Cancer Anorexia - Cachexia Syndrome

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ABSTRAK


Kata kunci: anoreksia, kaheksia, kanker, patogenesis, diagnosis, terapi.

ABSTRACT

Cancer anorexia-cachexia syndrome (CACS) is a devastating and debilitating aspect at any stage of malignancy. It presents primarily as anorexia, weight loss and muscle wasting secondary to inadequate oral intake and metabolic changes. This syndrome is highly prevalent among cancer patients, has a large impact on morbidity and mortality, and impinges on patient quality of life. The pathogenic mechanisms of CACS are multifactorial. It is suggested to be the result of tumor-host interactions and cytokines have a significant role. Diagnosis of cancer cachexia is complex and multifaceted and requires meticulous clinical examination of the patient. The challenge for clinicians is to know how best to manage the symptoms of weight loss and anorexia for optimal patient outcome. This article outlines the diagnosis of cancer cachexia, reviews its impact on patient quality of life and survival, and updates the reader on potential therapies that may suppress it.

Key words: anorexia, cachexia, cancer, pathogenesis, diagnosis, therapy.

INTRODUCTION

The cancer anorexia-cachexia syndrome is a hypercatabolic state characterized by anorexia and loss of body weight associated with reduced muscle mass and adipose tissue. Cancer anorexia-cachexia syndrome (CACS) is clinically characterized by a number of signs and symptoms interfering with energy intake (i.e., reduced appetite, early satiety, changes in taste/smell) and affecting nutritional status (i.e., increased metabolic rate, weight loss, hormonal alterations, muscle and adipose tissue wasting, functional impairment, fatigue). The syndrome may occur in 15% to 40% of patients with cancer and in more than 80% of patients with advanced illness and substantially impacts upon the quality of life and survival of affected patients. Cachexia occurs in the majority of cancer patients before death and...
it is responsible for the deaths of 22% of cancer patients. A study by Harnoko K et al in Persahabatan Hospital Jakarta found that 89.5% patients with advanced-stage non small cell lung cancer suffered from anorexia and weight loss >5%.4

The pathogenesis of CACS is multifactorial and incompletely understood.6,7 It evolves from complex tumor-host interaction, leading to an imbalance that favors catabolism over anabolism.7

Diagnosis of cancer anorexia is based on reduced appetite and characterized by objective symptoms including early satiety, taste alterations, nausea or vomiting. Assessment of the presence of anorexia is performed by using questionnaires or visual analog scale.8 While cancer cachexia is clinically manifested by an involuntary weight loss of greater than 5 percent of premorbid weight which is observed within a six-month period, especially when combined with muscle wasting.9

The optimal therapy for CACS is curing the underlying cancer. However, this goal is often not attainable with currently available treatments. An integrated therapy approach should be devised to treat CACS, and should include both nutritional intake and counseling, and pharmacologic approaches.8

DEFINITION

Anorexia is defined as the loss of the desire to eat, leading to reduced energy intake.8 In fact, it may consist of appetite loss, early satiety, a combination of both or altered food preferences.10 Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. In cancer, cachexia is a multi-organ syndrome characterized by weight loss (at least 5%), muscle and adipose tissue wasting and inflammation which are often associated with anorexia.4 Cancer cachexia reduces performance status, impairs quality of life, increases toxicity of anticancer therapy, decreases response to therapy and reduces survival.6,7

Cancer anorexia-cachexia syndrome is a syndrome characterized by clinical picture of anorexia, tissue wasting, loss of body weight accompanied by decrease of in muscle mass and adipose tissue, and poor performance status that often precedes death.3,11

EPIDEMIOLOGY

Anorexia has been detected at the point of cancer diagnosis in 13 – 55% of patients and prevalence in terminally-ill cancer patients is even higher at approximately 65%.8

The incidence of weight loss upon diagnosis varies greatly according to the tumor site (Table 1). In less aggressive forms of Hodgkin’s lymphoma, acute nonlymphocytic leukemia, and in breast cancer, the frequency of weight loss is 30 – 40%. More aggressive forms of non-Hodgkin’s lymphoma, colon cancer and other cancers are associated with a frequency of weight loss between 50 – 60%. Patients with pancreatic or gastric cancer have the highest frequency of weight loss at over 80%.8

