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REVIEW ARTICLE

Advances in pharmacotherapies in cancer-related cachexia*

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Abstract

Cancer-related cachexia is highly prevalent in patients with advanced cancer, affecting approximately 50%–80% of patients and seriously interfering with active therapy, quality of life, and survival time. There are currently no effective treatments for cachexia. Therefore, new therapeutic strategies are required. In recent years, advances in understanding the mechanisms underlying cachexia have been made, and new drugs have been developed to combat cachexia muscle wasting and weight loss due to cancer. In this systematic review, we discuss these novel targets and drug treatments.

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Cancer cachexia is a multifactorial and irreversible syndrome often associated with dysfunction, such as decreased appetite, loss of body mass, muscle wasting, and deterioration of nutritional status. It is characterized by loss of skeletal and visceral muscle mass, with or without body fat loss, which cannot be entirely reversed by conventional nutritional support [1]. The pathogenesis of cancer-related cachexia is complex, involving endocrine metabolic disorders caused by tumors, muscle wasting, abnormal energy metabolism mediated by cytokines, and anorexia regulated by the hypothalamus [2–3]. Approximately 50%–80% of patients with tumor progression suffer from cachexia, accounting for up to 20% of patients dying from cachexia instead of cancer [4]. Diagnosis, staging, and treatment of cachexia are challenging.

An international consensus on the criteria for cachexia diagnosis and staging was proposed in 2011, which divided patients with cachexia into precachexia, cachexia, and refractory cachexia [1]. American Society of Clinical Oncology (ASCO) provided evidence-based guidance for adult patients with cancer cachexia in 2020. Progesterone analogs and corticosteroids have been recognized clinically as short-term appetite enhancers. Dietary counseling allows patients and caregivers to obtain more scientific guidance on managing cachexia [5]. Personalized exercise plus nutritional support or multimodal intervention have been demonstrated to be feasible in clinical trials; however, no study has monitored these interventions for symptom improvement or survival benefits [6–7]. Currently, no effective therapeutic strategy can improve the outcomes of cancer cachexia. In the future, pharmacological interventions will continue to be the main target of cachexia treatment. In recent years, anamorelin, TCMCB07, and GDF15-targeting drugs have been demonstrated to prevent weight loss and alleviate skeletal muscle wasting *in vivo* and *in vitro*. In this review, we summarize the progress in the development of drugs for cachexia treatment.

ASCO-recommended pharmacological intervention

Megestrol acetate/medroxyprogesterone

Megestrol acetate (MA) was initially used for contraception and palliative care of advanced breast and endometrial cancers. Owing to its weight-gaining effects, MA is used for cachexia treatment. In 1993, MA was approved for the treatment of cachexia in many European and American countries [8]. The mechanism by which MA stimulates appetite and food intake is unknown and may be related to the concentration of neuropeptide Y, a central

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appetite stimulant located in the hypothalamus [9]. The ASCO recommended dosage of MA for cancer cachexia is 200–600 mg/day, with adverse effects, including edema, thromboembolism, and adrenal insufficiency.

It is unclear whether MA, alone or in combination with other drugs, has a therapeutic effect [5]. In 2018, Ruiz-García *et al* [10] found that oral MA resulted in weight gain but did not improve the patient's quality of life. A recent meta-analysis by Lim *et al* [11] highlighted the therapeutic effect of MA in cancer cachexia and showed that MA was generally well tolerated but did not improve the patient's weight or quality of life; the overall pooled mean change in weight gain was 0.75 kg, and patients using doses above 320 mg/day suffered weight loss, which may be associated with severe cachexia symptoms. These results do not support the use of MA in improving anorexia/cachexia symptoms [11]. The efficacy and optimal dose of MA for cachexia are controversial and need to be further observed in more extensive studies with long follow-up periods.

Corticosteroids

Corticosteroids can remarkably improve cancer-related fatigue and can be used as short-term appetite enhancers; however, they do not affect weight gain in patients. Appetite regulation mechanisms are associated with the expression of genes encoding hypothalamic neuropeptide Y, corticotropin-releasing hormone, and agouti-related peptide [12]. ASCO does not recommend a particular corticosteroid type but only recommends a 3–4 mg dexamethasone equivalent dose/day for cancer cachexia. The European Society for Medical Oncology (ESMO) clinical guidelines state that corticosteroids should not be used for more than 2–3 weeks and that their prolonged use has no increased clinical benefit [5, 13–14]. Long-term or high-dose use of corticosteroids can cause side effects, such as insulin resistance, muscle wasting, osteoporosis, and high blood sugar levels [15–16].

