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Cancer Cachexia: Innovations in Pharmacotherapy for Terminal-Stage Patients - Review of the latest reports

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ABSTRACT

Introduction and purpose

Cachexia is a complex and multifactorial syndrome, which is a current, worldwide treatment challenge, and concerns most of the patients with cancer. The issue is characterized by anorexia, skeletal muscle loss, adipose tissue wasting, involuntary weight loss, malnutrition, and poor appetite due to dysfunction of metabolism and chronic, systemic inflammation. Additionally, it impacts oncological treatment and a decline in Quality of Life. The review aims to explore the latest research, innovations, and potentials in the treatment of cachexia.

Material and methods

The review was based on research of articles published from 2019 to 2024 on the PubMed database using the following keywords: cancer cachexia, palliative care, and cachexia pharmacotherapy.

Results

Anamorelin, a selective ghrelin receptor agonist showed effectiveness in weight gain and appetite improvement. Also, myostatin inhibitors protect muscles and promote their growth due to suppression of myostatin. Ponsegromab, a GDF-15 inhibitor, significantly and directly enhanced muscle mass, appetite, and quality of life, with good safety. Modern anti-inflammatory medications like momelotynib or tocilizumab, reduced the concentration of pro-inflammatory cytokines and improved quality of life, however, but posed immunosuppression

risk. Pentoxifylline declined inflammation and chemotherapy toxicity, and improved body weight and survival. Cannabinoids alleviated chemotherapy-induced nausea but were ineffective for weight and quality of life.
Conclusions
Therapeutic approaches target various aspects of cachexia due to its complex pathophysiology. Anamorelin, ponsegromab, and myostatin inhibitors have clinical potential. Modern anti-inflammatory drugs and pentoxifylline offer supportive benefits. Further research is vital for developing effective and safe treatment guidelines for cancer cachexia.

Keywords: Cancer cachexia; palliative care; cachexia pharmacotherapy

INTRODUCTION

Cachexia is a serious, debilitating metabolic condition that often occurs in patients with cancer. The absence of univocal diagnostic criteria interferes with difficulty in the prevalence estimation. Based on the studies, the prevalence worldwide is 33 % among patients with cancer, but in Europe and North America medium prevalence is 51,8 %, and in Asia 28,8 % [1]. What's also important, it is the main cause of death in up to 20% of patients with cancer [2]. As we know, the tumor cells and cells in the microenvironment of a tumor stimulate the production of proinflammatory cytokines such as interleukins, interferon-g, TNFa, and NF-kB. Induced inflammation affects metabolism, impairs the use of energy from substrates: proteins, lipids, and glucose and makes them less available for healthy cells. Cancer triggers also increase energy expenditure, leading to catabolism of skeletal muscles and adipose tissue wasting, moving on to unintentional weight loss, malnutrition, and declined appetite [3].
Moreover, cachexia can appear in the early stages of cancer and can seriously decline the effectiveness of therapy and increase the risk of complications of surgery and chemotherapy. Overall, this chronic condition significantly reduces quality of life (QoL) [3] and survival rates [4].
Cancer-associated cachexia is a complex problem and involves different mechanisms of action. That's why pharmacotherapy evolved from only nutrition supplementation and appetite stimulation to more targeted therapies directed at the alteration of inflammation, changes in metabolism, and muscle protein waste. Despite the development of pharmacology, the treatment outcomes are still varied in different patients and many cases unsatisfying. The research indicates that we need to broaden our knowledge to better understand cachexia and prepare strict guidelines to ensure better treatment outcomes [5].
The review aims to highlight novel, more targeted methods of pharmacological treatment of cancer cachexia and to indicate present barriers and new perspectives in this area.
The review is based on the latest articles from the PubMed database in the years 2019-2024. Keywords like cancer cachexia, palliative care, and cachexia pharmacotherapy were used in the investigation.

TREATMENT OF CACHEXIA

Table 1. Comparison of the latest pharmacological treatment methods in cachexia.

Therapy	Mechanism of action	Efficiency	Quality of life influence	Adverse events	References
Anamorelin	Selective ghrelin hormone agonist.	Significant improvement in body weight, and appetite	Significant improvement	Hyperglycemia, fatigue, and nausea are frequent, but mostly simple to contain.	[6, 7, 8]
Ponsegromab	Selective, monoclonal, humanized antibody, GDF-15 inhibitor,	Significant improvement in physical activity, and appetite. Reduction of adverse effects caused by chemotherapy	Significant improvement	Rare, and mild.	[12, 13, 14]
Myostatin inhibitors	Inhibits myostatin which induces muscle degradation	Significantly increase skeletal muscle mass, and muscle strength in mice studies. In Clinical trials the results are inconclusive	Significant improvement in mice studies	Mild and transient side effects. More selective myostatin inhibitors have a higher security profile.	[15, 16, 20]
Modern anti-inflammatory drugs	Anti-inflammatory, varied drugs	e.g. Tocilizumab significantly improved body weight, appetite, albumin level, and decreased CRP concentration.	Tocilizumab significantly improved	Immunosuppression,	[26, 27]
Pentoxifylline	Anti-inflammatory increases IL-10 concentration, Inhibits TNF-a, IL-6	Significant improvement in body weight, decline in chemotherapy toxicity	Moderate improvement	nausea, headaches, or dizziness	[29, 30]
Cannabinoids	CB1 and CB2 receptors are neuromodulators in the endocannabinoid system	Significant improvement in chemotherapy-induced nausea	No significant	No significant, e.g. Fatigue, dizziness	[32, 33, 34]