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>Incidence of weight loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>83</td>
</tr>
<tr>
<td>Gastric</td>
<td>83</td>
</tr>
<tr>
<td>Esophagus</td>
<td>79</td>
</tr>
<tr>
<td>Head and neck</td>
<td>72</td>
</tr>
<tr>
<td>Colorectal</td>
<td>55 – 60</td>
</tr>
<tr>
<td>Lung</td>
<td>50 – 66</td>
</tr>
<tr>
<td>Prostate</td>
<td>56</td>
</tr>
<tr>
<td>Breast</td>
<td>10 – 35</td>
</tr>
<tr>
<td>General cancer population</td>
<td>63</td>
</tr>
</tbody>
</table>

In CACS, the incidence is variable and difficult to determine but in general the syndrome may occur in 15 – 40% of patients with cancer and in more than 80% of patients with advanced illness.3 Cachexia itself is a major cause of death in more than 20% of patients.8,10

ETIOLOGY

Cachexia can occur in the setting of cancer as well as in chronic infection, AIDS, heart failure, rheumatoid arthritis and chronic obstructive pulmonary disease. In CACS, this syndrome is caused by cancer particularly in patients with advanced illness.12,13 The cause of cancer cachexia is categorized into two groups: primary and secondary cachexia.14

Primary cachexia is brought about by tumor-induced metabolic change. The cancer itself generates tumor products that disturb
normal tissue repair. Catabolism is accelerated, whilst anabolism slows, leading to tissue loss. In addition, the cancer triggers a systemic inflammatory response. This inflammatory response includes an elevated metabolic rate and release of biomechanical products that suppress appetite and cause early satiety. The consequence of metabolic abnormalities is anorexia and loss of fat plus muscle mass.14

Secondary cachexia is caused by factors that compromise dietary intake leading to malnutrition including nausea, vomiting, stomatitis, taste and smell abnormalities such as those induced by chemotherapy, diarrhea, constipation, fatigue and mechanical obstruction such as tumor occluding the oesophagus.9,14

PATHOGENESIS

The pathogenesis CACS is multifactorial and incompletely understood.6 It evolves from complex tumor-host interaction, leading to an imbalance that favors catabolism over anabolism. The disturbances caused by this process include anorexia, hypermetabolism, tissue wasting, metabolic abnormalities and hormonal changes.7

Anorexia is related to disturbances of the central physiological mechanism controlling food intake. Under normal conditions energy intake is controlled primarily in the hypothalamus by specific neuronal populations, which integrate peripheral blood-borne signals conveying information on energy and adiposity status. In particular, the arcuate nucleus of the hypothalamus transduces these inputs into neuronal responses and via second-order neuronal signaling pathways, into behavioural responses. Anorexia might be considered secondary to defective signals arising from the periphery, perhaps due to an error in the transduction process or to a disturbance in the activity of the second-order neuronal signaling pathways. However, consistent data seem to suggest that cancer anorexia is mediated by the inability of the hypothalamus to respond appropriately to peripheral signals, indicating an energy deficit (Figure 1).2,8 Cytokines, including IL-1 and TNF-α, appear to mediate this ‘hypothalamic resistance’, by hyperactivating anorexigenic neurons and suppressing prophyagic neurons.5,6

Under physiologic conditions, the homeostasis of skeletal muscle mass is a dynamic process, in which a balance of protein degradation and protein synthesis is achieved. During cancer, progressive reduction of skeletal muscle mass occurs, although visceral protein reserves are preserved and the liver mass may actually increase. Whole-body protein turnover is increased, due to an increase in muscle protein catabolism and overall decrease in protein synthesis, despite the increase in hepatic acute-phase protein synthesis. There are three main proteolytic pathways responsible for protein catabolism in skeletal muscle. These are the lysosomal system, which is involved in proteolysis of extracellular proteins and cell-surface receptors; the cytosolic calcium-regulated calpains, which are involved in tissue injury, necrosis and autolysis; and the ATP ubiquitin-dependent proteolytic pathway. Of these, ubiquitin-dependent proteolysis is considered to be the most important for protein degradation in cancer cachexia.8,15