The Chinese Society of Clinical Oncology-recommended pharmacological intervention

Long-chain omega-3 polyunsaturated fatty acids (ω-3 LC-PUFAs), such as eicosapentaenoic and docosapentaenoic acids, are effective in maintaining body weight and lean body mass, improving appetite, and sensitizing chemotherapy and are recommended by the Chinese Society of Clinical Oncology for patients with cancer cachexia [17]. A recent case-control study conducted by Abe *et al* [18] examined the effects of ω-3 LC-PUFAs in patients with unresectable or recurrent biliary tract cancer or pancreatic cancer undergoing chemotherapy. The study enrolled 39 patients, and enteric nutritional supplements containing ω-3 LC-PUFAs were administered for 56 days. The results showed that patients had an increased skeletal muscle mass compared to the baseline (median 17.3 kg *vs.* 14.8 kg, $P < 0.01$) and increased chemotherapy tolerance [18]. This is consistent with the conclusions of some previous studies [19–20]. However, other clinical trials have shown that ω-3 LC-PUFAs do not provide any benefits [21–22]. The Food and Drug Administration (FDA)-mandated maximum daily intake dose of ω-3 LC-PUFAs is 5 g [23]. In these clinical trials, the daily intake of ω-3 LC-PUFAs and number of treatment days were heterogeneous. How omega-3 PUFAs exert their pharmacological effects in patients with cachexia deserves further exploration.

Prospective therapeutic drugs

Appetite-stimulating drugs

Anorexia is commonly observed in patients with cancer who have cachexia. If left untreated, cancer-related anorexia (CA) eventually develops into anorexia-cachexia syndrome (CACS). The occurrence of CACS is closely related to energy intake and regulation. Contributing factors to CACS involve inflammatory factors, ghrelin, leptin, and melanocortin, which enable the brain to receive early satiety and anorexia information and, at the same time, change the normal energy metabolism in the body [24–25]. The treatment of cancer cachexia is mainly based on these appetite-regulating targets.

Anamorelin

Anamorelin is an orally active, highly selective ghrelin receptor agonist that increases lean body mass by modulating growth hormone and insulin-like growth factor 1 [26]. In 2016, Temel *et al* [27] published the results of two phase III multicenter randomized clinical trials, ROMANA1 and ROMANA2, which included a total of 979 patients with stage III or IV non-small cell lung cancer cachexia. After 12 weeks of administration, an increase in median lean body mass was observed in the 100 mg/day anamorelin group compared with that in the placebo group (ROMANA1: anamorelin 0.9 kg versus placebo –0.47 kg, $P < 0.0001$; ROMANA2: anamorelin 0.65 kg versus placebo –0.98 kg, $P < 0.0001$). After the completion of ROMANA1 and ROMANA2, 513 patients entered ROMANA3, a 12-week anamorelin phase III safety extension study. In total, 221 patients completed 24 weeks of anamorelin treatment (100 mg/day). Compared to those in the placebo group, patients in the treatment group experienced increased significantly weight from the baseline over the entire 0–24-week period, and their anorexia-cachexia symptoms improved; however, there was no significant change in handgrip strength. Anamorelin has demonstrated good tolerability, safety, and effective therapeutic effects with long-term

administration [28].

Increased lean body mass and improvement in cachexia symptoms were observed in a double-blind phase II clinical trial in patients with advanced non-small cell lung cancer and cachexia and an open-label, single-arm open trial in patients with advanced gastrointestinal tumors with cachexia [29–30].

