REVIEW

Cancer cachexia, mechanism and treatment

Tomoyoshi Aoyagi, Krista P Terracina, Ali Raza, Hisahiro Matsubara, Kazuaki Takabe

Tomoyoshi Aoyagi, Krista P Terracina, Ali Raza, Kazuaki Takabe, Division of Surgical Oncology, Department of Surgery, Virginia Commonwealth University School of Medicine and the Massey Cancer Center, Richmond, VA 23298-0011, United States
Tomoyoshi Aoyagi, Hisahiro Matsubara, Department of Frontier Surgery, Graduate School of Medicine, Chiba University, Chiba 263-0022, Japan
Correspondence to: **Kazuaki Takabe, MD, PhD, FACS,** Division of Surgical Oncology, Department of Surgery, Virginia Commonwealth University School of Medicine and the Massey Cancer Center, West Hospital 7-402, 1200 East Broad Street, Richmond, VA 23298-0011, United States. ktakabe@vcu.edu
Telephone: +1-804-8289322
Fax: +1-804-8284808

Abstract

It is estimated that half of all patients with cancer eventually develop a syndrome of cachexia, with anorexia and a progressive loss of adipose tissue and skeletal muscle mass. Cancer cachexia is characterized by systemic inflammation, negative protein and energy balance, and an involuntary loss of lean body mass. It is an insidious syndrome that not only has a dramatic impact on patient quality of life, but also is associated with poor responses to chemotherapy and decreased survival. Cachexia is still largely an underestimated and untreated condition, despite the fact that multiple mechanisms are reported to be involved in its development, with a number of cytokines postulated to play a role in the etiology of the persistent catabolic state. Existing therapies for cachexia, including orexigenic appetite stimulants, focus on palliation of symptoms and reduction of the distress of patients and families rather than prolongation of life. Recent therapies for the cachectic syndrome involve a multidisciplinary approach. Combination therapy with diet modification and/or exercise has been added to novel pharmaceutical agents, such as Megestrol acetate, medroxyprogesterone, ghrelin, omega-3-fatty acid among others. These agents are reported to have improved survival rates as well as quality of life. In this review, we will discuss the emerging understanding of the mechanisms of cancer cachexia, the current treatment options including multidisciplinary combination therapies, as well an update on new and ongoing clinical trials.

Key words: Physical exercise; Pharmacological treatment; Cancer cachexia

Core tip: This review aims to present the clinical presentation, the mechanisms, and current treatment options, such as pharmacological treatment and physical exercise for cancer cachexia.

INTRODUCTION

Although there is no single universally agreed upon definition of cachexia, a recent consensus statement

states that cachexia is a complex metabolic syndrome associated with underlying illness, and is characterized by the loss of muscle with or without loss of fat mass. Cachexia is seen in many medical conditions, including cancer, acquired immunodeficiency syndrome (AIDS), chronic obstructive pulmonary disease, multiple sclerosis, chronic heart failure, tuberculosis, familial amyloid polyneuropathy, mercury poisoning (acrodynia) and hormonal deficiency[1,2]. Cancer cachexia is characterized by systemic inflammation, negative protein and energy balance, and an involuntary loss of lean body mass, with or without wasting of adipose tissue[3]. Clinically, cachexia is represented by significant weight loss in adults and failure to thrive in children[4], accompanied by alterations in body composition and a disturbed balance of biological systems[5-7]. Whilst the loss of skeletal muscle mass is the most obvious symptom of cancer cachexia, cardiac muscle is also depleted, though muscle of other visceral organs tend to be preserved. Though cachexia is seen in several disease states, the loss of muscle mass has been shown to occur most rapidly in cancer patients[8].

Cancer cachexia is an insidious syndrome that not only has a dramatic impact on patient quality of life, but is also associated with poor responses to chemotherapy and survival[9-11]. Indeed, cachexia occurs in the majority of terminal cancer patients and, according to Warren, is responsible for the death of 22% of cancer patients[12,13].