Cancer cachexia is also characterized by a marked reduction in adipose tissue, which is due to an increase in lipolysis rather than a decrease in lipogenesis. In addition, energy metabolism is dysregulated during tumor growth, leading to continual increased energy expenditure, possibly via changes in the expression of genes encoding the uncoupling proteins. These are a family of mitochondrial membrane proteins that mediate proton leakage and decrease the coupling of respiration to ADP phosphorylation, resulting in the production of heat instead of ATP.8

The dramatic changes that occur during tumor growth are triggered by a number of factors, including proteolysis-inducing factor, which induces protein degradation into amino acids in skeletal muscles, and lipid-mobilizing factor, which promotes breakdown of adipose...
tissue into free fatty acids. While proteolysis-inducing factor and lipid-mobilizing factor are produced by the tumor, other factors are released as a consequence of interactions between host cells and tumor cells, represented by a number of proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). \(^8,16\)

**CLINICAL CHARACTERISTICS**

Cancer cachexia is characterized by diminished nutrient intake and progressive tissue depletion, both of which lead to weight loss. Changes in body composition, increasing debility, fluctuations in resting energy expenditure, loss of appetite, and an ability to eat for mechanical reasons further characterize this syndrome. \(^13\)

**Changes in Body Composition**

A disproportionate and excessive loss of lean body mass (LBM) is the hallmark of cancer cachexia. Weight-losing patients with solid tumors suffered a loss of both fat and lean body mass. However, the loss of lean body mass, most notably skeletal muscle, was more dramatic. The response contrasts with that of simple starvation where the host preserves lean body mass in an effort to survive. \(^13\)

**Alterations in resting energy expenditure**

Alterations in resting energy expenditure (REE, also called basal metabolic rate) may contribute to the energy deficit that lead to wasting. An increase in REE has been observed in patients with lung cancer, hematologic malignancies, and sarcomas, and is thought to contribute to the weight loss observed in cancer cachexia. In one study of patients with lung cancer, 74% had an elevation in REE while 30% had a weight loss of 10% or more. \(^13,16\)

**Reduced Dietary Intake or Absorption**

Anorexia and poor oral intake contribute to the energy deficits observed in cancer cachexia. In one of the studies, caloric intake was significantly lower (300 kcal/day) in weight-losing cancer patients. Chemotherapy-related alterations in taste and smell may contribute to this loss of appetite. \(^13\)

In addition, a number of nonspecific factors that may contribute to decreased nutrient intake or absorption include chemotherapy and radiotherapy induced anorexia, nausea and vomiting; limited food intake due to dysphagia or abdominal pain or abdominal distention; early satiety due to an enlarged spleen or liver, an abdominal mass or abdominal distention (ascites); and malabsorption resulting from tumor invasion of the gastrointestinal tract or intestinal resection. \(^13\)

**Alteration in Nutrient Metabolism**

Cancer cachexia is often associated with important changes in nutrient metabolism. Many patients have a constellation of findings consisting of hyperglycemia, hypertriglyceridemia, and an exaggerated insulin response to a glucose load. Hypertriglyczeridermia occurs in combination with increases in very low density lipoprotein production and lipolysis and reduced activity of adipose tissue lipoprotein lipase. \(^12,16\) These changes may result from the interaction between increased cytokine release and insulin resistance. \(^13\)

Protein breakdown is increased in patients with cancer cachexia, leading to enhanced amino acid release from skeletal muscle despite the reduction in muscle mass and negative nitrogen balance. The plasma concentration of certain amino acids tends to be elevated, perhaps in part because of decreased skeletal muscle uptake due to insulin resistance. \(^13\)

