Communication



# Treating Cancer Cachexia Should Be Essential in Cancer Care

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# Treating Cancer Cachexia Should Be Essential in Cancer Care

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**Abstract: Background:** Cancer cachexia manifests as a multifaceted syndrome characterized by weight loss; appetite loss, muscle wasting, fatigue, weakness, and systemic disturbances, affecting patients' physical function and quality of life (QoL). Despite these negative effects, cancer cachexia treatments have often been limited to supportive care with the primary objective of symptom relief. **Methods:** We evaluated papers published in English from January 2010 to January 2024 searched over PubMed, and Google Scholar databases using search terms "cancer cachexia", "cachexia treatment", "essential care", and "immune disorder" and their combinations with suitable Boolean operators. Studies beyond 10 years and studies not reporting CAC, essential care, and anti-inflammatory interventions were excluded. **Results:** Essential care encompasses routine screening for cachexia using criteria such as the Global Leadership Initiative on Malnutrition (GLIM) or the Cachexia Score (CASCO), and therapeutic approaches that identify and inhibit mechanisms that are driving cachexia. Managing this multifactorial syndrome has involved a multimodal approach that has included non-steroidal anti-inflammatory drugs, nutritional support, physical activity, appetite-stimulating agents, and specific androgen receptor modulators. These approaches have not been successful. Instead, identifying drugs and biologics that are immunomodulators targeting the molecular and cellular immune dysfunction promoting cachexia is a strategy that could reduce symptoms and improve outcomes in cachectic cancer patients. **Conclusions:** This study emphasizes the integration of cancer cachexia management into routine cancer care. It also highlights the potential of targeted therapies, such as immunomodulators to address the underlying immune disorders driving cachexia

**Keywords:** Cachexia; Immunomodulation; Patient outcomes; Quality of life; Monotherapy; Weight loss

## Introduction

Cancer cachexia contributes to approximately half of the global cancer-related deaths, predominantly associated with pancreatic, gastric, and esophageal cancers [1,2]. It encompasses a complex syndrome characterized by the progressive reduction in mass of skeletal muscle, which may be partially manageable with nutritional support [1]. The main clinical manifestations include weight loss, appetite loss, muscle wasting, fatigue, weakness, and systemic disturbances [2]. Despite its high prevalence in patients with advanced cancer (up to 60%-80%), its occurrence and intensity vary, even in patients with the same type and stage of cancer [1,3].

Cancer cachexia represents a multifaceted challenge in oncology, extending beyond physical manifestations to deeply affecting patients' psychological well-being and overall quality of life (QoL) [1,4]. Cachexia is not merely a consequence of cancer but rather a complex interplay of various factors, including systemic inflammation, metabolic dysregulation, and neurologic alterations [2,4,5]. Its impact is profound, often resulting in a vicious cycle where weight loss and muscle wasting further exacerbate the disease prognosis, rendering patients more susceptible to treatment-related toxicities and complications [4]. Furthermore, cancer cachexia undermines the efficacy of conventional cancer therapies, reducing treatment response rates and compromising overall treatment outcomes leading to reduced effectiveness of chemotherapy, increased side effects, and treatment disruptions [1,4]. This

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underscores the potential benefit of identifying and incorporating effective cachexia treatments when initiating systemic anti-cancer regimens.

Despite the devastating impact of cancer cachexia on patients with late-stage cancer, treatments for it have often been limited to supportive care. There is a critical need to integrate cachexia management into routine cancer care to improve patient outcomes. Early intervention and comprehensive management strategies are essential for addressing the multifaceted aspects of cachexia and enhancing patient well-being [6]. Initiating an effective treatment for cachexia simultaneously with cancer treatment could reduce treatment toxicity, enhance cancer treatment delivery, and improve outcomes. The purpose of this perspective is to advocate for re-evaluating the clinical importance of effective treatments for cancer cachexia and consider it as 'essential' rather than 'supportive' in cancer care. While relieving symptoms is important, improving outcomes is the primary goal of cancer treatment – survival trumps all.

We evaluated papers published in English from January 2010 to January 2024 searched over PubMed, and Google Scholar databases with combinations of keywords and medical subject headings (MeSH) along with suitable Boolean operators. The search terms employed were "cancer cachexia", "cachexia treatment", "essential care", and "immune disorder". All published original articles were considered. Studies beyond 10 years were excluded from the search. Additionally, studies not reporting CAC, essential care, and anti-inflammatory interventions were not considered.

