Current and Future Care of Patients with the Cancer Anorexia-Cachexia Syndrome

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OVERVIEW

Many important advances have occurred in the field of cancer cachexia over the past decade, including progress in understanding the mechanisms of the cancer anorexia-cachexia syndrome (CACS) and the development of promising pharmacologic and supportive care interventions. However, no approved agents for cancer cachexia currently exist, emphasizing the unmet need for an effective pharmacologic therapy. This article reviews the key elements of CACS assessment in daily practice, the contribution of nutritional impact symptoms (NIS), the evidence for current pharmacologic options, and promising anticachexia agents in perclinical and clinical trials. It also proposes a model for multimodality therapy and highlights issues pertinent to CACS in patients with pancreatic, gastric, and esophageal cancer.

Many important advances have occurred in the field of cancer cachexia over the past decade, including progress in understanding the mechanisms of CACS and the development of promising pharmacologic and supportive care interventions. However, no approved agents for cancer cachexia currently exist, emphasizing the unmet need for an effective pharmacologic therapy. Patients with CACS may have different priorities; for many, preserving lean body mass (LBM) and function may be important, while for others, maintaining appetite to enjoy meals with their family may be the primary goal. Appetite and weight loss are also associated with important clinical outcomes such as decreased survival, fewer completed cycles of chemotherapy, more treatment side effects, and poorer health-related quality of life.1-3

CACHEXIA AND UPPER GASTROINTESTINAL CANCERS

A study by DeWys4 in 1980, of more than 3,000 patients enrolled in Eastern Cooperative Oncology Group chemotherapy trials, identified the high prevalence of weight loss in cancer and its association with decreased survival. The survival of patients with gastric and pancreatic cancer did not correlate with weight loss (even though 85% of these patients experienced weight loss, and one-third lost more than 10%). Possibly, weight loss may have lost its powerful predictive value in these patients because of their very poor prognosis.5 A subsequent retrospective study found weight loss in pancreatic and gastric cancer at presentation was associated with poorer quality of life and increased chemotherapy toxicity, even at lower doses.6 Outpatients with esophageal or pancreatic cancer have the highest nutritional risk scores, and more than 80% experience anorexia and weight loss even when they have a performance status (PS) of 1.7

ASSESSMENT OF PATIENTS

A consensus definition of cancer cachexia is important for clinical trial design and for identifying patients with the syndrome in clinical practice. Ideally, patients who are at risk should be identified early to provide the greatest opportunity for effective intervention. A delay could result in uncontrolled symptoms, poorer quality of life, and more rapid entry into the refractory stage of cachexia. A recent study of body composition imaging by CT of 368 patients shows 5% or less of patients gained muscle within 90 days of death, suggesting the anabolic opportunity for intervention probably exists early in the disease trajectory.8

Definition

Cancer cachexia is defined as a multifactorial syndrome characterized by ongoing loss of skeletal muscle mass (with or without loss of fat) leading to progressive functional impairment, which cannot be fully reversed by conventional nutritional support.9 Based on the current definition, detection of cancer cachexia centers on involuntary weight loss of more than 5% over 6 months (or 2% when evidence of sarcopenia is present).9,10 Recently, attempts have been made to incorporate anorexia severity, PS, and markers of inflammation, such as C-reactive protein, into staging criteria for the identifica-
tion of precachexia, cachexia, and refractory cachexia. A simple, objective, systemic inflammation–based approach using C-reactive protein and albumin has prognostic value independent of tumor stage, PS, and treatment in a variety of advanced tumors, but it has yet to be incorporated into the screening or staging of cancer cachexia. More research is required to identify simple patient-reported outcomes or biomarkers that could help classify patients into early and late stages of cachexia.

