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REVIEW

Cancer Cachexia: Definition, Staging, and Emerging Treatments

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Abstract: Cachexia is a multifactorial disease characterized by weight loss via skeletal muscle and adipose tissue loss, an imbalance in metabolic regulation, and reduced food intake. It is caused by factors of catabolism produced by tumors in the systemic circulation as well as physiological factors such as the imbalanced inflammatory activation, proteolysis, autophagy, and lipolysis that may occur with gastric, pancreatic, esophageal, lung cancer, liver, and bowel cancer. Cancer cachexia not only negatively affects the quality of life of patients with cancer but also reduces the effectiveness of anti-cancer chemotherapy and increases its toxicity, leading to increased cancer-related mortality and expenditure of medical resources. Currently, there are no effective medical interventions to completely reverse cachexia and no approved drugs. Adequate nutritional support is the main method of cachexia treatment, while drugs that target the inhibition of catabolism, cell damage, and excessive activation of inflammation are under study. This article reviews recent advances in the diagnosis, staging, and evaluation of cancer cachexia.

Keywords: cancer cachexia, disease staging, metabolic dysfunction

Introduction

The prevalence of cachexia is as high as 87% in patients with pancreatic and gastric cancer, 61% in patients with colon, lung, and prostate cancer and non-Hodgkin lymphoma, and 40% in breast cancer, sarcoma, leukemia, and Hodgkin lymphoma.[1] Overall, cachexia accounts for 20% of all cancer-related deaths and is a sign of poor prognosis. Cancer cachexia develops as a secondary disease in patients with cancer and causes progressive dysfunction, characterized by a systemic inflammatory response, negative protein-energy balance, and involuntary loss of lean body mass, with or without a decline in adipose tissue.[2] Clinically, cachexia manifests as a significant reduction in adult body weight or inhibited growth in children, accompanied by changes in body composition and disturbances in the balance of the biological system. Decreased skeletal muscle mass is the most obvious symptom of cancer cachexia and is accompanied by the depletion of fat and heart muscle. This review presents the definition and staging of cancer cachexia, before presenting the latest research in treatment and understanding this syndrome further.

Definition

The term "cachexia" originates from the Greek terms "kakos" and "hexis", meaning "poor physical state". Cancer cachexia is a multifactorial host-phagocytic syndrome characterized by a continuous decline in skeletal muscle mass, with or without fat

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loss. It leads to progressive functional impairment, weakens the effects of chemotherapy, and increases mortality in patients with cancer.[3–7] Another significant feature of this paraneoplastic syndrome is that conventional nutritional support cannot be completely reversed.[8] There is great heterogeneity in its presentation and severity, so its definition and diagnostic criteria are somewhat controversial.

In 2008, Evans[9] defined cachexia as a complex metabolic syndrome associated with underlying illness, characterized by loss of muscle with or without loss of fat mass (Table 1). The prominent clinical feature of cachexia is weight loss in adults (fluid retention correction) or growth failure in children (excluding endocrine disorders).[9] Because cancer cachexia cannot be easily distinguished from anorexia and other causes of weight/muscle mass loss, Fearon (2012)[10] proposed that cancer cachexia is a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that can be partially but not entirely reversed by conventional nutritional support (Table 1). Depletion of skeletal muscle is a key feature of cancer-associated cachexia, and its consequences include reduced antitumor efficacy,[11] increased chemotherapy toxicity,[12–14] complications from cancer surgery,[15] and mortality.[12,13,15-18] The physiological characteristics of the disease are negative nitrogen balance and negative energy balance due to reduced food intake and abnormally high metabolism. The diagnostic criteria defined by Evans are applicable to all types of chronic disease-related cachexia, when taking metabolism and nutrition into account. The diagnostic criteria presented by Fearon specifically target cancer-related cachexia, emphasizing weight loss factors and reduced muscle loss. Overall, weight loss, loss of appetite, growth disorders, and decreased muscle mass are the main symptoms of cachexia.

