Cancer Anorexia-Cachexia Syndrome: Current Issues in Research and Management

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ABSTRACT Cachexia is among the most debilitating and life-threatening aspects of cancer. Associated with anorexia, fat and muscle tissue wasting, psychological distress, and a lower quality of life, cachexia arises from a complex interaction between the cancer and the host. This process includes cytokine production, release of lipid-mobilizing and proteolysis-inducing factors, and alterations in intermediary metabolism. Cachexia should be suspected in patients with cancer if an involuntary weight loss of greater than five percent of premorbid weight occurs within a six-month period.

The two major options for pharmacological therapy have been either progestational agents, such as megestrol acetate, or corticosteroids. However, knowledge of the mechanisms of cancer anorexia-cachexia syndrome has led to, and continues to lead to, effective therapeutic interventions for several aspects of the syndrome. These include antiserotonergic drugs, gastroprokinetic agents, branched-chain amino acids, eicosapentanoic acid, cannabinoids, melatonin, and thalidomide—all of which act on the feeding-regulatory circuitry to increase appetite and inhibit tumor-derived catabolic factors to antagonize tissue wasting and/or host cytokine release.

Because weight loss shortens the survival time of cancer patients and decreases performance status, effective therapy would extend patient survival and improve quality of life. *(CA Cancer J Clin 2002;52:72-91.)*

INTRODUCTION

Anorexia, involuntary weight loss, tissue wasting, poor performance, and ultimately death characterize cancer cachexia—a condition of advanced protein calorie malnutrition.[1-9] Referred to as "the cancer anorexia-cachexia syndrome," anorexia, or loss of compensatory increase in feeding, is a major contributor to the development of cachexia.

The word "cachexia" is derived from the Greek words "kakos" meaning "bad" and "hexis" meaning "condition."[1] About half of all cancer patients suffer from this syndrome.[2]

In general, while patients with hematological malignancies and breast cancer seldom have substantial weight loss, most other solid tumors are associated with a higher frequency of cachexia. At the moment of diagnosis, 80 percent of patients with upper gastrointestinal cancers and 60 percent of patients with lung cancer have already experienced substantial weight loss.[2]

Cachexia is more common in children and elderly patients and becomes more pronounced as the disease progresses. The prevalence of cachexia increases from 50 percent to more than 80 percent before death and in more than 20 percent of patients, cachexia is the main cause of death.[2] Cachexia occurs secondarily as a result of a functional inability to ingest or use nutrients. This can be related to mechanical interference in the gastrointestinal tract, such as obstruction or malabsorption, surgical interventions, or treatment-related toxicity. And in patients receiving chemotherapy or radiation therapy, nausea, vomiting, taste changes, stomatitis, and diarrhea can all contribute to weight loss.[8]

Patients with cancer often experience psychological distress as a result of uncertainties about the disease, its diagnosis, treatment, and anticipated final outcome. This psychological state, which often coexists with depression, is bound to affect food intake.

Thus, cancer anorexia-cachexia syndrome is seen as a multidimensional (mal)adaptation encompassing a variety of alterations that range from physiological to behavioral and is correlated with poor outcomes and compromised quality of life.

DETECTION OF CACHEXIA

A patient's nutritional state is usually evaluated with a combination of clinical assessment and anthropometric tests, such as body weight, skin fold thickness, and mid-arm circumference.[10,11] But most clinicians rely on body weight as the major measure of nutritional status, using usual adult weights as a reference.

Although the range of body weight is wide, the range of individual weight fluctuations over time is known to be much narrower. It was shown that the 95% confidence intervals for change in body weight in healthy adults were approximately ±2% in one month, ±3.5% in three months, and ±5% within a six-month period of follow-up.[5,12] Therefore, any weight change occurring at a higher rate can be considered abnormal. Cachexia should be suspected if an involuntary weight loss of greater than 5 percent of premorbid weight is observed within a six-month period, especially when combined with muscle wasting. Often a weight loss of 10 percent or more, which indicates severe depletion, is used as a starting criterion for the anorexia-cachexia syndrome in obese patients. It was shown by body compartment analysis that patients with cachexia lose roughly equal amounts of fat and fat-free mass.[5,13] Losses of fat-free mass are centered in skeletal muscle and reflect decreases in both cellular mass and intracellular potassium concentration.[5,13]

Cancer patients with a known involuntary 5% weight loss have a shorter median survival rate than patients with stable weight.[14] Patients with weight loss also respond poorly to chemotherapy and experience increased toxicity.[12] It should be emphasized that cachexia can be an early manifestation of tumor-host interaction (i.e., pulmonary and upper aerodigestive cancers).

A number of laboratory tests to assist in evaluation of nutritional status are available, such as the measurement of short half-life proteins (transferrin and transthyretin) and analysis of urinary metabolites (creatinine), but many of these are of limited value among cancer patients because of the chronic nature of malnutrition.[10,11]

Serum albumin is one of the most common parameters used because of its low cost and accuracy, in the absence of liver and kidney diseases. Fat and muscle differ in their water composition and therefore, their electrical impedance.[10,11] Bio-electrical impedance analysis measures impedance between surface electrodes on the extremities in order to estimate total body lean mass. Although not

routinely used, this method can provide data that is helpful in evaluating investigational treatments and, in the future, may become more important in clinical practice than simple measurement of weight, which cannot discriminate lean tissues and fat mass.

PATHOGENETIC MECHANISMS OF CACHEXIA

Anorexia

Energy intake has been shown to be substantially reduced among weight-losing cancer patients.[15,16] Cancer patients may frequently suffer from physical obstruction of the gastrointestinal tract, pain, depression, constipation, malabsorption, debility or the side effects of treatment such as opiates, radiotherapy, or chemotherapy—any of which may decrease food intake.[6] Cancer-associated hypercalcemia is a fairly common medical emergency and leads to nausea, vomiting, and appetite loss.

However, there remains a large number of patients with cancer in whom there is no obvious clinical cause of reduced food intake.

Disruption of Leptin Regulation

Weight loss is a potent stimulus to food intake in healthy humans and animals (Figure 1). The persistence of anorexia in cancer patients therefore implies a failure of this adaptive feeding response, which is so robust in normal subjects.[17-20]

Leptin, a hormone secreted by adipose tissue, is now known to be an integral component of the homeostatic loop of body weight regulation.[21-28] Leptin plays an important role in triggering the adaptive response to starvation since weight loss causes leptin levels to fall in proportion to the loss of body fat.

Low leptin levels in the brain increase the activity of the hypothalamic orexigenic signals that stimulate feeding and suppress energy expenditure, and decrease the activity of anorexigenic signals that suppress appetite and increase energy expenditure.[17-20] Most of the orexigenic signals are known to be up-regulated through fasting in experimental animals. This suggests these signals play an important role in facilitating the recovery of lost weight.