**DIAGNOSIS**

Anorexia is defined as the loss of the desire to eat, and its diagnosis is based on reduced appetite, early satiety, taste alterations and nausea and by assessing its severity. Consequently, a visual analog scale is often used, which is a useful tool in epidemiologic or prospective studies but may prove unreliable if small changes in appetite need to be detected. Sometimes, the diagnosis of anorexia is based on the presence of reduced energy intake, but this could be misleading because the reduction of ingested calories might be the consequence of dysphagia or depression rather than because of anorexia. The use of questionnaires to diagnose anorexia is increasing rapidly, thus highlighting their utility and reliability. However, considering that questionnaires provide only a qualitative assessment of the presence of anorexia, it is also advisable to quantify the degree of anorexia by using a visual analog scale. \(^8\)

The diagnosis of cachexia cancer is complex
and multifaceted and requires meticulous clinical examination of the patient (Table 2). In ascertaining the patient history, the presence of unintentional weight loss of more than 5% of premorbid weight in a 6-month period should be noted. The presence of anorexia should also be ascertained, as it is commonly associated with cancer cachexia and will contribute to decreased energy intake. Recent chemotherapy or radiation treatment should be considered, as treatment-related toxicities may worsen anorexia and/or cachexia.

Table 2. Diagnosis of cancer cachexia.18

<table>
<thead>
<tr>
<th>Test</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical:</td>
<td></td>
</tr>
<tr>
<td>- Body Weight</td>
<td>Unintentional weight loss (&gt;5% during preceding 6 months)</td>
</tr>
<tr>
<td>- Skeletal muscle mass</td>
<td>Decreases biceps, quadriceps muscle mass</td>
</tr>
<tr>
<td>- Food intake recall or diary</td>
<td>Anorexia and/or decreased food intake</td>
</tr>
<tr>
<td>- Fatigue</td>
<td>Increased</td>
</tr>
<tr>
<td>- Range of motion</td>
<td>Usually impaired</td>
</tr>
<tr>
<td>- Quality-of-life surveys</td>
<td>Decreased scores</td>
</tr>
<tr>
<td>- Karnofsky Performance Scale</td>
<td>Decreased scores</td>
</tr>
<tr>
<td>Serum:</td>
<td></td>
</tr>
<tr>
<td>- Serum CRP (C-reactive protein)</td>
<td>Increased (acute-phase response)</td>
</tr>
<tr>
<td>- Serum fibrinogen</td>
<td>Increased (acute-phase response)</td>
</tr>
<tr>
<td>- Serum hematokrit</td>
<td>Decreased (anemia)</td>
</tr>
<tr>
<td>- Serum albumin</td>
<td>Decreased</td>
</tr>
<tr>
<td>Nutritional assessment:</td>
<td></td>
</tr>
<tr>
<td>- Indirect calorimetry</td>
<td>Increased in REE</td>
</tr>
<tr>
<td>- DXA</td>
<td>Decreased in LBM</td>
</tr>
</tbody>
</table>

Abbreviations: CRP, C-reactive protein; REE, resting energy expenditure; DXA, dual X-ray absorptiometry; LBM, lean body mass.

Physical examination may reveal skeletal muscle wasting, loss of body fat, and generalized weakness. Although most clinicians depend on body weight as a general measure of nutritional status, skinfold thickness, and arm muscle circumference and area may also be used to assess patients. It is important to examine such muscles as the gastrocnemius, vastus lateralis, rectus abdominis and biceps, as experimental data and clinical observations suggest that these type II fast-twitch muscles are most commonly affected in cancer cachexia. Involuntary weight loss in combination with loss of LBM should alert the clinician to the strong possibility of cancer cachexia.9,18

Screening cancer patients for cachexia has included obtaining blood to detect low serum albumin, low hematocrit, and fibrinogen levels, but these laboratory values are quite nonspecific for nutritional evaluation. Measurement of short half-life proteins (eg, transferrin and transthyretin) and urinary metabolites of protein breakdown (eg, creatinine) are of limited value, as they may be elevated in cancer patients with chronic malnutrition but in those with not cachexia. Increased acute-phase proteins such as CRP levels may be an especially helpful screening test, as elevated CRP has been positively correlated with weight loss and cancer cachexia. Although relatively nonspecific, CRP is a sensitive marker for inflammation that is both inexpensive and routinely available, making it useful in the diagnosis of cancer cachexia.4,9,18