**The Role of Essential Care in Cancer Cachexia Management**

Cachexia often remains overlooked and underdiagnosed, contributing to disease progression and heightened mortality rates [7]. While some clinical services for cancer cachexia management exist within conventional cancer care frameworks, there is no established standard protocol. With only a handful of institutions having a specialized cachexia clinic, cancer cachexia is generally managed under symptom control or palliative care [1]. Thus, optimizing the maximum available resources becomes crucial in enhancing patients' QoL and treatment outcomes [7].

Managing cancer cachexia in patients with advanced cancer is currently believed to require a multimodal approach. This approach addresses physical health through pharmacological (single or multiple drugs), medical, nutritional, and rehabilitative measures, alongside promoting psychological, emotional, and social well-being [8]. It emphasizes improving skeletal mass, appetite, and safety [9]. Evidence from a phase III randomized controlled trial (RCT) involving 332 patients, highlighted the benefits of combining interventions such as medroxyprogesterone acetate or megestrol acetate, eicosapentaenoic acid (EPA), L-carnitine, thalidomide, and nutritional supplements, which improved various parameters including lean body mass, energy expenditure, IL-6 levels, appetite, grip strength, and QoL [10]. Similarly, a non-blinded RCT with 32 participants demonstrated the potential of family-centered nutritional interventions to positively impact patients' nutritional status and alleviate eating-related distress [11]. Another RCT involving 207 patients demonstrated reduced symptom burden and enhanced QoL upon integrating consultative palliative care into standard oncology care, irrespective of prognosis [12]. Although some studies show the benefits of a multimodal approach, comprehensive data regarding the efficacy of multimodal interventions for cancer cachexia is lacking [13]. Regulators mandate agents that can prevent cachexia progression or demonstrate cachexia reversal effects [9]. In alignment with this, two phase III RCTs involving 484 and 495 patients, respectively, reported a significant improvement in lean mass, body weight, and anorexia symptoms following anamorelin (a ghrelin receptor agonist) treatment, although no improvement was noticed in handgrip strength [14]. Contrasting results were reported regarding the effect of anamorelin on the improvement of QoL. While a phase II RCT conducted on 180 patients showed improved QoL in patients treated with anamorelin, another open-label study involving 31 patients showed no improvement in QoL of patients treated with the same [15,16]. Thus, newer monotherapy approaches targeting the mechanisms of cancer cachexia might be more effective.

Cancer cachexia is a complicated syndrome where multiple symptoms often require simultaneous attention for comprehensive management [7]. Existing anti-cancer pharmacotherapies

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show limited efficacy in improving the significant muscle mass reduction seen in patients [4]. While future research into underlying mechanisms progresses, no approved drugs especially targeting cancer cachexia have been developed [1]. Further, managing cachexia itself is challenging due to the difficulty in balancing the risks, burdens, and costs with anticipated benefits while also ensuring patient consent [1].

**Current Therapeutic Approaches for Treating Cachexia**

Cancer cachexia includes multiple factors such as anorexia, skeletal muscle loss, metabolic alterations, and systemic inflammation. Addressing these logically requires comprehensive treatment approaches involving pharmacotherapies and multidisciplinary interventions, encompassing nutrition therapy, physical activities, and psychosocial interventions [4]. However, the authors believe that identifying pharmacologic or biologic agents that inhibit the immune dysfunction that promotes cachexia is the strategy most likely to have a positive impact on outcomes for cachectic cancer patients. Hopefully, this approach would impact the majority of patients with cachexia, but identification of an agent that is efficacious in a substantial subset of cachectic patients with a targetable biomarker would also be useful [17]. Among the existing drugs, corticosteroids, androgens, non-steroidal anti-inflammatory drugs (NSAIDs), cannabinoids, and progestins, have modest short-term symptom relief for some patients with cachexia [4] (Table 1).

**Table 1.** Current therapeutic approaches against cancer cachexia.

| Intervention | Targets | Impact on Patients | Ref. |
|---|---|---|---|
| IL-6 receptor antibody<br>TNF-$\alpha$ inhibitor<br>TGF-β antibody<br>GDF15 antibody | Inflammation | Reduced muscle wasting, improved appetite, increased survival | [18-21] |
| Immunomodulators | Immune disorder | Reduced muscle wasting, reduced fat loss, increased survival and QoL | [17] |
| NSAID<br>Polyphenols<br>Ginsenoside | Inflammation, ROS, Atrogin1, MuRF1 | Reduced muscle wasting and better QoL | [22-24] |
| ActRIIB3<br>Inhibitors of Activin A/Myostatin activin II receptor antibody | Activin A<br>Myostatin | Reduced muscle wasting and improved QoL | [25, 26] |
| IGF analog<br>EPA<br>β2-andregenergic agonist | Protein degradation | Reduced muscle wasting and improved QoL | [27-29] |
| Ghrelin<br>(ghrelin mimetic synthetic progestogen)<br>Cannabinoid | Food intake | Reduced muscle wasting, weight gain, improved appetite | [30-32] |
| Physical activity | Adiponectin and mTOR signaling | Muscle protein synthesis | [33, 34] |

