Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Outcomes of novel trials for cancer cachexia

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Cancer cachexia is a multifactorial syndrome characterized by involuntary loss of skeletal muscle and fat, reduced quality of life and decreased survival. Unlike starvation, weight loss cannot be fully reversed by increasing caloric intake. Interventions, such as nutritional counseling or currently available appetite stimulants such as megestrol acetate have limited benefits. Recently, there has been an increase in the understanding of the pathophysiology contributing to weight loss in patients with cancer. Clinical trials of various pharmacological therapies targeting the underlying pathophysiological derangements contributing to cancer cachexia are underway. A personalized approach may be needed for managing patients with anorexia–cachexia syndrome in conjunction with the best supportive care. The following narrative review will highlight novel therapies being investigated for the treatment of cancer cachexia, which can be used as a single-agent or combined in multimodal therapy.

Keywords: anorexia • cancer• cancer cachexia• clinical trials

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Cancer cachexia is characterized by an accelerated loss of skeletal muscle, with or without the loss of fat mass. Weight loss is associated with a decline in physical function [1], impaired body image [2], decline in quality of life, psychosocial distress for both patients and their family caregivers [3] and increased mortality [4].

Cachexia experienced by advanced cancer patients is irreversible despite adequate caloric intake or conventional nutritional support [5]. Decreased appetite or reduced caloric intake [6] is often associated with cancer cachexia and exacerbates weight loss. However, recent research has reported only a modest association between food intake and appetite loss, suggesting that patients may adapt by exercising conscious control over their eating in order to overcome their appetite loss [7]. In addition to reduced nutritional intake, cachectic patients often have evidence of systemic inflammation, decreased muscle strength, hypermetabolism with elevated resting energy expenditure (REE) and symptoms of fatigue [8,9], which can all contribute to the weight loss despite adequate caloric intake.

In 2010, a panel of international experts agreed to the following definition [8]: "*Cancer cachexia is defined as a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Its pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism.*"

In addition to a common definition, the expert panel has proposed a three-level staging system that includes a precachexia, cachexia, and a refractory cachexia stage [8]. The precachexia stage is characterized by the presence of metabolic changes without significant muscle wasting or functional impairment. When patients enter the stage of cachexia, weight loss and muscle wasting are found, weight loss can have a profound impact on a patient's quality of life, symptom burden and overall performance status. In the final stage known as refractory cachexia, patients

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are believed to be refractory to anticachexia treatment, exhibit a poor performance status, and have a prognosis of 3 months or less.

More research is needed to support that the cachexia syndrome progresses in distinct stages. One study applied the cancer cachexia stages to 207 patients with advanced non-small-cell lung or gastrointestinal cancer and classified patients according to either noncachectic, precachectic, cachectic and refractory cachexia stage [10]. The distinct stages were significantly correlated ($p < 0.05$) with overall symptom burden, quality of life, ability to tolerate chemotherapy and survival; however, prechachectic and cachectic patients behaved similarly with respect to clinical outcomes [10]. In addition, a preliminary case-control study of non-small-cell lung cancer patients supports a biological basis for classification of cachexia into distinct stages. Early-stage lung cancer patients exhibited evidence of a proinflammatory status with elevated TNF, increased C-reactive protein (CRP) and fibrinogen, and decreased albumin levels without changes in body composition [11]. Muscle biopsies showed no changes in skeletal muscle NF-κB or an increased activity of the ubiquitin proteasome system (UPS) [11]. These patients with precachexia had significantly reduced exercise capacity despite maintenance of muscle mass and unaltered indices of UPS activation supporting the concept that transition of systemic to local inflammation is required to initiate UPS-dependent muscle wasting.