Sophisticated analytical techniques may be used to diagnose cancer cachexia. For example, dual energy X-ray absorptiometry (DXA) scans and bioelectrical impedance analysis can assist in determining patient body composition, which is altered in cachexia. DXA uses alternating high-energy and low-energy X-rays to analyze the differences between bone and soft tissue attenuating at different X-ray levels. It can be used to determine the relative proportions of LBM, fat body mass, and total body water (TBW), and exposes each patient to less radiation than computed tomography (CT). In cancer patients with cachexia, both LBM and fat body mass will be decreased. Bioelectrical impedance analysis can assess both the nutritional status and the fluid deficits in patients with advanced cancer and is based on the principle that body tissues differentially oppose the flow of a small alternating current.4,9,18

Another diagnostic tool is indirect calorimetry that permits the assessment of REE and is an accurate and clinically feasible method of measuring energy expenditure. Because of the direct relationship between caloric burn and
oxygen consumption, measuring the volume of oxygen uptake (VO2) will elucidate patient’s caloric burn rate. Measurements of the oxygen consumption rate and the carbon dioxide production rate can be used to calculate the patient’s respiratory quotient and metabolic rate. These measurements permit more accurate monitoring of patients, especially if treatment of the cachexia is initiated.18

TREATMENT

The best way to treat CACS is to cure the cancer, but unfortunately this remains an infrequent achievement. Therefore, an integrated therapy approach is needed which includes both nutritional intake and counseling to prevent muscle and adipose tissue wasting, and pharmacologic approaches to fight anorexia and metabolic disturbances.8,9

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.9,17

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. 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.9

However, parenteral nutrition may facilitate administration of complete chemoradiation therapy doses for esophageal cancer and may have beneficial effects in certain patients with decreased food intake because of mechanical obstruction of the gastrointestinal tract. 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.9

The effects of caloric intake on tumor development and growth are still being debated. 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.9

Nutritional Counseling

In anorectic-cachectic cancer patients, intensive individualized nutritional intervention based on nutrition counseling attenuates the deterioration of nutritional status, and accelerates recovery of global quality of life and physical function. Food intake can be increased by providing frequent small meals and that are energy-dense and easy to eat. Patients should be encouraged to eat in pleasant surroundings and attention should be given to the presentation of food. It is advisable to avoid high-fat food, because fat delays gastric emptying and may exacerbate early satiety, a symptom of anorexia. Since changes in taste and smell occur in anorectic patients, extremes in food temperature and flavor should be avoided.8

Pharmacologic Approaches

Bearing in mind that anorexia and metabolic disturbances are involved, the development of different therapeutic strategies has focused on the two factors: improving appetite and neutralizing metabolic disturbances.4

Improving Appetite

Synthetic progestins such as megestrol acetate and medroxyprogesterone were the first agents studied for the treatment of CACS. The mechanism of action is not fully understood, however, there is evidence that these agents reduce activity of thyrosine hydroxyls and dopamine, which are negative modulators of NPY neurotransmission, and also downregulate NPY2 receptors, reducing negative NPY feedback inhibition, thereby, stimulating appetite. The oral dosages of megestrol acetate range from 160 mg to 1600 mg per day and medroxyprogesterone is given at doses of 300 – 4000 mg per day.4,19,20,21

Cannabinoids are present in marijuana. They stimulate appetite through their effect on hypothalamic cannabinoid-1 receptors and their association with leptin. Dronabinol is an oral synthetic derivative of tetrahydrocannabinol used for the treatment of chemotherapy-induced nausea and vomiting. Oral dronabinol 2.5 mg was administered three times daily, one hour after meals for four weeks.4,19
Cyproheptadine are used for appetite stimulation via serotonin antagonism. The oral dosage is given at doses of 8 mg three times daily. Other antiserotonic agents are ondansentron and mirtazapine.\textsuperscript{4,19,22}

Corticosteroids are widely used for their anti-emetic properties, appetite stimulation and increased euphoric effects. Dexamethasone 0.75 mg is administered orally four times daily, methylprednisolone 16 mg twice daily and prednisolone 5 – 10 mg twice daily.\textsuperscript{4,19}

