Modern Management of the Cancer Anorexia–Cachexia Syndrome

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The cancer anorexia–cachexia syndrome is common, occurring in 80% of patients with advanced-stage cancer, and it is one of the most frequent causes of death in patients with cancer. It is a complex problem involving abnormalities in protein, carbohydrate, and fat metabolism. Tumors have both direct and indirect effects that result in anorexia and weight loss. The disease burden does not necessarily correlate with the degree of cachexia. In addition to the physical manifestations, the resulting abnormalities have a significant psychologic effect on patients and their families. Although there is no treatment to reverse the process, pharmacologic and nonpharmacologic measures can enhance food intake and improve quality of life.

Introduction

The cancer anorexia–cachexia syndrome (CACS) is complex and incompletely understood. It increases with advancing disease and is one of the most common causes of death in patients with cancer [1,2•,3]. Anorexia is defined as the lack of desire to consume food. Cachexia is the wasting of body tissue, both fat and lean mass, out of proportion to the degree of anorexia. The normal process of preferential fat loss in response to starvation is not seen in these patients. Supplemental feeding by parenteral or oral routes does not result in reversal of the weight loss or of the metabolic abnormalities [4].

Pathophysiology and Assessment

Tumors produce both direct and indirect metabolic abnormalities that cause anorexia and weight loss which is mediated via tumor products and immune system alteration of cytokine production. These abnormalities centrally and peripherally promote lipolysis, protein loss, and anorexia, resulting in cachexia (Table 1). Because disease burden does not correlate with cachexia, patients with small tumors may have cachexia, whereas others with significant disease have minimal weight loss.

It is difficult to separate the symptom (anorexia) from the sign (cachexia) in the dynamic process leading to CACS. This process represents a continuum that often begins with anorexia even before the patient is diagnosed with cancer and ends with death accompanied by profound cachexia. In clinical assessment and treatment, it is important to view anorexia and cachexia separately, as it is often possible to stimulate appetite without promoting weight gain or increasing survival. To deny patients improved appetite and/or food intake because it will not provide physiologic improvement ignores the very important benefit of symptom control to quality of life.

Anorexia

Many nutritional challenges result in anorexia associated with cancer and its treatment. These include chemotherapy and other drugs, nausea and vomiting, malabsorption, gastrointestinal dysmotility, dry mouth, taste change, food aversion, pain, depression, fatigue, and social isolation [1]. It is probably rare for patients with anorexia to have only one specific symptom that, when controlled, alleviates the anorexia. Each specific problem should be evaluated and treated appropriately.

Cachexia

In the clinical setting, recording of weight and assessment by routine physical examination are sufficient. However, in a research setting, or if body compartment assessment is desired, two methods are common: 1) anthropometrics, or measures of skin-fold thickness that determine body fat content by a formula incorporating the measurement, weight, and height; and 2) bioimpedance, involving two sets of electrodes to measure impedance and determine lean body mass and fat content by a formula incorporating weight and height [5•]. Both approaches have been developed and validated on healthy individuals, making their accuracy in CACS questionable. Other methods, used primarily in the research setting, include calorie count,

Table 1. Biochemical/Metabolic Abnormalities in Cachexia

Metabolic process	Abnormality
Carbohydrate metabolism	Increased
	Cori cycle activity
	Hepatic gluconeogenesis
	Glucose consumption
	Glucose production
	Glucose intolerance
	Blunted insulin effect
	Decreased
	Skeletal muscle glucose uptake
	Body glycogen mass
Protein	Increased
	Branched-chain amino acid turnover
	Skeletal protein breakdown
	Liver protein synthesis
	Whole-body protein synthesis
	Decreased
	Muscle mass
	Skeletal protein synthesis
	Nitrogen balance
	Skeletal muscle amino acid uptake
	Changes in circulating amino acid pattern
Lipid	Increased
	Lipolysis
	Hyperlipidemia
	Hypertriglyceridemia
	Decreased
	Total body lipid
	Lipoprotein lipase activity
	Fat synthesis

densitometry, resting energy expenditure, dual-energy x-ray absorptiometry (DEXA), total body potassium, and isotope dilution total body water measurement.

Pharmacologic Treatment and Appetite Stimulants

Pharmacologic treatments and appetite stimulants are summarized in Tables 2 and 3 and described in the following sections.

