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Cancer Cachexia: Cause, Diagnosis, and Treatment

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Abstract

Patients with cancer frequently experience unintended weight loss due to gastrointestinal (GI) dysfunction caused by the malignancy or treatment of the malignancy. However, others may present with weight loss related to other symptoms not clearly associated with identifiable GI dysfunction such as anorexia and early satiety. Cancer cachexia (CC) is a multifactorial syndrome that is generally characterized by ongoing loss of skeletal muscle mass with or without fat loss, often accompanied by anorexia, weakness, and fatigue. CC is associated with poor tolerance of antitumor treatments, reduced quality of life (QOL), and negative impact on survival. Symptoms associated with CC are thought to be caused in part by tumor-induced changes in host metabolism that result in systemic inflammation and abnormal neurohormonal responses. Unfortunately, there is no single standard treatment for CC. Nutrition consequences of oncologic treatments should be identified early with nutrition screening and assessment. Pharmacologic agents directed at improving appetite and countering metabolic abnormalities that cause inefficient nutrient utilization are currently the foundation for treating CC. Multiple agents have been investigated for their effects on weight, muscle wasting, and QOL. However, few are commercially available for use. Considerations for choosing the most appropriate treatment include effect on appetite, weight, QOL, risk of adverse effects, and cost and availability of the agent. (*Nutr Clin Pract*. 2017;32:599-606)

Keywords

cancer; cachexia; weight loss; appetite stimulants; malnutrition; anabolic agents; corticosteroids; progestational agents; anti-inflammatory agents

Unintentional weight loss has long been associated with a negative impact on multiple outcomes in patients with cancer, including survival and quality of life (QOL).[1] Many patients may present with weight loss related to readily apparent reasons for inadequate nutrient intake such as tumor or treatment-induced abnormalities in gastrointestinal (GI) function or other treatment-related nutrition impact symptoms[2–4] (Table 1). However, multiple investigations have reported weight loss in patients with cancer for no clearly identifiable reason. For some patients, weight loss either occurred or continued despite reported adequate nutrient intake. Frequently, patients with cancer with weight loss also presented with other nutrition and medical abnormalities such as skeletal muscle loss and insulin resistance. Cancer cachexia (CC) is the term that has been applied to this collection of abnormalities associated with weight loss in tumor-bearing patients.[5] For many, inadequate nutrient intake has been associated with decreased appetite, but anorexia is not consistently reported from all patients with cancer with unintentional weight loss.[6] Indeed, there is a remarkably poor correlation between other tumor-associated metabolic abnormalities, weight loss, tumor type, and stage of malignancy.[5,6] A major reason for the lack of consistency in results from investigations of patients with cancer and weight loss is the lack of agreement on the definition of CC.[5–7] A consensus definition has been proposed by Fearon et al[5] in an attempt to standardize identification and treatment of cachectic patients. CC is defined as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutrition support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism.[5] This characterization acknowledges the multifactorial nature of CC and distinguishes the difference in weight loss associated with starvation, which primarily affects fat tissue, from that associated with CC, which targets skeletal muscle and other organ metabolism.[1]

Causes of CC

Unfortunately, no single cause of symptoms associated with CC has been identified.[1,8] Multiple abnormalities in

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Table 1. Identifiable Causes of Inadequate Nutrient Intake in Patients With Cancer.[2–4]

Cause of Inadequate Nutrient Intake	Abnormality Affecting Nutrient Utilization
Nutrition consequences of malignancy	Obstruction/perforation of GI tract Intestinal secretory abnormalities Malabsorption Intestinal dysmotility Fluid/electrolyte abnormalities
Treatment-related nutrition impact symptoms	
Chemotherapy	Anorexia Altered taste Learned food aversion Nausea, vomiting Mucositis, enteritis Malabsorption, diarrhea Ileus
Surgery	Malabsorption, diarrhea Adhesion-induced obstruction Odonophagia/dysphagia Fluid/electrolyte abnormalities Vitamin/mineral abnormalities
Radiation	Anorexia Altered taste Mucositis, enteritis Xerostomia Odonophagia/dysphagia Obstruction Perforation Stricture
Other	Opioid-induced constipation GI tract abnormalities associated with fungal, viral, or bacterial infection Fatigue Tumor-associated or treatment-associated pain Mood disorders (ie, depression)

