

MANAGING CANCER CACHEXIA

A guide to current therapy

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Top-line summary

Cachexia is a syndrome associated with many end-stage chronic conditions including cancer. It is characterized by profound loss of both muscle bulk and adipose tissue. Cachexia is considered to be a contributing factor in almost a quarter of cancer deaths. Patients with this condition may have an exaggerated loss of function, affecting activities of daily living. The etiologies of secondary cachexia are many, and should be identified and treated aggressively in any patient with cancer who presents with weight loss. Primary cachexia is characterized by an abnormal inflammatory response, increased resting energy expenditure, and activation of 3 main proteolytic pathways that cause a negative nitrogen balance. Treatment with pharmacologic agents has yielded conflicting and disappointing results, but newer approaches and agents hold promise for the future.

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The cancer cachexia syndrome, defined as “a wasting syndrome involving loss of muscle and fat caused directly by tumor factors, or indirectly by an aberrant host response to tumor presence,” is found in 80% of patients with advanced cancer, most commonly in those with lung and upper gastrointestinal malignancies.¹⁻³

Weight loss and anorexia (decreased appetite) are the hallmarks of this disorder. The former is strongly associated with poor outcomes throughout all stages and histologies of malignancy and the latter has been reported to be a prognostic factor independent of weight loss in patients with advanced cancers.^{4,5} Further, patients displaying these symptoms prior to treatment are less likely to be offered surgery, chemotherapy or radiotherapy, and exhibit poorer tolerance of these treatments.^{6,7} Cachexia is considered a contributing factor in almost a quarter of cancer deaths, and at least one study has suggested that cachexia itself may sometimes be a direct cause of death.⁸

Patients with advanced cancer have multiple reasons for their poor nutritional reserve, including disease-related complications such as dysphagia, pain, discomfort and malabsorption. Treatment-induced nausea and vomiting are often contributing factors.

ETIOLOGY

Secondary cachexia

A thorough assessment of weight loss in a patient with cancer begins by eliminating potentially correctable causes of what is sometimes referred to as

“secondary cachexia.” This involves comprehensive multidisciplinary evaluation of physical, biochemical, psychologic and social factors, listed in **Table 1** (page 10), which could potentially contribute to poor nutritional intake and weight loss. Should any of these be identified, prompt intervention can greatly impact on the patient’s quality of life and overall prognosis.^{1,4}

Primary cachexia

If no secondary cause is identified, or once all causes found have been treated effectively, the patient is deemed to have at least a component of “primary cachexia.” Several mediators are thought to contribute to this complicated metabolic disorder, which causes patients to suffer loss of appetite, weight loss, profound weakness, debilitating fatigue and ultimately, a markedly decreased ability to perform basic daily activities.^{1,10} While most cases of cancer cachexia have elements of both primary and secondary cachexia, the former should only be considered after all secondary causes have been identified and treated. The physiologic presentation of this syndrome is significant loss of skeletal muscle induced by activation of 3 main proteolytic path-





ways: the lysosomal system, the cytosolic calcium-regulated calpains and — likely the most important of the 3 in a wide range of catabolic conditions — the ATP ubiquitin-dependent proteolytic pathway. These lead to a negative nitrogen balance. There is also considerable loss of fat, mediated at least in part by tumour production of lipid-mobilizing factor, which acts through a β 3-adrenoceptor.¹¹ In simple starvation, however, lean body mass is preserved. Thus, to successfully manage primary cachexia, 2 separate metabolic processes must be addressed: decreased anabolism and increased catabolism. This explains why aggressive caloric supplementation alone has proven ineffective in reversing the weight loss in these patients. Also, resting energy expenditure has been found to be increased in cachectic patients,¹² whereas it would be decreased in the setting of starvation. Finally, increased glucose turnover is observed in cachexia, typically with no urinary ketosis — as opposed to starvation, in which glucose is low and associated with ketones in the urine.⁴ Although complex physiologic interactions are at play, the central feature defining primary cachexia is believed to be a cancer-induced systemic inflammatory process.^{1,4}

THERAPY FOR CACHECTIC PATIENTS

The optimal therapy for cachexia is to cure the underlying cancer whenever possible. Once significant weight loss

has set in, however, the disease is often in the advanced or terminal phase and realistic goals of treatment are palliative rather than curative. Furthermore, survival has been shown to be adversely affected by weight loss in patients with gastrointestinal and breast primary tumours, and even more so in those with lung cancer.⁵ An integrated therapeutic plan applicable to each individual patient should be devised to treat both cancer anorexia and cachexia, and should include both nutritional advice and pharmacologic prescription.

Diet

Most appropriate are small, frequent meals that are energy-dense but with low fat content, as fatty foods delay gastric emptying and can cause the sensation of early satiety. Extremes in taste and smell must be avoided. All meals should be enjoyed in a pleasant environment. The actual presentation of the food is important, as are its temperature and flavour. Assessment and advice from a qualified dietician who can pinpoint which foods are tolerated and which should be avoided usually help to improve the patient's nutritional intake, improving social family time and motivating the sharing of meals together.

Pharmacologic therapies

Several different pharmacologic approaches to treating patients with cancer cachexia have been reported. Agents with effects on appetite and weight continue to be studied. When choosing a pharmaceutical agent to combat loss of appetite and weight, the patient's wishes, medical condition and expected life span must be considered.