Current therapies focus on palliation of symptoms and the reduction of distress of patients and families rather than cure[14]. In many cases, cachexia remains a largely underestimated and untreated condition[4,15]. Approximately half of all patients with cancer experience cachexia[16,17], with the prevalence rising as high as 86% in the last 1-2 wk of life[18,19], and with 45% of patients losing more than 10% of their original body weight over the course of their disease progression[19]. Death usually occurs when there is 30% weight loss[5]. The best management strategy of cancer cachexia is to treat the underlying cancer as this will completely reverse the cachexia syndrome. Unfortunately, this remains an infrequent achievement with advanced cancers. A second option could be to counteract weight loss by increasing nutritional intake, but since in the majority of cachectic patients anorexia is only a part of the problem, nutrition as a unimodal therapy has not been able to completely reverse the wasting associated with cachexia.

In this review, we discuss the presentation, mechanisms, and current treatment options for cancer cachexia, including diet and exercise therapy to improve quality of life as well as prognosis for affected patients.

CANCER CACHEXIA AND MALIGNANT INFLAMMATION

Multiple mechanisms are involved in the development of cachexia, including anorexia, decreased physical activity, decreased secretion of host anabolic hormones, and an altered host metabolic response with abnormalities in protein, lipid, and carbohydrate metabolism[20]. Due to the complex clinical findings, guidelines for the diagnosis of cachexia have just recently started to appear[3]. Even so, there is great variation in definitions, which presents problems when comparing studies and informing clinical diagnoses[21,22] (Table 1).

One proposed mechanism of cancer cachexia is that it is an integrated physiological response of substrate mobilization driven by inflammation[23]. There is an increase in pro-inflammatory cytokine activity during cancer progression[24,25], and systemic inflammation is a hallmark of cancer cachexia, indicated by the production of acute-phase response (APR) proteins such as C-reactive protein (CRP) and fibrinogen[26,27]. CRP is considered to be an accurate measure of the pro-inflammatory cytokine activity[28] that has been implicated in muscle wasting[29]. The APR is related to the inflammation and weight loss seen in cachexia[30,31] and the reduced quality of life and shortened survival of cachexia patients[10,32-35]. These phenomena increase muscle catabolism and transfer amino acids from muscle anabolism toward the amino acid pool required for APR protein anabolism[36,37]. It has been suggested that eicosanoids also mediate inflammation in cancer cachexia[38-40].

There is considerable evidence that signaling through cytokines and myostatin/activin pathways has a role in cancer cachexia and anorexia[41-43] (Figure 1). Numerous cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6, and interferon-gamma (IFN-γ), have been postulated to play a role in the etiology of cancer cachexia[44-52]. The cytokines are transported across the blood-brain barrier where they interact with the luminal surface of brain endothelial cells causing release of substances that affect appetite[53]. Receptors of TNF-α and IL-1 are found in the hypothalamic areas of the brain, which regulate food intake. Anorexia induced by both TNF-α and IL-6 can be blocked by inhibitors of cyclooxygenase, suggesting that a prostaglandin, such as PGE2, may be the direct mediator of appetite suppression[54].

The role of TNF-α in mediating cancer cachexia is supported by evidence that intraperitoneal injection of a soluble recombinant human TNF-receptor antagonist improved food intake and weight gain in tumor-bearing rats[55]. TNF-α increases gluconeogenesis, lipolysis and proteolysis, decreases the synthesis of proteins, lipids and glycogen, induces the formation of IL-1[17], and stimulates the expression of Uncoupling proteins (UCP) 2 and UCP3 in cachectic skeletal muscle[8]. Despite the fact that TNF-α induces the symptoms of cachexia, its inhibition has not been shown to stop or to reverse cancer cachexia[49]. This indicates that though TNF-α may be involved in the development of cachexia, it is not solely responsible for the effects seen in cachectic