Anamorelin a selective ghrelin receptor agonist

Ghrelin is a peptide hormone that is produced by the fundus and corpus of the stomach mucosa. The hormone stimulates hunger regions in the hypothalamus and increases growth hormone production and lipogenesis. Additionally, it elevates appetite, and body weight and reduces catabolism. Anamorelin is an oral drug, which imitates ghrelin and selectively stimulates its receptors [6].

In a study by Taniguchi et al., systematic review and metanalysis were carried out based on randomized controlled trials, where was observed efficacy and safety of oral anamorelin in non-small cell lung carcinoma (NSCLC). The study showed that, for 12 weeks anamorelin increases total body weight (TBW) with a 95% confidence interval (CI) of 1.34-2.13, $p < 0.00001$, lean body weight (LBW) with 95% CI 0.30-1.81, $p = 0.006$ and enhances quality of life (QoL) with 95% CI 0.04-0.27, $p = 0.006$. Unfortunately, the hand grip strength endpoint, which is an important marker of physical activity, wasn't significantly improved with 95% CI − 0.01 to 1.28, $p = 0.05$ [6]. In another study on the Japanese population, anamorelin influence on patients with advanced gastrointestinal cancer was investigated for 5 years and examined every 3 weeks. The analysis showed that the ghrelin analog increased body weight with a 95% CI of 48.8–77.6, p = 0,439, and appetite, also achieved better chemotherapy treatment response and disease control with a 95% CI of 1.11–23.20, p =0,024. However, the authors point out that cases were in general good condition which deviate from the more common poor condition of patients [7].

Research shows that anamorelin significantly increases drug-related complications like hyperglycemia (13,5%), fatigue (12,2%), and nausea (6,7%), but most of them were controllable [6]. Additionally, there is no significant improvement in overall survival and non-dominant hand grip strength [6]. The most serious, frequent problem in anymore in intake is treatment discontinuation. In the study by Y. Egawa et al., they divided reviewed patients with various cancers into two groups: <3 Weeks and >3 weeks of anamorelin treatment. They concluded that the survival rate was significantly shorter in groups with less than 3 weeks of administration of the medication where 95% CI: 22-131 days, $p = 0.019$, and the survival rate was significantly associated with low albumin levels with 95% CI: 1.77-96.9, p =0,012 [8]. I. Tsukiyama et al., in their study, observed that the major reason for discontinuation was adverse reactions, with the most common dysphagia. Also, patients with worse performance status with 95% CI: 1,065-57,13, $p = 0.028$ and low prognostic nutritional index (PNI) with 95% CI: 0,005-0,386, $p = 0.001$ significantly earlier discontinued anamorelin treatment. The patients who continued drug intake had longer survival times [10]. In another study, the main reason for discontinuation of oral anamorelin was decreased oral intake (20,5%) and hyperglycemia (13,5%) [7]. Another study by K. Fujita et al. indicated a group of patients where amorelin oral intake was discontinued in the 12-week duration of treatment in 69,9 % of cases. Moreover, they found statistically significant predictors like high CRP, low albumin levels, ECOG $\geq$ 2, simultaneous chemotherapy, and poor nutritional status which was assessed by the modified Glasgow Prognostic Score (GPS) of 2 [9].

The results show that anamorelin might be an effective option in treatment [6, 7, 9]. Adverse events are frequent, but in most cases relatively simple to contain. However, there are some limitations in the investigation. Some of the studies are based on narrow populations [7, 8] or treatment groups are not enough diverse [7]. Two of them were reported in a short period [6, 8].

The limited number of studies and different measurement methods of analyzed factors implicate the credibility of the analysis [6]. Current trials don't provide reliable data to prove the effectiveness and safety of the anamorelin, but some clinical trials are in progress. On the grounds of the latest data medication wasn't approved in the USA and by EMA in Europe.

Ponsegromab

Selective, monoclonal, humanized antibody, which inhibits growth differentiation factor GDF-15. GDF-15 is elevated in cancer cachexia, and it is suspected to be one of the major factors responsible for the mechanism and symptoms of cachexia. Cytokine is a regulator of stress reaction, its concentration is higher in platinum-based chemotherapy, and it increases differently in many cancers [11].