Anamorelin also showed a significant increase in dose-related hunger scores and caloric intake in healthy male subjects [31]. Anamorelin was approved for the first time in Japan on December 11, 2020, and is indicated for patients with non-small cell lung cancer, gastric cancer, pancreatic cancer, and colon cancer cachexia. It is currently the only cancer cachexia treatment drug approved for marketing [32]. At present, the Clinical Pharmacology Research Center of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, is conducting a phase I clinical trial to evaluate the safety, pharmacokinetics, and pharmacodynamics of anamorelin hydrochloride (CTR20171102). Anamorelin is ineffective in improving handgrip strength, walking ability, and other active functions, suggesting that cachexia cannot be entirely treated with a single drug [33]. This evidence indicated that anamorelin is currently the most promising drug for cancer cachexia treatment.

Ruxolitinib

Ruxolitinib, the first Janus kinase 1 and 2 inhibitor approved by the FDA in 2011, is used to treat patients with intermediate- or high-risk myelofibrosis [34]. In the COMFORT-I trial for myelofibrosis, a significant weight gain was observed in the ruxolitinib-treated group. Weight gain was not solely due to the therapeutic effect of the drug on myelofibrosis-linked symptoms. Ruxolitinib significantly increases body weight by blocking the production of leptin, an early satiety feedback signal in the Janus kinase 2/signal transducer and activator of tranions 3 (JAK2/STAT3) pathway. [35–36]. A phase I clinical trial (NCT04906746) exploring the dose-limiting toxicity of ruxolitinib in non-small cell lung cancer with cachexia is ongoing.

TCMCB07

TCMCB07, a melanocortin-4 receptor antagonist, reduces metabolism and energy expenditure by inhibiting hypothalamic melanocortin signaling and brain inflammatory factors. TCMCB07 significantly increased the body weight and fat mass of mice with cachexia and effectively crossed the blood-brain barrier when administered peripherally [37]. TCMCB07 exhibited not only good safety and tolerability at both high and low doses but also showed concomitant dose-related weight gain in a trial using dogs [38]. A phase I clinical trial (NCT04906746) to explore the safety, tolerability, and pharmacokinetics of TCMCB07 in healthy individuals is ongoing.

Inhibition of muscle wasting pathways

Since the discovery that blocking the ActRII receptor downstream of transforming growth factor-β (TGF-β) superfamily signaling pathways can alleviate muscle wasting and prolong the survival time of mice with cachexia, the biological role of the TGF-β superfamily in skeletal muscle has attracted extensive attention [39]. Activin, myostatin, growth and differentiation factors (GDFs), follistatin (FST), bone morphogenetic proteins, and STAT and Smad protein families are all components of the TGF-β superfamily and play a vital role in muscle wasting. Activin, myostatin, and FST promote muscle wasting by interacting with the ActRII receptors [40–41]. GDF15, also known as macrophage inhibitory cytokine 1, is the key factor regulating cachexia symptoms via glial-derived neurotrophic factor receptor α-like (GFRAL). Elevated GDF15 serum levels are associated with anorexia, muscle wasting, weight loss, regulation of body energy balance, and poor prognosis, indicating it might be a promising therapeutic target for cachexia [42–43].

Ponsegromab

Ponsegromab (PF-06946860) is a selective humanized anti-GDF15 monoclonal antibody that blocks GDF15/GFRAL-mediated signaling. A randomized, double-blind, phase I clinical trial of PF-06946860 in patients with cancer cachexia was completed on August 9, 2022; it explored the improvement in cachexia symptoms and appetite scores (NCT05546476) [44]. Two clinical trials comparing ponsegromab to placebo in patients with cancer cachexia are ongoing: one to evaluate its efficacy, safety, and tolerability (NCT05546476), and the other to assess its effect on appetite (NCT04803305).

3P10

3P10, an anti-mouse monoclonal antibody derived from a library of hybridoma clones generated from mice immunized with the GFRAL extracellular domain, can bind to GFRAL and prevent the GDF15-driven interaction between Ret proto-oncogene (RET) and GFRAL on the cell surface. 3P10 reversed skeletal muscle wasting in mice with cachexia by blocking GDF15/GFRAL/RET signaling, the mechanism of which is likely related to the inhibition of lipid mobilization and oxidation pathway. Surprisingly, researchers found that 3P10 also improved motor function and increased forelimb grip strength; the expression of muscle atrophy genes, including *Bnip3*, *Fbx032*, and *Gadd45a*, was completely prevented in mice with cachexia treated with 3P10 [45]. The weight regulatory mechanism of the GDF15/GFRAL/RET signaling pathway may be related to the sympathetic nervous system, independent of leptin, ghrelin, and other food intake-related factors, and weight increase does not depend on increasing caloric intake. GDF15 not only regulates body weight but also has anti-inflammatory effects, the mechanism of which has not been fully

elucidated. GDF15 has shown remarkable effects in the treatment of obesity, diabetes, and cancer cachexia [46].