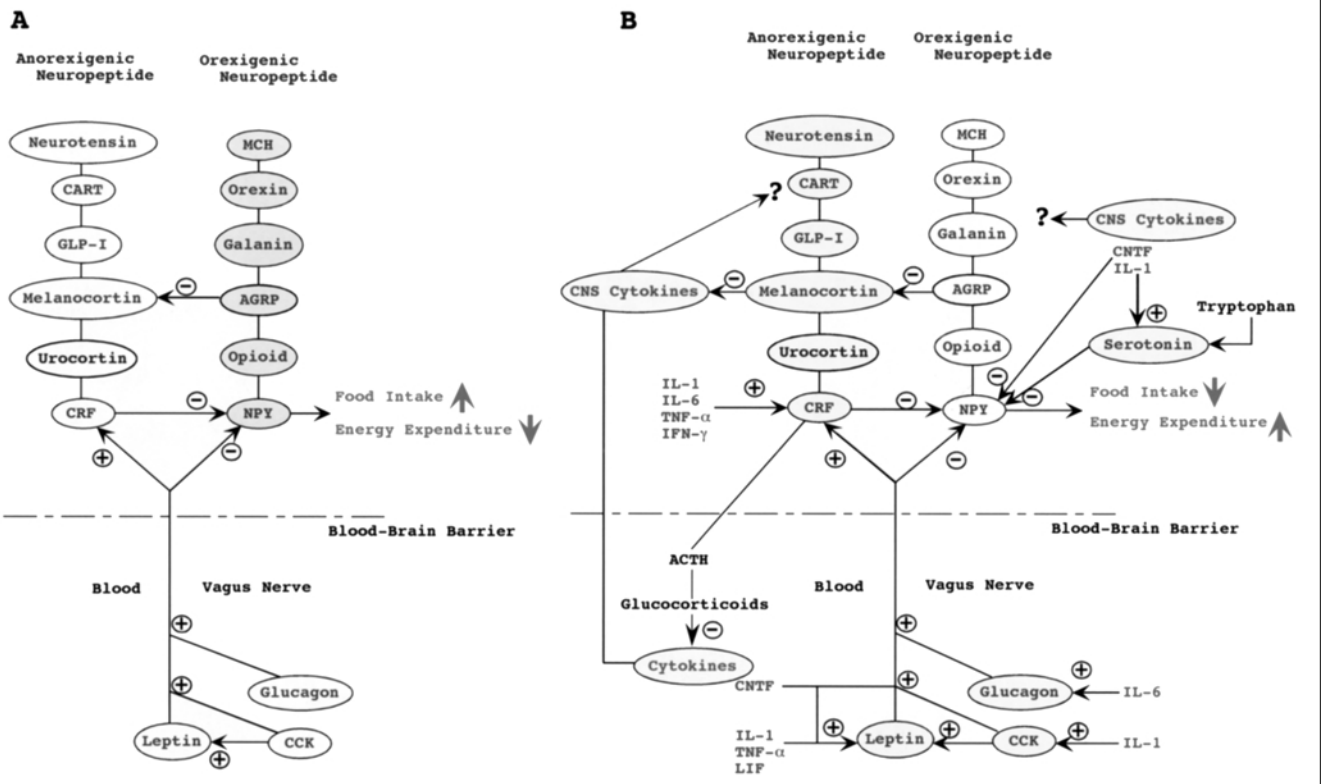
Cancer-induced anorexia may result from circulating factors produced by the tumor or by the host in response to the tumor (Figure 1). Several cytokines have been proposed as mediators of the cachectic process, among which are tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon-γ (IFN-γ).[1,4,29-37] High serum levels of TNF-α, IL-1, and IL-6 have been found in some (but not all) cancer patients, and the levels of these cytokines seem to correlate with the progression of the tumors.[38-40]

Chronic administration of these cytokines, either alone or in combination, is capable of reducing food intake and reproducing the distinct features of the cancer anorexia-cachexia syndrome.[1,4,38-41] These cytokines may produce long-term inhibition of feeding by stimulating the expression and release of leptin and/or by mimicking the hypothalamic effect of excessive negative feedback signaling from leptin, leading to the prevention of the normal compensatory mechanisms in the face of both decreased food intake and body weight (Figure 1).[4,16,32] Therefore, the weight loss seen in cancer patients differs considerably from that seen in simple starvation (Table 1).

Disruption of Neuropeptide Y Regulation

Another mechanism is related to neuropeptide Y (NPY)—a 36-amino acid peptide that is abundantly distributed in the

FIGURE **1**



A simplified model of the hypothalamic neuropeptide circuitry in response to starvation (A) and cancer anorexia-cachexia (B). Leptin acts as part of a feedback loop to maintain constant stores of fats. This is achieved by hypothalamic neuropeptides downstream of leptin that regulate food intake and energy expenditure. A loss of body fat (starvation) leads to a decrease in leptin, which in turn leads to a state of positive energy balance wherein food intake exceeds energy expenditure. This compensatory response is mediated by increased production, release, and/or action of neuropeptide Y (NPY) and other orexigenic neuropeptides, as well as decreased activity of anorexigenic neuropeptides such as corticotropin-releasing factor (CRF) and melanocortin (A). In tumor-bearing states, cachectic factors such as cytokines elicit effects on energy homeostasis that mimic leptin in some respects, and the increased hypothalamic actions of these mediators induce anorexia and unopposed weight loss (B). This could be accomplished through persistent inhibition of the NPY orexigenic network and stimulation of anorexigenic neuropeptides although the exact nature and hypothalamic pathways participating in the response remain to be determined. Serotonin may also play a role in the development of cancer anorexia. Increased levels of plasma and brain tryptophan, the precursor of serotonin, and IL-1 may underlie the increased serotonergic activity.

AGRP = Agouti-related peptide.

MCH = Melanin-concentrating hormone.

CART = Cocaine- and amphetamine-related transcript.

GLP-I = Glucagon-like peptide-I (7-36) amide.

CCK = Cholecystokinin.

CNS = Central nervous system.

IL-1 = Interleukin-1.

IL-6 = Interleukin-6.

TNF-α = Tumor necrosis factor-alpha.

IFN-γ = Interferon-gamma.

CNTF = Ciliary neurotrophic factor.

Source: *Inui A. Cancer anorexia-cachexia syndrome: Are neuropeptides the key? Cancer Res 1999;59:4493-4501* with modification.