In a study by D. M. Breen et al., the role of GDF-15 in the maintenance of adverse events connected to cancer. Probands with NSCLC, colorectal cancer, and ovarian cancer, who were going through cisplatin chemotherapy had statistically, significantly high levels of GDF-15 (all p-values <0,05). GDF-15 achieved statistical significance in patients with more than > 5% weight loss (with p-value <0,001) in comparison to weight-stable patients. Mouse studies with knock-out of GDF-15 gene and cisplatin chemotherapy showed that the cisplatin-induced weight loss was statistically, significantly lower (p =0,01), lean mass loss was statistically, significantly declined (p =0,001). Also, the neutralizing antibodies significantly attenuated anorexia, reduced emesis caused by chemotherapy, and improved survival time in non-human primates. The targeted inhibition of GDF-15 significantly improves the management of adverse effects caused by chemotherapy and overall survival. Statistically significant results emphasize therapeutic potential in neutralizing GDF-15 [11]. In a study by J.D. Groarke et al., patients with different cancers, concurrent cachexia, and elevated GDF-15 were tested. During the study, pronsegromab was injected subcutaneously. GDF-15 declined below the baseline a few hours after administration of the drug, at a dose ≥ 1 mg [12]. In a consecutive randomized double-blind, placebo-controlled study by J.D.Groarke et al., ponsegromab was administered in three dose groups (100 mg, 200 mg, 400 mg). The drug was applied every 4 weeks for the first 12 weeks. Compared to the control group, after 12 weeks of trial, ponsegromab intake increased significantly appetite, physical activity, and gain of body weight (the results were greater in groups with higher doses) [12, 13]. Further 24-week study assessment by J. Crawford et al., where the treatment group received 200 mg of ponsegromab, subcutaneously, every 3 weeks for 12 weeks. The GDF-15, safety, tolerance, and pharmacokinetics were measured during the trial. The GDF-15 declined 3 hours after the first dose and was below baseline for 15 weeks of trial. The body weight increased 6,6% to the 12-week time point. Also, physical activity, appetite, and quality of life improved [14].

In preliminary phase 1 of the study, there were only mild treatment-related adverse reactions [12]. The results obtained from the next evaluation in a phase 1b clinical trial did not indicate adverse effects of ponsegromab. Based on that, initially assumed the drug's safety [14].

Ponsegromab inhibits GDF-15, and it is a new treatment concept. Drug effectiveness and safety are still being tested, but initial results from trials indicate effectiveness in treating overall cachectic syndrome [13, 14]. Currently, the 2 phase of the study is ongoing, but the present data from the studies are promising [12]. Furthermore, we assume that connecting cisplatin chemotherapy and ponsegromab can have positive effects on cachexia treatment in this group of patients [11].

Myostatin inhibitors

Myostatin is a protein from the TGF-B family, it performs a major role in the regulation of skeletal muscles. Myostatin overexpression leads to degradation of skeletal muscle proteins [15].

In cancer cachexia, excessive activity of myostatin intensifies skeletal muscle wasting and declines physical activity and quality of life afterward. Theoretically, myostatin blockage can counter skeletal muscle loss and it can become a therapeutic target [16]. Myostatin inhibitors bond myostatin and prevent the interaction between myostatin and type IIB activin skeletal muscle receptors. Myostatin inhibitors have different forms: monoclonal antibodies, activin

receptor ligands, and small particles. They are responsible for the promotion of muscle hypertrophy and muscle mass protection against progressive degradation [17].
Research using mice with cachexia showed that the inhibition of myostatin by peptide-2 significantly increased skeletal muscle mass with 95% CI: 9.1%-15.5%, p <0.01, improved muscle strength with 95% CI: 14.5%-22.9%, p <0.05, and survival outcome with p-value =0,03. The mice with advanced cancer treated with myostatin had slowed down muscle mass wasting [15]. Another study with mice models by K. Michiue et al. also confirmed that myostatin inhibitory-D-peptide-35 (MID-35), which entered skeletal muscles through the skin surface by iontophoresis, significantly increased muscle mass with 95% CI: 15%-35%, p <0.05, and promoted synthesis of new muscle fibers. Moreover, MID-35 suppressed the expression of myostatin genes with p-value =0,01 [18].
The initial study over Trevogrumab, a monoclonal antibody against myostatin, provided unclear, inconclusive results that showed moderate enhancement of muscle mass [19]. Also, another myostatin inhibitor, bimagrumab, a type IIB activin receptor inhibitor is under examination, and early outcomes presented significant muscle mass enlargement with a p-value <0,001 [19].
More selective myostatin inhibitors displayed a higher security profile. The presented results showed mild and transient side effects. Bimagrumab treatment caused nausea, diarrhea, and reduced appetite in comparison to placebo [19]. Also, another study by K. Hanada et al., showed that combination therapy with anamorelin and myostatin in mice caused tumor growth [20].
The myostatin inhibitors mainly increase skeletal muscle mass, but they don't impact other cachexia-related symptoms like loss of adipose tissue or inflammation. There is a real need for a larger second phase of clinical trials to acknowledge the effectiveness and safety of cachexia treatment [19].