In clinical practice, managing patients with anorexia–cachexia syndrome is challenging, and often, a multimodal individualized approach is required [12,13]. In addition to specific pharmacological therapies for cancer cachexia, symptoms that impact appetite and can result in weight loss, must be managed. These nutrition-impact symptoms include nausea, constipation, early satiety, pain and depression. In addition to maximizing supportive care measures, psychological support for patients and family member should be provided emphasizing the social aspects of food intake and the pleasure of tasting meals over the amount. Consultation with a nutritionist should be offered and may improve caloric intake and in some cases, that is, early-stage disease or when starvation is a significant contributor, may result in weight gain. Randomized controlled trial in patients undergoing radiotherapy for colorectal cancer [14] and head and neck tumors [15] showed that dietary counseling produced a sustained improvement in symptoms, function and quality of life. In patients with advanced cancer and cachexia, nutritional counseling alone is inadequate to reverse weight loss. Once best supportive care is provided to cancer patients to control symptoms, specific anticachexia pharmacological interventions may be more effective.

Several drugs have been shown to stimulate appetite including megestrol acetate and glucocorticoids, but often an increase in appetite is not accompanied by meaningful improvements in fat-free mass or performance status.

Megestrol acetate is appetite stimulant that has predominantly progestational and anti-gonadotropic effects [16]. In 2013, a Cochrane review of megestrol acetate for the treatment of cachexia syndrome reported benefits as an appetite stimulant and slight weight gain in roughly a fourth of cancer patients [17], but side-effects are significant and include a dose-dependent increased risk of thromboembolic disease, adrenal insufficiency and hypogonadism in male patients [18].

In cancer patients, glucocorticoids have been shown to be an appetite stimulant in randomized controlled trials. A 2005 systematic review reported that glucocorticoids including dexamethasone, methylprednisolone, and prednisolone improved appetite and quality of life in the short term but the benefits waned over time [19]. Side effects of glucocorticoids include insulin resistance, immunosuppression, muscle myopathy and adrenal insufficiency, when abruptly discontinued, limit their efficacy in treating cancer cachexia.

The following narrative review will highlight recent developments in research examining pharmacological interventions for cancer cachexia. A PubMed search of novel pharmacological agents with the potential to prevent or treat cancer cachexia and may be combined with other drugs as a component of multimodal therapy was conducted. For each agent, preliminary clinical studies will be reviewed, and if available, randomized-controlled double-blind studies will be highlighted.

Clinical trials

■ Omega-3 fatty acids

Successes

Fish oil contains omega-3 (n-3) fatty acids, including eicosapentaenoic acied (EPA) and/or docosahexaenoic acid (DHA), has been shown to reduce inflammation and may benefit cancer patients suffering from weight loss. The supplementation of n-3 fatty acids from fish oil decreases proinflammatory eicosanoids from n-6 acrachidonic acid (e.g., leukotriene B4, thromboxane A2, prostaglandin E2) and increases the production of beneficial eicosanoids (e.g., thromboxane A3, prostaglandin E3, leukotriene B5) [20]. N-3 fatty acid supplementation has been shown to decrease proinflammatory cytokines in healthy individuals [20,21].

Early trials, which were small and non-blinded, reported positive effects of supplementation with fish oil alone or in combination with nutritional supplements on anorexia–cancer cachexia syndrome [22–25].

One placebo-controlled study of 60 patients with solid tumors who were supplemented with fish oil (170 mg EPA, 115 mg of DHA, and 200 mg of vitamin E) for 40 days versus placebo reported a survival advantage ($p < 0.025$) and increased performance status, but no significant effect on body weight or albumin level [22]. In a study of 20 patients with unresectable pancreatic adenocarcinoma, who were supplemented with two cans of fish-oil-enriched nutritional supplement per day in addition to normal meals, reported that administration of fish oil-enriched supplement resulted in significant weight gain at 3 weeks (median 1 kg; $p = 0.024$) and 7 weeks (median 2 kg; $p = 0.033$), increased dietary intake of almost 400 kcal/day ($p = 0.002$), as well as improved appetite and performance status [23]. In another study, EPA administered with an energy- and protein-dense oral supplement for a duration of 8 weeks did show stabilization of weight loss in patients with pancreatic cancer with an increase in both caloric intake ($p< 0.05$) and activity level ($p = 0.08$) [25].