Dronabinol

Dronabinol (delta-9-tetrahydrocannabinol) is a synthetic cannabinoid, a class of naturally occurring substances derived from the *Cannabis sativa* plant and used for centuries for its medicinal properties. Cannabis was widely used in medicine for a multitude of ailments from asthma to syphilis, but primarily for pain. In the early 20th century, it fell out of favor due to its unpredictable qualities and was replaced by drugs with greater efficacy.

After oral administration of dronabinol, time to peak concentration is 2 to 4 hours, with a variable duration of action: 4 to 6 hours for psychoactive effects, and 24 hours for appetite effects. Two studies have evaluated the appetite-stimulating effects of oral dronabinol in advanced cancer-associated anorexia [6,7]. In nine hospitalized patients, three doses were evaluated to determine weight gain, anti-emetic utility, and toxicity. The lowest dose, 0.1 to 0.12 mg/kg four times daily, was the only one tolerated without dose-limiting psychotomimetic effects. Significant weight gain was seen with dronabinol, and continued loss with placebo [6]. In another study, 13 of 18 evaluable patients had improved appetite with dronabinol, 2.5 mg three times daily 1 hour after meals (those over 60 years were started at twice-daily dosing and increased after 2 days if the drug was well tolerated) [7]. Four developed psychotomimetic side effects, but appetite response was not dependent upon the euphoria associated with the drug, as noted in some anti-emetic studies. The low dose and timing seem important in preventing the significant side effects seen in other studies. Dronabinol has also been found to stimulate appetite and weight gain in AIDS-related anorexia and wasting [8].

Current status

Doses of dronabinol starting at 2.5 mg, three times daily, are tolerable and improve appetite in cancer anorexia. Elderly patients should be started at a lower dose and titrated up if that dose is tolerated. Once-daily dosing has not been studied but may be useful in advanced cancer. The drug could be given at bedtime to avoid some psychotomimetic effects and perhaps still produce appetite stimulation for 24 hours.

Marijuana

Recently, marijuana has been advocated for medicinal use. Smoked cannabis preparations have not been evaluated for their appetite-stimulating properties in cancer patients. There are over 400 chemicals in marijuana; more than 60 are cannabinoids. Delta-9-tetrahydrocannabinol (THC) is the principle psychoactive component. The other cannabinoids are delta-8-THC, cannabinol, and cannabidiol, comprising 1% to 2% of the total concentration. Because of the large number of substances and multiple cannabinoids in marijuana, these different substances may work synergistically, additively, or possibly even antagonistically when they are ingested together in a smoked marijuana preparation [9].

Current status

THC plasma levels from smoked marijuana depend on dose, overall duration of ingestion (number of fractions/

Table 2. Assessment of Anorexia

Identifiable cause	Possible treatment
GI dysmotility (early satiety)	Prokinetic agent
Constipation/bowel obstruction	Laxative regime
Nausea/vomiting	Anti-emetic, prokinetic
Depression	Antidepressant
Dry mouth	Sour/bitter lozenges, artificial saliva, stimulation of saliva production (*ie*, pickles, sports gum)
Food aversion	Biofeedback, reconditioning exercises, avoidance, dietary modification
Inability to take oral nourishment	Enteral/parenteral feedings

Table 3. Useful Appetite Stimulants

Agent	Starting dose	Continuation
Cannabinoids		
Dronabinol	2.5 PO three times daily after meals	Escalate as tolerated to 5 mg three times daily
Corticosteroids		
Dexamethasone	4 mg PO daily after food	Escalate to 8 mg twice daily
Prokinetic agents		
Metoclopramide	10 mg PO four times daily 30 min before meals and at bedtime	—
Progestational agents		
Megestrol acetate	80 mg PO twice daily after meals	Escalate to 200 mg PO four times daily, as tolerated

PO—oral.

unit of time), inhalation duration, volume inhaled, breath-holding after inhalation, and the individual's preference for effect, making it difficult to prescribe accurately. Tobacco and marijuana smoke are quite similar, except for the nicotine in tobacco and the cannabinoids in marijuana [9], making marijuana potentially harmful in chronic use and in patients with lung disease. At this time, marijuana cannot be considered a useful treatment for CACS [10••].