TABLE **1**

Characteristics of Cancer Versus Starvation Cachexia

Variable	Starvation	Cancer
Energy intake	↓	↓(→*)
Energy expenditure (resting)	↓	↑
Body fat	↓	↓
Skeletal muscle	→	↓
Liver	↓†	↑‡

*There are several reports that cancer patients or animal models show seemingly normal food intake. However, in most cases this should be considered insufficient compensatory food intake in the face of decreased body weight.
†Atrophy.
‡Increased size and metabolic activity.

brain, including the hypothalamus, and is situated downstream from leptin in this pathway.[25,27] NPY is the most potent feeding-stimulatory peptide and consists of an interconnected orexigenic network that includes galanin, opioid peptides, melanin-concentrating hormone (MCH), orexin, and agouti-related peptide (AGRP) (Figure 1). NPY may stimulate feeding on its own and also via stimulation of the release of the other orexigenic peptides.

Previous studies demonstrated that NPY feeding systems are dysfunctional in anorectic tumor-bearing rats. NPY injected intrahypothalamically stimulated feeding less potently in rats bearing methylcholanthrene-induced sarcoma than in controls. This was observed prior to the onset of anorexia and became more severe as the rats developed anorexia.[42] The level or release of NPY in the hypothalamus is also reduced in tumor-bearing rats, whereas it is increased in fasting animals and in nutritional controls that have their food restricted to match their body weight to the carcass weight of tumor-bearing rats.[43,44] IL-1β administered directly into cerebral ventricles antagonizes NPY-induced feeding in rats at a dose that yields estimated pathophysiological concentrations in the cerebrospinal fluid such as those observed in anorectic tumor-bearing rats.[45-47] IL-1β decreases hypothalamic NPY mRNA levels that are specific to and not associated with a generalized reduction in the brain levels.[46]

The hypothalamic NPY system is thus one of the key neural pathways disrupted in anorexia induced by IL-1β and other cytokines. However, no change or even increase in NPY mRNA levels were reported in the hypothalamus of tumor-bearing rats,[48,49] suggesting the involvement of other orexigenic and/or anorexigenic signals in anorexia and body weight loss.

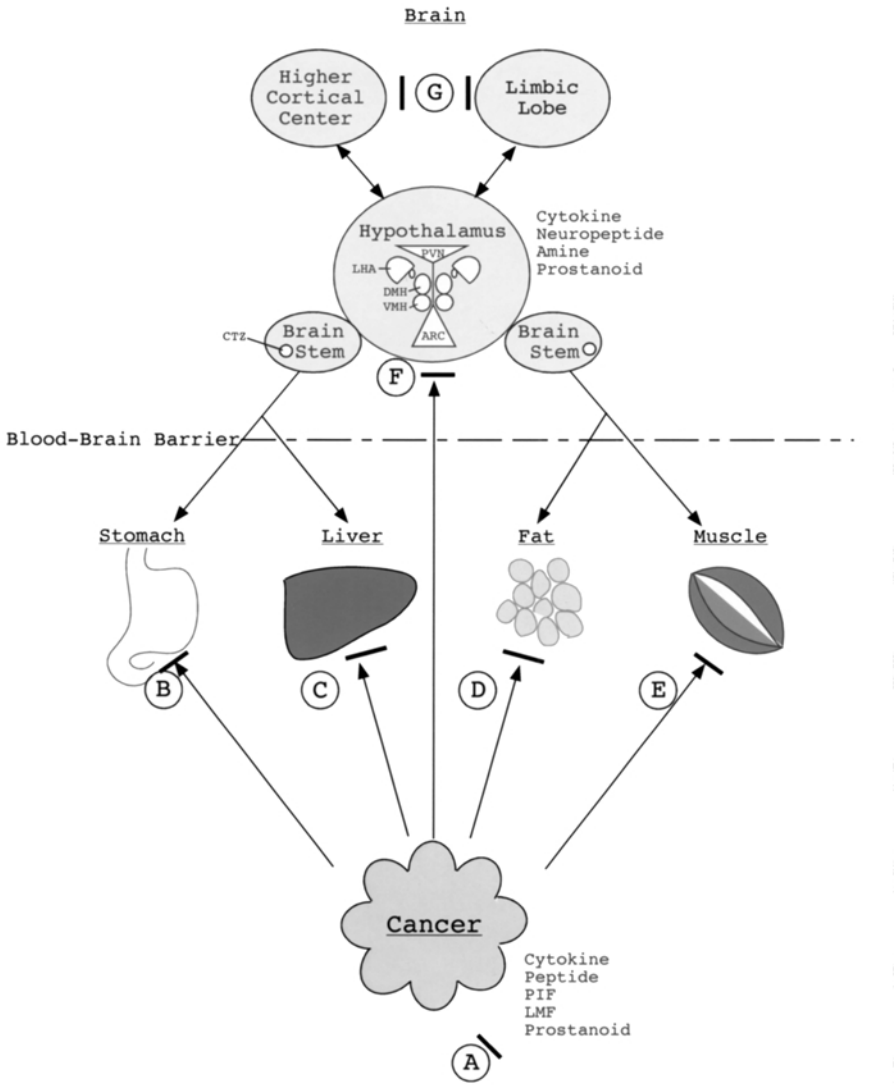
Aberrant Melanocortin Signaling

It was recently reported that aberrant melanocortin signaling may be a contributing factor in anorexia and cachexia[50-52] (Figure 1). Melanocortins are a family of regulatory peptides that includes adrenocorticotropin (ACTH) and the melanocyte-stimulating hormones (MSH). This group of peptides and their receptors help regulate appetite and body temperature, and are also important in memory, behavior, and immunity.[25-27] Despite marked loss of body weight, which would normally be expected to down-regulate the anorexigenic melanocortin signaling system as a way to conserve energy stores, the melanocortin system remained active during cancer-induced cachexia. Central melanocortin receptor blockade by AGRP or other antagonists reversed anorexia and cachexia in the animal models, suggesting a pathogenetic role for this system.[50-52]

Hypermetabolism

Hypermetabolism, defined as an elevation in resting energy expenditure, is a cardinal feature

FIGURE **2**



The potential modalities of pharmacological intervention of cancer anorexia-cachexia syndrome. Agents were classified as those established (First-line) or those unproven/investigational (Second-line), depending on their site or mechanism of actions. (A), inhibitors of production/release of cytokines and other factors; (B), gastroprokinetic agents with or without antinausea effect; (C), blockers of Cori cycle; (D)(E), blockers of fat and muscle tissue wasting; (F), appetite stimulants with or without antinausea effect; and (G), anti-anxiety/depressant drugs. These agents should be selected on an individual basis according to the cause of cachexia or the state of the patient.