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Abbreviations: EPA, eicosapentaenoic acid; IGF, insulin-like growth factor; IL-6, Interleukin-6; mTOR, mammalian target of rapamycin; MuRF1, muscle ring finger 1; NSAID, non-steroidal anti-inflammatory drug; QoL, quality of life; ROS, reactive oxygen species; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha.

Drugs like anamorelin, and selective androgen receptor modulators have demonstrated improvement in muscle mass for patients with cachexia and without reversing cachexia [4,35]. Similarly, myostatin inhibitors also target muscle wasting, providing symptomatic relief [36]. Anti-inflammatory cytokine treatments like anti-IL6 therapy, and anti-IL1 therapy for cancer cachexia have also shown promising results [37]. Patients with advanced cancer have anabolic potential that can be harnessed using drugs, with some showing a net muscle gain exceeding 15%, presenting an opportunity for nutritional interventions to manage cachexia emphasizing strategies such as optimizing caloric and protein intake through dietary counseling, oral nutritional supplements, enteral feeding, or, when necessary, parenteral nutrition [36,38]. Additionally, integrating physical activity and exercise therapy into treatment plans can improve muscular fitness, potentially supporting anabolism and enhancing QoL [39]. The American Society of Clinical Oncology (ASCO) recommends the above approaches and has provided guidelines for managing cachexia in patients with advanced cancer, primarily involving symptom management (Figure 1).

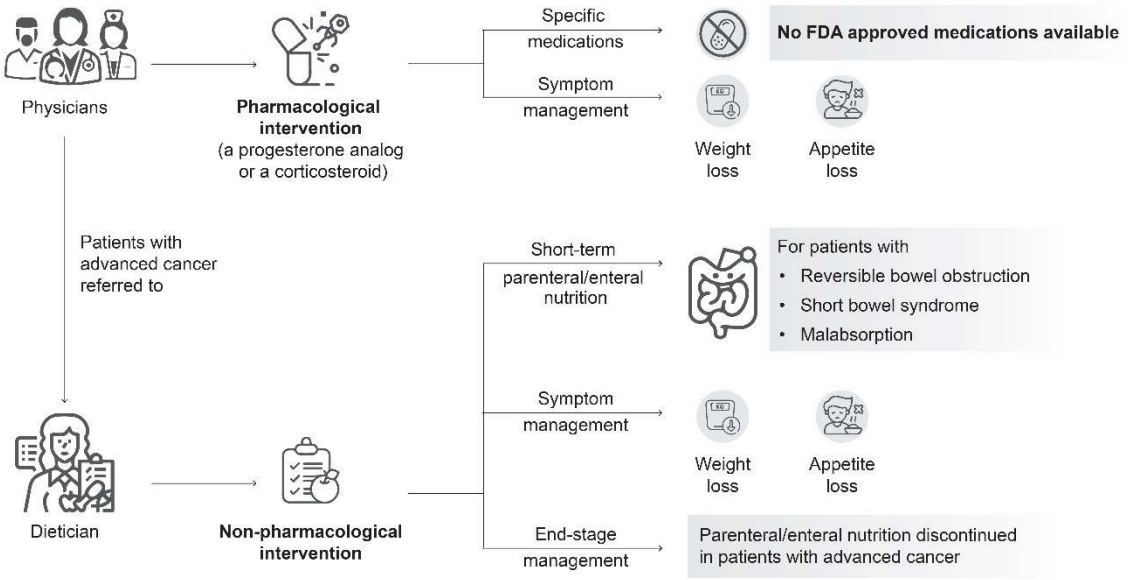


**Figure 1.** ASCO recommendations for the management of cancer cachexia.

Recent research on R-ketorolac, an immunomodulator, has shown a reduction in adipose tissue and skeletal muscle loss without affecting cyclooxygenase (COX) activity, which is pivotal for inflammation and pain regulation, suggesting that this agent could have a significant impact in managing cachexia [17]. This is particularly important since long-term NSAID use is related to the side effects of COX-1 inhibition [40]. The combination of R-ketorolac and chemotherapy in murine models demonstrated a 100% survival rate, highlighting the potential of immunomodulation as a therapeutic approach addressing the altered immune response underlying cachexia [17]. Immunomodulation represents a new direction to develop effective treatments for cancer cachexia.