Setbacks

Subsequent larger, randomized trials reported no significant benefit of supplementation of EPA on lean body mass (LBM) [26–28]. In a study of 60 patients with advanced cancer, administration of high doses of fish oil (1.8 g of EPA and 1.2 g DHA) over a period of 2 weeks reported no significant differences in symptoms or nutritional parameters including appetite, fatigue, nausea or caloric intake compared with placebo. The majority of patients were not able to swallow more than ten capsules of fish oil due to burping or aftertaste [26].

In a study of 518 patients with either advanced gastrointestinal cancer or lung cancer who were randomized to pure EPA 2–4 g daily versus placebo, there was no statistical improvements in survival, weight or other nutritional variables after 4 weeks of supplementation; however, a trend for weight gain ($p = 0.066$) was reported at 8 weeks favoring the treatment arm with a small increase in mean weight of 1.2 kg with 2 g and 0.3 kg with 4 g supplementation of EPA [27].

In a study examining protein supplement enriched with (n-3) fatty acid and antioxidants compared with isocaloric isonitrogenous control supplement reported no significant benefit with (n-3) fatty acid supplementation, with both supplements being equally effective in the intention-to-treat group comparisons. However, when taken in sufficient quantities, the (n-3) fatty acid-enriched protein supplement did show increase in net gain of weight ($p < 0.001$) and LBM ($p = 0.001$) in a *post hoc* dose analysis [28].

Three systematic reviews have concluded that there is either insufficient evidence or that fish oil has no benefit on weight loss, symptom burden or quality of life [29–31].

Future studies

Recent studies examining fish oil supplementation to prevent the development of cancer cachexia during an earlier stage have been more encouraging [32–35]. In a double-blind randomized study of enteral nutrition enriched with 2.2 g EPA versus enteral nutrition alone provided 5 days preoperatively (orally) and 21 postoperative days (jejunostomy) following esophageal cancer surgery, reported preservation of LBM when patients were supplemented with EPA [32]. In a study that included stage III non-small-cell lung cancer patients receiving concurrent chemotherapy, protein supplementation with (n-3) polyunsaturated fatty acids (2.0 g EPA + 0.9 g DHA per day) had an improved weight maintenance including fat-free mass after 3 and 5 weeks ($p < 0.05$) [33]. In another study of newly referred patients with non-small-cell lung cancer from the time of initiation of chemotherapy, 2.2 g EPA per day of fish oil supplementation resulted in the maintenance of weight (0.5 ± 1.0 kg) as opposed to weight loss (-2.3 ± 0.9 kg) in patients who received standard of care ($p = 0.05$) [35].

The inconsistent results may be explained by the recent attempts to improve compliance with fish oil supplementation and provide interventions earlier in the progression of cancer cachexia [36]. Murphy and colleagues suggest that future studies should allow patients a choice of supplementation format (capsules or liquid) or use EPA-enriched parenteral or enteral nutrition to ensure compliance. In addition, supplementation with n-3 fatty acids from krill or flaxseed oil may decrease the inconvenience for patients taking too many pills and minimize aftertaste.

■ Melatonin

Melatonin (*N*-acetyl-5 methoxytryptamine) is a hormone synthesized in diverse tissues including the pineal gland [37] from the amino acid tryptophan and locally secreted in the gastrointestinal system in response to feeding [38]. It is involved as a messenger of light and regulates the circadian rhythm with the highest production of melatonin occurring at night. Melatonin has a diverse range of actions regulating inflammation, autonomic function and absorption of nutrients, which may target the underlying pathophysiology of cancer cachexia.