First-line treatments

- Glucocorticoids (F) (A)
- Progesterones (F) (A)

Second-line treatments

- Cannabinoids (F)
- Cyproheptadine (F)
- Branched-chain amino acids (E) (F)
- Metoclopramide (B) (F)
- Eicosapentanoic acid (D) (E) (A)
- 5′–deoxy-5-fluorouridine (A)
- Melatonin (A)
- Thalidomide (A)
- β2-adrenoceptor agonists (E)
- Non-steroidal anti-inflammatory drugs (A) (F)
- Others
  - Anabolic steroids (E)
  - Pentoxifylline (A)
  - Hydrazine sulfate (C)

ARC=Arcuate nucleus of the hypothalamus; VMH=Ventromedial nucleus of the hypothalamus; DMH=Dorsomedial nucleus of the hypothalamus; LHA=Lateral hypothalamic area; PVN=Paraventricular nucleus of the hypothalamus; CTZ=Chemoreceptor trigger zone; PIF=proteolysis-inducing factor; LMF=Lipid mobilizing factor.

of cachexia, but not of starvation.[5] Hypermetabolism may be the direct cause of weight loss in some cachectic patients, although there are conflicting reports about total energy expenditure in malignant disease.[53] Total energy expenditure involves resting energy expenditure (approximately 70 percent), voluntary energy expenditure (25 percent), and energy expenditure in digestion (5 percent). Voluntary energy expenditure may be decreased in cachexia, which may manifest clinically as apathy, fatigue, and depression.[5,53,54] However, it is clear that there is an imbalance between energy intake and expenditure, with food intake being relatively inadequate to meet the body's current requirements. This imbalance is important as the mechanism of weight loss and also as a possible guide to nutritional requirements.

The orexigenic and anorexigenic signals are known to respectively decrease and increase sympathetic nervous activity, which regulates energy expenditure by activating thermogenesis in brown adipose tissue in rodents and possibly in muscle in humans, through induction of the mitochondrial uncoupling protein (UCP) (Figures 1 and 2).[21-28] It has recently been suggested that activation of UCP in muscle and white adipose tissue by cytokines might be a molecular mechanism underlying the increase in heat production and muscle wasting.[4,55]

Altered Carbohydrate Metabolism

A variety of changes in nutrient metabolism have been described in patients with cancer. Most solid tumors produce large amounts of lactate, which is converted back into glucose in the liver, a process known as the Cori cycle.[6,35] Gluconeogenesis from lactate uses ATP molecules and is very energy inefficient for the host. This futile cycle may be responsible, at least in part, for the increased energy expenditure. A 40% increase in hepatic glucose production has been reported in weight-losing cancer patients, which may also be a consequence of meeting the metabolic demands of the tumor and therefore, it contributes to the development of the cachectic process.[6,35,56]

Altered Lipid Metabolism

Fat constitutes 90 percent of a healthy adult's fuel reserves, and fat loss might account for most of the weight loss in cancer cachexia as it does in starvation. Abnormalities described include enhanced lipid mobilization, decreased lipogenesis, and decreased activity of lipoprotein lipase (LPL), the enzyme responsible for triglyceride clearance from plasma.[6,35,53] Cytokines inhibit LPL, which would prevent adipocytes from extracting fatty acids from plasma lipoproteins for storage, resulting in a net flux of lipid into the circulation.[35]

A lipid mobilizing factor (LMF) has recently been isolated from a cachexia-inducing murine tumor and from the urine of weight-losing cancer patients.[1,35,57,58] The LMF showed an apparent molecular weight of 43kDa and was homologous with the plasma protein Zn-α_2-glycoprotein in amino-acid sequence. Studies in animal models suggested that production of LMF by cachexia-inducing tumors may account for the loss of body fat and the increase in energy expenditure, but not for anorexia.[58] LMF acts directly on adipose tissue with the release of free fatty acids and glycerol through an elevation of the intracellular mediator cyclic AMP in a manner similar to that produced by the natural lipolytic hormones.[35]

These alterations in fat metabolism lead to decreased fat storage and severe cachexia in animal models and humans,[58] especially when combined with decreased food intake.

Altered Protein Metabolism

During starvation, glucose utilization by the brain is normally replaced by ketone bodies derived from fat, leading to decreased glucogenesis from amino acids by the liver and conservation of muscle mass.[58] In cancer cachexia however, amino acids aren't spared and there is depletion of lean body mass. This characteristic is thought to be responsible for the reduced survival time of cachectic cancer patients.[36,37,59]

Both reduced rates of protein synthesis and increased rates of protein degradation have been observed in biopsies of skeletal muscle from cachectic cancer patients.[36,60] However, whole body protein turnover is significantly increased in weight-losing cancer patients because of the reprioritization of liver protein synthesis, commonly known as the acute-phase reactant response.[6,61]

Approximately 40 percent of patients with pancreatic cancer exhibit an acute-phase response at diagnosis and this increases to around 80 percent at the time of death.[62] The presence of an acute-phase protein response is strongly associated with shortened survival in patients with pancreatic cancer,[62] as well as those with lung and renal cancer.[63,64] It may be that the demand for amino acids to manufacture acute-phase proteins is met by the breakdown of skeletal muscle, and in the face of inadequate protein intake this may lead to accelerated wasting and demise.[6,9,65]

Loss of skeletal muscle mass in both cachectic mice and cancer patients has been shown to correlate with the presence in the serum of a proteolysis-inducing factor (PIF) that is capable of inducing protein degradation as well as inhibiting protein synthesis in isolated skeletal muscle.[1,35,58,66-68] PIF is a sulfated glycoprotein produced by tumors, with a molecular weight of 24kDa. It appears to activate the ubiquitin-dependent proteolytic pathways that break down most skeletal muscle proteins in a variety of wasting conditions.[36,69]

PIF was shown to be excreted in the urine of patients with cancer cachexia, but not in those with similar tumor types without cachexia.[68] Production of PIF appears to be associated specifically with cancer cachexia, and it was undetectable in the urine of patients with other weight-losing conditions, such as major burns, multiple injuries, or surgery-associated catabolism and sepsis. When PIF was administered to non-tumor-bearing mice, weight loss due to a selective depletion of the nonfat mass occurred despite normal food and water intake, suggesting that anorexia and cachexia may not be inextricably linked.[58,68]

Cytokines may not induce muscle protein catabolism directly but may affect muscle repair processes.[69] A recent study demonstrates that TNF-α and IFN-γ activate the transcription factor, nuclear factor kappa B (NF-κB), which leads to decreased expression of MyoD, a transcription factor important for replenishing wasted muscle.[70]