Table 1 Cancer cachexia

Treatment	Description	Physiologic benefit	Possible mechanism	Ref.
Megestrol acetate	Active progesterone derivative	Improves appetite, caloric intake, nutritional status, quality of life	Unknown; possible neuropeptide Y release	[80-92]
Medroxyprogesterone	Active progesterone derivative	Improves appetite, food intake Weight stabilization	Decreases serotonin, IL-1, IL-6, TNF-α	[93-96]
Ghrelin	Gastric peptide hormone	Improves lean + total body mass, hand grip, cardiac function (CHF cachexia only)	Growth hormone receptor secretagogue	[105]
Delta-9-tetrahydrocannabinol	Cannabinoid	MIXED May improve food intake, weight gain	Possible endorphin receptor activation, Inhibition of prostaglandin, IL-1	[85,106-110]
Melanocortin antagonists	Adrenocorticotropic hormone antagonist	UNTESTED; prevention of anorexia, loss of lean body mass or basal energy (animal only)	Neuropeptide Y alteration or melanocortin-4 receptor antagonism	[112,113]
Thalidomide	Immunomodulatory	Limits weight and lean body mass loss	Decreases TNF-α, pro-inflammatory cytokines, nuclear factor kappa B, cyclooxygenase 2, angiogenesis	[124-126]
Etanercept	Immunomodulatory	Limits fatigue; improves adjuvant therapy adherence	Decreases TNF effect	[127]
Eicosapentaenoic acid/omega-3-fatty acids	Lipid	MIXED; may improve weight, appetite, quality of life	Decreases pro-inflammatory cytokines, proteolysis inducing factor	[129,130,133,137,140-142,146-152]
Rikkun-shito	Herbal Japanese medicine	Improves median survival with gemcitabine (pancreatic cancer); improves anorexia, GI dysmotility, muscle wasting, anxiety	Unknown	[154,155]
Corticosteroids	Immunomodulatory	Improves appetite and quality of life	Various mechanisms	[156,157]
Formoterol	β2-adrenergic agonist	UNTESTED	Protein and muscle degradation antagonism	[170]
Erythropoetin	Glycoprotein hormone	Improves patient's metabolic and exercise capacity	Decreases production of IL-6	[171-173]
ACE inhibitors	Heart medications	Reduce wasting of muscle mass	Inhibit TNF-α production	[174]
β-blockers	Heart medications	Preserved body weight, and lean and fat mass, and improved the quality of life	Normalized Akt phosphorylation	[175]

IL: Interleukin; TNF: Tumor necrosis factor.

patients.

IL-1 concentrations increase in the cachectic state and have been known to cause similar effects to TNF-α[56]. IL-1 induces anorexia in cachectic patients as it causes an increase in plasma concentrations of tryptophan, which in turn increases serotonin levels, causing early satiety and suppressing hunger[57]. Increased tryptophan leading to associated increased serotonin production from the hypothalamus has been linked to anorexia[57,58]. A conflicting study showed that IL-1 did not affect food intake or weight loss, suggesting that IL-1 has a local effect on a particular tissue or the exogenous doses of IL-1 must be larger in order to see characteristics of cachectic state[59].

IL-6 is an important mediator in the defense mechanism of humans through its regulation of immune responses[60]. Concentration levels of IL-6 increase transferrin in cancer patients[28]. Levels of IL-6 were observed to be higher in patients with cachexia than weight-stable patients. Although IL-6 may have an important role in the development of cachexia, it is not considered to be solely responsible, working through indirect action, indicated by the failure of IL-6 administration to reproduce cachexia in animal model[17]. As such, it is likely that a complex interplay of these factors is responsible for cachexia, rather

than each working in isolation[61]. However, since there is limited variation in levels of circulating cytokines[62], and circulating cytokines are produced by isolated peripheral mononuclear cells, it is speculated that local production in affected tissues is more important and relevant to cachexia than systemic circulation of these factors[63].

Signal transducers and activators of transcription 3 (STAT3) is a member of the STAT family of proteins. STAT3 function as essential signal transducing effector proteins of cytokine-induced pathways that control the development, proliferation, differentiation, homeostasis of many cell types[64]. STAT3 activation is a common feature of muscle wasting. STAT3 is activated in muscle by IL-6 and by different types of cancer and sterile sepsis[65]. It is not certain whether the cytokine production is primarily from tumor or host inflammatory cells. It has been hypothesized that either tumor cell production of pro-inflammatory cytokines or the host inflammatory cell response to tumor cells is the source of the APR proteins seen in many malignancies and in cachexia[66].