In animals, melatonin stimulates appetite [39], and modulates intestinal transit and nutrient absorption in the GI tract [40]. In addition, it may possess antitumor activity [41]. Female nurses who work the night shift have been reported to have an increased risk of breast cancer [42] and colon cancer [43]. Preliminary trials show improvement in efficacy when given in conjunction with arterial chemoembolization for patients with

hepatocellular carcinoma [44]. Melatonin may have a role in the treatment of symptoms including appetite, fatigue, mood and weight loss and may protect non-cancerous cells for the toxicity secondary to radiation and chemotherapy [45,46].

Successes

Preliminary trials in a diverse group of metastatic cancer patients randomized to either supportive care alone or supportive care plus 20 mg of melatonin for a period of 3 months, the group treated concomitantly with melatonin had lower levels of TNFα than cancer patients receiving only supportive care [47]. A subsequent trial by the same group reported that melatonin supplementation for patients with solid tumors refractory to chemotherapy showed improvements in fatigue, anorexia–cachexia and depression [48]. In addition, a randomized trial examining the benefits of supplementing melatonin at night in patients receiving standard chemotherapies for advanced solid tumors reported decreased symptoms, less adverse effects and improved survival compared with usual care [49]. Although preliminary randomized trials were promising, enthusiasm for melatonin was tempered by the absence of double-blind or placebo-controlled studies.

Setbacks

Recently, a randomized, double-blind, 28-day trial of melatonin 20 mg versus placebo was conducted in advanced gastrointestinal or lung cancer patients. Patients were stratified according to those actively receiving treatment versus those who were not, and the clinical outcomes included appetite scores, weight, symptom burden as measured by the Edmonton Symptom Assessment Scale, and quality of life, measured by the Functional Assessment for Chronic Illness therapy [50]. The study concluded that 20 mg of melatonin supplementation at night did not improve appetite, increase weight, alter CRP or improve overall quality of life for patients with advanced cancer [50]. Of note, the study was stopped after interim analyses secondary to futility. In addition, analysis of the whole group of advanced cancer patients noted significant association of weight gain with improvements in appetite or depression, and the authors hypothesized that melatonin supplementation may not have a marked improvement in symptoms when accompanied by optimal symptom management, which was provided for both arms of the trial.

Future direction

Limitations of the study included the short duration of treatment (4 weeks), and advanced nature of the cancer in the patient population [50]. However, it was noted that interventions such as megestrol acetate [51,52] and ghrelin [53] have demonstrated improvements in weight in an advanced cancer patient population in a similar interval. For cachectic patients with advanced cancer and poor prognosis, interventions for weight loss should show clinical benefit in a short period of time in order to be useful for patients. In addition, the heterogeneity of the patient population and functional status was cited as a limiting factor, although the majority of patients enrolled in the study had a good performance status with a Karnofsky score between 70 and 90, and patients were restricted to either gastrointestinal or lung malignancies.

Side effects of melatonin are minimal with sleepiness and fatigue being the most common. Rarely, muscle and joint pain, leukopenia, and abnormalities of liver enzymes have been noted [54]. Other toxicities when melatonin is used on a long-term basis include impaired sexual drive, nightmares and worsened depression [55]. Doses as high as 1 g/day have been used over 30 days without major toxicities [56]. Since melatonin is not categorized as a drug, production is unregulated with concerns regarding the purity and dosage, accuracy may hinder research. Studies examining the potential benefits of melatonin in preventing weight loss earlier in the disease trajectory of patients with cancer are needed.

■ Nonsteroidal anti-inflammatory drugs

One of the critical underlying pathophysiological factors, which result in the development of cancer cachexia, is an aberrant inflammatory response. The exact mechanism is unclear but involves the host's pro-inflammatory cytokine response, which may include TNF, IFN-γ and IL-6. Anti-inflammatory agents targeting the inflammatory response may alter the development of cachexia. The pro-inflammatory cytokines, which have been modified by the administration of non-steroidal anti-inflammatory drugs (NSAIDs), include C-RP and IL-6 [57,58]. In tumor bearing rats, indomethacin has been shown to inhibit TNF and ubiquitin-mediated pathway of protein degradation [59]. In animals, studies have shown that celecoxib, a COX-2 inhibitor, may palliate cachexia via suppression of systemic inflammation [60].