Gastrointestinal Dysfunction

Abnormalities in the mouth and the digestive tract, either as a result of a disease or its treatment, may interfere with food ingestion. Changes in taste and smell in cancer patients have been documented.[53,71] Changes in the capacity to recognize and taste sweetness in foods occur in over one-third of patients, while bitterness, sourness, and saltiness are less frequently affected.[72,73] The decreased recognition threshold for bitter taste correlates well with meat aversion. Learned aversions to specific foods may develop due to unpleasant experiences coinciding with exposure to that particular food.[53] In cancer patients, this usually occurs in association with chemotherapy.[74] It was suggested that these changes in taste and smell correlate with decreased nutrient intake,

a poor response to therapy, and tumor progression, including metastasis.[73] The possible role of zinc-deficiency,[53] alterations in brain neuro-transmitters such as NPY, and opioid peptides that affect taste and nutrient selection[4,75] in the etiology of cachexia needs to be clarified (Figure 1). Direct involvement of the gastrointestinal tract or accessory digestive organs with tumors can cause problems with digestion and nutrient absorption, and consequently lead to malnutrition and cachexia. Dysphagia and odynophagia are particularly marked in cancers of the head and neck and esophageal cancer.[71] Tumors in the gastrointestinal tract and hepatobiliary tract, as well as the extrinsic pressure exerted by metastatic cancers, are often complicated by partial or total digestive obstruction leading to nausea and vomiting.

Satiety signals from the gastrointestinal tract help regulate appetite and food intake (Figure 1). Early satiety is a characteristic in cachectic cancer patients even without direct involvement of the gastrointestinal tract. This may be associated with increased activity of proinflammatory cytokines, such as IL-1β and central corticotropin-releasing factor (CRF), a potent anorexigenic signal.[76,77]

Convergent information suggests that CRF may be involved in triggering changes in gastrointestinal motility observed during stress exposure. CRF may induce delayed gastric emptying and gastric stasis that are observed in cancer patients, as well as in nonneoplastic states, such as infection and anorexia nervosa.[53,78,79] This may result in early satiety and negatively influence food intake.

Anticancer treatments can also be a major cause of malnutrition.[53,71] Chemotherapy can cause nausea, vomiting, abdominal cramping and bloating, mucositis, and paralytic ileus. Several antineoplastic agents such as fluorouracil, adriamycin, methotrexate, and cisplatin may induce severe gastrointestinal complications.[80] Enterocytes are rapidly dividing cells, which make them prone to the cytotoxic effects of both chemotherapy and radiotherapy. Both treatments are responsible for erosive lesions that occur at various levels of the digestive tract, resulting in impairment of feeding, digestion, and nutrient absorption.

TREATMENT OF CACHEXIA

The best way to treat cancer cachexia is to cure the cancer, but unfortunately this remains an infrequent achievement among adults with advanced solid tumors.[6] Therefore, the next therapeutic option is to increase nutritional intake and to inhibit muscle and fat wasting by manipulating the metabolic milieu outlined above with a variety of pharmacological agents (Figure 2).

It is essential to identify causes of reduced food intake, such as nausea and vomiting directly related to treatment, oral mucositis, and gastrointestinal obstruction, as well as to utilize appropriate palliative interventions for relieving these conditions.

A detailed discussion of these issues is beyond the scope of this article, but should be considered before choosing the treatment suited to the patient. Treatment should be directed at improving the quality of life, and for many patients, this means improving appetite and food intake.[53]

Hypercaloric Feeding

It was hoped that enteral or parenteral nutritional support would circumvent cancer anorexia and alleviate malnutrition. However, the inability of hypercaloric feeding to increase lean mass, especially skeletal muscle mass, has been repeatedly shown.[5]

The place of aggressive nutritional management in malignant disease also remains

ill-defined and most systematic prospective studies that have evaluated total parenteral nutrition combined with chemotherapy or radiotherapy have been disappointing.[81,82] No significant survival benefit and no significant decrease in chemotherapy-induced toxicity have been demonstrated. Indeed, an increase in infections and mechanical complications has been reported.[6,83]

However, parenteral nutrition may facilitate administration of complete chemoradiation therapy doses for esophageal cancer[84] and may have beneficial effects in certain patients with decreased food intake because of mechanical obstruction of the gastrointestinal tract.[81,82] Home parenteral nutrition can also be rewarding for such patients. If the gut can be used for nutritional support, enteral nutrition has the advantage of maintaining the gut-mucosal barrier and immunologic function, as well as the advantage of having low adverse side effects and low cost.[53,81,82]

The effects of caloric intake on tumor development and growth are still being debated.[85] A clear benefit from nutritional support may thus be limited to a specific, small subset of patients with severe malnutrition who may require surgery or may have an obstructing, but potentially therapy-responsive tumor.[71,81,86] A novel approach is to supplement substances such as omega-3 fatty acids that reduce IL-1 and TNF-α production and may improve the efficacy of nutritional support.[71,81]

Glucocorticoids

Glucocorticoids are widely used in the palliative setting for symptoms associated with cancer.[86-91] There have been a number of randomized, placebo-controlled trials demonstrating the symptomatic effects of different types of corticosteroids.[92-95] Most studies have shown a limited effect of up to four weeks on symptoms such as appetite, food intake, sensation of well-being, and performance status.[87,90,91]

Corticosteroids have been shown to have a significant antinausea effect and to improve asthenia and pain control. However, these studies have failed to show any beneficial effect on body weight. Prolonged treatment may lead to weakness, delirium, osteoporosis, and immunosuppression—all of which are commonly present in advanced cancer patients.[88]

Prednisolone, at a dose of 5 mg three times (15 mg) daily, and dexamethasone, at 3 to 6 mg daily, have been shown to improve appetite to a greater extent than placebo. Methylprednisolone given intravenously at a dose of 125 mg daily may improve quality of life.[6,94] There is no indication that any one glucocorticoid is superior in its appetite-stimulating ability.[86] When prescribing, it is recommended to begin with an initial one-week trial and continue treatment if there is a response. The entire daily dose may be given in the morning with breakfast or on a divided schedule after breakfast and lunch. This decreases hypothalamic-pituitary-adrenal (HPA) axis suppression and the insomnia associated with use later in the day.

Prescribing an intermediate-acting glucocorticoid (prednisone, predonisolone, methylprednisolone) may cause less HPA axis suppression than a long-acting drug (dexamethasone). Peptic ulceration is a concern, particularly in patients at risk. Prophylactic histamine-2 receptor antagonists are prudent when commencing long-term glucocorticoids.[86] The mechanism of action of glucocorticoids on appetite includes the inhibition of synthesis and/or release of proinflammatory cytokines such as TNF-α and IL-1, which decrease food intake directly or through other anorexigenic mediators, such as leptin, CRF, and serotonin[4] (Figure 1). Glucocorticoids can enhance NPY levels in

the hypothalamus, which appear to be responsible, at least in part, for the increased appetite and food intake.[20,25] NPY-induced feeding is known to be dependent on circulating glucocorticoid levels.