Glucocorticoids

Glucocorticoids (GCs) play a major role in the treatment of cancer [11,12]. Several controlled studies have evaluated their appetite-stimulating properties. In one study, 116 patients with advanced gastrointestinal malignancies were randomized to placebo; oral dexamethasone, 0.75 mg four times daily; or dexamethasone, 1.5 mg four times daily. At 2-week follow-up, appetite in the dexamethasone group improved significantly more than in the placebo group (57% vs 44%), and strength improved, favoring the dexamethasone group (26% vs 15%). Weight gain and performance status did not change, and improvement was not maintained at the same level at 4-week follow-up. The dose was not a determinant of response [13]. In another study, dexamethasone, 0.75 mg four times daily, had effects that were comparable with those of megestrol acetate, 800 mg daily, for weight gain and appetite stimulation. However, the side effect profile was different [14].

In 58 patients with anorexia, prednisolone, 30 mg daily, slowed appetite loss more than placebo (two of 17 vs 11 of 17, $P<0.02$) [15]. No treatment side effects were observed. Prednisolone was compared with placebo in 41 patients with advanced cancer and anorexia or weight loss [16]. In a double blind with in-patient crossover trial, participants were randomized to prednisolone, 15 mg daily, for 2 weeks, and placebo for 2 weeks. Appetite and sense of well-being were statistically better with prednisolone than with placebo. However, no difference was observed in weight gain or food intake. No side effects were reported. These results may have been affected by the low dose.

In another trial comparing oral methylprednisolone with placebo, 31 patients received methylprednisolone, 32 mg daily, and then placebo [17]. Statistically significant improvement was seen in appetite (77% vs 10%) and food consumption (65% vs 50%) with methylprednisolone, compared with placebo. There was no improvement in nutritional status, measured by body weight, tricep skin-fold thickness, arm muscular circumference, and albumin. Side effects were minimal, with two patients developing Cushingoid facies, two developing anxiety, and one experiencing mild fluid retention. No side effects required discontinuation of the medication.

The side effect profile of GCs is significant [18]. Dexamethasone treatment for longer than 3 weeks has been associated with toxicity in 75% of patients, whereas shorter duration decreased this toxicity to 5% [19]. Patients with total cumulative doses over 400 mg had 75% toxicity, versus 13% for lower doses. The risk of peptic ulceration is a concern, particularly in those with other risk factors

[20,21]. Although controversial, prophylactic histamine-2 receptor antagonists are prudent (famotidine, 20 mg orally at night) when commencing long-term GCs.

The effect of GCs on mental status can be detrimental or advantageous [22], and their use should be monitored closely. Major mental disturbances are uncommon (5%), but mild complications are frequent (3% to 50%). Affective disorders and global cognitive impairment are most common. This is particularly important in advanced cancer, where mild baseline mental status changes may exist. Psychiatric disturbances usually occur within the first 2 weeks of treatment and are reversible with dose reduction or discontinuation.

Current status

There is no indication that one GC is superior in its appetite stimulating ability to any other; choice of agent should be based on cost, degree of mineralocorticoid activity, side effects, potential drug interactions, and ease of administration. Dexamethasone may be better for nerve compression treatment and have a more favorable side effect profile than prednisolone [18]. When prescribing GCs for anorexia, the physician should begin with an initial 1-week trial and continue treatment if there is a subjective or objective response. The entire daily dose should be given in the morning with breakfast or on a divided breakfast and lunch schedule after food. This strategy decreases hypothalamic-pituitary-adrenal (HPA) axis suppression and the insomnia associated with later-day use. Intermediate-acting GCs (*ie*, prednisone, prednisolone, or methylprednisolone) cause less HPA axis suppression than a long-acting drug (dexamethasone); however, one study suggests that dexamethasone may have a better side effect profile, compared with prednisolone.

Megestrol acetate

Progestational agents have been available since the late 1940s and routinely used in the palliative treatment of breast cancer. Studies have documented their appetite-stimulating effect in both hormonally and non-hormonally sensitive cancers [23]. A dose-ranging study showed improvement as the dose increased from 160 mg/d to 800 mg/d. Above 800 mg, there was no greater efficacy, and side effects became intolerable [24]. However, benefit has been reported with a considerably lower dose of 40 mg twice daily [25].

In a recent placebo-controlled study (*N*=33), patients with advanced cancer were given 160 mg of megestrol acetate (MA) twice daily. Appetite improved significantly within 7 days in the megestrol group compared with the placebo group. Unfortunately, no significant difference was seen in weight gain, subjective assessment of food intake, mood, or quality of life [26]. Another study (*N*=41) compared MA, 160 mg three times daily, and placebo to the same dose of MA and ibuprofen, 400 mg three times daily [27••]. Patients in the megestrol/placebo group lost weight (median, 2.8 kg), whereas those in the megestrol/study period. The megestrol/ibuprofen group also showed an improvement in quality of life.