Table 1 Definitions of Cancer Cachexia

Study	Criteria
Evans et al[9]	Weight loss of at least 5% in 12 months or less in the presence of underlying illness, plus three of the following criteria: -Decreased muscle strength (lowest tertile) -Fatigue -Anorexia -Low fat-free mass index -Abnormal biochemistry • Increased inflammatory markers (CRP>5.0mg/l, IL-6>4.0pg/mL); • Anemia (HGB<12g/dl); • Low serum albumin (Alb<3.2g/dl)
Fearon et al (EPCRC)[10]	-Weight loss>5% over past 6 months (in absence of simple starvation); or -BMI<20 and any degree of weight loss>2%; or -Appendicular skeletal muscle index consistent with sarcopenia (male<7.26kg/m^2; female<5.45kg/m^2) and any degree of weight loss>2%
SCRINIO[21]	-Weight loss ≥10%; and -Presence of at least 1 symptom of anorexia, fatigue, or early satiation.

Abbreviations: CRP, C-reactive protein; IL-6, interleukin-6; HGB, hemoglobin.

With the trend of patients with cancer becoming obese and overweight in recent years, the European Society of Clinical Nutrition (ESPEN)[19] has recommended the higher cut-off value of 22 kg/m^2 for BMI in the elderly. A study conducted by Martin[20] assessing cancer-related weight loss criteria also proved that the value of weight loss percentage independent of BMI is limited and proposed a risk assessment model based on BMI corrected for weight loss. To facilitate clinical practice, the SCRINIO working group[21] proposed a third definition in which patients with cachexia are classified based on weight loss (<10%, pre-cachexia; ≥10%, cachexia) and whether there is at least one symptom of anorexia, fatigue, or early satiety (Table 1). Because systemic inflammation and decreased muscle content are not classified as important diagnostic factors, these definitions have stronger clinical practicality and expand the diagnosis of cancer cachexia by stressing its universality.

Staging

Cancer cachexia is divided into three consecutive clinical stages:[10] pre-cachexia, cachexia, and refractory cachexia, though patients may not experience all three stages. The incidence and severity of cachexia are highly heterogeneous and depend on the type, location, and stage of the tumor. At present, there are no specific biomarkers for early stage cachexia identification. Staging is determined according to the clinical manifestations and characteristics of the patient. The refractory cachexia phase is determined by the patient's underlying disease and overall condition; diagnosis of this stage requires a low WHO performance status score and a survival period of less than 3 months.[10] The focus of treatment for refractory cachexia moves from aiming to cure and control to maintaining the patient's

quality of life. This type of grading system can provide patients with more suitable treatment options at all stages of disease development, and allows for targeted research and treatment for each stage.

Evaluation

Cancer cachexia is a multi-dimensional disease, and the condition of each patient must be fully evaluated to determine their overall status to optimize the treatment decision. Cancer cachexia assessment mainly includes nutritional status, weight/content of body weight, quality of life, and related biomarkers. Insufficient intake is a common phenomenon, screening for malnutrition in patients with advanced cancer is critical. The Patient-Generated Subjective Global Assessment (PG-SGA),[22] a modified for patients with cancer, is a validated screening tool for malnutrition. The PG-SGA questionnaire has a comprehensive design, that assesses factors such as patient weight, calorie intake, functional status; and temperature, muscle status, body fat status and whether edema is present or absent. The Mini Nutritional Assessment (MNA)[23] is a validated, rapid screening tool of nutritional status, that evaluates diet history, weight, mid-arm circumference and nutritional risk factors. In clinical practice, the MNA that assesses elderly malnutrition is more practical as it can be completed within 10 minutes. Other screening tools include the Malnutrition Screening Tool[24] and Nutritional Risk Screening 2002,[25] but only the PG-SGA is adapted to patients with cancer.[26]