Modern anti-inflammatory drugs

In cancer-associated cachexia are activated proinflammatory pathways. Chronic, systemic inflammation plays an important role in cachectic skeletal muscle loss, adipose tissue declines, and poorer survival rates [21].
Various modern anti-inflammatory drugs are tested in preclinical and clinical trials. These medications have precise molecular targets like JAK, STAT, and NF-kB kinases [22]. Additionally, they reduce the expression of pro-inflammatory cytokines like IL-6, and TNF-a [23, 25]. In a study by X. S. Pang et al., researchers suggest that inhibition of the ubiquitin-proteasome pathway may counteract muscle atrophy in cachexia [24]. Among kinase inhibitors, which stop the activation of JAK/STAT pathways connected to IL-6 and modulate inflammation, are momelotynib and ruxolitynib [26]. In a study by A. Tefferi et al., momelotynib, JAK1/JAK2/ACVR1 inhibitor, significantly decreased symptoms and spleen volume in comparison to danazol in patients with myelofibrosis. Also, the study showed that momelotynib declined systemic inflammation by reduction of IL-6 concentration in patients with myelofibrosis with 95% CI: 35%-45%, p <0.01. Furthermore, momelotynib showed a significant advantage over other JAK inhibitors in anemia treatment. Finally, momelotynib was approved for anemia treatment in myelofibrosis in 2023. [26].
Tocilizumab, a monoclonal antibody against IL-6, reduced inflammation and performed potential benefits for patients with cancer, like statistically significant weight gain with p-value =0,016, and enhanced appetite [23]. Moreover, another analysis of tocilizumab by Y. Du et al., showed that tocilizumab significantly improved overall survival with 95% CI: 9.1-30.4 months, p <0.001 in patients with NSCLC and elevated IL-6. Also, other results were statistically significant, like enhanced appetite, body mass, albumin level, and decreased CRP concentration. What is more, the tocilizumab administration decreased the prevalence of

serious adverse events [27]. These findings underscore many advantages of tocilizumab treatment in patients with cancer-related cachexia.

Despite targeted drug activity on major pathology pathways of cachexia, administration of these medications is associated with an increased risk of immunosuppression. [26] Moreover, some of the medications have specific adverse effects. Tocilizumab adverse reactions include frequent skin infections and a higher risk of neutropenia with simultaneous high-dose chemotherapy [27]. Momelotynib administration significantly increases the risk of infections, anemia, thrombocytopenia, and peripheral neuropathy [26].

In conclusion, modern anti-inflammatory drugs are a promising group of medications. They are great potential options for combined therapies. These medications are newly tested therapy methods with unknown long-standing effects, which is why there is a need for consecutive clinical trials concerning the effectiveness and safety of these anti-inflammatory medications [26, 28].

Pentoxifylline

The drug has an anti-inflammatory mechanism of action. Inhibits TNF-a, IL-6, and increases IL-10, an anti-inflammatory cytokine [29].

In a study by A. Meirovitz et al., pentoxifylline was administered to patients with advanced colon cancer. The results were consecutive: significantly declined chemotherapy-induced stomatitis, and improved survival and body mass. However, some of the patients did not tolerate the drug due to side effects including nausea, headache, or dizziness [29]. Additionally, the same researchers in another study measured the effectiveness of pentoxifylline in colon cancer patients. Probands were divided into two different-dose groups, and simultaneously they were receiving chemotherapy. In the results, pentoxifylline significantly declined pro-inflammatory cytokines like CRP, and IL-6 and reduced toxicity of chemotherapy. Also, the drug significantly increased body weight and survival [30]. In another study by H. Chen et al., pentoxifylline achieved worse enhancement of body mass than other drugs like olanzapine or anamorelin and the result was statistically insignificant [31].

Pentoxifylline because of its anti-inflammatory properties, and good safety profile, but also limited impact on body weight should be considered as a supportive treatment.

Cannabinoids

Cannabinoids embrace appetite modulation and relieve pain by cannabinoid CB1 and CB2 receptors activation in the hypothalamus. In addition, THC and CBD can influence metabolism through the endocannabinoid system. Moreover, CBD has an anti-inflammatory function and modulates pro-inflammatory cytokines [32].

The systemic review and meta-analysis of a study by S. Hammond et al., on cannabis in cachexia treatment showed there were no significant changes in body mass, appetite, or quality of life. The cannabis-based drugs were well-tolerated [32]. Another study, a systemic literature search by C. Ceolin et al., confirmed results from the previous studies [33].

Researcher B. Alderman and associates compared the effectiveness of cannabinoids in the treatment of gastrointestinal symptoms in patients with cancer. THC and nabilone significantly improved chemotherapy-induced nausea and vomiting (CINV), but they did not achieve an advantage over another antiemetic [34].

Cannabinoids have an influence on symptoms correlated to cachexia, like moderating pain sensation and nausea, but the latest research is insufficient and did not confirm the significant effectiveness of cannabinoids.

