The landscape of cancer cachexia in advanced non-small cell lung cancer: a narrative review

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Contributions: (I) Conception and design: All authors; (II) Administrative support: T Yamada; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: S Morita-Tanaka; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background and Objective: Cancer cachexia presents with weight loss, anorexia, and fatigue and worsens the prognosis and quality of life of cancer patients. We aimed to summarize the current relevant discourse in the literature about cancer cachexia in the setting of non-small cell lung carcinoma and the possible current and future treatments.

Methods: We conduct a narrative review of the literature on the landscape of cancer cachexia in the context of non-small cell lung cancer, multimodality therapy, markers, imaging, tumor biology, pathology, chemoprevention, and technical advances.

Key Content and Findings: The need for appropriate intervention for cancer cachexia is increasing as the prognosis of patients with advanced non-small cell lung cancer is improving with advances in treatment. Tumor cells play a role in the pathogenesis of cachexia, where they release factors that elicit the production of inflammatory cytokines by the immune system resulting in decreased appetite, abnormal energy metabolism, and skeletal muscle degeneration. Comorbid chronic lung diseases are associated with pulmonary cachexia and sarcopenia and commonly occur in the context of lung cancer, further contributing to the increased incidence of cachexia in patients with lung cancer. Currently, a ghrelin-like agonist, anamorelin, is approved for the treatment of cancer cachexia and is used in clinical practice in Japan. The role that nutritional and exercise therapies can play as added treatments must be further explored.

Conclusions: Cancer cachexia remains a poorly understood phenomenon, and awareness must be raised through educational activities for health care providers and patient family members. In addition, new therapeutics targeting cancer cachexia, such as GDF-15 antibodies, are in development, and further progress is expected.

Keywords: Cancer cachexia; non-small cell lung cancer; immune-checkpoint inhibitor; anamorelin

Introduction

Background

Cancer cachexia mainly presents in the form of weight loss, anorexia, and fatigue, worsening the life expectancy and quality of life (QOL) of cancer patients (1). The prognosis of patients with advanced non-small cell lung cancer (NSCLC) is improving with advances in treatment, including novel molecular targeted therapy targeting KRAS G12C mutations (2). Therefore, the need for appropriate intervention for cancer cachexia is increasing. Inflammatory cytokines are produced by the immune system in response

to factors produced by tumor cells. They play an important role in the pathogenesis of cancer cachexia, resulting in decreased appetite, abnormal energy metabolism, and skeletal muscle degeneration. These different phenomena further contribute to weight loss, a reportedly poor prognostic factor in patients with advanced NSCLC (3). Pharmacological therapies, such as corticosteroids and progesterone agents, have been used to alleviate symptoms associated with cancer cachexia in some countries, and there have been reports of some efficacy, whereas adverse events and other issues abound (4-6). In contrast, although the development of specific novel agents for cachexia has been attempted, it has not been successful for a variety of reasons, such as effects and toxicity (7).

In 2021, Japan became the first country in the world to approve anamorelin, a ghrelin-like agonist, for the treatment of cancer cachexia. Anamorelin continues to be used in daily clinical practice because of its therapeutic effects on cachexia. However, there is no established protocol for non-pharmacological treatment options, and clinical trials are currently underway in the world. In addition, the awareness of cancer cachexia remains low, and further educational activities for healthcare providers and patient family members are warranted.

Objectives

In this review, we provide an overview of patients with advanced lung cancer complicated with cachexia. We highlight the basic science concepts pertaining to cachexia, the advances in treatment, and the future of lung cancer treatment in the context of cancer cachexia. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-561/rc).

Methods

We searched published articles using the PubMed, published in the English language up to June 2022. We specifically searched using the key words "cancer cachexia", "non-small cell lung cancer", and in this context for "non-small cell lung cancer", "pulmonary cachexia", "Sarcopenia", "COPD", "ghrelin", and "clinical application". Our focus was to include mainly literature published from 2010 onwards. We also performed secondary review of bibliographies of several key meta-analyses (*Table 1*).

What is cachexia?