Adapted with permission from Mattox TW. Treatment of unintentional weight loss in patients with cancer. *Nutr Clin Pract*. 2005; 20:400-410.
GI, gastrointestinal.

protein, fat, and carbohydrate metabolism as well as peripheral hormone and neuropeptide metabolism have been reported primarily in experimental and animal models and, to a lesser extent, investigations of humans that suggest a central role of tumor-induced inflammation.[1,6,8] However, the contribution of cytokine activity to these abnormalities is not conclusive. Although several investigations in animal models have demonstrated the negative effects of tumor necrosis factor α (TNFα), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon γ (IFNγ) on protein, fat, and carbohydrate metabolism as well as appetite regulation, the association between elevated cytokine levels and symptoms of CC is not consistent.[1,6,8] Other metabolic abnormalities thought to contribute to increased resting energy expenditure (REE) reported in some patients with cancer with reduced weight include increased hepatic glucose production, increased lipolysis with increased production of glycerol and free fatty acids, and increased whole-body protein turnover compared with healthy volunteers and patients with cancer who did not experience weight reduction.[1,6,8] Increased liver activity due to inefficient and metabolically expensive metabolism is also thought to contribute to increased energy expenditure. For example, tumor cell–produced lactate and its subsequent use as a gluconeogenic substrate via the Cori cycle is a futile cycle that has been reported in tumor-bearing patients and is hypothesized to contribute to development of hypermetabolism.[1,8] Altered conversion of white adipose tissue to brown adipose tissue has also been hypothesized to contribute to increased energy expenditure. Characteristic sarcopenia seen in many patients with CC is thought to be caused in part by increased circulating proteolysis-inducing factor (PIF) activation of abnormal skeletal muscle protein degradation by the ubiquitin-proteasome pathways, but the role of PIF in human investigations is not clear.[1,6,8] Other implicated abnormalities include insulin resistance and decreased circulating levels of insulin-like growth factor 1.[1] Fat loss has been associated with upregulated fat mobilizing factors such as zinc-α-2 glycoprotein. Changes in appetite are associated with hypothalamic changes that affect neuropeptide (neuropeptide Y) and peripheral hormone (ghrelin, leptin) metabolism. The normal metabolic effect of elevated circulating leptin concentrations is decreased appetite while elevated ghrelin concentrations stimulate appetite. These peripheral signals regulate activity of neuropeptide Y and agouti-related protein, which promote increased appetite, or pro-opiomelanocortin and melanocyte-stimulation hormones, which decrease appetite. Decreased hypothalamic response to peripheral signals to increase appetite is thought to be an underlying cause of anorexia seen in CC.[1,8]

Diagnosis of CC

A variety of criteria have been used to characterize CC in an attempt to facilitate a standard for clinical trials and development of therapeutic agents, as well as provide clinical guidance for timing and choice of treatment.[9–11] Many of the early criteria focused on weight loss and appetite. For example, one of the earliest criteria used for clinical trials were developed by the North Central Cancer Treatment Group.[9] CC was defined as a 5-pound weight loss in the preceding 2 months and/or an estimated daily caloric intake of <20 calories per kilogram, a desire by the patient to increase his or her appetite and gain weight, and the physician's opinion that weight gain would be beneficial for the patient. However, later investigations of CC acknowledged the role of body composition and other metabolic alterations on the degree of clinical abnormalities and outcomes accompanying weight loss. Others have attempted to incorporate these data into a more comprehensive classification.[10,11] Fearon and others[10] reported a framework that included a continuum of 3 diagnostic stages: precachexia, cachexia, and refractory cachexia. Risk