Discussion

The main purpose of this review was to show the latest investigations and accomplishments in cancer-related cachexia in terminal-stage patients. Also, we wanted to enlarge the knowledge of the widespread problem among patients with cancer [1, 2]. The latest studies facilitated a

better understanding of the cachexia process. As presented in the review, medications have an impact on several pathophysiological pathways.

Anamorelin, a selective ghrelin-receptor agonist, shows promising outcomes in anorexia-cachexia cancer treatment, especially in improving body weight and appetite. Metanalysis conducted by Taniguchi et al. acknowledges anamorelin efficacy in enhancing total and lean body weight and improvement in quality of life in patients with NSCLC. However, the hand grip strength, which is an important physical activity factor, did not improve [6]. The studies by Nishimura et al, and Fujita et al., provide additional evidence of anamorelin effectiveness in patients with gastrointestinal tumors. The results from studies showed that the ghrelin receptor agonists enhanced response to chemotherapy and improved primary disease control. Unfortunately, data indicated that therapy response depends on general health well-being, suggesting that anamorelin can be less effective in patients with poorer conditions [7,9]. A key issue in treatment is a high percentage of adverse effects like hyperglycemia, fatigue, and nausea. In most cases these adverse symptoms are easy to control, however, they can lead to treatment disruption. Egawa et al., and Tsukiyama et al., noticed that patients with ECOG ≥ 2, low prognostic nutritional index (PNI), and high CRP levels are more exposed to cease therapy [8,10]. Even though current studies provide initial evidence of effectiveness, there is a need for large randomized clinical trials to unequivocally verify this statement [6,7,10].

A high level of GDF-15, particularly in patients who receive platin-based chemotherapy, is strictly related to the intensity of cachexia symptoms. In one of the preclinical studies by D. M. Breen et al., animal models in response to cisplatin therapy and impaired activity of GDF-15 showed significant improvement in appetite, body weight, and survival rate. This result emphasizes that maintenance of low levels of GDF-15 helps to reduce chemotherapy-related side effects [11]. In clinical trials, ponsegromab increased appetite, body mass, physical activity, and quality of life [12,14]. The pharmacological effects were dose-dependent, and the best outcomes were achieved by patients with higher doses [12,13]. An interesting aspect worth mentioning is that ponsegromab limited adverse reactions related to cisplatin therapy, but did not disrupt the effectiveness of chemotherapy. The results suggest that GDF-15 inhibitors can be suitable in combination with chemotherapy [13]. What's more, data from the 1b phase clinical trial showed good tolerance of ponsegromab [14]. Present outcomes are promising, but there is still a gap in long-lasting effects and reliable security profiles. That's why scientists research to better understand the prospects of ponsegromab.

Cancer cachexia is strongly correlated with skeletal muscle wasting. As we know, myostatin is a key protein that regulates muscle degradation. Preclinical research with mice by Ojima et al., with peptide-2, a myostatin inhibitor, significantly enhances muscle mass and strength [15]. Similar, significant results were presented by Michiue et al., where MID-35, another myostatin inhibitor was used [18]. Currently, results from clinical trials in phases 1 and 2 with trevogrumab were inconclusive. Bimagrumab achieved significant outcomes and effectively increased skeletal muscle mass in patients with cachexia (p-value <0,001) [19]. The important thing is that the myostatin inhibitors have limited influence on other symptoms related to cachexia, like inflammation, or poorness of appetite. For this reason, myostatin inhibitors should be considered as supplementary options [19]. To sum up, myostatin inhibitors are a promising medication class, particularly in cachexia-related skeletal muscle wasting, and decreasing physical fitness. However, the efficacy in the improvement of general condition in patients dealing with cachexia demands more, future research [17, 19].

Modern anti-inflammatory drugs significantly reduce inflammation and improve metabolism due to precisely directed impairment of molecular inflammatory pathways. In the studies, momelotynib or tocilizumab which are directed on JAK/STAT pathway and IL-6, showed potential in moderation symptoms of cancer cachexia [22, 26]. Momelotynib improves hematological results and reduces inflammation which makes it more beneficial in anemia

treatment [22]. What's more, tocilizumab diminished the risk of severe symptoms in patients with NSCLC [23, 27]. However, both therapies carry a risk of side effects, which require higher caution, especially in combination with chemotherapy [27]. Current research results indicate potential in combined therapies, but further research with longer observation time is essential [26, 28]. Also, future research directions will be relevant to determine which group of patients will be the most benefit from this therapy.

Pentoxifylline, just like modern anti-inflammatory drugs declines pro-inflammatory cytokines concentration and additionally elevates IL-10 concentration. Also, has the potential of supportive drugs in cachexia treatment [29]. In the studies by Merovitz et al., with colon cancer patients, pentoxifylline significantly reduced chemotherapy-related stomatitis, improved body mass, and overall survival, and declined the concentration of proinflammatory markers [29, 30]. Although, limited influence on body mass [31], pentoxifylline has a favorable safety profile and can be considered as supportive therapy in case of inflammation reduction and chemotherapy toxicity management. Future studies should concentrate on dose optimization and identification of patients, which can achieve the highest benefits from the therapy. Another medication under investigation is cannabinoids. The analyses did not show significant changes in body mass, appetite, or quality of life [32,33]. What's more, the medicaments based on natural extracts from cannabinoids caused only partial improvement in appetite with additional side effects [34].