Several studies examining NSAIDs in the treatment of cachexia have been conducted but the vast majority are small, include a heterogeneous cancer population, intervene at different time of trajectory of illness, and have poor methodological quality. The following discussion will highlight select studies conducted on NSAIDs as a single intervention for cancer cachexia.

Successes

One unblinded study involving a mixed population of 135 cancer patients with malnutrition and expected survival of more than 6 months were randomized to treatment with 100 mg indomethacin, 20 mg of prednisolone, or placebo until death [61]. No serious adverse events were noted in

patients receiving indomethacin. The study reported no significant differences regarding body weight, hand grip strength or arm circumference but did have significantly improved functional ability ($p = 0.03$), decreased CRP levels and improved survival in the indomethacin and prednisolone group (log rank, $p < 0.03$) [61].

A retrospective case-control study matched 151 cancer patients treated with indomethacin with 145 cancer patients not receiving NSAIDs. The patients treated with indomethacin had greater body weight, which comprised of preserved total body fat ($p < 0.005$), but no significant change in LBM, higher food intake ($p < 0.0006$), lower CRP ($p < 0.0001$) and resting energy expenditure ($p < 0.003$) [62].

A second prospective, randomized, double blind, placebo-controlled pilot study examined celecoxib effect on weight loss in head, neck, and gastrointestinal cancers [63]. The study was conducted over a 21-day course of treatment and reported that patients receiving celecoxib experienced statistically significant ($p = 0.05$) improvements in both weight (mean + 1.0 kg) and body-mass index, while patients on placebo developed weight loss (mean -1.3 kg). No serious adverse events were noted, but the study had limitations including a small sample size of only 11 head and neck or gastrointestinal cancer patients.

Setbacks

Adverse reactions associated with NSAIDs including gastrointestinal complaints such as dyspepsia are common. More serious adverse events include symptomatic GI ulcers, bleeding, or perforations may rarely occur. In addition, renal failure, hepatic dysfunction, and increased cardiovascular events have been reported. Selective COX-2 inhibitors reduce the risk of gastrointestinal complications compared with traditional NSAIDs, but their increased risk for cardiovascular events have been highlighted [64]. NSAIDs, by inhibiting prostacyclin synthesis, may induce fluid retention, which could account for some of the weight gain [65].

Several limitations exist to make definitive conclusions on the use of NSAIDs for cancer cachexia. The evidence to support the use of NSAIDs for cancer cachexia is limited by small sample size in many of the studies and multiple outcomes that were measured that makes it difficult to recommend NSAIDs for the treatment of cancer cachexia. Because of the potential for significant side effects and lack of large, well-designed randomized-controlled, double-blind trials, more research is needed. A systematic review concluded that the evidence is 'too frail' to recommend NSAIDs for cachexia outside of clinical trials [66].

Future directions

The use of NSAIDs as a single agent to treat cancer cachexia may be less effective than in combination therapy. Recent research expanding the current knowledge of the multiple underlying mechanisms resulting in cancer cachexia has led to researchers adopting multimodality treatment as a potential treatment for cachexia. With regards to NSAIDs, researchers often combine anti-inflammatory therapies with appetite stimulants or other forms of nutritional support. In addition, future research needs to explore the relative benefits of COX-2 selective inhibitors versus older NSAIDs as well as their safety.

Multimodality therapy

Since many past efforts at treating cancer cachexia with single agents have failed, multiple pharmacological interventions targeting the various pathophysiological mechanisms simultaneously have been advocated. A number of trials have recently been published exploring multimodality therapy for cancer cachexia. Virtually all multimodality interventions incorporate pharmacological agents, which modulate aberrant inflammation.