of progression across the stages is dependent on a variety of factors, including tumor type and stage, presence of inflammation, inadequate food intake, and response to antitumor treatment. Precachexia is defined as <5% involuntary weight loss in the presence of other metabolic abnormalities such as anorexia or impaired glucose control. Cachexia is defined as >5% involuntary weight loss over the preceding 6 months or a body mass index (BMI) <20 kg/m^2 and ongoing weight loss >2% or signs of sarcopenia and ongoing weight loss >2%. Sarcopenia has been defined by a variety of assessment tools, including mid-arm muscle area or circumference, appendicular skeletal muscle index determined by dual-energy x-ray absorptiometry, lumber skeletal muscle index determined by oncological computerized tomography, or whole-body fat-free mass index without bone determined by bioelectrical impedance.[2,10] Refractory cachexia is defined by the patient's clinical presentation such as rapidly progressive cancer unresponsive to treatment, low performance status (World Health Organization [WHO] score 3 or 4), and a life expectancy <3 months. The clinical utility of this multiple-stage classification is not clear, particularly the ability to distinguish between no cachexia and precachexia.[12] Addition of biological indicators of inflammation such as C-reactive protein may be helpful. However, use of both percentage weight loss and BMI may be more useful as indicators of the clinical impact of degree of weight loss in patients with cancer.[11,12]

Treatment of CC

No single treatment plan for CC exists because of the multifactorial characteristics of the syndrome. However, 3 areas that appear to be key to treating CC are appropriate antitumor treatment, nutrition intervention, and supportive pharmacologic intervention. Successful response to appropriate oncologic therapy should result in improved CC symptoms. Patients who respond poorly to oncologic therapy are frequently those with progressive CC symptoms.

Nutrition intervention includes appropriate nutrition screening and assessment, which should begin early in the course of the disease to reduce or delay negative effects on therapy and QOL.[2,13] Nutrition impact symptoms should be appropriately treated to minimize the role of GI dysfunction in precluding adequate oral intake. For example, antiemetic or prokinetic therapy should be maximized for treatment of nausea/vomiting or delayed gastric emptying. Treatment of pain and symptoms of depression should be maximized as well. The role of single nutrients such as amino acids and other micronutrients and effect on CC is not clear.[14] However, liquid nutrition supplements may be useful for helping to increase caloric intake.

A large assortment of pharmacologic agents has been investigated for potential orexigenic activity, as well as their effects on cytokine and hormonal metabolism and other anabolic or catabolic pathways in an attempt to reverse symptoms of CC and improve QOL. However, success with use of available agents is extremely variable, frequently providing minimal effectiveness as an aggressive nutrition support intervention for many patients with CC.[15] Although there appears to be a positive effect on appetite for many patients, minimal increase in lean body mass (LBM) and total body weight occurs for many patients who respond, but many patients continue to lose weight throughout the course of their disease despite pharmacologic intervention. Although weight gain may not be a reasonable goal for many patients, prevention of further weight and LBM loss as well as improved appetite and QOL may be achievable for others. More recent data suggest use of combination therapy may more effective than a single-agent approach.[13] The ideal pharmacologic agent for treating CC should have sustained positive effects on appetite, support body cell mass maintenance or repletion, and improve QOL while minimizing adverse effects and negative effects on tumor treatment. Unfortunately, no currently available pharmacologic agent meets all criteria. Hence, choice of pharmacologic agent(s) for treating CC should be based on the patient's clinical condition, including GI status, as well as the patient's and the caregiver's goals for therapy.

Appetite Stimulants

Progesterone Analogues

Numerous investigations have reported orexigenic activity associated with progestational agents such as megestrol acetate (MA) and medroxyprogesterone (MPA).[16,17] MA has received the most attention in randomized controlled trials of patients with cancer. Improvement in QOL has been demonstrated in several large prospective studies in patients with CC treated with MA, but a survival benefit has not been shown.[15] A recent Cochrane Database review reported a beneficial effect of MA on appetite improvement and a small effect on weight gain compared with placebo, but no difference in effect compared with other drugs investigated in comparison trials. Improved QOL with MA was evident compared with placebo, but there was no difference compared with other drugs investigated in comparison trials.[16] A more recent investigation suggests a potentially better role for MPA or MA in combination with other agents as a more effective treatment for CC. Both MPA and MA were studied in CC patients to determine the effects of therapy on LBM, REE, and fatigue.[17] Secondary end points included appetite, QOL, grip strength, Glasgow Prognostic Score for systemic inflammation, and proinflammatory cytokines. Patients were randomized to 1 of 5 treatment groups. Group 1 received MPA or MA, which were considered equivalent treatments. Group 2 received an oral supplement fortified with the ω-3 fatty acid, eicosapentaenoic acid (EPA). Group 3 received L-carnitine. Group 4 received thalidomide, a cytokine inhibitor, and group 5 received MPA or MA, EPA-enriched nutrition supplement, L-carnitine, and thalidomide. In addition, all patients received a multicomponent antioxidant cocktail. Group 5 demonstrated a significant increase in LBM, decrease in REE, and improved fatigue. In addition, appetite was significantly improved in group 5. IL-6 levels significantly