Assessment Tools
A brief standardized assessment that includes NIS such as nausea, depression, and severe pain should be performed on all oncology patients who are at risk for CACS (Fig. 1). Unfortunately, the American Society of Clinical Oncology’s Quality Oncology Practice Initiative does not currently include any specific questions about appetite, and without systematic inquiry, symptoms such as anorexia may not be identified by oncologists, since patients volunteer few symptoms relative to their total symptom experience. The 10-item Edmonton Symptom Assessment Scale (ESAS) has shown a high prevalence of multiple symptoms in ambulatory patients with cancer, similar to the symptom burden reported in palliative care populations. The ESAS assesses symptom severity, including appetite, but does not include other CACS-relevant symptoms such as constipation, early satiety, or dysgeusia. A more comprehensive evaluation requires an additional assessment measure such as the Patient-Generated Subjective Global Assessment (PG-SGA): an American Dietetic Society–endorsed questionnaire that identifies additional reversible factors contributing to poor oral intake. A recently validated brief version, the a-PG-SGA, can be completed in less than 5 minutes and provides additional diagnostic and prognostic value for patients with cancer. Using these simple tools for symptom and nutritional assessment, along with a history of 5% or more weight loss during the past 6 months would identify many patients with CACS.

Role of Body Composition
Because of the high prevalence of obesity in the general population, many patients may have a normal or elevated body mass index even though they report weight loss and experience profound muscle wasting. Body composition assessment by dual-energy x-ray absorptiometry (DEXA) scan or CT scan may identify patients with occult muscle wasting, consistent with sarcopenia. Patients with the combination of sarcopenia and obesity have a worse prognosis and a higher risk of chemotherapy-related adverse effects. The information derived from routine CT images can provide potentially clinically relevant information beyond assessment of tumor size and response.

Several studies using routine CT imaging in patients with pancreatic cancer have demonstrated relationships between body composition, LBM, impaired lung function, and clinical outcomes. For patients entering a palliative care program, sarcopenia in patients who were overweight was an independent adverse prognostic indicator. Another longitudinal study in patients with locally advanced pancreatic cancer showed that baseline obesity and loss of visceral adipose tissue (VAT) were associated with worse survival. In particular, patients with diabetes who have pancreatic cancer experience accelerated VAT loss and reduced survival compared to those patients without diabetes. In patients receiving neoadjuvant chemotherapy for potentially resectable pancreatic cancer, skeletal muscle loss and VAT loss were correlated with disease-free and progression-free survival, respectively. Although quantification of LBM or fat is not yet conducted in daily clinical practice, CT imaging is emerging as a useful measure of body composition and could influence clinical decision making and chemotherapy dosing in future.

Other modalities have been used for body composition analysis, including bioimpedance (BIA), which relies on the different electrical properties of fat and muscle and—although not as accurate as CT imaging or DEXA—is relatively easy to use and nonburdensome for patients. Additional information provided by BIA such as the ratio of resistance and reactance (phase angle) may be useful for prognostication in several tumor types including pancreatic cancer.

CURRENT MANAGEMENT
The clinical assessment and management should focus on nutrition (quantity and composition), symptoms contributing to poor oral intake, weight and body composition, and identification of any reversible metabolic abnormalities (Figs. 2 and 3).

Symptom Management
NIS such as nausea, depression, severe pain, dysgeusia, gastroparesis, and constipation can contribute to decreased caloric intake and weight loss in patients with CACS (Fig. 3). In addition, comorbid metabolic abnormalities such as hypogo-
nadism, thyroid dysfunction, and vitamin B12 and D deficiencies may contribute to fatigue, muscle weakness, and poor appetite. Other causes of weight loss that have a predominant starvation component such as gastrointestinal obstruction should be identified, especially if they are reversible and respond to endoscopic or surgical treatment (e.g., stent placement or endoscopic dilation for esophageal obstruction).

A retrospective study of 151 patients with solid tumors referred to a specialized cachexia clinic found a median of three NIS and five or more NIS in 15% of patients. Early satiety was the most common symptom, and it improved in many
with 10 mg metoclopramide every 4 hours orally. Patients with advanced cancer often have gastroparesis and dyssmotility; metoclopramide enables the stomach to accommodate more food and improves motility.\(^{31,32}\) Although rare, tardive dyskinesia is an irreversible side effect, so the benefits of treatment beyond 3 months should be considered carefully since the duration and total cumulative dose of metoclopramide increase the risk of tardive dyskinesia.