History of cachexia

The mention of cachexia dates back to the time of Hippocrates in ancient Greece as a condition in which a patient becomes emaciated and weak as a result of persistent and progressive chronic diseases, such as cancer, respiratory diseases, cardiac diseases, and collagen diseases. The English word cachexia is derived from the Greek words "*kakos*" meaning bad and "*hexis*" meaning condition. There was no effective treatment for cachexia, and it was considered a condition that developed in the terminal stage of the diseases. However, the pathophysiology, diagnostic criteria, and treatment methods have remained poorly understood, and until recently, cachexia was regarded as a "sign of death".

Disease patterns have changed as medical advances have established effective treatments for many diseases. Malignant neoplasms have replaced infectious diseases as the leading cause of death (8), and according to the International Agency for Research on Cancer, the World Health Organization's specialized agency for research on cancer, the worldwide incidence and mortality of cancer in 2018 were approximately 18.1 million cases and 9.6 million deaths, respectively. Of all cancers, lung cancer ranked first in both incidence and mortality (9).

Drug therapy for lung cancer has advanced remarkably over the years with the introduction of platinum-based drugs in the 1980s, followed by the approval of the molecularly targeted drugs from 2013 for EGFR, ALK, ROS1, KRAS, MET, and RET, and the immune checkpoint inhibitor (ICI) nivolumab in 2015 by the U.S. Food and Drug Administration (FDA). The prognosis for drug-sensitive patients has dramatically improved: the 5-year survival rates for advanced NSCLC preceding the advent of ICI ranged from 1 to 8%. The 5-year survival rates for patients treated with nivolumab, however, were reported to be 16% for squamous cell cancer and 15% for non-squamous NSCLC. Patients with high expression of PD-L1 within the tumor were reported to have a 5-year survival rate of 43% (10). In addition, the 5-year survival rate for patients with treatment-naïve advanced NSCLC treated with pembrolizumab monotherapy was reported as 23.2% (11).

With the progress of drug therapy and the improvement of overall survival, overcoming cancer cachexia, the poor prognostic factor with a major impact on QOL, has become the next main challenge. Research aimed at the development

Table 1 Details of the search method for this narrative review

Items	Specification
Date of search	July 21st, 2022
Databases and other sources searched	PubMed and ClinicalTrial.gov
Search terms used	"cancer cachexia", "non-small cell lung cancer", and in this context for "non-small cell lung cancer", "pulmonary cachexia", "sarcopenia", "COPD", "ghrelin" and "clinical application"
Timeframe	Mainly literature published from 2010 onwards
Inclusion and exclusion criteria	• Inclusion criteria:
	(I) Only English-language article
	(II) Original publications, including the clinical trial, literature review, and review paper were included
	• Exclusion criteria:
	(I) Non-English-language article
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Study selection and full-text articles were assessed by first authors (Tanaka Satomi and Tadaaki Yamada) and the consensus was obtained by other authors