Progestational agents, e.g. megestrol acetate and medroxyprogesterone

Many trials have reported an effect on appetite and weight gain; however, the additional weight is attributed to increased body fat stores and not lean body mass. In addition, these agents carry a side effect profile of thromboembolism, nausea and drowsiness, especially with higher doses.¹³⁻¹⁷

Glucocorticoids

The mechanism of appetite stimulation by glucocorticoids, including dexamethasone, methylprednisolone and prednisolone, is unknown but is thought to be due to anti-inflammatory activity. Studies report positive but short-lived effects on clinical outcomes such as appetite and quality of life, with minimal or no effect on weight gain. Side effects such as muscle wasting and immunosuppression make the long-term use of glucocorticoids less appropriate.^{13,15}

Word origins

The words “cancer” and “carcinoma” are derived from the Greek word “karkinos,” meaning “crab;” the suffix “-oma” denotes a “neoplasm.” This analogy was first invoked by Hippocrates, who wrote that a malignant tumour of the breast resembled the body of a crab and the surrounding vessels its legs.⁹ Physicians caring for cancer patients in the advanced stages of their illnesses understand this analogy from a different perspective. They may state that these patients appear as though their body mass has been viciously destroyed from within by the claws of a multitude of internal crustaceans.

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Cannabinoids

No definitive data suggests effectiveness in cancer patients of cannabinoids, e.g. dronabinol. To date, no randomized controlled trial of dronabinol alone or combined with megestrol acetate has shown superior benefit in promoting weight gain and appetite.^{18,19}

Anti-inflammatory agents

Anti-inflammatory agents, including omega-3 fatty acids and thalidomide, decrease tumour necrosis factor (TNF)-alpha levels, but results regarding weight gain and appetite stimula-

DISCOURSE

tion are conflicting. The omega-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been shown to suppress production of proinflammatory cytokines and arachidonic acid-derived mediators. Preliminary studies of EPA suggested a benefit to cancer patients; however, subsequent larger comparative studies failed to replicate the results.²⁰⁻²² A randomized pla-

cebo-controlled trial evaluated the safety and efficacy of thalidomide (200 mg daily) in patients with advanced pancreatic cancer and weight loss of at least 10% of pre-morbid weight. The thalidomide group showed a significant difference in weight loss compared with the placebo group, indicating the drug's ability to safely reduce loss of weight and lean body mass in the patients studied.²³

TABLE 1. Potential contributing factors to secondary cachexia^{1,4}

type of disturbance	clinical problem
psychologic factors	anxiety depression and/or decreased motivation insomnia spiritual distress cognitive impairment and/or delirium
social factors	family distress financial stress
loss of muscle mass	prolonged inactivity and/or deconditioning aging
eating difficulties	decreased appetite altered taste and/or smell alternative cancer diet
oral pathology	denture problems mouth sores thrush xerostomia
esophageal odynophagia and/or dysphagia	physical obstruction neurogenic dysfunction esophageal candidiasis
gastric problems	early satiety nausea and vomiting
intestinal problems	intestinal obstruction constipation
malabsorption	exocrine pancreatic insufficiency fistula chronic diarrhea
symptoms of advanced disease	pain dyspnea
exogenous protein loss	frequent paracentesis or thoracentesis nephrotic syndrome
concurrent medical illness	heart failure chronic or acute infections chronic lung disease diabetes mellitus liver cirrhosis thyroid dysfunction adrenal insufficiency hypogonadism

Anabolic agents

To date only limited published data support effectiveness of anabolic agents such as oxandrolone, nandrolone decanoate and fluoxymesterone.¹⁵

Ghrelin

An orexigenic (appetite stimulating) peptide predominantly secreted from gastric cells, ghrelin's role is still controversial in the cancer cachexia syndrome. It stimulates the release of growth hormone and increases appetite. In anorectic-cachectic cancer patients, it may also improve the intake of nutrients, possibly preserving muscle mass.^{24,25}

Other pharmacologic approaches

Newer novel therapies under investigation include the selective androgen receptor modulators (SARMs), insulin-like growth factor I (IGF-I) variants such as mechano growth factor, anti-myostatin antibodies, angiotensin converting enzyme (ACE) inhibitors, aldosterone antagonists and insulin treatment.²⁶

Other supportive drug therapies include:

- metoclopramide, which enhances gastric emptying
- antiemetic drugs, including serotonin antagonists and corticosteroids
- supplementary pancreatic enzymes
- adequate analgesia

Additional therapies


The potential impact of the following interventions cannot be underestimated — they must be considered part of any treatment intervention.

An appropriately devised physiotherapy program to build muscle bulk, improve muscle strength and endurance is vital for maintaining independence. Resistance exercises and cardiovascular training are cornerstones of this intervention.

An ergonomically focused assessment by an occupational therapist is invaluable to aid a patient in adapting

in his home environment to the limited mobility and loss of independence that may accompany cachexia. Use of aids such as a built-up toilet seat or a bath bench can make the difference in ability to continue daily activities, alone or with the help of an assistant. Correctly designed working surfaces ease the strain of having to bend over to perform a task.

RESEARCH AND TEAMWORK

The cancer cachexia syndrome is a clinical problem affecting many patients with cancer and other end-stage diseases. Correct identification of treatable, reversible causes must be aggressively sought and, when found, appropriately treated. Innovative research into novel therapies directed at primary cachexia is ongoing: well-structured clinical trials are mandatory, as is support for these trials through enrollment of eligible patients. Professional inputs and interventions from multiple members of the cancer care team can all have a profound influence on the treatment of patients with cachexia and should be considered the standard approach. 

Disclosure

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- Final Program and abstract book: 4th Cachexia Conference, Tampa, FL, December 6-9, 2007.

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