Progestational Drugs

Megestrol acetate (MA) and medroxyprogesterone acetate (MPA) are synthetic, orally active derivatives of the naturally occurring hormone progesterone. In several clinical trials, these compounds have been found to improve appetite, caloric intake, and nutritional status.[86-90,96-102]

Megestrol has demonstrated a dose-related benefit from dosages ranging from 160 mg (40 mg orally four times daily) to 1600 mg on appetite, caloric intake, body weight gain (mainly fat), and sensation of well-being, with an optimal dosage of 800 mg daily.[97] Increasing dosages from 160 mg of megestrol to 800 mg per day improves response to a level beyond which no further improvement occurs. It is recommended that a patient be started on the lowest dosage (160 mg/day) and the dose be titrated upwards according to the clinical response.[87,91]

Quality of life measures such as the Karnovsky index may or may not be influenced by progesterone agents.[89,91,102] Medroxyprogesterone has similarly been shown to increase appetite and food intake with stabilization of body weight at a dose of 1000 mg (500 mg twice) daily.[91] Although the drug may be used at 500 to 4000 mg daily, side effects increase above oral doses of 1000 mg daily.[86] Medroxyprogesterone can also be given in a depot formulation. Oncologists are increasingly prescribing megestrol or medroxyprogesterone oral suspensions rather than tablets for their patients because of improved compliance and decreased cost.[91,103]

There is, at present, considerable evidence of the effect of synthetic progestins on appetite and body weight, the two clinical hallmarks most widely identified in the cancer anorexia-cachexia syndrome.[104] However, further issues to be clarified are the optimal treatment duration, the best time to start treatment during the natural history of the disease, and the eventual impact on the overall quality of life.[104]

Both megestrol and medroxyprogesterone can induce thromboembolic phenomena, breakthrough uterine bleeding, peripheral edema, hyperglycemia, hypertension, adrenal suppression, and adrenal insufficiency (if the drug is abruptly discontinued).[86-89,96-100] Although patients rarely need to stop taking these drugs because of adverse effects, these drugs should not be prescribed in cases of thromboembolic/thrombotic disease, heart disease, or for patients at risk for serious fluid retention.[86] The mechanism of action of progestational drugs remains to be clarified, but might be related to glucocorticoid activity.[87] Megestrol may induce appetite via stimulation of NPY in the hypothalamus, modulation of calcium channels in the ventromedial hypothalamus (VMH)—a well known satiety center[19-28,34] which reduces the firing tone of VMH neurons—and inhibition of the activity of proinflammatory cytokines such as IL-1, IL-6, and TNF-α.[91,105,106]

Serum levels of such cytokines were reported to be decreased in cancer patients after megestrol or medroxyprogesterone treatment.[91]

Cyproheptadine and Other Antiserotonergic Drugs

Cyproheptadine is an antiserotonergic drug with antihistaminic properties that has been shown to have an appetite-stimulant effect in a number of human conditions.[90,91]

A randomized, controlled trial found mild appetite stimulation in patients with advanced cancer, although it did not prevent progressive weight loss.[107] Considerable evidence, both in

humans and experimental animals, suggests that anorexia may be mediated by increased serotonergic activity in the brain. Its blockade, therefore, might be beneficial in reducing symptoms (Figure 1).[108,109]

Serotonin (5HT) is a known satiating factor. It suppresses food intake when injected into the VMH of animals, where it may play a critical role in anorexia associated with cancer. Cyproheptadine appeared to stimulate appetite and to decrease diarrhea in patients with advanced carcinoid tumors.[110] $5HT_3$ receptor antagonists, such as ondansetron and granisetron, have entered widespread clinical use as antiemetics for cancer chemotherapy.

Ondansetron improved the ability of patients to enjoy food although it failed to prevent weight loss.[111] Future clinical trials with other antiserotonergic drugs are needed to define the role of the serotonergic system in the development and treatment of cancer cachexia.

Branched-chain Amino Acids

Peripheral muscle proteolysis, as occurs in cancer cachexia, works to metabolize amino acids required for the synthesis of liver and tumor protein. The administration of amino acids may theoretically serve as a protein-sparing metabolic fuel by providing substrate for both muscle metabolism and gluconeogenesis.[88]

Branched-chain amino acids (BCAA: leucine, isoleucine, and valine) have been used with the aim of improving nitrogen balance, particularly muscle protein metabolism.[88]

It was reported that BCAA-enriched total parenteral nutrition resulted in improved protein accretion and albumin synthesis.[112] BCAA may also serve to counteract anorexia and cachexia by competing for tryptophan, the precursor of brain serotonin, across the blood-brain barrier and thus blocking increased hypothalamic activity of serotonin (Figure 1).

It is known that increased plasma levels of tryptophan can lead to increased CSF tryptophan concentrations and increased serotonin synthesis during cancer.[109] Oral supplementation of BCAA successfully decreased the severity of the anorexia in cancer patients.[113]

Prokinetic Agents

Many patients with advanced cancer have symptoms of delayed gastric emptying and gastric stasis. Autonomic failure with decreased gastrointestinal motility is a recognized complication of cancer cachexia and is capable of causing anorexia, chronic nausea, early satiety, and constipation leading to reduced caloric intake.[114]

The prokinetic agent, metoclopramide, 10 mg orally before meals and at bedtimes, may relieve anorexia and early satiety with minimal side effects.[7,53] It has been the most extensively used drug in patients with cancer for the prevention and treatment of chemotherapy-induced emesis.[91]

Slow-release metoclopramide taken every 12 hours is significantly better than rapid-release metoclopramide taken every six hours, confirming the need for continued gastric stimulation for effective control of chronic nausea and early satiety.[115] The role of other prokinetic agents, including domperidone and potentially erythromycin derivatives that lack antibacterial activity, need to be examined in randomized trials in cancer patients.[79,89]

Eicosapentanoic Acid

The polyunsaturated fatty acid, eicosapentanoic acid (EPA), has been widely studied in animals and has demonstrated inhibition of lipolysis and muscle protein degradation associated with a cachexia model.[7,58,87,88] It countered the metabolic actions of LMF and PIF by interfering with their second-messenger production (cyclic

AMP and arachidonic acid, respectively), and resulted in a reversal of tumor-induced cachexia without changes in food intake in animal models.[58,116,117]

In a recent open label study conducted with pancreatic cancer patients, a supplement of fish oil capsules [18% EPA + 12% DHA (docosahexaenoic acid), 12 tablets per day taken orally] was investigated for three months. Patients showed decreased fatigue and a low body weight gain, as well as a reduction of acute-phase protein while taking the capsules.[118] The reduction of acute-phase response (C-reactive protein) was also related to the suppression of IL-6 production.[119] The effect appeared to be specific to the fish-oil supplement because it was not observed in patients receiving another polyunsaturated fatty acid, γ-linolenic acid.[58,118]