of cancer cachexia treatment methods has progressed, and in 2021, the world's first ghrelin-like drug with anti-cancer cachexia action, "anamorelin", was launched in Japan (*Figure 1*).
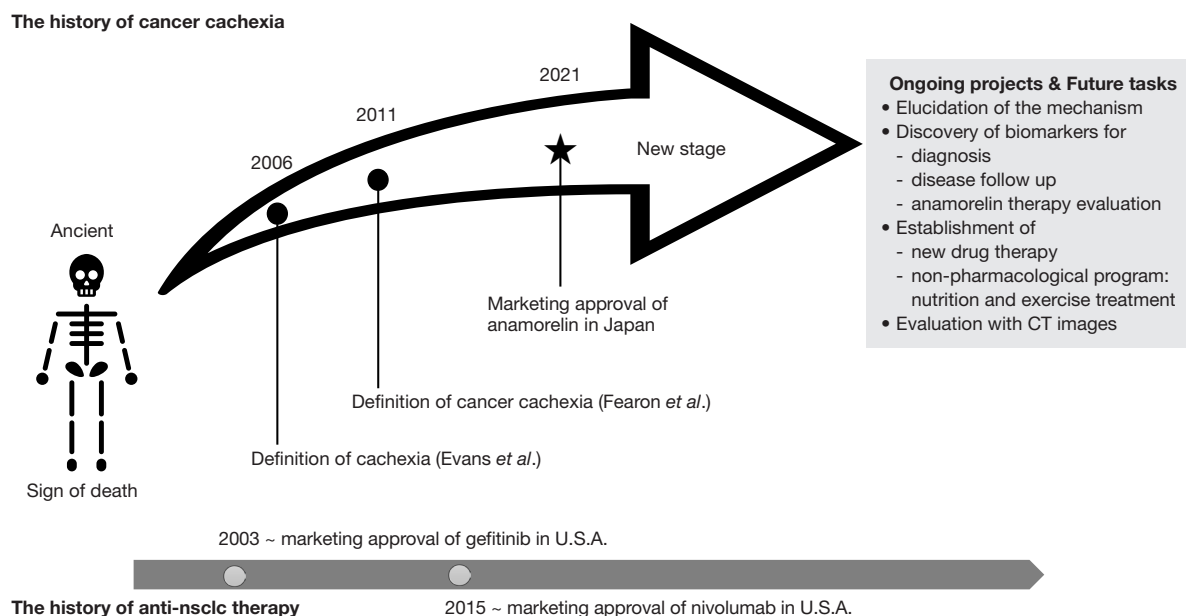
Definition of cachexia

The definitions and diagnostic criteria of "cachexia" and "cancer cachexia" were established in 2006 and 2011, respectively. The definition and diagnostic criteria for cachexia were proposed by Evans *et al.* at the 2006 Cachexia Consensus Conference held in the USA. Cachexia was defined at this conference as "a syndrome of complex metabolic abnormalities associated with an underlying disease, characterized by a decrease in skeletal muscle mass with or without a decrease in fat mass". Clinical manifestations include weight loss in adults, growth retardation in children, anorexia, inflammation, insulin resistance, and muscle proteolysis. Cachexia is distinct from starvation, age-related loss of muscle mass, depression, malabsorption disorders, and hyperthyroidism. The diagnostic criteria are listed as follows: duration that is consistent with that of chronic disease, presence of weight loss of 5% or more within 12 months, or body mass index (BMI) less than 20 kg/m^2 when weight change is not known, and the presence of three or more of the following items: (I) muscle weakness, (II) fatigue, (III) anorexia, (IV) low lean body mass (LBM), and (V) abnormal biochemical

data (12). The definition and diagnostic criteria for cancer cachexia were published five years later in a consensus report in the European Palliative Care Research Collaborative (EPCRC). The consensus report defined cancer cachexia as "a multifactorial syndrome characterized by a persistent loss of skeletal muscle mass (with or without fat loss) that cannot be completely reversed by conventional nutritional therapy and that progresses to functional impairment." The diagnosis of cancer cachexia is as follows: (I) weight loss of 5% or more within the past 6 months, (II) weight loss of 2% or more when BMI was less than 20 kg/m^2 within the past 6 months, (III) weight loss of >2% in cases of concomitant sarcopenia within the past 6 months (1). Cancer cachexia has three stages: precachexia, cachexia, and refractory cachexia. Intervention starting from the precachexia stage is recommended. Given the multifactorial nature of the syndrome, a combination of pharmacotherapy and non-pharmacologic interventions, such as nutrition and exercise, is recommended. However, standard prescriptions for nutritional and exercise interventions are yet to be established.

Mechanism of cachexia

The pathogenesis of cachexia is complex and not fully understood. At present, the development of cancer cachexia is thought to be due to the release of various factors in

Figure 1 The history of cancer cachexia and anti-non-small cell lung cancer therapy. With the progress of non-small cell lung cancer drug therapy, overcoming cancer cachexia, a poor prognostic factor for advanced cancer, has become the next major challenge. The definitions and diagnostic criteria of "cachexia" and "cancer cachexia" were established in 2006 and 2011, respectively. Research aimed at the development of cancer cachexia treatment methods has progressed, and in 2021, the world's first ghrelin-like drug with anti-cancer cachexia action, "anamorelin", was launched in Japan. NSCLC, non-small cell lung cancer.