A randomized-controlled, double-blinded study of 73 patients with gastrointestinal cancer and an expected survival greater than 2 months were randomized to treatment with megestrol acetate (480 mg) with placebo versus megestrol with ibuprofen (1200 mg daily) for 12 weeks [67]. The combination arm reported significant gain in weight (median 2.3 kg, $p < 0.001$), decrease in CRP, improvement in appetite at the onset of treatment, and quality of life, while the megestrol with placebo arm reported a decrease in weight (median 2.8 kg) [67]. Of note, 46 (63%) of the patients enrolled in the study dropped out due mainly to disease progression and only 27 patients were available for evaluation at 12 weeks.

In a small trial evaluating 2 g of fish oil/celecoxib (200 mg twice daily) versus fish oil/placebo, 22 patients with advanced and progressive lung cancer with weight loss >10% were randomized to equal groups [68]. Both groups were also treated with aspirin (75 mg daily) and an oral food supplement. The arm that included celecoxib, was noted to have significant improvements in body weight ($p = 0.05$), handgrip strength ($p = 0.002$), and decreased CRP ($p = 0.005$); however, no difference in symptoms of fatigue or appetite was reported [68].

A recent Phase III trial involving advanced gynecological tumors, randomized patients to either a combination of megestrol acetate, carnitine, celecoxib and antioxidants versus megestrol acetate alone [69]. The combination regimen significantly ($p = 0.032$) increased LBM, decreased REE, improved symptoms of fatigue and overall quality of life [69]. However, grip strength, appetite, and ECOG performance status did not show significant improvements in the combination regimen compared with megestrol acetate alone.

Other combinations of pharmacologic agents studied include fish oil with melatonin. A total of 24 patients with

advanced cancer who were not candidates for systemic chemotherapy and had documented weight loss were randomized to 4.9 g of EPA and 3.2 g of DHA or 18 mg/day of melatonin for 4 weeks [70]. The study reported no significant changes in biochemical markers of cachexia. In the fish oil group, five of 13 patients (38%) showed weight maintenance or gain while only three or 11 patients in the melatonin group (27%) patients had positive outcomes. Interestingly, after 4 weeks, 63% of patients who received combined interventions experienced increased weight or maintenance [70].

Finally, a large randomized study involving 332 patients with complications of cancer anorexia/cachexia syndrome were assigned to one of five arms: arm 1: medroxyprogesterone (500 mg/day) or megestrol acetate (320 mg/day); arm 2: fish oil supplementation with eicosapentaenoic acid; arm 3: l-carnitine (4 g/day); arm 4: thalidomide (200 mg/day); and arm 5: a combination of the first four interventions over a period of 4 months [71]. Final analysis of the five arms reported significant superiority in the multimodality treatment group (arm 5) including significant increase in LBM, decrease in resting energy expenditure and symptoms of fatigue, increase in appetite, spontaneous physical activity and performance status [71]. Toxicity was reported to be minimal even with multiple pharmacological interventions.

Setbacks

There are no published studies reporting negative outcomes with multimodality therapy for cancer patients with anorexia–cachexia syndrome. However, a recent study does highlight the limitations of the mantra that 'more is better' with regards to treatment of cancer cachexia. In a randomized, noninferiority study in patients with advanced stage tumor at any site and >5% weight loss compared a combination of carnitine and celecoxib with or without the addition of megestrol acetate reported no significant difference in LBM [72]. Of note, all patients also received treatment with polyphenols 300 mg/day, lipoic acid 300 mg/day, carbocysteine 2.7 g/day, vitamin E, A, and C for a duration of 4 months. More research is needed to examine the optimal combination of agents for multimodal therapy for cancer cachexia, which maximizes benefits and minimizes potential adverse effects.