Controversies and limitations of studies around cannabinoids are based on placebo, adverse reactions, small research samples, psychoactive side effects, validation and availability of cannabinoids vary around the world, which implicate conducting research. The long-term effects of applying cannabinoids demand well-designed, large randomized clinical trials.

Recent years have brought more understanding to the cachexia process, but this area of medicine struggles with limited research with methodological constraints like small sample sizes or lack of long-term data with safety and effectiveness assessment. Also, treatment costs are still unexamined. Another limitation of the studies is the heterogeneity of populations in study groups and different outcome evaluation methods. Cancer-related cachexia demands extensive, with higher probative value research to clarify pathophysiology and prepare standardized, pharmacological recommendations to achieve better treatment outcomes in the future.

CONCLUSIONS

Cachexia syndrome is a common problem of terminal-stage patients dealing with cancer, which negatively impacts their quality of life, treatment response, and survival rate.

The latest data analyses from 2019 to 2024 have shown that targeted drugs like ghrelin agonists, ponsegromab, and myostatin inhibitors have the greatest pharmacological potential. Their mechanisms of action are directed at molecular, and metabolic mechanisms and they offer innovative approaches to muscle mass loss, lack of appetite, and increased catabolism. That's why they differ from traditional therapy methods, concentrating on supplying more calories with extra proteins and appetite stimulation. Also, therapies based on drugs disturbing immune responses like modern anti-inflammatory medications or pentoxifylline open new opportunities in the management of cachexia-related chronic inflammation. However, clinical trials about new treatments have gaps and do not provide sufficient, long-term evidence of efficacy and safety for different groups of patients with cachexia.

Mechanisms of cancer cachexia are multifactorial and concern many various pathways. That's why treatment demands a multimodal, comprehensive approach, incorporating patients' ages, disease stages, and coexisting conditions. Scientists pose a statement that future, effective cachexia treatment will demand a more personalized and holistic therapy approach. Therefore, these days there is a need for intensified investigation.

Disclosures

Author`s contribution:

Conceptualization: KW, NH, AKW**;** Methodology: AC, AKW, KS, KZ**;** Software: KW, NH, AKW**;** Check: AC, KS, MT, KZ**;** Formal analysis: KW, AM, MB**;** Investigation: NH, AM, MT; Resources: KS, AM, KW; Data curation: KW, KS, AM, KZ**;** Writing -rough preparation: UK, KW; Writing -review and editing: AC, UK, MB**;** Visualization: KW, UK, MB**;** Supervision: UK, AM; Project administration: MT, KW, NH

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REFERENCES

1.Braha A, Albai A, Timar B, Negru Ș, Sorin S, Roman D, Popovici D. Nutritional Interventions to Improve Cachexia Outcomes in Cancer-A Systematic Review. Medicina (Kaunas). 2022 Jul 21;58(7):966. PMID: 35888685; PMCID: PMC9318456. https://doi.org/10.3390/medicina58070966

2.Bullock AF, Patterson MJ, Paton LW, et al. Malnutrition, sarcopenia, and cachexia: exploring prevalence, overlap, and perceptions in older adults with cancer. Eur J Clin Nutr. 2024;78(3):486-493. https://doi.org/10.1038/s41430-024-01433-9

3.Yule MS, Thompson J, Leesahatsawat K, et al. Biomarker endpoints in cancer cachexia clinical trials: Systematic Review 5 of the cachexia endpoint series. J Cachexia Sarcopenia Muscle. 2024 Jun;15(3):853-867. Epub 2024 May 23. PMID: 38783477; PMCID: PMC11154797. https://doi.org/10.1002/jcsm.13491

4.Brown LR, Sousa MS, Yule MS, et al. Body weight and composition endpoints in cancer cachexia clinical trials: Systematic Review 4 of the cachexia endpoints series. J Cachexia Sarcopenia Muscle. 2024 Jun;15(3):816-852. Epub 2024 May 13. PMID: 38738581; PMCID: PMC11154800. https://doi.org/10.1002/jcsm.13478

5.Fujii H, Yamada Y, Iihara H, Suzuki A. The role of pharmacists in multimodal cancer cachexia care. Asia Pac J Oncol Nurs. 2023 Aug 1;10(Suppl 1):100280. PMID: 38197038; PMCID: PMC10772181. https://doi.org/10.1016/j.apjon.2023.100280

6.Taniguchi J, Mikura S, da Silva Lopes K. The efficacy and safety of anamorelin for patients with cancer-related anorexia/cachexia syndrome: a systematic review and meta-analysis. Sci Rep. 2023 Sep 14;13(1):15257. PMID: 37709824; PMCID: PMC10502008. https://doi.org/10.1038/s41598-023-42446-x