CATABOLISM

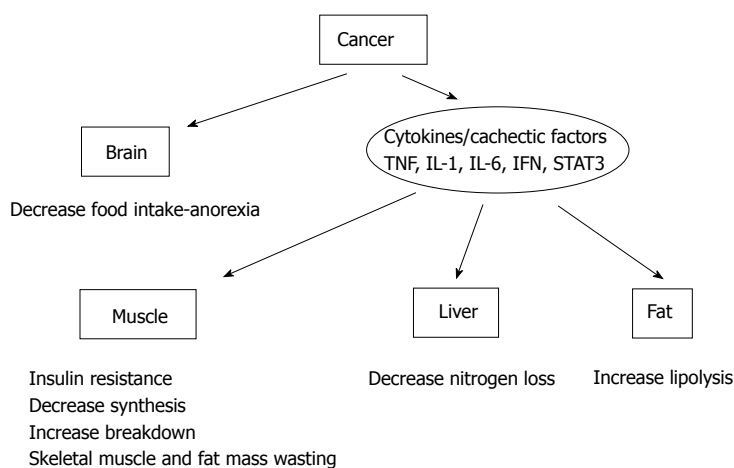A number of factors in cancer patients are known to

Figure 1 Role of tumor-induced systemic inflammation with metabolic pathways in organs affected by cancer cachexia. IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; STAT3: Signal transducers and activators of transcription 3.

increase the catabolic response, leading to unsustainable levels of fat and muscle mobilization and levels of muscle depletion that cause significant morbidity and mortality.

The metabolic changes found in cachexia resemble those of infection rather than starvation and are multifactorial and complex[67]. Although the weight loss brought on by starvation is mainly from adipose tissue stores, the weight loss of cancer cachexia is caused by loss of both skeletal muscle and adipose tissue mass[68]. In patients with cachexia there is an increase in muscle protein catabolism leading to a net loss of muscle mass. This imbalance of protein synthesis and degradation is one of the most obvious aspects of metabolism disruption in cancer cachexia. It has been widely observed that the rate of muscle protein catabolism increases in cachexia, whilst anabolism of new proteins decreases, resulting in net protein breakdown[8,69-71].

Increased energy expenditure may also contribute to the wasting process. Resting energy expenditure (REE) is increased in the cachectic state, with futile metabolic cycling accounting for much of this increase[72]. About 70% of the total energy expenditure in sedentary people arises from the REE[1]. The REE in cancer patients is strongly determined by the type of tumor. For example, patients with pancreatic and lung cancer had increased REE compared with healthy subjects[73,74]. Patients with gastric and colorectal cancer were reported to have no elevation of REE[73], though it seems that these results reflect how close the patients were to death at the time of measurement. In malnourished patients near death there is an increase in REE and in protein catabolism which could relate to the utilization of the last skeletal muscle mass[75].

Although skeletal muscle is the most important site for thermogenesis in the adult human, brown adipose tissue (BAT) is also known to have an important role in cachexia. Non-shivering thermogenesis takes place in BAT, and in a single study using autopsy samples of peri-adrenal tissue examined by light microscopy, BAT was observed in 20 of the cachectic cancer patients (80%) compared to 2 of the age-matched subjects (13%)[76].

UCPs, related to the regulation of mitochondrial proton gradients and the production of reactive oxygen species in skeletal muscle and adipose tissue, may also play a role in the increased REE observed in cachexia[8]. There are three UCPs: UCP1 found only in BAT, UCP2 found in most tissues, and UCP3 found only in BAT and skeletal muscle[77]. In particular, the expression of UCP2 and UCP3, associated with energy expenditure and metabolism in skeletal muscle, is upregulated in the cachectic state, indicating involvement of these mechanisms[8]. Expression levels of mRNA of UCP1 in BAT were significantly elevated over controls in mice bearing cachexia inducing tumors, while expression levels of UCP2 and -3 did not change in BAT, but were significantly increased in skeletal muscle[78]. This may also be applicable to cancer patients, since UCP-3 mRNA levels are increased in muscle only when weight loss is associated with cancer. UCP-2 mRNA levels in muscle seem unaffected by cancer either with or without weight loss[79]. The increase in UCP3 mRNA might enhance energy expenditure and contribute to tissue catabolism.

PHARMACOLOGICAL TREATMENT

Megace
Megestrol acetate (MEGACE) and medroxyprogesterone (MPA) are synthetic, orally active derivatives of the naturally occurring hormone, progesterone.