Tilorone

Tilorone, a broad-spectrum antiviral drug with a history of more than 50 years, induces interferon production *in vivo* after oral administration. Tilorone and its analogs have anticancer activity [47–48]. Sartori *et al* [49] found that the BMP signaling pathway is one of the mechanisms regulating muscle wasting. In cachexia-related mouse models, elevated interleukin 6 (IL-6) activates STAT3, and the activated IL-6/STAT3 signaling pathway promotes the transcription of Noggin, a BMP signaling pathway inhibitor in mouse muscle tissue. High Noggin expression inhibits the BMP-Smad1/5/8 signaling pathway, resulting in abnormal neuromuscular junctions, which can promote tumor-related muscle wasting and dysfunction. By enhancing the activity of the BMP signaling pathway, tilorone can significantly improve muscle mass, improve motor neuron transmission dysfunction, and reduce the expression of key muscle atrophy-related genes, including *Fbxo32*, *Trim63*, and *Fbxo30*. Moreover, tilorone has no effect on tumor growth in mice with cachexia; however, it can prolong their survival by approximately 58% and is expected to be developed as a cachexia treatment drug.

mRNA therapy

Since 2020, mRNA therapeutics have undergone rapid development in the field of vaccines for infectious diseases, and mRNA therapeutics have been developed for cancer treatment [50]. Recently, Korzun *et al* [41] first reported a method for treating metastatic ovarian cancer and cachexia-induced muscle wasting using FST messenger RNA (mRNA) delivered by lipid nanoparticles (LNPs). Intraperitoneal injection of LNP-containing FST mRNA into metastatic ovarian cancer model mice triggered FST production in cancer clusters. FST is a highly targeted and regulated member of the TGF-β superfamily. FST binds to ActA with high affinity and irreversibility, thereby inhibiting the binding of ActA to ActRIIB receptors and reversing muscle wasting. FST mRNA LNP therapy has good tolerability and safety and avoids immunogenicity and dose-related toxicity that may be caused by recombinant protein supplementation. Both mRNA therapeutics and vaccines are promising cancer treatments [51].

Inflammatory factor-inhibiting drugs

A recent meta-analysis showed that inflammatory cytokines, including IL-6, IL-8, and TNF-α, were significantly elevated in the serum of patients with cancer cachexia and that elevated levels of IL-6 and TNF-α were associated with weight loss [52]. MABp1 is a human-derived monoclonal antibody that neutralizes IL-1α. Hickish *et al* [53] randomized patients with advanced colorectal cancer to receive MABp1 or a placebo treatment at a ratio of 2:1. In this phase III clinical trial, a composite endpoint was innovatively designed as the primary endpoint: patients with stable or increased lean body mass and stability or improvement in two of the three symptoms, including pain, fatigue, and anorexia. When administered for eight weeks, patients who met the primary endpoint in the MABp1 group had better clinical treatment response rates and longer median survival times than those in the placebo group.

In 2010, clazakizumab (ALD518), a humanized IL-6 antibody, was found to improve anemia symptoms in patients with stage II non-small cell lung cancer cachexia. Nonetheless, no follow-up phase III clinical trials have been conducted [54].

TNF-α-related drugs, including pentoxifylline, etanercept, infliximab, and melatonin, have not shown therapeutic efficacy in the treatment of cachexia [55]; therefore, existing targeted drugs against TNF-α and IL-6 have limited benefits in cachexia treatment. However, many new drugs that inhibit the secretion of TNF-α and IL-6 from macrophages and tumor cells are being developed, and clinical trials are ongoing.