Side effects can prohibit higher doses, particularly in patients with poor performance status. At lower doses, MA is usually well tolerated, with mild side effects, rarely requiring drug withdrawal. The most common side effect is fluid weight gain; others include flushing, vaginal bleeding, impotence, and deep vein thrombosis. MA should not be used in thromboembolic/thrombotic or heart disease, or in patients at risk for serious complications due to fluid retention. Possible MA withdrawal syndrome has been reported [28]. In a patient with AIDs treated with 80 mg four times daily, concern over extreme appetite increase prompted a dose reduction to 80 mg twice daily, but weight gain continued. Subsequent abrupt discontinuation was associated with depression, rapid appetite decline, and energy loss lasting 10 to 14 days. Laboratory evidence of pituitary-adrenal axis suppression indicates that MA may result in adrenal insufficiency upon drug withdrawal [29,30•].

Current Status

Megestrol acetate has been evaluated in many clinical trials and shown to be very useful for appetite stimulation in cancer patients. As with many appetite-stimulating agents, the significant weight gain is not in lean body mass. As noted previously, MA should not be used in thromboembolic/thrombotic or heart disease, or in patients who are at risk for serious complications due to fluid retention because many studies have reported fluid weight gain.

Metoclopramide

Cancer is associated with autonomic nervous system dysfunction (Nelson K, *et al*., Submitted manuscript). Commonly, gastrointestinal (GI) abnormalities such as delayed gastric emptying cause early satiety. Upper gastrointestinal (UGI) dysmotility and its effect on appetite in advanced cancer have been reported [31]. Early satiety ranks in the top ten symptoms for prevalence and severity [2], occurring in 43% of an advanced cancer population. The mainstay of treatment in early satiety and anorexia possibly due to UGI dysmotility is a prokinetic agent. These drugs act to increase the myoelectric contractions of the stomach by sensitization of smooth muscle to acetylcholine. They accelerate both liquid and solid emptying.

Current status

Metoclopramide is appropriate for early satiety and anorexia due to gastric stasis. A dose of 10 mg four times daily has been reported to stimulate appetite in cancer patients with early satiety [32]. Side effects, caused by the central effects of antidopaminergic properties, are more common in young women.

Oxandrolone

Oxandrolone is a synthetic oral anabolic steroid. Most anabolic agents are derived from or closely related to test-

guinea pig muscle was reported in 1938. Anabolic steroids (AS) were first developed in the 1950s to provide the anabolic advantages of testosterone with less androgenic activity. However, the dissociation of these effects is incomplete and variable.

Oxandrolone can be given orally with rapid and complete absorption and relatively little hepatic metabolism. It has low androgenic effects such as acne and hirsutism. Studies for cachexia have been done in the AIDs population. In one study, in which oxandrolone, 5 mg/d, was compared with 15 mg/d and placebo, those in the placebo group had a mean weight decrease of 2.5 pounds, whereas the 5-mg group maintained their weight, and the 15-mg group gained 1.5 pounds over 16 weeks. In addition, oxandrolone, 15 mg/d, promoted subjective improvement in appetite, strength, and physical activity [33]. In another open study of 20-mg daily dosage in AIDS wasting, statistically significant increased body weight, body cell mass, fat, and intracellular water were observed, along with decreased extracellular fluid at 90 days, measured by bioimpedance in 17 participants. The treatment was not associated with any adverse events.

Current status

Studies of anabolic agents in oncology practice are few, old, and often contradictory regarding efficacy. Most indicate that the positive nitrogen balance is short-lived and that AS weight gain seems to depend on adequate nutritional intake and physical activity. This may limit the usefulness of these agents in cancer; they are now used primarily in the research setting.

Thalidomide

Endogenous cytokines are known to cause catabolic effects in a variety of illnesses. To inhibit their production or effect would seem advantageous in preventing cachexia. Thalidomide inhibits tumor necrosis factor, a cytokine thought to be involved in CACS. Its nutritional efficacy was studied in AIDs wasting in 28 patients, who received thalidomide, 100 mg four times daily, or placebo for 12 weeks [34]. Therapeutic failure occurred in 10 of 14 patients from the placebo group and in three of 14 from the thalidomide group. Weight gain occurred in one patient on placebo and eight on thalidomide. In another study of AIDs weight loss, 300 mg of thalidomide produced an average weight gain of 4.5% of usual body weight, compared with only 0.9% in the placebo group [35]. Side effects of thalidomide include peripheral neuropathy, sedation, skin rashes, constipation, and neutropenia.