MEGACE was first synthesized in England in 1963. Developed as an oral contraceptive, the agent was first tested in the treatment of breast cancer in 1967 and, was later tested for the treatment of endometrial cancer. MEGACE is currently used to improve appetite and to increase weight in cancer-associated anorexia. From September 1993, MEGACE was approved by the Food and Drug Administration in the United States for the treatment of anorexia, cachexia or unexplained weight loss in patients with AIDS. MEGACE has been found to improve appetite, caloric intake and nutritional status in several clinical trials[80-90]. Recently a meta-analysis of 35 trials, comprising 3963 patients, for the effectiveness of MEGACE was conducted[91], demonstrating a benefit of MEGACE compared with placebo, particularly with regard

to appetite improvement and weight gain in cancer. Higher doses were more related to weight improvement than lower doses. Quality of life improvement in patients was seen only when comparing MEGACE *vs* placebo[91]. The mechanism for the associated weight gain is mostly unknown, although MEGACE may stimulate the synthesis, transport, and release of neuropeptide γ, known to produce appetite-stimulating effects in rats[92].

MPA has similarly been shown to increase appetite and food intake with a stabilization of body weight[93]. There is evidence that high-dose synthetic progestins have effects on both appetite and body weight, the two clinical hallmarks most widely identified in patients with cancer anorexia and cachexia[94]. MPA has been shown to reduce the *in vitro* production of serotonin and cytokines (IL-1, IL-6 and TNF-α) by peripheral blood mononuclear cells of cancer patients[92,93,95,96]. These findings have also been replicated in the clinical setting, with IL-1, IL-6, and TNF-α levels in serum reported to be decreased in cancer patients after MEGACE or MPA treatment[93].

Ghrelin

Ghrelin, a 28-amino-acid gastric peptide hormone, was first identified in the rat stomach in 1999 as an endogenous ligand for the growth hormone secretagogue receptor[97]. The functions of ghrelin include food intake regulation, gastrointestinal (GI) motility, and acid secretion in the GI tract. Many GI disorders involving infection, inflammation, and malignancy are correlated with altered ghrelin production and secretion[98]. Circulating levels of ghrelin are noted to be increased when human melanoma cells are implanted in nude mice[99]. In a similar manner, circulating levels of both acyl and des-acyl ghrelin are elevated in cachectic cancer patients with gastric cancer[100,101] and lung cancer[102,103]. The levels of acyl-ghrelin are reported to be 50% higher in cancer patients with cachexia[104]. These elevated levels of ghrelin could represent a counter regulatory mechanism to fight anorexia associated with tumor growth, representing an endocrine response to the so-called "ghrelin resistance" found in cancer patients. This is the rationale behind the clinical studies of high dose ghrelin as a treatment to counteract anorexia in cancer.

An experimental study showed that repeated administration of ghrelin improves cardiac structure and function and attenuates the development of cardiac cachexia in chronic heart failure, with ghrelin thought to regulate energy metabolism through growth hormone dependent and growth hormone independent mechanisms[105]. For cancer cachexia, a phase Ⅱ randomized, placebo-controlled, double-blind study, using an oral ghrelin mimetic was conducted[105]. This study demonstrated an improvement in lean body mass, total body mass and hand grip strength in cachectic cancer patients[105].

Cannabinoids

Cannabinoids, which are present in marijuana, are a class of diverse chemical compounds that activate cannabinoid receptors on cells that repress neurotransmitter release in the brain. Cannabinoids have a definite effect on weight gain and, bearing this in mind, have been used to increase food intake in cancer patients. The main effective constituent of cannabis is delta-9-tetrahydrocannabinol[106,107], but the mechanism by which cannabinoids exert their effects has yet to be clarified. It has been postulated that they may act *via* endorphin receptors, through inhibition of prostaglandin synthesis[108], or by inhibiting IL-1 secretion[85]. Despite high expectations for cannabinoids to be effective against cancer-related anorexia/cachexia syndrome, both of the two separate randomized clinical trials carried out by Jatoi *et al*[109] and Strasser *et al*[110] have failed to show benefit as compared to MEGACE or placebo, respectively.