decreased in groups 4 and 5. Systemic inflammation and QOL improved in groups 3, 4, and 5. The authors concluded that the most effective treatment was a progestin in combination with the other medications and supplements as a multimodal intervention to counter tumor-induced altered metabolism associated with CC.

The inclusion criteria for many investigations of progestational agents help provide a contextual background for the study results in addition to providing a characteristic profile for identifying potential adult candidates for progestional agents. In general, patients included in the investigations had a diverse collection of primary malignancies and may or may not have continued antitumor treatment. Inclusion criteria frequently included >5% weight loss with or without anorexia, advanced incurable disease, no hormonally active disease, Eastern Cooperative Oncology Group performance >2, life expectancy >3 months, and a functional GI tract that allowed oral intake. The mean age of study patients was often >60 years. The attrition rate of patients during the investigations was frequently >30% and sometimes >50%. Reasons for not completing the investigation period included treatment toxicities, worsening clinical status, or death. Last, the treatment duration varied between investigations. The study period for many investigations lasted <8–12 weeks.[16]

MA is generally well tolerated, but most of the adverse effects associated with its use as an appetite stimulant in patients with cancer have been reported with short-term use, usually <12 weeks. Risk of adverse effects with longer use is not well reported. Adverse effects reported include hyperglycemia and adrenal insufficiency.[18] An association with a small increase in the risk of developing edema and impotence in men as well as higher rates of venous thrombolic episodes have been reported as well.[2,16,18]

Corticosteroids

Corticosteroids have been widely used for treatment of a variety of symptoms in patients with cancer, including appetite stimulation. Several mechanisms of action have been proposed, including hypothalamic-pituitary-adrenergic (HPA) axis modulation, modulation of proinflammatory cytokines, reduction of peritumoral edema and tumor mass or function, and modulation of adrenergic activity in the dorsal horn.[19] Improved appetite and QOL have been reported in multiple comparison trials of corticosteroid therapy compared with placebo, but the effect is short lived (<4 weeks), and long-term use is associated with negative nitrogen balance, net calcium loss, glucose intolerance, and immunosuppression.[19]

Corticosteroids have been successfully used for the treatment of anorexia and other supportive care symptoms in palliative care patients.[20] Fifty home hospice patients with advanced cancer were studied after corticosteroid therapy was initiated for the treatment of symptoms such as weakness, anorexia, headache, drowsiness, nausea and vomiting, dyspnea, and confusion. Significant improvements occurred in all symptom categories except drowsiness. Dexamethasone was the agent most frequently used with a mean daily dose of 7 mg and a range of 4–16 mg/d. Similar results were reported in a prospective, randomized double-blind, placebo-controlled investigation of dexamethasone in patients with advanced cancer.[21] Patients were randomized to receive either dexamethasone 4 mg orally twice daily or placebo for 14 days. The treatment group had a significant improvement in cancer-related fatigue, anorexia, and QOL.

In general, any nutrition advantage with the long-term use of corticosteroids is negated by the risk of adverse effects, such as muscle wasting and immunosuppression.[19,22] However, terminal patients with poor performance status could be considered potential candidates for corticosteroid intervention because the positive pharmacologic effects on other symptoms associated with end-stage cancer may outweigh the risks associated with the negative adverse effects.[22]