Although nutritional supplementation alone cannot attenuate the development of weight loss in cachectic patients, the inclusion of EPA significantly increased weight gain and lean body mass, leading to an improvement in performance status.[120]

In a randomized, controlled study, patients with advanced cancer who received a mixed fish-oil preparation showed increased survival relative to patients who received placebo. This improvement was observed in both weight-losing and non-weight-losing subgroups of patients.[121]

Cannabinoids

Appetite stimulation and body weight gain are well-recognized effects of the use of marijuana and its derivatives. Dronabinol is the synthetic, oral form of tetrahydrocannabinol (THC), which is the active ingredient responsible for this effect.[86-88,90]

Dronabinol and Marinol (in the United States) and Nabilone (in Canada) have been used as antiemetics in cancer, with many studies demonstrating their efficiency in treating chemotherapy-induced nausea and vomiting.[90]

Several studies of THC in advanced cancer-associated anorexia have shown some improvement in mood and appetite with either no or some improvement in body weight.[122,123]

Randomized, controlled trials are needed to better determine the efficacy and usefulness of THC in cancer cachexia.

It has been shown that almost 20 percent of the cancer patients receiving chemotherapy along with dronabinol as an antiemetic experienced side effects, such as euphoria, dizziness, somnolence, and confusion resulting in a dose reduction or less frequently in withdrawal of the treatment.[88] The drug could be taken at bedtime to avoid some psychotomimetic effects and might produce long-lasting appetite stimulation for 24-hour periods.[86] The mechanism by which cannabinoids exert their effect has yet to be clarified. It was postulated that they might act via endorphin receptors, by inhibiting prostaglandin synthesis or by inhibiting IL-1 secretion.[88] Recent studies demonstrate that endogenous cannabinoids are present in the hypothalamus, which may tonically activate CB1 cannabinoid receptors to maintain food intake and form part of the neural circuitry regulated by leptin.[124]

5′-Deoxy-5-Fluorouridine

The fluorinated pyrimidine nucleoside, 5′-deoxy-5-fluorouridine (5′-dFUrd) has been shown to effectively attenuate the progression of cachexia in mice bearing murine or human cancer cell lines.[125,126]

5′-dFUrd is a cytostatic agent that is converted upon metabolization into the active 5-fluororacil (5-FUra) by pyrimidine (thymidine and uridine) phosphorylases, which are very active in tumor tissue.

Although concomitant inhibition of tumor growth was observed in these models, it was not sufficient to account for the preservation of body weight. 5′-dFUrd reversed a progressive weight loss, hypoglycemia, and increased production of acute phase proteins with no change in tumor size or even some tumor growth.[125]

The mechanisms of the anticachectic activity of 5′-dFUrd include inhibition of production of IL-6 and PIF.[126] Chemotherapy could be expected to have a role in cachexia not only by decreasing tumor mass, but perhaps also by modulating the production by cancer cells or immune cells of chemical mediators.[89,127]

Unfortunately, few studies have been conducted with the aim of trying to define the potential symptomatic role of low-toxicity chemotherapy on cachexia, as well as on asthenia or pain.[127] Such clinical studies are warranted and should include 5′-dFUrd.

Emerging Drugs

The reported clinical trials on emerging drugs are generally small. Larger, randomized studies are necessary to assess the efficacy of these drugs in the treatment of cancer cachexia.

Melatonin

Melatonin is the pineal hormone that is able to decrease the level of circulating TNF-α in patients with advanced cancer. In a recent controlled trial of 100 patients with metastatic solid tumors, loss of more than 10 percent body weight was less common among those treated with melatonin (20 mg daily) than among patients in the placebo group.[128]

Addition of melatonin to the chemotherapy regimen of cisplatin plus etoposide improved the response rate and survival rate, and reduced myelosuppression, neuropathy, and cachexia among lung cancer patients in poor clinical condition.[129]

Thalidomide

Initially developed as a sedative and an anti-inflammatory agent, thalidomide was withdrawn from use when its teratogenic effect was recognized. It is now prescribed for new indications, except in susceptible populations (women of child-bearing potential and their spouses, and those with peripheral neuropathy).[86]

Thalidomide also inhibits TNF-α in animals and humans with cancer, AIDS, and other diseases. A significant improvement in well-being and weight gain occurs in AIDS patients with modest doses of thalidomide (300 mg).[130]

It was also reported to improve insomnia and restlessness as well as nausea in advanced cancer patients and it has improved appetite as well, resulting in an enhanced feeling of well-being in one-half to two-thirds of patients studied.[131]

These results together with the recent finding that thalidomide is able to inhibit growth of the tumor through an inhibition of neoangiogenesis,[132] suggest the unique role of thalidomide both as an anticachectic and antineoplastic agent.

β2-agonists

Beta 2 adrenoceptor agonists may have an important effect on protein metabolism in skeletal muscle, favoring protein deposition even in sedentary populations.[88,89] It was reported that clenbuterol suppresses the activation of muscle proteolysis through its action on the ubiquitin-dependent proteolytic system during tumor growth in tumor-bearing animals.[133]

Although no controlled trials are reported

in cancer patients, it was shown to significantly improve muscle strength after knee surgery when compared with placebo.[134]

Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are very widely used in patients with cancer for the treatment of fever and pain. Ibuprofen, taken at a dose of 400 mg three times daily, has been shown to reduce levels of acute phase proteins, IL-6, and cortisol and to normalize whole-body protein kinetics to some extent in cachectic colorectal cancer patients.[135,136] It may reduce resting energy expenditure and stabilize weight and quality of life in pancreatic cancer patients.[137,138]

The related anti-inflammatory agent indomethacin, taken at a dose of 50 mg twice daily, has been shown to stabilize performance status and prolong survival of patients with metastatic solid tumors in a large controlled trial.[139] These agents may therefore have some role in the palliation of cachexia and fever,[140] although concern remains about gastrointestinal side effects. NSAIDs act by inhibiting prostaglandin production by the rate-limiting enzymes known as cyclo-oxygenases, COX-1 and COX-2. The recent discovery and introduction into clinical practice of selective inhibitors of COX-2 (celecoxib and rofecoxib) that are devoid of gastrointestinal toxicity yet maintain a high anti-inflammatory activity, suggest that these agents will be therapeutic alternatives to conventional NSAIDs.[91]

These COX-2 inhibitors were recently shown to have anti-angiogenic and anti-tumor activities in animal models.[141]

Others

Pentoxifylline, a methylxanthine derivative, is a phosphodiesterase inhibitor that inhibits TNF-α synthesis by decreasing gene transcription.[88] A randomized, controlled trial in patients with solid tumors, however, showed no increase in appetite or body weight gain among patients taking pentoxifylline (400 mg three times daily for two months) compared with patients receiving placebo.[142]

Hydrazine sulfate inhibits phosphoenol-pyruvate carboxykinase, a key enzyme in gluconeogenesis.[6] It was hoped that interrupting the Cori cycle would normalize some aspects of carbohydrate metabolism in cachectic cancer patients. However, large, randomized, placebo-controlled trials did not show any benefit in advanced lung and colorectal cancer patients.[143-145] Based on its lack of efficacy and significant neurotoxicity, hydrazine sulfate is not used by mainstream oncologists, although it is still promoted by some alternative medicine practitioners.