Melanocortin antagonists

The melanocortin-4 (MC4) receptor subtype plays a pivotal role in body weight regulation[111]. Acute and chronic stimulation of MC4 receptors produces anorexia, weight loss, and an increase in metabolic rate, the cardinal features of disease-associated cachexia. Knock-out or antagonism of MC4 receptors in animal models of cachexia protects from anorexia and the loss of both lean and fat body mass, and it is suggested that an MC4 antagonist may be beneficial in wasting diseases, which are poorly treated by available therapies[112]. The MC4 receptor is involved in the anorexigenic cascade leading to a decrease in neuropeptide γ and, therefore, a decrease in food intake. The use of MC4 antagonists has been proven to be effective in preventing anorexia associated with cachexia, loss of lean body mass and basal energy in animal models[112,113]; however, there is no clinical data at this time. Future clinical trials are needed to prove the efficacy of this antagonist in the treatment of human cachexia.

Thalidomide and etanercept

TNF-α, IL-6, and IFN-c have all been implicated in the pathogenesis of cachexia, and in cachectic tumor bearing murine models treatment with anti-TNF-α, anti-IL-6, and anti-IFN-c antibodies can attenuate the disease process, although it cannot stop or reverse cancer cachexia[49,114-120]. There is also some evidence that cytokines play a role in the pathogenesis of cachexia[121]. It has been suggested that by mimicking the hypothalamic effect of excessive negative feedback signaling from leptin by persistent stimulation of anorexigenic peptides, or by inhibition of the neuropeptide Y pathway, cytokines could induce anorexia[122]. Thus modulating cytokine expression in cancer patients may also affect cancer associated anorexia. Therapeutic strategies have been based on either blocking cytokine synthesis or their action[123].

Thalidomide (a-N-phthalimidoglutaramide) has complex immune-modulatory and anti-inflammatory properties. It has been shown to down-regulate the production of TNF-α and other pro-inflammatory

cytokines in monocytes, to inhibit the transcription factor nuclear factor kappa B (NFκB), down-regulate cyclooxygenase 2, and to inhibit angiogenesis[124,125]. One randomized placebo-controlled trial in patients with cancer cachexia showed that the drug was well-tolerated and effective at attenuating loss of weight and lean body mass in patients with advanced pancreatic cancer[126].

Etanercept, a soluble p75 tumor necrosis factor receptor: FC (TNFR: FC) fusion protein for plasma cytokines, has been used over the last decade for the treatment of immune-mediated rheumatic diseases. In a clinical pilot study, patients with several advanced malignancies treated with etanercept combined with docetaxel had less fatigue and improved tolerability to anti-tumor treatment, although etanercept alone did not show effects[127].

Omega-3-Fatty acides (N-3-FA), eicosapentaenoic acid

Eicosapentaenoic acid (EPA) is one of several omega-3 polyunsaturated fatty acids found abundantly in fish oil. Polyunsaturated fatty acids have been proposed to reduce cachexia-associated tissue wasting[128] as well as tumor growth[129,130]. EPA down-regulates the production of pro-inflammatory cytokines in both healthy individuals and patients with cancer. Furthermore, the effects of proteolysis inducing factor, a cachectic factor produced by cancer, are also inhibited by EPA.

Three systematic reviews have been published regarding n-3-FA. Only one of these formulated a weak recommendation of n-3-FA for patients with advanced cancer and weight loss[131], stating that there was fair evidence to recommend its use (recommendation grade B). The other two reviews found no clear advantages from treatment with n-3-FA. A meta-analysis by Colomer *et al*[131] contained 17 trials[61,132-146], and attempted to evaluate the effectiveness and safety of n-3-FA in relieving symptoms associated with the cancer cachexia syndrome. They reported that EPA improved various clinical, biochemical, and quality of life parameters after 8 wk of treatment. Dewey *et al*[147] showed that data were insufficient to determine whether oral EPA is better than placebo in their analysis of 5 trials[130,137,140,148,149]. Comparison of EPA *vs* MEGACE as an appetite stimulant provided no evidence that EPA improved cachexia-related symptoms[147]. Mazzotta *et al*[150] systematically reviewed several databases including publications until 2006 in order to identify the clinical efficacy of EPA and Docosahexaenoic Acid (DHA), another Omega-3-fatty acid, for the management of cachexia in cancer patients. They analyzed 10 studies and 7 RCTs[133,137,140-142,151,152] and found no clear advantage of either EPA or DHA on weight, lean muscle mass, symptoms, quality of life, or survival. Studies that reported statistically significant differences were found to have only a small clinical difference, not enough to justify the use of EPA or DHA alone as a treatment option. However, it does seem clear that multidimensional treatments represent the most useful approach for cachexia in advanced cancer[150].