Cannabinoids

Cannabinoids have been investigated in patients with cancer for antiemetic and appetite-stimulant activity.[23] Dronabinol is the synthetic oral form of tetrahydrocannabinol (THC), which is the active agent in marijuana thought to be responsible for these effects. The mechanism of action of dronabinol is not completely understood, but its activity is likely mediated by cannabinoid receptor–related processes.[24] A recent multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-in-Cachexia-Study-Group found no difference in patients' appetite or QOL between dronabinol and placebo.[25] In addition, there were no differences in body weight between groups at baseline or week 6 or in weight loss. Another randomized trial of 469 patients with advanced cancer and cachexia compared dronabinol with MA and demonstrated MA to be superior for appetite improvement and weight gain.[26] Furthermore, combination therapy with both agents was not superior to treatment with MA alone. Adverse effects reported in this investigation included dizziness, ataxia, and confusion. A recent meta-analysis of investigations evaluating the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adult patients with cancer reported a similar adverse effects.[27] Patients who received cannabinoids had a higher chance of reporting dizziness, dysphoria, euphoria, "feeling high," and sedation. In addition, significantly more participants reported these adverse events with cannabinoids compared with the antiemetic prochlorperazine.

The role of medical marijuana for treatment of CC is not clear.[23,28] Investigations of effects of smoked or vaporized cannabis on appetite or cachexia in patients with cancer are lacking. However, clinical concerns with pulmonary administration of marijuana in patients with cancer include potential for injury to large airways or increased symptoms of bronchitis, which may negatively affect antitumor treatments. In addition, immunocompromised patients who smoke marijuana may be at risk

for invasive pulmonary aspergillosis because of natural aspergillus contamination. The routine use of dronabinol or medical marijuana as an appetite stimulant is not recommended because of the inconsistent evidence for successful clinical use in patients with cancer.[2,28]

Olanzapine and Mirtazipine

Seratonin 5-HT_2 and 5-HT_3 receptor blockade is thought to be the etiology of increased appetite and weight gain in patients without cancer receiving the atypical antipsychotic olanzipine. However, additional mechanisms have been proposed.[29] A recent investigation in adult patients with cancer assessed the effect of olanzapine on metabolic cytokine response and relationship to weight.[30] The authors reported no change in leptin, ghrelin, and growth hormone levels throughout the study period. There was also no relationship between cytokine response and weight. Improved weight gain, appetite, and QOL was reported in patients with advanced GI or lung cancer who received olanzapine and MA compared with single-agent MA.[31]

Mirtazapine is a tetracyclic antidepressant that antagonizes presynaptic α2-adrenergic receptors, resulting in increased norepinephrine and serotonin release. Mirtazapine also antagonizes serotonin 5-HT2 and 5-HT3 receptors.[29] Mirtazapine has been investigated for its effects on pain, QOL, nausea, anxiety, insomnia, appetite, and weight gain in patients with advanced cancer. Improved appetite and QOL were reported in nondepressed patients with CC or anorexia who received 15–30 mg mirtazapine in an open-label single-institution phase II trial.[32] However, the effect on weight gain was variable. Further clinical data are needed before either olanzapine or mirtazapine can be recommended for routine use as a treatment for CC.

Ghrelin

Ghrelin, a potent orexigenic peptide hormone produced by the stomach, has been shown to increase appetite and caloric intake in healthy individuals and in animal models of CC.[33] An early concern with use in patients with cancer was promotion of cellular proliferation and invasion of certain types of cancer. However, a subsequent investigation in adults with CC reported a marked increase in caloric intake and no side effects.[34] A recent randomized, placebo-controlled, double-blind, double-crossover study demonstrated that ghrelin was safe and well tolerated but unfortunately did not show any change in nutrition intake.[35] The clinical utility of ghrelin is hindered by its short half-life and parenteral dosage form. However, anamorelin is an investigational ghrelin receptor agonist that can be administered orally that has demonstrated positive effects on appetite and LBM.[33,36] The efficacy and long-term safety of anamorelin as a treatment for CC needs further study before routine use can be recommended.[37]

Anabolic Agents

Anabolic agents are used in an attempt to improve muscle anabolism. Multiple studies have reported anabolic agent use in other clinical conditions or diseases such as human immunodeficiency virus (HIV), infection, or burns, but few published investigations characterize use in patients with CC.