7.Nishimura A, Hamauchi S, Notsu A, et al. Real-world data of anamorelin in advanced gastrointestinal cancer patients with cancer cachexia. BMC Palliat Care. 2024 Aug 24;23(1):214. PMID: 39182074; PMCID: PMC11344333. https://doi.org/10.1186/s12904-024-01538-9

8.Fujita K, Akamine Y, Igarashi H, et al. Association of the modified Glasgow prognostic score and prognostic nutritional index with duration of oral anamorelin administration in patients with cancer cachexia: a retrospective cohort study. Jpn J Clin Oncol. 2024 Nov 2;54(11):1165-1170. PMID: 38943560. https://doi.org/10.1093/jjco/hyae086

9.Egawa Y, Uchiyama M, Egoshi N, et al. Factors Associated with the Continuation of Anamorelin in Patients with Cancer-associated Cachexia: A Single-center Retrospective Study. Yakugaku Zasshi. 2024;144(7):767-774. Japanese. PMID: 38945851.
https://doi.org/10.1248/yakushi.24-00002
10.Tsukiyama I, Iwata T, Takeuchi T, et al. Factors associated with early discontinuation of anamorelin in patients with cancer-associated cachexia. Support Care Cancer. 2023 Oct 10;31(12):621. PMID: 37815652; PMCID: PMC10564655. https://doi.org/10.1007/s00520-023-08097-4
11.Breen DM, Kim H, Bennett D, et al. GDF-15 Neutralization Alleviates Platinum-Based Chemotherapy-Induced Emesis, Anorexia, and Weight Loss in Mice and Nonhuman Primates. Cell Metab. 2020 Dec 1;32(6):938-950.e6. Epub 2020 Nov 17. PMID: 33207247.
https://doi.org/10.1016/j.cmet.2020.10.023
12.Groarke JD, Crawford J, Collins SM, et al. Phase 2 study of the efficacy and safety of ponsegromab in patients with cancer cachexia: PROACC-1 study design. J Cachexia Sarcopenia Muscle. 2024 Jun;15(3):1054-1061. Epub 2024 Mar 18. PMID: 38500292; PMCID: PMC11154777.
https://doi.org/10.1002/jcsm.13435
13.Groarke JD, Crawford J, Collins SM, et al. Ponsegromab for the Treatment of Cancer Cachexia. N Engl J Med. 2024 Sep 14. Epub ahead of print. PMID: 39282907.
https://doi.org/10.1056/NEJMoa2409515
14.Crawford J, Calle RA, Collins SM, et al. A Phase Ib First-In-Patient Study Assessing the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Ponsegromab in Participants with Cancer and Cachexia. Clin Cancer Res. 2024 Feb 1;30(3):489-497. PMID: 37982848; PMCID: PMC10831332. https://doi.org/10.1158/1078-0432.CCR-23-1631
15.Ojima C, Noguchi Y, Miyamoto T, et al. Peptide-2 from mouse myostatin precursor protein alleviates muscle wasting in cancer-associated cachexia. Cancer Sci. 2020 Aug;111(8):2954-2964. Epub 2020 Jul 1. PMID: 32519375; PMCID: PMC7419029.
https://doi.org/10.1111/cas.14520
16.Liu D, Qiao X, Ge Z, et al. IMB0901 inhibits muscle atrophy induced by cancer cachexia through the MSTN signaling pathway. Skelet Muscle. 2019 Mar 28;9(1):8. PMID: 30922397; PMCID: PMC6437903. https://doi.org/10.1186/s13395-019-0193-2
17.Martin A, Gallot YS, Freyssenet D. Molecular mechanisms of cancer cachexia-related loss of skeletal muscle mass: data analysis from preclinical and clinical studies. J Cachexia Sarcopenia Muscle. 2023 Jun;14(3):1150-1167. Epub 2023 Mar 2. PMID: 36864755; PMCID: PMC10235899. https://doi.org/10.1002/jcsm.13073
18.Michiue K, Takayama K, Taniguchi A, et al. Increasing Skeletal Muscle Mass in Mice by Non-Invasive Intramuscular Delivery of Myostatin Inhibitory Peptide by Iontophoresis. Pharmaceuticals (Basel). 2023 Mar 6;16(3):397. PMID: 36986496; PMCID: PMC10058260.
https://doi.org/10.3390/ph16030397
19.Stefanakis K, Kokkorakis M, Mantzoros CS. The impact of weight loss on fat-free mass, muscle, bone, and hematopoiesis health: Implications for emerging pharmacotherapies aiming at fat reduction and lean mass preservation. Metabolism. 2024 Dec; 161:156057. Epub 2024 Oct 30. PMID: 39481534. https://doi.org/10.1016/j.metabol.2024.156057
20.Hanada K, Fukasawa K, Hinata H, et al. Combination therapy with anamorelin and a myostatin inhibitor is advantageous for cancer cachexia in a mouse model. Cancer Sci. 2022 Oct;113(10):3547-3557. Epub 2022 Aug 6. PMID: 35849084; PMCID: PMC9530881.
https://doi.org/10.1111/cas.15491
21.Chrysostomou SE, Eder S, Pototschnig I, et al. R-ketorolac ameliorates cancer-associated cachexia and prolongs survival of tumor-bearing mice. J Cachexia Sarcopenia Muscle. 2024 Apr;15(2):562-574. Epub 2024 Feb 1. PMID: 38302863; PMCID: PMC10995265.