Altogether, there is not enough evidence to support a net benefit from n-3-FA in treating cachexia from advanced cancer. On the other hand, adverse effects were infrequent and not severe. More research is needed not only on drugs such as eicosapentaenoic acid or other n-3-FA, but also on multimodal approaches combining drugs and non-drug interventions.

Herbal medicine (kampo)

Kampo is the Japanese herbal medical practice, which is an adaptation of traditional Chinese medicine that came to Japan between the 7th and 9th centuries. Kampo has been shown to have significant clinical benefits for cachexia[153]. Fujitsuka *et al*[154] reported that Rikkun-shito, a Kampo formula, improved anorexia, gastrointestinal dysmotility, muscle wasting, and anxiety-related behavior. Rikkun-shito improved anorexia-cachexia and prolonged survival of tumor-bearing rats in this study. Moreover, Rikkun-shito significantly prolonged median survival of pancreatic cancer patients with ascites who were treated with gemcitabine. These studies suggest that Rikkun-shito may be useful in clinical practice for cachectic cancer patients. Although the mechanisms of how the herbs demonstrate these effects are unclear and remain to be elucidated, they deserve further studies as new potential therapy agents for cancer treatment[155].

Corticosteroids

Corticosteroids are one of the most widely used appetite stimulants. In randomized controlled studies, they have been shown to improve appetite and quality of life compared with placebo[156]. MEGACE and corticosteroids seem equally effective, although for long-term use, corticosteroids result in more serious adverse effects such as protein breakdown, insulin resistance, water retention, and adrenal suppression[157]. Therefore, corticosteroids are not suitable for long-term use and should be used in a limited fashion, such as during the pre-terminal phase of cachexia.

Non-steroidal anti-inflammatory drugs

There are four studies investigating the relationship between non-steroidal anti-inflammatory drugs (NSAIDs) and cancer cachexia[158-161]. These studies demonstrated improved quality of life, performance status, inflammatory markers, weight gain and survival. Notably these reviews show that side effects of NSAIDs use were not remarkable in these reports that were evaluated.

However, two reports concluded data were insufficient for recommending the widespread use of NSAIDs in practice[162,163]. This reflection arises from the large heterogeneity observed in terms of study design, number of patients, type of cancer, clinical parameters, definition of effect criteria, and the weakness of the many individual studies.

β2-adrenergic agonists

β2-adrenergic agonists are potent muscle growth promoters in many animal species resulting in skeletal muscle hypertrophy[164-167], and reduction of the body fat

content[168,169]. The wide variety of physiologic functions controlled by β-adrenergic receptors suggest that the mechanisms underlying effects on carcass composition may be extremely complex.

Formoterol is a long-acting β2 agonist approved for the management of asthma and chronic obstructive pulmonary disease. Formoterol exerts a selective, powerful protective action on heart and skeletal muscle by antagonizing the enhanced protein degradation, which is a characteristic of cancer cachexia. β2-agonists are also proposed to have a protective action against the apoptosis of skeletal muscle. Formoterol may be potential therapeutic tool in pathologic states[170].

Others
Other drugs that are investigated to be used for cancer cachexia include Erythropoetin[171-173], ACE inhibitors[174], and β-blockers[175].

Chemotherapy
At the present time, cancer cachexia cannot be cured. However, several recent randomized trials using combinations of newer chemotherapy agents have shown promising results. Combination chemotherapy was initially assessed with low-efficacy regimens designed for symptomatic management in the palliative setting until effective regimens were discovered that were found to improve survival in the adjuvant setting[176]. Regimens combining multiple drugs are expected to be successful. In a phase II study, the combined administration of anti-oxidants, pharmaco-nutritional support, progestagen and anti-cyclooxygenase-2 drugs, was shown to be safe and effective for cancer cachexia[177]. Based on those results, an ongoing randomized phase III study began recruiting patients in 2005, with the aim of including more than 300 cachectic cancer patients. Findings to date reinforce the use of multi-modal therapies in the treatment of the cachexia-anorexia syndrome in cancer. Usually the response to therapy is better with early intervention during active adjuvant or palliative cancer therapy, compared to treatment when the patient has progressed to become refractory to anti-cachexia treatment. One of the challenges to undertaking "upfront" randomized trials for cachexia is that the systemic chemotherapy for cancer treatment itself can aggravate weight loss, and for anti-cachexia therapy to show benefit it has to "compete" with chemotherapy.