Oxandrolone is an oral anabolic androgenic steroid approved by the U.S. Food and Drug Administration (FDA) for counteracting the protein catabolism associated with long-term corticosteroid use and for the relief of bone pain frequently accompanying osteoporosis.[38] However, oxandrolone has an FDA orphan drug designation for use as an adjunctive therapy for patients with AIDS who have HIV-wasting syndrome.[39] Very few studies have reported on the use of oxandrolone in patients with cancer. The effects of oxandrolone and MA on LBM, weight, and QOL were investigated in patients with solid tumors and weight loss.[40] Patients were randomized to receive either oxandrolone 10 mg twice daily or MA 800 mg daily for 12 weeks. There was a significant increase in weight in the MA group compared with the oxandrolone group; however, there was a trend for an increase in LBM in the oxandrolone group compared with the MA group that was not statistically significant. There was no difference in QOL. Other important considerations for use of oxandrolone in patients with cancer include a contraindication for use in testosterone-sensitive malignancies such as prostate or male breast cancer.[38]

The anabolic steroid fluoxymesterone was investigated in a comparison trial that included a progestin and corticosteroid for effect on CC.[41] Patients with advanced cancer and a history of weight loss or anorexia were randomized in a double-blind study to receive MA 800 mg daily, dexamethasone 0.75 mg orally 4 times daily, or fluoxymesterone 10 mg orally twice daily. Appetite, nausea, vomiting, drug toxicities, and QOL were evaluated. Fluoxymesterone had the least effect on appetite compared with those who received MA, although those who received MA or dexamethasone reported a similar effect on appetite. Degree of weight gain was not significantly different between the MA group and the other groups. However, there was a trend for improved weight gain in those who received MA compared with those who received fluoxymesterone. The trend for weight gain was similar when the MA group was compared with those who received dexamethasone. There was no difference in QOL between the 3 groups. The dexamethasone group experienced a higher rate of drug discontinuation because of toxicities such as heartburn and insomnia compared with MA, while the MA group had a higher rate of venous thrombolic episodes compared with those who received dexamethasone.

Cytokine Inhibitors

Cytokine inhibitors have the potential to be effective agents for treating CC by modulating catabolic inflammatory conditions

associated with anorexia and weight loss. Thalidomide has been shown to counter TNFα and IL-6 production.[42,43] Thalidomide was investigated as a potential treatment for weight loss in patients with cancer in a randomized, placebo-controlled trial of 50 patients with pancreatic cancer. Patients were randomized to receive thalidomide 200 mg/d or placebo for 24 weeks.[42] The authors reported thalidomide was well tolerated and effective at attenuating loss of weight and LBM. However, a recent meta-analysis of investigations of adult patients with cancer who received thalidomide evaluated the effectiveness for treatment of CC.[43] The authors reported inadequate evidence to recommend routine clinical use of thalidomide for CC treatment. Adverse effects identified included peripheral neuropathy, paresthesia, rash/cutaneous reaction, somnolence, and venous thrombolic episodes.

Pentoxifylline is a phosphodiesterase inhibitor used in the treatment of peripheral vascular disease that also inhibits TNFα synthesis by decreasing gene transcription. However, patients with a history of cancer-related anorexia or weight loss who were randomized to receive pentoxyfylline 400 mg 3 times daily or placebo demonstrated no difference in appetite or weight gain between the 2 groups.[44] Further investigations are necessary to clarify the role of pentoxyfylline as a routine treatment for CC.