response to activation of the humoral immune system, and not a direct effect of tumorigenesis. These factors include cytokines, blood cells, and humoral factors secreted by tumor cells. Tumor cell-derived cytokines, such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF), and interferon-γ (IFNγ), are known to be involved in the insulin-like growth factor 1 (IGF1)-Akt-forkhead box O (FoxO), transforming growth factor-β (TGF-β)-myostatin, NF-κB, and glucocorticoid pathways. Immune cells such as macrophages, neutrophils, bone marrow-derived suppressor cells, and T-cells that function in response to tumorigenesis are also implicated in cancer cachexia (13,14).

The balance of the appetite center, which is regulated by growth differentiation factor-15 (GDF-15), leptin secreted by adipocytes, and ghrelin secreted by gastric wall cells, is disrupted by inflammatory cytokines during cancer progression. Dysregulation of these processes promotes the state of appetite suppression. GDF-15, also referred to as macrophage inhibitory cytokine-1, is a divergent member of the TGF-β superfamily which regulates cell growth, differentiation, and death. GDF-15 is widely expressed in normal cells and its concentration in circulating blood is increased in inflammation, wound formation, cardiac

and renal diseases, and malignancies (15). Elevated blood concentration of GDF-15 in cancer patients since the early stage of cachexia has been reported as a poor prognostic factor in patients with anorexia and weight loss due to cancer cachexia (16,17). In addition, its overexpression in skeletal muscles can promote muscle atrophy (18). In animal studies of cachexia, mice treated with anti-GDF-15 antibody experienced increased body weight, muscle mass, and fat mass (16).

GDF-11, another member of the TGF-β family of molecules, is a homologous protein of myostatin, a known inhibitor of skeletal muscle growth. Interestingly, GDF-11 and myostatin have more than 50% of their amino acid sequences in common (19). The concentration of GDF-11 in the circulating blood is associated with the degree of skeletal and cardiac muscle atrophy (20). Increased endogenous secretion of glucocorticoids, a class of corticosteroids, occurs in stressful conditions, and glucocorticoids have long been used in cancer therapy. In skeletal muscles, glucocorticoids cause increased protein catabolism and decreased synthesis (21).

Parathyroid hormone-related protein (PTHrP) in adipose tissue has been reported to be associated with
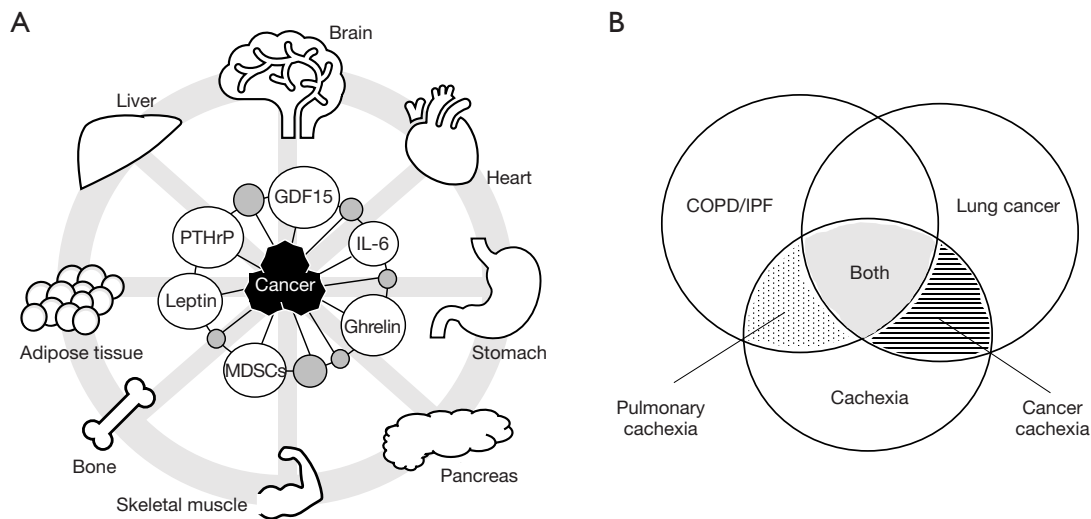
Figure 2 The role of multiple factors associated with cancer cachexia. (A) The relationship between cancer cachexia and multiple organs. These diverse factors, such as GDF-15, IL-6, ghrelin, and leptin, cause cachexia pathology by acting on systemic organs, such as the skeletal muscle, adipocytes, brain, liver, bone, and pancreas, myocardium, and gastrointestinal tract. (B) Lung cancer, pulmonary disease, and cachexia. It has been speculated that one of the reasons for the high incidence of cachexia in lung cancer is related to its occurrence secondary to chronic lung diseases, such as COPD or IPF, in addition to the rate of disease progression of advanced cancer. GDF-15, growth differentiation factor-15; PTHrP, parathyroid hormone-related peptide; MDSCs, myeloid-derived suppressor cells; IL-6, interleukin-6; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis.