Current status

Thalidomide was initially developed as a sedative and anti-inflammatory agent. It was widely used internationally in pregnant women but never sold in the United States because of safety concerns. In 1961 it was withdrawn from the international market when its teratogenic effect (phocomelia) was recognized [36]. It is now prescribed for new indications, avoiding susceptible populations (women of childbearing potential and their spouses, and those with peripheral neuropathy). The US Food and Drug Administration (FDA) approved thalidomide for AIDs-associated anorexia in 1995 and subsequently granted permission to study its use in cancer anorexia–cachexia. The usual starting dose is 50 mg at bedtime. Use of thalidomide in CACS is limited to clinical trials and strictly monitored individual patients.

Patenteral/enteral nutrition

Indications for parenteral nutrition in patients with cancer are limited based on available evidence (Table 4) [37]. In many studies a negative effect, such as decreased survival or increased infection rate, was actually reported [38]. Although efficacy has been disappointing, the studies have often been poorly designed and thus cannot reveal a possible subpopulation, albeit small, that may benefit from nutritional support. Studies of enteral nutrition are few, but this method of replenishment may be associated with fewer complications when the GI tract is functionally intact. Nevertheless, enteral nutrition is not free of risk.

Nonpharmacologic Management

Nonpharmacologic measures are an important aspect of anorexia management in patients with cancer. Some measures act directly to improve appetite and intake, whereas others act indirectly by improving quality of life. Before considering appetite stimulants, the physician should make an "appetite review" consisting of the following steps: 1) evaluation of current food intake to assure that calorie count is sufficient, if possible; 2) discontinuing offending agents such as distasteful food supplements, unnecessary medications, and noxious food; 3) evaluation of food preparation methods and advice on enhancing intake; and 4) finding foods that taste good to the patient and encouraging these.

In addition, it is important to treat other symptoms that may inhibit proper food intake such as pain, nausea, odynophagia, dysphagia, or constipation. Whenever possible, a consultation with an experienced and qualified nutritionist should be arranged. Finally, appropriate complementary and alternative (CAM) techniques can be considered. Traditional medical professionals are often uninformed about such techniques. This lack of knowledge may compromise their ability to provide high-quality, comprehensive symptom management, whether through lack of awareness of potentially useful techniques or potentially dangerous ones [39••,40•].

Conclusions

Cancer-associated anorexia and cachexia are serious problems in the cancer population, affecting the physical, psychosocial, and spiritual domains. The current literature does not provide effective treatments to modify

Table 4. Indications and Complications for Enteral/ Parenteral Feeding

Indications
Patients in well-designed clinical trials evaluating nutritional support in cancer
Anorectic/cachectic patients with therapy-responsive tumor who are beginning treatment
Patients with hypophagia due to obstruction with potentially therapy-responsive tumor
Patients with complications from treatment for a responsive malignancy
Patients with surgically resectable tumors receiving preoperative treatment for malnutrition
Complications
Enteral
Nausea, vomiting
Abdominal pain
Diarrhea
Aspiration pneumonia
Parenteral
Infection—systemic, IV lines
Thrombosis
Metabolic abnormalities

IV—intravenous.

cachexia in any meaningful way; however, appetite stimulants help to alleviate anorexia and may stabilize weight loss for a time. Based on available studies, dronabinol, megestrol acetate, metoclopramide, and glucocorticoids are useful agents. Newer agents under investigation may help patients with CACS, but, for now, treatment decisions should be based on the clinical situation. Although anorexia and cachexia are a common part of the natural history of cancer, patients should be asked about these problems and managed appropriately.

References and Recommended Reading

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A comprehensive resource on all forms of complementary and alternative medicine with many links to useful sites. It is worth visiting on a regular basis to keep abreast of new developments in the field.

40.• National Center for Complementary and Alternative Medicine. Accessed at http://nccam.nih.gov./

This NIH website provides viewers with a complete listing and categorization of the currently reported complementary and alternative techniques. Most physicians would be surprised at the sheer number of methods classified as complementary or alternative. This site deserves attention, particularly by physicians, as it helps to understand the full spectrum of treatments patients are using or considering.