## Changing Perspectives on Treatment Paradigms

### *Understanding Cancer Cachexia Phases*

Cancer cachexia manifests in three phases: pre-cachexia, cachexia, and refractory cachexia, although not all patients progress through each of these phases [41]. Pre-cachexia is marked by

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cachexia-associated derangement without weight loss [5]. The cachexia stage involves significant loss of weight (>5%), decreased food or energy intake, and increased systemic inflammation [42]. Refractory cachexia is linked to unresponsiveness to cancer treatments, reduced functional ability, and a life expectancy of three months or less [5].

*Assessing Cancer Cachexia in Patients*

Initial treatment steps should include routine screening for cachexia using validated assessment tools like the GLIM (Global Leadership Initiative on Malnutrition) criteria or the CASCO (Cachexia Score). The GLIM criteria diagnose malnutrition through a two-step process involving risk screening and severity assessment based on various criteria including loss of weight and muscle mass, low body mass index (BMI), reduced food intake/metabolism, and disease burden or inflammation [43]. The CASCO categorizes cachexia severity numerically into mild (0-25), moderate (26-50), severe (51-75), and terminal (76-100) based on criteria like weight loss and composition, disturbances related to inflammation or metabolism, immunosuppression, reduced physical performance, anorexia, and QoL [44]. This grading system aids in treatment selection, supported by studies classifying patients into pre-cachexia and cachexia phases using comprehensive frameworks [41]. Aligning with this, a study classified 40 patients having non-small-cell lung cancer (stage III) into pre-cachexia and cachexia phases using both cancer-specific and general frameworks. The cancer cachexia features frameworks include weight loss, reduced food intake, and inflammation. The general frameworks include BMI, energy expenditure, fat-free mass (FFM), anorexia, muscle strength, and biochemical features. Additional parameters such as physical activity, QoL, and survival were evaluated and were subsequently followed by risk assessment conducted using Kaplan–Meier survival functions [42].

*Interdisciplinary Approach to Cancer Cachexia Management*

Failure of previous approaches in cancer cachexia management has prompted a comprehensive approach to enhance the QoL, improve treatment tolerance, and consequently, better the disease prognosis [7]. This involves an interdisciplinary team of oncologists, physicians, psychiatrists, psychologists, anesthesiologists, physiotherapists, nurse specialists, counselors, and dieticians. However, effective management also requires standardization of assessment tools and criteria for diagnosis and monitoring of cancer cachexia, facilitating specialized training and coordination among health care providers, and allocation of resources to provide essential care and support to patients with cachexia [7].

*Tailoring Treatment in Cancer Cachexia*

Treatment objectives vary among patients, with personalized nutrition consultation playing a crucial role. For some individuals, the goal is to preserve physical function, maintain autonomy, and reduce fatigue, while others may prioritize the psychosocial aspects of cachexia or anorexia, such as distorted body image and the inability to eat with family members [45]. The patient's nutritional requirements are calculated following this assessment, considering factors like preferences and habits. Subsequently, a tailored diet plan is prescribed, integrating preferred foods and accommodating patient habits while ensuring nutritional adequacy [46]. As patients with cancer age, the adoption of diverse treatment approaches exacerbates physical and psychological stress, potentially impeding treatment continuity. Therefore, the approach to treating cancer cachexia should be tailored to suit the patient's condition and lifestyle, thereby facilitating consistent maintenance [4].

**The Promise of Immunomodulation**

Emerging research focuses on the intricate interplay between the immune system and metabolic pathways implicated in cachexia pathogenesis. Recent studies have identified pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-$\alpha$), interleukin-6 (IL-6), interferon-gamma (IFN-$\gamma$), and GDF-15 as key mediators of cachexia-associated inflammation [47–49]. Immunomodulatory

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agents, including monoclonal antibodies and small molecules, seek to modulate the activity of these cytokines, thereby attenuating systemic inflammation and its detrimental effects on metabolism and muscle mass [47,50].