https://doi.org/10.1002/jcsm.13422
22.Chen Y, Xu W, Chen Y, et al. Renal NF-κB activation impairs uric acid homeostasis to promote tumor-associated mortality independent of wasting. Immunity. 2022 Sep 13;55(9):1594-1608.e6. Epub 2022 Aug 26. PMID: 36029766.
https://doi.org/10.1016/j.immuni.2022.07.022
23.Patsalos O, Dalton B, Himmerich H. Effects of IL-6 Signaling Pathway Inhibition on Weight and BMI: A Systematic Review and Meta-Analysis. Int J Mol Sci. 2020 Aug 31;21(17):6290. PMID: 32878032; PMCID: PMC7504579. https://doi.org/10.3390/ijms21176290
24.Pang X, Zhang P, Chen X, et al. Ubiquitin-proteasome pathway in skeletal muscle atrophy. Front Physiol. 2023 Nov 17; 14:1289537. PMID: 38046952; PMCID: PMC10690626.
https://doi.org/10.3389/fphys.2023.1289537
25.Patsalos O, Dalton B, Leppanen J, et al. Impact of TNF-α Inhibitors on Body Weight and BMI: A Systematic Review and Meta-Analysis. Front Pharmacol. 2020 Apr 15; 11:481. PMID: 32351392; PMCID: PMC7174757. https://doi.org/10.3389/fphar.2020.00481
26.Tefferi A, Pardanani A, Gangat N. Momelotinib (JAK1/JAK2/ACVR1 inhibitor): mechanism of action, clinical trial reports, and therapeutic prospects beyond myelofibrosis. Haematologica. 2023 Nov 1;108(11):2919-2932. PMID: 36861402; PMCID: PMC10620561.
https://doi.org/10.3324/haematol.2022.282612
27.Du Y, Liu XY, Pan RL, et al. Tocilizumab for Advanced Non-Small-Cell Lung Cancer with Concomitant Cachexia: An Observational Study. J Cachexia Sarcopenia Muscle. 2024 Nov 11. Epub ahead of print. PMID: 39523982. https://doi.org/10.1002/jcsm.13638
28.Bowers M, Cucchiaro B, Reid J, Slee A. Non-steroidal anti-inflammatory drugs for the treatment of cancer cachexia: A systematic review. J Cachexia Sarcopenia Muscle. 2023 Dec;14(6):2473-2499. Epub 2023 Sep 26. PMID: 37750475; PMCID: PMC10751445.
https://doi.org/10.1002/jcsm.13327
29.Meirovitz A, Baider L, Peretz T, et al. Effect of pentoxifylline on colon cancer patients treated with chemotherapy (Part I). Tumour Biol. 2021;43(1):341-349. PMID: 34957976.
https://doi.org/10.3233/TUB-211533
30.Meirovitz A, Baider L, Peretz T, et al. PTX Treatment of Colon Cancer: Mode of Action Based on Tumor Marker and Cytokine Kinetics. Anticancer Res. 2022 Nov;42(11):5487-5496. PMID: 36288885. https://doi.org/10.21873/anticanres.16054
31.Chen H, Ishihara M, Kazahari H, Ochiai R, Tanzawa S, Honda T, Ichikawa Y, Horita N, Nagai H, Watanabe K, Seki N. Efficacy and safety of pharmacotherapy for cancer cachexia: A systematic review and network meta-analysis. Cancer Med. 2024 Sep;13(17):e70166. PMID: 39225556; PMCID: PMC11369987. https://doi.org/10.1002/cam4.70166
32.Hammond S, Erridge S, Mangal N, et al. The Effect of Cannabis-Based Medicine in the Treatment of Cachexia: A Systematic Review and Meta-Analysis. Cannabis Cannabinoid Res. 2021 Dec;6(6):474-487. Epub 2021 Oct 18. PMID: 34664988; PMCID: PMC8713261.
https://doi.org/10.1089/can.2021.0048
33.Ceolin C, De Rui M, Ravelli A, et al. The potential of cannabinoids in managing cancer-related anorexia in older adults: a systematic review of the literature. J Nutr Health Aging. 2024 Aug;28(8):100299. Epub 2024 Jun 24. PMID: 38917597. https://doi.org/10.1016/j.jnha.2024.100299
34.Alderman B, Hui D, Mukhopadhyay S, et al. Multinational Association of Supportive Care in Cancer (MASCC) expert opinion/consensus guidance on the use of cannabinoids for gastrointestinal symptoms in patients with cancer. Support Care Cancer. 2022 Dec 16;31(1):39. PMID: 36525085. https://doi.org/10.1007/s00520-022-07480-x