However, nutrition screening tools cannot assess muscle mass[27] or body composition. The most commonly used parameters to assess body composition in patients with cancer include anthropometric methods, bioelectrical impedance analysis (BIA), computed tomography (CT) and dual-energy X-ray absorptiometry (DXA). The anthropometric method[28] is a method for evaluating the composition of the human body by measuring skinfolds, weight, height, and body area. Although this is a simple method, it has poor accuracy and cannot distinguish between lean body mass and fat tissue. BIA[29] is used to estimate the percentage of body fat, fat mass, fat-free mass and total fat content based on electrical properties, and uses an equation to calculate body fluid; however, BIA is not as accurate as DXA in assessing the body composition of patients with cancer. DXA[30] evaluates human body composition by predominantly scanning appendicular muscles. The radiation dose and cost are low, however, this approach does not differentiate subsets of adipose tissue into intramuscular, visceral, and subcutaneous or lean body mass into muscle, organ tissue, and tumor tissue. Therefore, lean body mass is often overestimated with this approach. In general, CT[31] scans are used to assess axial skeletal muscle mass by identifying standard skeletal markers (usually the third lumbar vertebra) to assess body composition. This approach has high accuracy and specificity as the scanning can distinguish individual tissue composition; it is the gold standard for evaluating body composition. The imaging has high accuracy and specificity. Magnetic resonance imaging (MRI)[32] is a high-precision method for measuring the composition of the human body. It is equivalent to CT imaging,[33] and does not expose patients to ionizing radiation, but it is costly. Other methods for assessing the overall composition of the body include water density (underwater weighing) and air plethysmography (Bod Pod),[34,35] but they cannot distinguish between local fat or muscle. Upper-arm grip is the preferred method of assessing muscle strength,[10,36] which can indirectly reflect muscle mass and function. The quality of life is usually used to assess the psychosocial and functional characteristics of patients.[37]

Biomarkers of cancer cachexia are research hotspots. Lipid and protein mobilization factors produced by tumors help to activate the inflammatory cascade, which in turn stimulates the adrenal glands to release cortisol and catecholamines; this leads to changes in protein metabolism through direct cytokine activation breakdown of proteins, carbohydrates, and lipids. A variety of inflammatory markers and cytokines are potential biomarkers of cachexia, including hemoglobin, albumin, C-reactive protein (CRP), ghrelin, adiponectin, leptin, insulin-like growth factor 1 (IGF-1), interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor-α (TNF-α). Albumin and CRP levels are currently considered to be the best indicators of cancer cachexia.[38] In order to quantify cancer cachexia systematically, scoring systems have been developed, including the modified Glasgow Prognostic Score (mGPS),[39,40] cancer cachexia scoring system (CASCO),[41,42] and cachexia staging score (CSS).[43] However, biomarkers are affected by a variety of factors such as sex, age, and underlying diseases.[44] The score corresponds with either non-malignant, pre-cachexia, cachexia, or refractory cachexia to effectively predict the survival of patients with the syndrome.

Treatment

It has been proven that cancer cachexia can be separated from underlying diseases by mechanical means, as the

targeted blockade of cachexia signals can prolong survival while tumors continue to grow.[45,46] In order to achieve the overall goals of improving muscle mass, improving the state of the body, and increasing the tolerance of anti-tumor therapies, the treatment of cancer cachexia must follow a comprehensive, individualized, structured, and continuous treatment model. For end-stage cachexia, palliative treatment strategies are better than other therapy options.[47] For certain catabolically active underlying diseases (advanced lung cancer,[48] bile duct cancer,[2] etc.), the first choice of treatment is to inhibit catabolic drugs. To maximize the quality of life for patients, it is important to establish a continuous treatment system based on drug therapy and supplemented with nutrition, exercise, and psychological counseling.

As the basis for the treatment of cancer cachexia, drug therapy reduces tumor-related inflammation, increases anabolic metabolism, reduces catabolism, stimulates appetite, achieves weight and muscle gain, improves physical fitness scores, and extends survival. Megestrol acetate (MA) is the only drug approved by the FDA for the treatment of AIDS-related cachexia. Its representative drug is medroxyprogesterone acetate (MPA), which increases the release of neuropeptide Y in the hypothalamus to reduce and inhibit pro-inflammatory cytokines and stimulate appetite; this leads to increased food intake, weight gain, and an improved quality of life.[49,50] However, the application of MPA is limited due to its association with increased peripheral thromboembolic events, fluid retention, adrenal insufficiency, hypogonadism, hyperglycemia, and hypertension. In addition to MPA, many of the following compounds have been put into clinical and preclinical research:

1. Cannabinoids interact with endorphin receptors, interfere with IL-1 synthesis, activate cannabinoid receptors in the leptin neural circuit, and inhibit prostaglandin synthesis. They can increase the intake of energy storage and improve the nitrogen balance in the body,[51] but can also produce serious central nervous system adverse reactions such as hallucinations, dizziness, and psychosis.[52]
2. Cyproheptadine, a 5-HT inhibitor, is a kind of tissue serotonin that produces mild appetite stimulation and a certain degree of sedation.[53] Because the results of current clinical trials involving this drug are inconsistent, it should be used with caution in clinical applications.[54]
3. Non-Steroid Anti-Inflammation Drugs (NSAIDs) include COX-2 inhibitors such as celecoxib, indomethacin, and ibuprofen. They can reduce tumor-related inflammation and TNF-α levels, increase lean weight and grip strength, and improve life treatment and mGPS score.[55,56] To date, only preliminary clinical trial results have been positive,[57] as these drugs are not widely used outside of clinical trials.
4. Immunomodulatory preparations mainly include TNF-α inhibitors (infliximab), IL-6 antagonists (ALD518), IL-6R antagonists (tocilizumab), and TNF-α and IL-6 dual-target OHR/AVR118. Current clinical trials have confirmed that infliximab has no significant effect on improving body weight and physical fitness.[58] Conversely, ALD518 has been shown to delay lean body mass loss in non-small cell lung patients with cancer in a Phase II clinical trial.[59] Tocilizumab has been shown to significantly improve weight and nutritional status, and to reduce the inflammatory response. Many clinical trials and case reports[60–62] indicate that OHR/AVR118 can improve cachexia functional status, stabilize weight, and stimulate appetite.[63]
5. Growth hormone releasing peptides and their receptor agonists include ghrelin, anamorelin, and macimorelin, which stimulate growth hormone secretion,[64] inhibit pro-inflammatory cytokines, and inhibit NF-κB[65,66] to improve weight and appetite and increase muscle mass quickly.[67,68] Although its half-life is less than 30min and there is limited clinical utility,[69] ghrelin may stimulate tumor growth;[70] therefore further data is needed based on Phase 3 clinical trials, to understand the potential risks. Anamorelin, a novel orally active ghrelin receptor agonist, has been associated with positive results in patients with cachexia who have non-small cell lung cancer. The two double-blinded phase II trials (ROMANA 1 and ROMANA2[71]) assessed the efficacy and safety of anamorelin (100mg/d for 12 weeks) in patients with cachexia who have advanced NSCLC. Anamorelin significantly increased total body weight. These results were obtained by assessing the least-squares mean change ± standard error in the anamorelin group vs placebo group - ROMANA 1: 2.20 ± 0.33kg vs 0.14± 0.36kg, respectively, $p<0.0001$; for ROMANA 2:0.95 ±0.39 kg vs −0.57 ±0.44 kg,

respectively, p<0.0001. The increase in body weight was especially seen in those with a low-BMI (<20kg/m^2) patients.[72] The weight increase, however, failed to improve handgrip strength. ROMANA3[73] also confirmed that anamorelin is well tolerated and increased body weight over 24-week period in the anamorelin vs placebo group (least-squares mean change ± standard error: 3.1 ±0.6kg vs 0.9±0.7kg, respectively, p<0.0001). In a real world setting, anamorelin not only stimulates food intake, but it also reversed loss of muscle tissue and lean body weight.[69]

6. Selective androgen receptor modulators, such as enobosarm, selectively act on the androgen receptors of skeletal muscle and bones, thereby minimizing irritation to other organs such as the prostate, skin, and liver. These modulators can increase lean body mass and improve activity tolerance.[74,75] Related phase 3 clinical trials are underway (NCT 01355484, NCT 01355497).
7. Anabolic catabolic transforming agents (ACTAs), such as spindolol, are a class of non-specific β-1 and β-2 adrenergic blockers with β2 adrenergic receptor intrinsic sympathomimetic activity. As a strong HT-1A receptor agonist, spindolol can bind to HT-1A receptors in the brain. It can increase muscle content, weight, and improve grip.[76] Initial preliminary data is promising, but more research is required to indicate the efficacy and to provide a safety data disclosure.
8. As a methylxanthine derivative, the drug pentoxifylline inhibits the characteristics of systemic inflammation and TNF-α by inhibiting phosphodiesterase; its efficacy has not been proven in cancer cachexia.[77]
9. Glucocorticoids, such as the drugs prednisone acetate and dexamethasone, inhibit pro-inflammatory cytokines like TNF-α and IL-1 to increase appetite and improve nausea, but cannot eliminate muscle loss.[78] Those increase in body weight was mainly due to an increase in fat mass and water retention, and was not associated with an increase in lean body mass nor skeletal muscle. Adverse reactions such as insulin resistance, adrenal insufficiency, and sleep disorders have been observed, and there is no evidence of clinical application.
10. Melanocortin-4 receptor (MC-4R) is a member of the melanocortin receptor family, a group of G-protein-coupled receptors that secrete a peptide in the ventromedial nucleus of the hypothalamus. These substances play an important role in regulating food intake. In a mouse model, MC-4R activation has been shown to reduce foraging behavior, increase basal metabolic rate, and reduce lean body mass.[79] The effectiveness of MC-4R antagonists has also been demonstrated in murine models.[80] However, clinical trials have not yet begun.
11. Other compounds: growth hormone,[81] olanzapine,[82] bortezomib,[83] the JAK/STAT3 inhibitor ruxolitinib, and the myostatin/activin inhibitor BYM338 are all potential drugs that have not been validated in clinical trials.