Immunomodulation offers a multi-effect approach to cachexia management. Beyond symptom control, these therapies hold the potential to improve functional capacity and enhance survival [22,50]. Notably, administering R-ketorolac and anti-human GDF15 inhibitory antibodies has enhanced survival in mouse models. These approaches target the underlying immune dysregulation, they target the root causes of cachexia rather than merely managing its manifestations [17,51,52]. These findings emphasize that treating cancer cachexia could significantly improve survival in murine models, implying its potential clinical application. Effective treatment of cancer cachexia could therefore offer hope to the patients, making it essential to prioritize care for cachexia. However, translating promising preclinical findings into effective clinical therapies poses challenges. Optimizing treatment regimens, identifying suitable patient populations, and managing potential side effects require careful consideration [50]. Considering these challenges, immunomodulation represents a paradigm shift in cachexia management. By intervening in the complex immune-metabolic pathways driving the syndrome, these therapies offer hope for improved patient outcomes. Continued research efforts are essential to elucidate the full potential of immunomodulatory interventions and their role in reshaping the landscape of cachexia treatment.

**Future Directions in Managing Cancer Cachexia**

Cancer cachexia significantly impacts the well-being of patients. Its complexity and multifactorial nature pose considerable challenges in management. However, a novel targeted therapy approach to immunomodulation with agents like, R-ketorolac, which has shown promise in pre-clinical studies [17]. A 'proof of concept' trial is being conducted with ketorolac to test whether immunomodulation can reverse cancer cachexia in pancreatic ductal adenocarcinoma (PDAC) patients [53]. The use of combination drug therapies also has shown promise, but to date, no novel drug or combination has been approved for treating cancer cachexia in the United States or European Union [1,10].

Consequently, researchers are also exploring a multimodal approach that combines pharmacological and non-pharmacological approaches to address the various mechanisms of the disease simultaneously. This approach aims to improve calorific intake, muscle and fat mass, and physical ability. A multimodal intervention comprising physical exercise, nutritional supplements, and anti-inflammatory agents was incorporated into a randomized phase II clinical trial [54,55]. Results showed that the multimodal approach exhibited feasibility and tolerability in patients undergoing chemotherapy for advanced-stage lung or pancreatic cancer [54]. Subsequently, the phase III trial with multimodal exercise, nutrition, and anti-inflammatory medication for cachexia (MENAC) intervention consisting of ibuprofen, a home-based exercise program, nutritional supplements, and advice has been completed. The results of this randomized trial were presented at the 2024 annual meeting of the ASCO [56] [2024]. A marginally significant short-term effect of weight stabilization at a 6-week follow-up period in patients treated with exercise, nutrition, and ibuprofen versus a median weight loss of 1 kg in the comparator group that received conventional care [57].

The realization of multimodal therapy remains challenging without parity between human and animal studies, effective therapies targeting the root cause instead of symptoms, standardized diagnostic tools, and risk assessment, with limited success alongside a huge cost burden. This calls for further research to refine diagnostic criteria and develop specific and effective treatments to improve outcomes for patients with cancer cachexia. Ideally, single pharmacologic or biologic agents inhibit multiple causative mechanisms or a single mechanism in a subset of cachectic patients identified by a biomarker.

**Strengths and Limitations of this Treatment Strategy**

This article presents a comprehensive overview of cancer cachexia, highlighting its multifaceted nature and the challenges associated with its management. Strengths of the study include its

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thorough examination of various aspects of cancer cachexia, from its clinical manifestations to the potential interventions, including pharmacological and non-pharmacological approaches. It also discusses a paradigm shift in the intent of treating cancer cachexia that focuses on identifying strategies that inhibit cachexia as a means for improving survival rather than focusing primarily on symptom relief. It emphasizes emerging research on immunomodulation as a promising therapeutic avenue. While the study provides insights into various treatment modalities, a few limitations are evident. It acknowledges the lack of approved drugs specifically targeting cancer cachexia, highlighting the ongoing challenges in managing the condition effectively. Additionally, the reliance on preclinical findings and ongoing clinical trials underscores the gaps in translating promising research into clinical practice.

## Conclusions

This study highlights the potential benefit of a paradigm shift in cancer cachexia management, emphasizing the integration of cachexia as an essential aspect of routine cancer care rather than merely supportive care. The authors advocate a novel approach incorporating specific therapeutic agents such as immunomodulators like R-ketorolac, to address immune system disorders, the underlying cause of cancer cachexia, and to enhance patient outcomes. The study also underscores the significance of further research and the development of specific and effective therapies through immunomodulation to pursue complete reversal of this lethal syndrome, rather than solely alleviating some cachexia symptoms.

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