Fatigue is frequently associated with infection. It may predate the episode of infection and may outlast the infection by weeks or months. Anxiety, depression, or other mood disturbances are common in patients with cancer. There is an association between depression and fatigue in patients with cancer; however, a causal relationship has not been established. Hypogonadism may also contribute to fatigue. Much of the research on the role of hypogonadism in fatigue has been done on HIV-positive men. Testosterone deficiency is associated with loss of muscle mass, fatigue, reduced libido, and anemia. In patients with HIV with testosterone deficiency, treatment with androgenic anabolic steroids, including testosterone and its derivatives, has been found to increase muscle mass, energy levels, and libido. A randomized 10-week trial of 47 patients with COPD with testosterone deficiency showed that testosterone plus resistance training had additive benefits. Both lean body mass and leg muscle strength increased significantly. Recently published studies have found a high prevalence of hypogonadism in patients with cancer and in patients receiving high doses of opioids. In both these studies, the presence of hypogonadism was associated with fatigue. Therapeutic trials of androgen replacement therapy in these patients for fatigue management are currently in progress.

**Pharmacologic**

Medications such as MA and dexamethasone may alleviate some of the symptoms of fatigue in patients with advanced cancer. Corticosteroids have been shown to decrease fatigue via unknown mechanisms. The duration of benefit is between 2–4 weeks, and treatment may be suitable for patients with a short life expectancy. Prolonged use may induce myopathy and infection, thereby further contributing to fatigue. The usual starting dose in most studies is prednisone 20–40 mg per day or its equivalent.

Psychostimulant medications have been shown in studies to ameliorate fatigue in patients with AIDS and multiple sclerosis. In a randomized double-blinded placebo-controlled trial of ambulatory patients with HIV, two psychostimulants—pemoline and methylphenidate—were shown to improve fatigue scores and quality of life. In patients with cancer, the most commonly used psychostimulant is methylphenidate. Dextroamphetamine, pemoline, and modafinil have also been used, although there have been no controlled comparisons of any of these drugs. Methylphenidate has been used in cancer patients to treat opioid induced somnolence, reduce pain intensity, treat depression, and improve cognition. Preliminary evidence suggests that psychostimulants may have a role in fatigue management in patients with cancer. Clinical trials are in progress. Modafinil, which is licensed for treatment of narcolepsy, is a novel psychostimulant that has been shown to be effective for management of fatigue in multiple sclerosis. Further research is warranted to evaluate its role in fatigue management in advanced chronic disease.

Donepezil, a centrally acting acetylcholinesterase (AChE) inhibitor approved for use in Alzheimer’s disease, may have a role in some patients with fatigue. Preliminary studies in patients with cancer have suggested at least short-term benefit in treating opioid-related sedation as well as improvement in fatigue scores. Randomized controlled trials are currently in progress.

**Nonpharmacologic approaches**

A multidisciplinary approach to management benefits patients with advanced cancer and other disease such as CHF.

Patients with heart failure have a wide array of options should standard medical therapy (diuretics, angiotensin-converting enzyme [ACE]-inhibitors, beta blockers, aldosterone antagonists,
digoxin) fail to improve fatigue and functional capacity. However, more invasive emerging therapies, such as ventricular assist devices or resynchronization pacing should be carefully discussed with the primary team before implementation, because of their considerable impact on complexity of care and hospital discharge.

*Patient education.* Patients with symptoms of fatigue need to be counseled about the nature of symptoms, likely etiology of their fatigue, options for management, and the expected outcome. This will help patients and their families set realistic expectations. As the disease progresses, patients will need to adapt to progressive limitations in physical function and activity. Patient preferences for information and willingness to participate in exercise and other treatment options should be ascertained.

*Exercise programs.* In patients with cancer, muscle abnormalities have been found even when lean body mass is constant and caloric intake normal. Excessive amounts of lactate have been found in tumor-free muscle tissues and it is unclear whether lactate is part of the pathogenic mechanism or consequent to it. Tumor-free muscle from tumor-bearing animals show alterations in the activity of various enzymes, distribution of isoenzymes, and synthesis and breakdown of myofibrillar and sarcoplasmic proteins. Patients with breast cancer who underwent electrical stimulation of the abductor pollicis muscle via the ulnar nerve were found to have impaired maximal strength, decreased relaxation velocity, and increased fatigue compared to normal controls. In addition, medications such as corticosteroids and cyclosporine may contribute to myopathy. Deconditioning resulting from inactivity and prolonged bed rest results in loss of muscle mass and reduced cardiac output. This in turn decreases endurance and activities of daily living. There is good evidence to support the effectiveness of exercise in patients with fatigue. Exercise improves fatigue through an adaptive cardiorespiratory response, maintenance of muscle mass, improvement in mood, and quality of sleep. Several studies have shown that endurance exercise training improves fatigue and physical performance in patients with cancer undergoing chemotherapy or in those who have undergone bone marrow or stem cell transplantation. Patients with multiple sclerosis who underwent an 8-week progressive resistance training program reported decreased fatigue and disability. There are also similarities between COPD and CHF with regard to muscle dysfunction and the impact of exercise.

Although there is abundance of data to support exercise, selection of the most appropriate program for patients with various types of advanced disease and different levels of performance status are not well defined. Any exercise program should be initiated gradually.

*Psychosocial interventions.* Patients should be counseled about stress management and methods to deal with depression and anxiety, which are commonly associated with fatigue. Clinical studies testing interventions to reduce stress and increase psychosocial support in cancer patients have shown reduction in fatigue levels, although in many of these studies fatigue was a secondary endpoint.

*Nutrition and hydration.* Patients may have decreased oral intake due to a variety of causes related to their illness or treatment. Referral to a nutritionist for dietary planning may be indicated if decreased intake is judged to be one of the causes of fatigue.

*Future treatment approaches*

Several promising approaches to fatigue management have been identified. Cytokine antagonists may be exploitable in combating the components of cancer-related fatigue and may also inhibit tumor growth. Pentoxifylline and bradykinin antagonists inhibit the release of cytokines, while others, such as COX-2 inhibitors, nonselective COX inhibitors, α-melanocyte-stimulating hormone, and monoclonal antibodies inhibit cytokine action. Thalidomide has been shown to improve the sensation of well-being in patients with cancer cachexia, and may also be helpful in cancer-related fatigue. Other potential treatment approaches that warrant research include human growth hormone, and L-carnitine supplementation.

REFERENCES


SYMPTOM CONTROL: CACHEXIA, ANOREXIA, FATIGUE

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