increased metabolism and decreased LBM (22). Anti-PTHrP antibodies have been reported to suppress cancer cachexia (23). These diverse factors cause cachexia pathology by acting on multiple organs, such as the skeletal muscle, adipocytes, brain, liver, bone, pancreas, myocardium, and gastrointestinal tract (*Figure 2A*) (24).

Lung cancer and cancer cachexia

Respiratory disease and cachexia, and pulmonary rehabilitation and nutritional support

Cancer cachexia occurs in 50–80% of patients with advanced cancer (25). Gastrointestinal, head and neck, and lung cancers are the most common causes of cancer cachexia (26). Gastrointestinal and head and neck cancers are directly involved in feeding, digestion, and absorption, whereas lung cancer has a less direct impact on nutritional intake. Cancer cachexia in advanced lung cancer may occur as a complication of commonly comorbid chronic lung diseases, such as chronic obstructive pulmonary disease (COPD) and idiopathic interstitial pneumonia. Cachexia is a complication of various chronic diseases, as well as cancer, and is frequently seen in COPD, congestive heart failure, cancer, and chronic kidney disease (27). The frequency

of COPD and emphysema in lung cancer patients has been reported as 38.4% and 58.2%, respectively (28). The prevalence of cachexia in patients with COPD is relatively high, ranging from 5% to 15%. In addition, cachexia is known as an independent risk factor for mortality in COPD patients (27,29). A randomized controlled trial comparing administration of ghrelin versus placebo control in patients with severe COPD with a BMI of 21 kg/m^2 showed that ghrelin treatment was associated with a significant reduction in dyspnea on exertion during respiratory rehabilitation (30).

Idiopathic pulmonary fibrosis (IPF), a group of refractory interstitial pneumonia that confer poor prognosis, occurs in approximately 10–20% of patients with lung cancer (31,32). A worse prognosis has been reported in patients with IPF and signs suggesting muscle atrophy and sarcopenia, such as a low cross-sectional area of the erector spinae muscle (33).

The progression of chronic lung diseases causes chronic systemic inflammation, leading to weight loss, sarcopenia, malnutrition, and ultimately, a state of pulmonary cachexia. It has been speculated that one of the reasons for the high incidence of cachexia in lung cancer is related to the complications of chronic lung diseases, in addition to the rate of disease progression of advanced cancer (*Figure 2B*).

Pulmonary rehabilitation and nutritional support

constitute one of the standard interventions for patients with chronic lung disease. High intensity exercise training was shown to be effective in improving lower limb muscle strength and exercise performance in COPD patients with low muscle mass and moderate airflow obstruction. Specific nutritional supplementation showed additional effects on nutritional status, inspiratory muscle strength, and physical activity (34). Despite proven physiological, symptom relief, psychosocial, and health economic benefits of pulmonary rehabilitation and nutritional support for patients with chronic respiratory diseases, these interventions are under-utilized worldwide. This is due to a lack of funding, resources, and reimbursement, as well as a lack of awareness and knowledge among healthcare professionals, payers, and patients.