Other therapeutic drugs

The following targets and drugs have been observed to significantly alleviate cancer cachexia muscle wasting in animal experiments: Calore *et al* [56] found that IMO-8503 can inhibit cancer-induced cachexia by antagonizing Toll-like receptor 7/8/9 (TLR7/8/9). Chiappalupi *et al* [57] targeted receptor for advanced glycation end-products (RAGE) prevents muscle wasting and prolongs survival in cancer cachexia, which was expressed only in cachexia atrophic myofibers. Murphy *et al* [58] demonstrated that mitochondrial assembly receptor (MasR) agonist AVE 0991 can alleviate weight loss and muscle wasting in cancer cachexia mice via substituting the angiotensin-coverting enzyme 2/angiotensin-(1-7)/MasR [ACE2/Ang-(1-7)/MasR] axis activated by AVE 0991 for the ACE/Angiotensin II/angiotensin type 1 (ACE/Ang II/AT1) axis.

Androgens and antidepressants have been tested in clinical trials to treat cachexia. Izumi *et al* [59] performed a prospective, randomized, non-placebo-controlled trial (the ARTFORM study) in male patients with advanced cancer and low serum testosterone levels. Unfortunately, androgen replacement therapy did not improve the quality of life [59]. Mirtazapine is a controversial drug that improves appetite and frequently causes adverse effects, such as drowsiness and hallucinations, during routine use. Hunter *et al* [60] recently studied 120 patients with incurable solid tumors with cachexia and anorexia who were randomly allocated to receive mirtazapine 15 mg/day at night *vs.* placebo for four weeks. The primary endpoint of appetite and secondary endpoints, including quality

Table 1 Clinical trials currently underway to treat cancer cachexia

Status	Start date	Study design	Estimated enrolment	Enrolled patients	Phase	Clinical trial identifier
Not yet recruiting	9-Sep-2022	1. Ponsegromab 2. Placebo	168	Patients with cachexia and elevated GDF15 levels in NSCLC, PAAD, and CRC	Phase II	NCT05546476
Recruiting	25-Dec-2021	1. Olanzapine 2. Placebo	164	Incurable solid cancer patients with anorexia and cachexia	Phase III	NCT05243251
Recruiting	1-Jun-2022	1. Mirtazapine 2. Megestrol acetate	80	Patients with advanced tumours and anorexia-cachexia	Phase II	NCT05380479
Recruiting	17-Dec-2020	Pancrelipase	30	Borderline resectable, locally advanced, and advanced PAAD patients with cachexia and exocrine pancreatic insufficiency	Phase II	NCT04098237

of life, fatigue, depressive symptoms, body weight, lean body mass, handgrip strength, and inflammatory markers, were not significantly different between the mirtazapine and placebo groups. These results do not support the use of mirtazapine tablets as appetite stimulants in patients with non-depressive cancer-related cachexia or anorexia [60]. National Comprehensive Cancer Network (NCCN) palliative care clinical guidelines recommend oral mirtazapine of 7.5–30.0 mg/day for patients with depression or anorexia when the life expectancy is several days to weeks, whereas, for patients with a life expectancy of months to years, oral olanzapine of 5.0 mg/day is recommended [61]. We summarize currently underway clinical trials of pharmacological treatments for cancer cachexia in Table 1.

Conclusion

Many studies have shown that the mechanism of cancer-related cachexia is complex and requires further research. Current research on drugs for cachexia treatment mainly focuses on blocking the muscle protein degradation pathway and stimulating an increase in appetite in patients. Multimodal combination therapies, including appetite-enhancing drugs, exercise interventions, and dietary supplements, have been used in many clinical trials. However, no ideal benefit has been observed. In addition, there is no uniform standard for assessing the therapeutic effects of clinical trial interventions, which makes it difficult to compare results across trials. Although cachexia muscle wasting cannot be completely alleviated, improving patients' appetite, weight, and muscle mass can undoubtedly buy time to perform the antitumor treatment. Developing new drugs or exploring multidimensional combinations to improve treatment tolerance and quality of life is the main direction of cachexia treatment.

In addition to the early detection of precachexia and early intervention, clinicians should also pay attention to the mental health status of patients, as depression and anxiety can also aggravate anorexia and weight loss.

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Conflicts of interest

The authors declared no conflict of interest.

Author contributions

Ze Ouyang: Conceptualization, writing, and original draft preparation. Weili Tao: Writing, reviewing, and editing. Corresponding authors: Supervision and funding acquisition. All the authors have read and agreed to the published version of the manuscript.

Data availability statement

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