Future directions

The ideal combination of pharmacological and nonpharmacological agents to treat the anorexia–cachexia syndrome is unclear. Exercise has been incorporated into multimodality treatment for cancer cachexia and a feasibility study examining exercise in combination with EPA and COX-2 inhibitor is ongoing [73], and other combinations of multimodal therapy incorporating exercise for the treatment of cachexia are in progress [74]. Exercise with progressive resistance has been reported to enhance muscle growth, strength and mass in athletes, older adults and patients with cancer and may downregulate proinflammatory cytokine activity [75]. Physical activity has been shown to be beneficial and improve quality of life in cancer patients; however, most studies are conducted in early stage breast cancer patients. Some preliminary evidence is emerging in other malignancies such as lung cancer that exercise is beneficial [76]. Unfortunately, less than half of patients with lung cancer who attempted the exercise program were able to complete the intervention, but those who completed the program reported improvement in symptoms [76]. The benefits of aerobic exercise versus resistance training for cancer patients with weight loss are unclear and more research is needed.

Future studies on multimodality treatment for cancer cachexia need to refine and tailor treatment for each individual patient. For patients with increased proinflammatory cytokines, nonpharmacological interventions such as exercise combined with pharmacological therapy that modulates the proinflammatory response such as NSAIDs and fish oil might be considered. For patients with poor appetite and a limited prognosis of a few weeks, a consultation with a nutritionist in conjunction with an appetite stimulant such as a corticosteroid should be considered. Tailoring therapy for individual patients should be based on a thorough assessment of symptoms such as early satiety and underlying pathophysiology that is contributing to the weight loss as well as the patient's goals of care. Some patients may be more concerned about improving their appetite and enjoying meals with their family, while others may be interested in gaining LBM and improving their physical function. These detailed assessments are currently only possible in clinics dedicated to the management of cancer cachexia. More research is needed on the feasibility of multimodality in oncology clinics for patients with cancer cachexia.

Next generation

Androgens, including testosterone, exert anabolic effects on muscle including increasing muscle mass and strength [77]. The prevalence of hypogonadism in male cancer patients has been reported to be as high as 90% [78]. A recent study has shown that hypogonadism to be more common in cachectic patients with cancer than cancer patients without weight loss [79]. In male patients with hypogonadism, testosterone replacement has been reported to decrease cytokine levels [80], and reduce inflammatory markers [81], and in male cancer patients, testosterone replacement has the potential to

improve symptoms of fatigue, muscle mass and strength and libido [82].

Recently, selective androgen receptor modulators have been developed that selectively activate the androgen receptor resulting in greater anabolic effects and minimizes androgenic effects that may result in side effects such as prostate enlargement, deepening of the voice, acne, and terminal hair growth, especially in women. Preliminary studies show a potential benefit in increasing muscle mass in cancer patients with cachexia [83].

Ghrelin, a peptide secreted mainly from the stomach, is an important orexigenic hormone that enhances appetite and increases food intake in humans [84]. Cancer patients with cachexia are reported to have increased ghrelin levels [85], and researchers have hypothesized that cancer patients with weight loss are resistant to ghrelin. In one study, an infusion of ghrelin was shown to increase appetite and food intake [86] but not in another similar study possibly because of the prolonged weekly administration interval [87]. A double-blind randomized trial comparing two doses of daily ghrelin in patients with advanced gastrointestinal cancer showed improved appetite and decreased loss of whole body fat ($p < 0.04$) in the high dose group [88].

Since ghrelin has a half-life of 30 min, it must be administered parenterally as a continuous infusion limiting its use. A ghrelin mimetic has been developed, RC-1291/ONO-7643, and is undergoing clinical trials. A small, multicenter, double-blind, placebo-controlled crossover study of ONO-7643, the ghrelin mimetic showed significant increase in body weight compared with placebo (0.77 vs -0.33 kg), increased food intake, and improved appetite scores [89]. In another study, the ghrelin mimetic was administered over a 12 week period in a randomized, placebo-controlled trial of 81 patients with mixed cancer with weight loss >5% reported, increased total body mass with a trend toward increased lean muscle mass [90]. Ghrelin and ghrelin mimetics have a potential for increasing IGF-1 levels and concerns regarding tumor progression exist, although preclinical models show no adverse effects [91]. In these preliminary trials, ghrelin [88] and ghrelin mimetics [89] were well tolerated and safe. Efficacy and safety need to be confirmed in larger randomized controlled trials.