Impact of weight loss in patients with advanced NSCLC

It has been reported that weight loss associated with cancer progression is a poor prognostic factor for patients with NSCLC. In the TORG0912 study, we observed weight change in 406 untreated advanced NSCLC patients with Eastern Cooperative Oncology Group-Performance status (ECOG-PS) 0–2 (median age 67 years, male to female ratio 2:1, mean BMI 21.79 kg/m^2) who were prospectively followed for 12 months. The group with greater weight loss showed increased muscle weakness and a marked deterioration in life expectancy, QOL, and PS (3). In addition, another Japanese cachexia team prospectively observed untreated advanced NSCLC patients over 70 years of age during initial chemotherapy and reported significant decreases in BMI, skeletal muscle index, and shuttle walk distance at 12 weeks following the start of observation (35).

Efficacy of ICIs in advanced NSCLC patients with cancer cachexia

Complications of cachexia and sarcopenia are also known to affect treatment response in patients with advanced NSCLC. By measuring the cross-sectional area of the psoas major muscle on computed tomography (CT) images, we retrospectively evaluated the presence of sarcopenia in 38 patients with advanced NSCLC who received the ICIs, nivolumab or pembrolizumab. Progression free survival (PFS) in patients without sarcopenia was significantly greater than that in patients with sarcopenia (36). Similarly, recent studies have reported that advanced NSCLC patients with cancer cachexia-sarcopenia showed poor prognosis after treatment with immune checkpoint inhibitors (37-39).

Next, in a retrospective study of 235 patients with advanced NSCLC treated with a combined therapy of ICIs and cytotoxic anticancer agents, we reported that patients with PD-L1 expression <50% and cachexia experienced significantly lower PFS and overall survival (OS) than patients without cachexia (40). These results indicate that the presence of sarcopenia and cancer cachexia in advanced NSCLC may affect the efficacy of immunotherapy-containing regimens. In addition, inflammatory/prognostic scores, such as modified Glasgow prognostic score, prognostic nutritional index, nutritional index, and neutrophil/lymphocyte ratio, are associated with cancer cachexia (41,42) and prognosis of advanced NSCLC patients (42-45).

Such muscle weakness may cause a decline in activities of daily living (ADL) in older lung cancer patients, which may significantly hinder treatment adherence, maintenance, and effectiveness.

Early intervention, such as exercise and nutrition, to maintain muscle strength may improve life expectancy and prognosis. A previous clinical trial demonstrated that early palliative care led to significant improvements in both QOL and mood among patients with metastatic NSCLC (46). However, at present, standard prescriptions and non-pharmacological approaches for patients have not been established.

Development of novel therapeutic strategy with anamorelin for cancer cachexia

Discovery of ghrelin

Ghrelin was discovered by Kojima *et al.* in 1999. Ghrelin is a peptide hormone present in the stomach that increases appetite and acts as an endogenous ligand for the growth hormone secretagogue receptor (GHS-R1a) (47). Ghrelin binds to GHS-R1a to exert its bioactivity. GHS-R1a is expressed not only in the central nervous system but also in various peripheral tissues and exhibits additional bioactivities, such as promotion of lipogenesis, involvement in glucose metabolism, regulation of gastrointestinal motility, suppression of inflammatory cytokine production, and protection of the cardiovascular system (48). Ghrelin is also known to promote protein synthesis in skeletal muscles through the following pathways: (I) ghrelin acts on the hypothalamus and enhances the secretion of growth hormone (GH); (II) secreted GH acts on the liver and promotes the secretion of IGF-1; (III) IGF-1 acts on skeletal muscles to promote protein synthesis (49).