NON-PHARMACOLOGICAL TREATMENT

Dietary treatment
Since cancer cachexia differs from starvation, at the present time no single modality therapies using traditionally applied nutritional regimens has succeeded in demonstrate any efficacy in improving weight gain, including gain in lean body mass, in patients diagnosed with cancer cachexia[178]. The average calorie deficit in a weight-losing patient is reported to be approximately 200 kcal per day in the setting of advanced cancer[132] and 250-400 kcals/d in those patients with cancer cachexia[178]. An average supplementation of 1 calorie/mL has not been shown to improve the nutritional status of patients receiving chemotherapy[140,179].

The average protein intake in patients with cancer cachexia is about 0.7-1.0 g/kg per day[140]. Food energy intake needs to increase by 300-400 kcal per day and protein intake to increase by up to 50% to have an effect on anabolic resistance (recommended intake 1.0-1.5 g/kg per day). The analysis of a randomized trial found that in addition to oral nutritional support, the use of parenteral nutrition resulted in a short (6-8 wk) but significant (*P* < 0.001), prolongation of survival when nutritional goals were achieved[180]. A meta-analysis of oral nutritional interventions in malnourished patients with cancer suggests that oral nutritional interventions have no effect on survival and that the effect on body weight and energy intake is inconsistent, though statistically significant improvements in some aspects of QOL may be achieved. In this study, nutritional intervention was associated with a significant increase in energy intake (430 kcal per day) and a weight gain of 1.9 kg. There was a beneficial effect on appetite and global quality of life[181].

Physical exercise
Physical exercise has been suggested as a promising countermeasure for preventing cachexia[182]. Unfortunately, only a few studies, in both clinical and experimental settings, have been performed to define the effectiveness of exercise against cachexia.

The rationale for the use of exercise relies on the known dramatic reduction of muscle strength and endurance during cachexia[183-186]. Since it is also reported that exercise increases insulin sensitivity, protein synthesis rate, and anti-oxidative enzyme activity[187] it may lead to a suppression of the inflammatory response and enhancement of immune function[188]. There is significant evidence that endurance exercise (*e.g.,* a high number of repetitions performed over extended time periods against relatively low resistance) ameliorates cancer-related fatigue[189]. A randomized trial has also reported that, in patients with advanced-stage cancer, exercise is feasible and that although fatigue is not reduced, physical performance is improved significantly[190]. Combination of resistance and aerobic muscle training has been suggested to be incorporated into cachexia treatment programs[191]. Exercise training is able to increase both strength and endurance in healthy conditions, depending on the type of exercise, and moreover, it has been proven to act as an excellent anabolic drive for skeletal muscle in combination with anabolic steroids or other muscle anabolic drugs[192].

FUTURE DIRECTIONS
Additional directions for study in the field of cancer

cachexia may come from the results of Bossola *et al*[193] who showed hyper-expression of mRNA for ubiquitin and increased proteolytic activity of proteasomes prior to weight loss in cancer patients. This finding could open a new research area in the field of early intervention and of prevention of cancer induced weight loss. Further research is also needed into cancer anorexia, due to the frequent finding of reduced food intake in cancer patients, and the lack of any current powerful therapies to improve appetite and daily caloric intake.

CONCLUSION

Cancer cachexia has been regarded as a non-curable disease, and has been estimated to be responsible for the death of over 20% of cancer patients. The management of cancer cachexia has improved dramatically in the past decade, as the mechanisms involved in the development and progression of the condition continue to be elucidated. Currently all treatments for cancer cachexia are considered palliative, but new agents have improved patient survival as well as their quality of life. Regular anti-neoplastic agents have the ability to treat cancer, but in many cases worsen cachexia. Future progress in the field will be realized through development of treatment agents with the ability to affect cancer progression as well as improve patient quality of life.

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