Other NIS can also be effectively managed with readily available inexpensive medications. Constipation, often exacerbated by medications such as opioids and ondansetron may contribute to early satiety and can be effectively managed with laxatives, although few published trials compare bowel regimens.\(^{33}\) Depressed mood may decrease appetite and should be managed with counseling and antidepressants if indicated. Mirtazapine and olanzapine are useful agents for both depression and nausea.\(^{34}\) A small single-arm trial of mirtazapine in nondepressed patients with CACS produced weight gain of 1 kg or greater in about one-quarter of participants within 4 weeks.\(^{35,36}\) There are no consistently effective therapies for dysgeusia; however, a trial of zinc sulfate may be justified\(^{37,38}\) because this supplement has few side effects in comparison to dronabinol, which is also shown to have benefit for chemosensory perception.

**PHARMACOLOGIC INTERVENTIONS**

**Current Agents**

**Progestational agents.** Systematic reviews indicate that megestrol acetate (MA) plays a role in CACS by increasing appetite and body weight compared to placebo.\(^{39-41}\) However, these improved outcomes found in a minority of patients should be weighed against potentially serious side effects and a failure to show better quality of life compared to other interventions.\(^{42}\) In addition, the weight gain MA-induced weight gain may be predominantly fat or fluid, rather than muscle.\(^{43}\)

An updated Cochrane review in 2013\(^{42}\) evaluated 35 trials (23 with cancer), including 928 patients with gastrointestinal or pancreatic cancer. Approximately one in four patients taking MA for cachexia (e.g., to treat cancer or AIDS) had an increase in appetite, while one in 12 experienced weight increase. Safety was evaluated in 3,180 patients. Dyspnea, edema, impotence, and thromboembolic phenomena were more common in patients taking MA, and deaths were increased, especially with higher doses. Since the median treatment duration was 8 weeks and follow-up length was short, the authors suggest adverse events may become even more relevant with prolonged use. Although some earlier studies showed improvement in fatigue as a secondary endpoint,\(^{44,45}\) there are concerns prolonged suppression of gonadal and adrenal function by MA could exacerbate symptoms such as fatigue and poor libido.\(^{46}\) Symptomatic adrenal suppression may be particularly problematic in pediatric patients with cancer, and stress-dose hydrocortisone is suggested for patients with acute illness or undergoing surgery.\(^{47}\)

Because of the increased risk for mortality and thromboembolism, patients should be informed of the potentially serious side effects. MA should be reserved for patients placing a high priority on improved appetite, since MA may have an

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**FIGURE 3. Mechanisms of Anorexia in Cancer**

- **Cancer Cachexia**
- **Hypoadrenalism**
- **Severe pain**
- **Gastroparesis and early satiety**
- **Chronic Nausea**
- **Depression**
- **Dygeusia**
- **Constipation**

**Poor appetite or decreased calorie intake**

- **Hypothyroid**
- **Gastrointestinal obstruction**

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antianabolic effect by decreasing muscle size.\textsuperscript{48} Given that increased mortality is associated with higher doses of MA, it may be prudent to start at lower doses and monitor response. The optimal dose for weight gain is more than 400 mg/day, although improvements in appetite have been reported at 160 mg/day\textsuperscript{4}.