Clinical development and challenges of anamorelin

In 2001, peripheral administration of ghrelin to healthy volunteers showed a significant increase in appetite and food intake (50). However, the short half-life of ghrelin of approximately 10 min and the need for intravenous administration were problematic for its clinical application. To overcome these problems, anamorelin, a ghrelin agonist, was developed as a ghrelin-like compound that can be orally administered. Anamorelin is a low-molecular-weight compound with a molecular weight of 583.16 and a half-life of approximately 9 hours in blood, making it feasible for daily oral administration. In clinical trials done in Japan (ONO-7643-04) investigating anamorelin in patients with NSCLC and gastrointestinal cancer, treatment with 100 mg/day of anamorelin once daily for 12 weeks showed a significant increase in LBM; the change from baseline was 1.38±0.18 and −0.17±0.17 kg in the anamorelin and placebo groups, respectively (P<0.0001). In addition, the LBM of anamorelin group increased one week after anamorelin treatment and it continued thereafter with no safety concern. Appetite was determined using the QOL Questionnaire for Cancer Patients Treated with Anticancer Drugs (QOL-ACD), and the scores also improved from the first week of treatment, and the effect was maintained until the 12th week. In contrast, the study did not show any improvement in non-dominant handgrip strength or 6-min walking distance (51). Following these results, the anamorelin was launched in Japan in 2021. However, it was not licensed in Europe and the US due to lack of adequate data on patient benefits and safety. Currently, two phase III SCALA studies on anamorelin are underway in the US, Europe, Russia, and Australia for treatment of malignancy-associated weight loss and anorexia in adult patients with advanced NSCLC (NCT03743051 and NCT03743064).

Regarding the introduction of anamorelin therapy, attention should be paid to two points: side effects and selection of treatment eligibility. In terms of side effects, adverse cardiovascular events, such as first-degree atrioventricular block, tachycardia, and hypertension, have been reported. From the results of nonclinical studies (49,52), anamorelin has been reported to have an inhibitory activity on ligand binding to sodium channels and L-type calcium channels and is known to inhibit sodium channel currents in human cardiomyocytes. Therefore, it should be noted that anamorelin is administered with caution or is contraindicated in patients with cardiac diseases, such as congestive heart failure, myocardial infarction, and angina pectoris, as well as severe heart conduction disorders, including complete atrioventricular block. In addition, because the drug is metabolized via CYP3A4, concomitant use with drugs that inhibit the activity of this enzyme is contraindicated. Particular attention should be paid to patients with comorbid chronic respiratory diseases, as frequently used drugs, such as clarithromycin, itraconazole, and voriconazole, are among the contraindications. In addition, caution must be taken when determining patient eligibility for clinical trials of anamorelin. In this study, patients with an ECOG-PS of 0–2 and an expected prognosis of at least 4 months were included. Therefore, the use of anamorelin in patients with poor PS should be judged with caution. The Japanese Association of Supportive Care in Cancer formulated a guideline for the proper use of anamorelin, considering the above precautions. Currently, anamorelin is available for patients with cachexia in daily practice but is not routinely used in Japan.

In contrast, the IGF-1 molecule secreted from the liver as a result of anamorelin administration is known to be a tumor growth factor. There was a concern about the enhancement of tumorigenicity during the drug development process; however, preclinical studies and clinical trials have shown no enhancement of tumorigenic effects with anamorelin administration (53).

Clinical interventional study for cancer cachexia

The aforementioned clinical trials showed that anamorelin treatment did not restore muscle strength or improve physical activity in patients with advanced cancer (51). To date, efficacy and tolerability have not been proven for the multidisciplinary treatment of patients with cancer cachexia using non-pharmacological therapies. Currently, randomized controlled clinical trials are underway in Japan and Europe to evaluate the efficacy of concurrent anamorelin and non-pharmacological treatment in the form of exercise and nutritional therapy. The Nutritional and Exercise Treatment for Advanced Cancer (NEXTAC) study, a multicenter study in Japan aiming to assess the efficacy of early nutritional and exercise interventions in older patients with advanced NSCLC/pancreatic cancer, is underway. The goal of this study is to establish interventions for muscle strength and physical function in patients with cancer cachexia. A phase I trial (NEXTAC-ONE) prospectively evaluated the feasibility of exercise therapy and its impact on QOL in 30 patients with advanced-stage untreated NSCLC and pancreatic cancer. These patients were aged 70 years or older, belonged to ECOG-PS 0–1, scored >90 points on the Barthel index, and were scheduled for induction of first-line