Anabolic steroids increase muscle mass in noncancer patients, and this has led to their illicit use for athletic advantage. Nandrolone decanoate treatment resulted in a decrease in weight loss in patients with lung cancer.[146] However, in a large, randomized, controlled trial comparing megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer cachexia, fluoxymesterone was clearly inferior.[147]

Nutritional, Psychological, and Behavioral Therapies

The management of cachexia in advanced cancer patients should first attempt to maximize oral intake by allowing the patient flexibility in type, quantity, and timing of meals.[90]

Professional teams of oncology physicians, nurses, and dietitians, along with patients and families, can diagnose specific needs and plan individualized treatment for improved nutritional health.

Counseling, which any member of the health care team may provide, is an effective and inexpensive intervention and should be combined with other nutritional interventions.[148]

Nursing interventions to counteract cachexia should be aimed at minimizing the negative factors of nausea, vomiting, diarrhea, pain, fatigue, changes in taste, or food preferences that may influence appetite.[149]

Encouraging patient and family interaction and providing emotional and educational support may be helpful. When family members can provide the patient's favorite foods, food intake usually improves and family bonds are strengthened.

Communication among physicians and other health care professionals provides the patient with a multidisciplinary approach to care. The patient record will be an excellent resource to document a plan of care and patient responses to treatment.[149] Psychological distress and psychiatric disorders are common among cancer patients and have a prevalence ranging from 10 to 79 percent of patients depending upon the group studied.[10,150] These problems are also as common among the family members of people with cancer.

The use of psychological and behavioral interventions in cancer is increasing and recent studies have suggested that some of these techniques may affect quality of life and, perhaps, survival rates.[10,150]

Evaluations of relaxation, hypnosis, and short-term group psychotherapy have suggested some benefit with regard to anorexia and fatigue, although the population most likely to benefit from these interventions has not yet been determined.[10,150]

Anorexia and cachexia may result in a secondary depression, or the depression may be a prime contributor to the anorexia and subsequent weight loss. Benzodiazepines can be helpful for persistent fear and anxiety and antidepressant drugs are increasingly used in depressed cancer patients.

Assessment of the patient's quality of life is also important and psychometric instruments relevant to this quality-of-life domain need to be designed and validated.[91,150]

CONCLUSIONS

In recent years, cancer cachexia has been understood as a result of major central nervous system (CNS) and metabolic abnormalities due to a combination of tumor by-products and host cytokine release rather than a simple increase in energy consumption by the tumor and starvation on the part of the patient.

Under normal circumstances, animals and humans respond to starvation with a complex neuroendocrine response that ultimately leads to an increase in appetite, a relative sparing of lean body mass and burning of fat stores, and an overall decrease in the basal metabolic rate.[18-20,50,151] In contrast, cachexia refers to a pathological state of malnutrition wherein appetite is diminished concomitantly with an increase in metabolic rate and a relative wasting of lean body mass (Figure 1). The resulting malnutrition and loss of lean body mass reduces the quality of life for the affected individual and compromises recovery by decreasing tolerance to therapy and increasing postsurgical complications.

Therefore, it is best to think of the clinical features as a continuum of severity that ranges from mild anorexia to severe cachexia and to concentrate on early therapeutic intervention. Attempts at drug therapy for cachexia with a variety of agents have been met with limited success. The most widely used agent, megestrol acetate, has shown some promise in reversing weight loss although this may be due to the increase in fat mass and subtle water retention rather than the preservation of lean body mass.

It is generally recommended that megestrol acetate be chosen for long-term use (weeks to months) and glucocorticoids for a shorter period of use for appetite stimulation.[86,147]

Glucocorticoids show a rapid onset of effect on appetite, as well as an improvement in fatigue and sense of well-being. There also appears to be a basis for recommending antiserotonergic drugs, gastroprokinetic agents, BCAA, EPA, cannabinoids, melatonin, and thalidomide, which act on the feeding-regulatory circuitry to increase appetite, and inhibit tumor-derived catabolic factors that antagonize tissue wasting and/or host cytokine release.

Most of these second-line drugs have different sites and/or mechanisms of actions (Figure 2). Therefore, these agents could be used soon after failure of the first-line drugs according to the cause of cachexia or the state of patient. Appetite stimulants could alleviate anorexia and be tolerable at doses that at least stabilize weight loss for some period of time.[86]

If there is associated early satiety or opioid-induced nausea and anorexia, a prokinetic agent should be considered. BCAA and EPA could be used as part of the nutritional support.[71]

Although most of the suggested treatments have received insufficient evaluation to be recommended as any more than second-line treatments, they should be used not only on an individual basis in a carefully monitored therapeutic trial, but also as part of a randomized, controlled study.

Furthermore, several new and exciting drugs are reaching the stage of clinical trials,[4,5,33,52,88,91,152,153] including melanocortin antagonists, growth hormone secretagogues (synthetic agonists of ghrelin, a newly-identified orexigenic peptide), and cytokine antagonists or inhibitors. These agents open the possibilities of combined drug therapy that may simultaneously address the different aspects of cancer cachexia and lead to more targeted pharmacological interventions. Previous studies have repeatedly shown that both physicians and patients desire effective treatments for the prominent clinical problem of cancer anorexia-cachexia syndrome. Caregivers often note that when friction occurs between themselves and the individual for whom they are caring, it often occurs over the issue of eating.[154] These caregivers report that they find it hard to cope with the patient who relentlessly loses weight and strength and yet persistently refuses adequate food intake.

We need to define carefully the subgroups of cachexia in terms of not only tumor type and extent, but also the mechanism of cachexia in hopes that it will be possible to identify those patients who will more likely benefit from available therapies.

The outcomes of drug studies in cancer cachexia should also focus on the symptomatic and quality-of-life advantages rather than simply on nutritional end points, since the survival of cachectic cancer patients may be limited to weeks or months due to the incurable nature of the underlying malignancy.

Effective communication with patients and their families is essential and is an important component of treatment. CA

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