**Corticosteroids.** Although small randomized trials have shown corticosteroids improve symptoms of anorexia and fatigue,\textsuperscript{49,50} only recently have two randomized, placebo-controlled trials confirmed their efficacy. In patients with advanced cancer (predominantly head and neck or gastrointestinal tumors), 4 mg dexamethasone twice daily for 14 days significantly improved fatigue ($p = 0.008$) and anorexia ($p = 0.013$) compared to placebo, with similar adverse events.\textsuperscript{51} Notably, the physical domain of health-related, rather than the psychologic, quality of life improved. A prior positive trial in advanced gastrointestinal cancers had speculated the benefits of corticosteroids were largely caused by mood elevation.\textsuperscript{17} A second recent study compared 7 days of 16 mg methylprednisolone twice daily to placebo and similarly showed improvements in fatigue and anorexia but no difference in the primary outcome of pain intensity.\textsuperscript{52}

Despite improvement in appetite and fatigue in the short term, no studies have demonstrated any benefit on LBM, and prolonged use can cause proximal myopathy.\textsuperscript{53} Although dexamethasone is considered preferable over other corticosteroids because of its lower mineralocorticoid effect, common toxicities include candidiasis, edema, cushingoid changes, depression, and anxiety.\textsuperscript{54} Based on recent placebo-controlled clinical trials and the rapid onset of effect, dexamethasone seems most appropriate for short-term use in patients near the end of life.

**Cannabinoids.** Cannabinoids such as dronabinol and nabilone are approved for chemotherapy-related nausea in patients not responding to conventional antiemetics.\textsuperscript{55} Dronabinol is also approved for treatment of anorexia in patients with AIDS,\textsuperscript{56} but unfortunately, the evidence for any benefit in cancer cachexia is very limited. A multicenter randomized trial of 289 patients with advanced cancer compared the effects of cannabis extract delta-9-tetrahydrocannabinol (2.5 mg twice daily) and placebo on appetite and quality of life.\textsuperscript{57} Consistent with other symptom intervention studies, there was a significant placebo effect and improved appetite in all three groups but no differences between the groups ($p > 0.15$). A lack of intrapatient dose escalation may be considered a limitation; however, the dose was based on an earlier phase II study showing a higher risk of adverse psychotropic effects and dropouts in patients taking higher doses of dronabinol (5 vs. 2.5 mg).\textsuperscript{58}

A multicenter randomized controlled trial (RCT) of 469 patients compared MA and dronabinol combination therapy to either agent alone for appetite stimulation in patients with lung or gastrointestinal cancer.\textsuperscript{59} MA was superior to dronabinol alone, and combination therapy did not provide any additional benefit. Despite the consistently negative results in large trials, a recent single RCT showed dronabinol improved taste and protein consumption in patients with cancer who had dysgeusia.\textsuperscript{60}

**Fish oil or eicosapentanoic acid.** Despite eicosapentanoic acid (EPA) showing initial benefits for CACS and fatigue in patients with pancreatic cancer,\textsuperscript{61} three systematic reviews found insufficient evidence for EPA in the management of cancer cachexia.\textsuperscript{62-64} Although no serious adverse effects were reported, abdominal discomfort, belching, nausea, and diarrhea often affected quality of life. More recently, there is renewed interest in fish oil after two small RCTs showed improved weight and muscle mass in patients with non–small cell lung cancer (NSCLC) at initiation of first-line chemotherapy.\textsuperscript{65,66}

**Thalidomide.** A recent Cochrane review of thalidomide in cancer cachexia found insufficient evidence for clinical practice.\textsuperscript{67} Unfortunately, the review follows a study in patients with esophageal cancer showing no benefit and poor tolerability to thalidomide,\textsuperscript{68} despite earlier trials in pancreatic\textsuperscript{49} and esophageal cancer\textsuperscript{70} that found improvements in LBM and minimal side effects after 4 weeks of 200 mg/day. More recently a phase II trial found improved appetite and minimal side effects with doses of 50 and 100 mg.\textsuperscript{71} More trials are probably warranted; however, other studies of thalidomide have experienced difficulty in patient accrual.\textsuperscript{72}

**New Agents**

Despite a number of promising interventions on the horizon, enobosarm and anamorelin are the only agents completing phase III RCTs.