ω-3 Fatty Acids

The ω-3 fatty acids EPA and docosahexaenoic acid (DHA) have been investigated in patients with cancer-related anorexia and weight loss.[2,45–48] Investigations of EPA in tumor-bearing animals and clinical trials of patients with cancer have reported multiple anti-inflammatory properties, including attenuation of protein degradation induced by PIF, inhibition of IL-6 production, and inhibition of tumor-derived fat mobilizing factor.[46] Initial clinical trials of fish oil provided alone or as a part of a liquid nutrition supplement in patients with CC reported positive effects on appetite, weight gain, and performance status.[2,45,46] However, early systematic reviews concluded that there were not sufficient data to determine if oral EPA is superior to placebo and suggested a limited role for use of ω-3 fatty acids as a single-agent treatment for CC.[45–47] A more recent systematic review of randomized controlled clinical trials of EPA and DHA supplementation in patients with cancer receiving treatment reported a beneficial role for ω-3 fatty acids.[48] Treatment regimens included radiation therapy, chemotherapy, or a combination of the 2. Ten studies met inclusion criteria. Supplements for ω-3 were provided as a soft-gel supplement or as a part of a nutrition supplement enriched with fish oil. The authors reported that EPA and DHA provided as fish oil in doses ranging from 600 mg/d to 3.6 g/d promoted weight maintenance or gain during treatment, improved or minimized loss of LBM as assessed by bioelectrical impedance analysis, and improved QOL as defined by physical function scores and global health status. This lack of consistency in clinical data is acknowledged in guidelines for nutrition in patients with cancer by both the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN). However, both groups suggest use of ω-3 fatty acid supplementation as an option for patients with cancer experiencing progressive, unintentional weight loss.[2,49] In general, adverse effects of supplemental ω-3 fatty acids are mild and frequently associated with GI symptoms such as mild abdominal discomfort, flatulence, nausea or vomiting, transient diarrhea, or steatorrhoea.[2,47] Others include fish aftertaste or fish belching.[2,47] Safety concerns with fish oil supplementation include increased risk of bleeding. However, combined intakes of up to 5 g/d EPA and DHA appear to be safe for most adults.[2]

Melatonin

Melatonin is a hormone produced primarily by the pineal gland. Oral dosage forms are commonly used as a treatment for insomnia. Although melatonin has an active role in circadian cycle regulation, anticancer and anticachectic effects thought to be related to cytokine and TNFα inhibition have been reported.[50] Previous investigations demonstrated melatonin given 20 mg/d orally resulted in less weight loss and greater survival rates.[50] However, a recent investigation in adult patients with advanced lung or GI cancer reported contradictory results.[50] Patients were randomized to receive melatonin 20 mg or placebo. Appetite score, weight response, QOL, and other symptoms were evaluated. The investigation was closed after initial interim analysis because there were no differences in appetite, weight, other symptoms, or QOL between groups. Mild adverse effects such as dizziness, headache, nausea, and sedation have been reported with melatonin use.[51] Further studies are needed before melatonin can be recommended for routine use as a treatment for CC.

Summary

Treatment of CC is challenging for both the patient and the healthcare provider because unfortunately, no single agent successfully treats CC. Identifying treatable nutrition-related problems and then determining an appropriate treatment in an attempt to minimize further weight loss and perhaps promote weight gain and improve QOL is challenging. Nutrition consequences of oncologic treatments should be identified early with nutrition screening and assessment. This process is necessary for creating a nutrition care plan to minimize weight loss and sarcopenia. Nutrition impact symptoms should be identified and appropriately treated. A mild physical exercise program tailored to the patient's performance status may support maintenance of muscle strength and minimize muscle loss.[2,22] However, options are limited for those patients who continue to lose weight and muscle mass despite apparent adequate nutrient intake. Determining the best treatment for unintentional weight

loss and sarcopenia in patients with cancer according to current clinical evidence remains difficult. Cost of therapy compared with expected benefit is an important consideration to both patients and healthcare providers. In general, nutrient supplements are not considered reimbursable expenses by many third-party payers. Although multiple agents have been studied and others are currently being investigated as new potential treatments for CC, choices for pharmacologic intervention based on recommendations from evidence-based sources include progestational agents or corticosteroids for appetite stimulation and a source of EPA as a potential cytokine inhibitor.[2,49,22] Expected length of therapy should dictate choice of appetite stimulant. A corticosteroid such as dexamethasone should be reserved for shorter treatment periods of 1–3 weeks to minimize adverse effects associated with long-term use. A progesterone analogue such as MA should be considered when therapy is expected to last longer (weeks to months). ω-3 Fatty acids may be used in patients with advanced cancer undergoing treatment who are at risk of weight loss or are malnourished.

Statement of Authorship

T. Mattox contributed to the conception/design of the review; contributed to the acquisition, analysis, or interpretation of the data; drafted the manuscript; critically revised the manuscript; agrees to be fully accountable for ensuring the integrity and accuracy of the work; and read and approved the final manuscript.

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