Ghrelin, an orexigenic peptide predominantly secreted from gastric cells, is a unique hormone that stimulates the release of growth hormone and increases appetite.\textsuperscript{4,8,23,24}

Melarcotin (MC4) antagonists has proved to be effective in preventing anorexia, loss of lean body mass and basal energy expenditure in experimental animal suffering from cachexia. MC4 receptor is involved in the anorexigenic cascade, modulating food intake by two different mechanisms which are both leptin-dependent and leptin-independent.\textsuperscript{4}

### Neutralizing Metabolic Disturbances

Pentoxifylline, a methylxanthine derivative, is a phosphodiesterase inhibitor that inhibits TNF synthesis by decreasing gene transcription.\textsuperscript{4}

Thalidomide is an agent reintroduced into cancer research secondary to its anti-inflammatory anti-tumor effects, specifically reducing the production of TNF. The agent is given at an oral doses of 100 mg every night.\textsuperscript{4,19,25}

Anti-cytokine antibodies and cytokine receptor antagonists or soluble receptors have led to some interesting results. The use of anti-cytokine strategies such as etanercept (fusion protein directed against p75TNF receptor) combined with an antitumor agent (docetaxel) had less fatigue and improved tolerability of the anti-tumor treatment.\textsuperscript{4}

Anti-inflammatory/anabolic cytokine such as interleukin-15 (IL-15) has been reported to be an anabolic factor for skeletal muscle. This cytokine is able to decrease protein degradation, decrease the rate of DNA fragmentation and increase uncoupling protein 3 (UCP3) expression in skeletal muscle, these being the most important trends associated with muscle wasting during cancer cachexia.\textsuperscript{4}

### Other Therapeutic Approaches

Anabolic steroids have a selective effect that induces an increased lean muscle and body mass with the benefit of less androgenic activity. Fluoxymesterone, an oral anabolic corticosteroid, administered at a dose of 10 mg twice daily to advanced cancer. Another anabolic agent such as oxandrolone administered at a dose of 15 mg orally per day promoted subjective improvement in appetite, strength, physical activity and negligible weight gain over the course of 16 weeks.\textsuperscript{4,16,19}

β2-adrenergic agonists, such as formoterol, have important effects on protein metabolism in skeletal muscle, favoring protein deposition. The mechanism is based on both and activation of the rate of protein synthesis and an inhibition of the rate of muscle proteolysis. Formoterol treatment resulted in a decrease in the mRNA content of ubiquitin and proteasome subunits in gastrocnemius muscle in which the main anti-proteolytic action of the drug may be based on inhibition of the ATP-ubiquitin-dependent proteolytic system.\textsuperscript{4,16}

β-blockers can reduce body energy expenditure and improve efficiency of substrate utilization. Patient with CHF treated with β-blockers can increase total body fat mass and partially reverse cachexia.\textsuperscript{4,16}

ω-3-Polyunsaturated fatty acids (ω-3-PUFA), present in large amounts in fish oil, actively reduce either tumor growth or the associated tissue wasting, particularly that of the adipose mass.\textsuperscript{4,15} Eicosapentaenoic acid (EPA) is a polyunsaturated acid that inhibits muscle protein degradation by altering lipid and protein metabolism in cachexia and also exerts anti-cytokine primarily TNF and IL-1.\textsuperscript{16,19,25,26}

Branched-chain amino acids (BCAA) such as leucine, isoleucine, and valine have been used with the aim of improving nitrogen balance, particularly muscle protein metabolism. 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.\textsuperscript{7} Glutamine is an amino acid that has been used to enhance immunoregulation of tumor growth and compensating for the uptake of the amino acid by the tumor. Whereas
N-acetylcysteine can be used to increase the availability of cysteine in the treatment of catabolic states in cancer cachexia.\textsuperscript{4,9,16}

Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, indomethacin, and cyclooxygenase (COX) inhibitors, act by inhibiting prostaglandin production that may have an effect on tumor growth. While nitric oxide inhibitors (e.g. N-nitro-L-arginine), if combined with anti-oxidants, prevent the decrease in body weight, the muscle wasting and skeletal muscle molecular abnormalities.\textsuperscript{4,9,27}