In addition to hormone therapy, β-blockers may potentially benefit cancer patients with cachexia by inhibiting activation of the sympathetic system, decreasing REE, and inhibiting proinflammatory cytokine production. Patients with congestive heart failure [92] and children with burns [93] have undergone pilot studies that show potential weight gain with the administration of β-blockers. Preliminary studies report that both atenolol and propranolol decrease REE in cachectic patients with solid tumors [94], but no studies have been published examining the benefits of β-blockers for patients with cancer cachexia and more research is needed.

Paradoxically, β-adrenoreceptor agonists may also play a role in some patients with cancer cachexia via anabolic effects on skeletal muscle. β-agonists have been shown to increase skeletal mass and decrease body fat [95], which has been used by athletes to increase muscle strength [96]. Limited studies exist examining β-agonists for the treatment of cachexia in cancer patients and they have potential side effects including tachycardia and muscle tremors.

Future perspective

For patients in the precachexia stage, interventions directed at controlling aberrant inflammation may prove to be effective at maintaining weight, which may be the primary goal. In patients with advanced cancer and refractory cachexia, optimizing supportive care such as appropriate analgesics to control pain, a prokinetic agent to treat early satiety and nausea, and psychosocial support for both patient and family need to be provided in conjunction with interventions specifically directed at reversing cancer cachexia. The distinct stages of the anorexia–cachexia syndrome – precachexia to cachexia to refractory cachexia – need further validation and biomarkers should be developed to help characterize these stages.

In addition, cancer patients with cachexia need to be evaluated ideally in cachexia clinics that can provide the 'best supportive care' and carry out assessments of factors such as REE, hormonal evaluations and accurate measurements of body composition, which can be cumbersome, in order to treat cachexia effectively and support high-quality clinical trials. In the absence of strong clinical evidence, treatment should be personalized to each patient's unique medical scenario based on a careful assessment of symptom burden and review of patients' goals of care, and treatment tailored to maximize benefit and minimize potential risks of pharmacological interventions for anorexia–cachexia syndrome.

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Executive summary

Background

- Cancer cachexia, the loss of skeletal muscle (with or without the loss of fat mass) is a multifactorial syndrome characterized by negative protein and energy balance.
- Recently, a three level staging system has been proposed for cancer cachexia: precachexia to cachexia to refractory cachexia.
- Limited pharmacological interventions exist for the treatment of cancer cachexia and mainly include corticosteroids and megestrol acetate that do stimulate appetite but not accompanied by improvements in fat-free mass or performance status.

Novel therapies

- Supplementation with omega-3 fatty acids found in fish oil show promise for the treatment of cancer cachexia.
- Future studies of omega-3 fatty acids should be designed to promote compliance and be introduced earlier in the progression of cancer cachexia.
- Initial studies of melatonin for cancer cachexia were promising, but a well-designed, randomized, double-blind trial reported no significant benefits for patients with advanced gastrointestinal or lung malignancies.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) may benefit cancer patients with cachexia and the use of NSAIDs as a single agent may be less effective than in combination therapy.
- Future research should evaluate the relative the benefits of COX-2 inhibitors versus older NSAIDs in the treatment of cancer cachexia.

Future perspective

- Multimodality treatment appears to be promising for the treatment of cancer cachexia and research needs to identify the combination of agents that works best.
- Androgens and selective androgen receptor modulators, ghrelin and ghrelin mimetics, as well as β-blockers are under investigation as novel agents for the treatment of cancer cachexia.

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