These drugs have the potential to treat cancer cachexia preferentially. However, there are numerous interactions between different mediators when complex inflammatory cascades are activated, suggesting that a single target drug cannot be used as a cure. Most patients with cancer-related cachexia must choose a targeted intervention point to maximize the effect on the syndrome.

According to the ASCO Guideline,[16] dietary assessment and counseling for patients with advanced cancer who suffer from insufficient intake due to various factors is the first recommendation based on robust evidence,[84–86] with goals of dietary structure adjustment (high energy and high protein diet), increased meal frequency, and oral nutritional supplements (β-hydroxy-β-methylbutyrate,[87] eicosapentaenoic acid,[88] L-carnitine,[89] omega-3 fatty acids[90]). If the terminal patient with cancer cannot eat for a long time, artificial feeding must be carried out. The enteral route should be given priority, but parenteral nutrition can be applied when the enteral route is insufficient or not feasible.[91] However, parenteral nutrition cannot improve the overall survival of patients with cancer cachexia,[92,93] and as a high-calorie high-protein and nutrient-dense feeding generally does not affect body composition in these patients.[94] Moreover, if the patient has difficulty digesting and absorbing nutrients, the caregivers have a tendency to repeat feeding, which can induce the patient vomiting, and cause complications such as regurgitation, aspiration, pneumonia. Often, the patient ends up feeling frustrated and to blame. In addition, proper physical exercise can preserve muscle mass and function[95] while reducing systemic inflammation[96–98] and decreasing systemic catabolism,[97,99] all of which prevent the symptoms of cancer cachexia. It can also delay muscle

breakdown and insulin resistance,[100] as well as provide adequate psychological support and intervention to improve quality of life.[101]

Research is currently underway on the correlation between cachexia treatment and cancer treatment. For example, studies have shown that cachexia tumor cell proliferation and excessive muscle-protein catabolism share a common mechanism. Specifically, dual-specific mitogen-activated protein kinase kinase-1 (MAP2K1) and MAP2K2 function downstream of RAS GTPases and RAF proto-oncogene serine/threonine protein kinase (RAF) to induce phosphorylation of MAPK1 and MAPK3, thereby conveying input promotion from growth factors for tumor cell proliferation. This signaling pathway also appears to be involved in the activation of excess muscle protein catabolism when tumor growth is present.[70,102] Therefore, MAP2K inhibitors may have both anti-cachexia and anti-tumor activity. These types of interactions should be explored through further research.

The diagnosis of cachexia in patients with cancer has made significant progress over time, evolving from the label "unintentional weight loss" to "cancer cachexia" in the clinical environment. With the continuous development of this field, genomics and metabolomics may be used to assist diagnosis. Classification and reclassification provide each patient with a more individualized and refined systemic treatment strategy. However, it must be acknowledged that the overall quality of clinical trials related to cancer cachexia is not high. In recent years, whether the trials have produced clinical benefits (improved grip strength, climbing stairs) is also controversial as the end point of the study.[103] Clinical trials and nutrition interventions for related new drugs are continuously being carried out and promoted, and regular efforts are being made for better treatment. The multimodal cachexia intervention, consisting of drug, nutritional supplements and adequate exercise, is feasible and safe for patients with cancer cachexia.[104]

Ethics Statement

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Disclosure

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