Angiotensin-converting enzyme (ACE) inhibitors, like captopril, seem to act by decreasing the production of TNF-\(\alpha\). A highly lipophilic ACE inhibitor imidapril attenuated the development of weight loss.\textsuperscript{4,16}

Anti-anemic drugs (i.e. erythropoietin) can improve metabolic and exercise capacity via an increased erythrocyte count together with the decreased production of the cachexia-inducing cytokines.\textsuperscript{4}

Adenosine triphosphate (ATP), a directly hydrolyzable source of energy, could potentially tip the balance towards weight gain and preservation of lean body mass. Creatine administration may result in an increase in skeletal muscle phosphocreatine content, which may protect the tissue during catabolic conditions.\textsuperscript{4}

Proteolytic system inhibitors such as peptide aldehyde, lactacystin and \(\beta\)-lactone can effectively block up to 90\% of the degradation of both normal and short-lived cellular proteins.\textsuperscript{4}

Anti-myostatin is a promising therapeutic strategy for cachectic patients. Myostatin, a transforming growth factor beta (TGF-\(\beta\)), induces cachexia through an NF-\(\kappa\)B-independent mechanism by antagonizing hypertrophy signaling through regulation of the AKT-FoxO1 pathway.\textsuperscript{3,28}

Corticotropin-releasing factor 2 receptor (CRF2R) has many biological activities including modulation of the stress response and has been involved in the prevention of skeletal muscle wasting that results from a variety of physiological stimuli.\textsuperscript{4}

**PROGNOSIS**

The presence of early satiety at any stage of the diseases can significantly increase the risk of death by 30\%. The extent of body weight loss negatively influences survival not only by itself, but also by delaying initiation and/or completion of aggressive anti-tumor therapy (Table 3).\textsuperscript{8}

Cancer patients with cachexia-induced weight loss (\(\geq 5\%\) body weight lost involuntary) experienced shorter median survival times than cancer patients without weight loss. The patients with weight loss had poorer responses to chemotherapy and experienced more treatment toxicities.\textsuperscript{18}

**Table 3. Effect of weight loss expressed as % of premorbid weight on median survival expressed in weeks.**\textsuperscript{8}

<table>
<thead>
<tr>
<th>Tumor</th>
<th>No WL</th>
<th>0–5% WL</th>
<th>5–10% WL</th>
<th>&gt;10% WL</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>20</td>
<td>17</td>
<td>13</td>
<td>11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Prostate</td>
<td>46</td>
<td>30</td>
<td>18</td>
<td>9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Colorectal</td>
<td>43</td>
<td>27</td>
<td>15</td>
<td>20</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Abbreviations: NSCLC, non-small-cell lung cancer; WL, weight loss.

Cachexia can have a significant effect on patients with small tumor burdens. In a recent study of early-stage (T1N0M0) renal cell carcinoma patients, the presence of cachexia was associated with markedly worse disease-spesific survival. The 5-year survival rate in patients with high grade (3 or 4) tumors, with and without cachexia, was 55\% and 75\% respectively. In patients with head and neck squamous cell carcinoma, weight loss of greater than 10\% had a strong prognostic impact on 1-year survival and could be used to predict mortality after recurrent oral cavity and oropharyngeal carcinomas. Survival was poorest in patients with greater than 10\% weight loss at the time of recurrent and best for patients with no weight loss.\textsuperscript{18}

**CONCLUSION**

Cancer anorexia-cachexia syndrome is frequently seen in patients with advanced cancer. It is characterized by anorexia and loss of body weight associated with reduced muscle mass and adipose tissue. The pathogenesis of CACS is multifactorial and cytokine plays a major role in this disorder, thereby, representing a suitable therapeutic target. Weight loss in CACS is a marker for both progression of the syndrome and poorer prognosis. Successful treatment of this syndrome may require not only nutritional counseling and supplementation but also treatment with anti-cachexia agents to reverse...
the proteolysis, lipolysis, anorexia, acute-phase response, and inappropriately elevated resting energy expenditure.

REFERENCES