**Androgens.** Hypogonadism is common in male patients with cancer and is associated with increased symptom burden including fatigue, anorexia, and diminished libido.\textsuperscript{41-45} Although testosterone replacement has improved muscle mass and strength in HIV-positive men,\textsuperscript{46} it has not been studied in large, RCTs for patients with cancer. A preliminary, double-blind, placebo-controlled trial of testosterone replacement in men with advanced cancer who had hypogonadism showed significant improvement in fatigue after 10 weeks ($p = 0.003$) but no effect on appetite or weight.\textsuperscript{47}

Selective androgen receptor modulators theoretically produce greater anabolic effects with fewer side effects such as prostatic hypertrophy. A phase II RCT of enobosarm for patients with advanced cancer who had cachexia found increased LBM and physical function compared to baseline with minimal side effects.\textsuperscript{73} Preliminary results from a phase III placebo-controlled trial showed an increase in LBM ($p = 0.036$) in patients with NSCLC on enobosarm treated with platinum plus taxane.\textsuperscript{74} Physical function as assessed by stair-climb power was not significantly better in patients receiving enobosarm. Final results are awaited.

**Ghrelin and ghrelin mimetics.** Ghrelin, an orexigenic hormone, enhances appetite and food intake in humans. A phase
II RCT of ghrelin in patients with advanced cancer showed improved appetite and decreased fat loss with higher doses; however, its development for CACS is hindered by the subcutaneous mode of administration and daily frequency. Because ghrelin has the potential for increasing insulin-like growth factor 1, which could theoretically cause tumor progression, the initial efficacy and safety from early studies should be confirmed in large RCTs. An oral ghrelin mimetic anamorelin has made the furthest progress toward approval thus far, after early-phase trials showed increased food intake, appetite, and LBM in patients with cancer. In addition, a pooled analysis of two phase II trials confirmed the benefits and few adverse effects of 12-week therapy. An encouraging preliminary report from the multicenter phase III trials suggests muscle mass (p = 0.0001) and appetite are improved in NSCLC.77

Myostatin and proinflammatory cytokine inhibitors. Myostatin is an extracellular cytokine that negatively regulates muscle mass. The results of early-phase clinical trials are awaited following promising animal studies that showed targeting the myostatin pathway reversed muscle wasting, increased grip strength, stimulated appetite, and prolonged survival, independently of tumor progression.78,79

Multimodal therapy for the cancer anorexia-cachexia syndrome. Even though new single agents show potential for improving outcomes, a more effective approach might be simultaneous, multifaceted therapy targeting the different mechanisms contributing to CACS (Fig. 4).81 Several studies have used a combination of pharmacologic agents for CACS.

A progestin in combination with an EPA, L-carnitine, and thalidomide significantly increased appetite, LBM (p = 0.007), and spontaneous physical activity, although there was no placebo arm.82 Beta blockers and insulin have also been used as multimodality therapy in combination with nonsteroidal anti-inflammatories (NSAIDs), showing bene-

**FIGURE 4. A Proposed Model for Management of Cancer Anorexia-Cachexia Syndrome**

Abbreviations: REE, rested energy expenditure; NSAID, nonsteroidal anti-inflammatory.
fits in reducing elevated resting energy expenditure and attenuation of weight loss and also improvements in survival ($p = 0.03$). Although NSAIDs have been combined with other agents and have demonstrated improvement in some clinical outcomes, a systematic review concluded that the risk of side effects and insufficient evidence suggest NSAIDs should be restricted to clinical trials. 85

**CONCLUSION**

Because the causes of muscle wasting and poor caloric intake in patients with CACS are multifactorial, a comprehensive multidimensional approach using pharmacologic and non-pharmacologic interventions is most likely to be effective in reversing or stabilizing weight loss and muscle wasting. Ideally, treatment should be individualized, taking into account the patient’s overall condition, the principal mechanisms of their weight loss, and their goals of care. New anticachexia agents have shown promise in preclinical and early-phase studies, but their efficacy and safety need to be confirmed in larger phase III RCTs. Clearly there is an unmet need for an effective pharmacologic agent, and even though we now have several promising candidates, any specific anticachexia intervention would still need to be incorporated into a multimodality approach.

**Disclosures of Potential Conflicts of Interest**

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