anticancer therapy (54). A physiotherapist, dietitian, and nurse provided counseling to promote daily physical activity throughout the 8-week intervention. Investigators assessed patient attendance and compliance with counseling, as well as the effectiveness of the intervention. Intensity of exercise was set at three levels (≤2,000 steps, >2,000 steps/<8,000 steps, and ≥8,000 steps) and was tailored to each patient based on their baseline average number of steps per day during the screening period. The median age of the patients was 75 years [70–84], and 12 (40%) patients met the criteria for cachexia at inclusion. Twenty-eight (93%) patients participated in all courses, resulting in 6 (15%) patients with increased indoor activities and 15 (52%) patients with increased outdoor activities. There were significant differences in physical activity, QOL, and mental activity between the patients who increased their activity and those who did not. We conclude that the NEXTAC program of exercise therapy is feasible and well tolerated by older patients with advanced-stage cancer. In fact, many patients showed behavioral changes and improved QOL (55). A multicenter randomized phase II trial (NEXTAC-TWO) is currently underway to test the usefulness of exercise therapy by evaluating two similar patient groups (UMIN000028801) (56). A multicenter, randomized phase II trial (NEXTAC-THREE) is also underway (JPRN-jRCTs 041210053). In European countries, a phase III study Multimodal-Exercise, Nutrition and Anti-inflammatory medication (MENAC) for the treatment of advanced NSCLC and advanced pancreatic cancer in patients aged 18 years and older with Karnofsky Performance Status >70 is also ongoing (NCT02330926) (57).

Current status of cancer cachexia treatment

Nutrition impact symptoms that can be intervened

Many NSCLC patients have a high symptom burden and are at risk of malnutrition prior to starting systemic anticancer therapy, suggesting that the improvement of nutritional conditions might enhance clinical outcomes (58). However, simple nutritional interventions did not improve clinical outcomes, including nutritional outcomes and QOL (59).

Practical interventions for cancer cachexia have not yet been well established. Management should appropriately address treatable factors associated with cancer. Symptoms that produce secondary hunger are termed nutrition impact symptoms and are thought to be caused by complications such as chemotherapy-related oral mucosal damage, diarrhea, nausea, and vomiting, as well as cancer-related depression (60). These complications for most cases are manageable by therapeutic intervention. The aforementioned TORG0912 trial showed that weight loss itself is a poor prognostic factor in patients with advanced cancer (3), and it is important to intervene appropriately through patient/family communication and QOL active weight follow-up.

Patient and family education

In a survey of cancer patients and their families in Japan, 8.2% of patients and 14.5% of family members reported being aware of the term cancer cachexia (61). Moreover, anorexia and weight loss were not reported or discussed with healthcare professionals when the main symptoms of cancer cachexia occurred in 42.4% and 57.9% of cases, respectively (62). Although the data were obtained before the launch of anamorelin, it is clear that there is insufficient awareness regarding cancer cachexia, highlighting the need for proper patient and family education.

Prospects for cancer cachexia

Development of novel therapeutics

New anti-cachectic agents are under development following anamorelin. Visugromab, a neutralizing antibody against GDF-15, is currently attracting attention as a novel therapeutic target against cachexia. GDF-15 has been reported to induce anorexia by acting on the brain's feeding center and to be involved in the reduction of LBM and fat mass in cancer patients (17). Visugromab has been evaluated for tolerability in a phase 1 study and is currently being evaluated in a phase 2 study. Bermekimab, an anti-IL-1α antibody targeting inflammatory cytokines, was evaluated in a phase 1 study (NCT01021072) in patients with advanced cancer to identify the appropriate dose of the antibody drug, as well as its antitumor effects and response to cachexia. In this study, no dose-limiting toxicity of Bermekimab was observed until 3.75 mg/kg, and disease control was obtained (63). They also reported that Bermekimab was well tolerated, with gains in LBM [1.0±2.5 kg, mean 0.4 kg (SD: –0.5 to 2.6)] in patients with metastatic non-small cell lung cancer (64). A phase III study in patients with advanced colorectal cancer refractory to treatment with oxaliplatin plus irinotecan treatment showed that Bermekimab treatment resulted in changes in LBM and improvement in subjective symptoms, such as pain, fatigue, and anorexia (65). Bermekimab is currently in clinical trials for inflammatory diseases, including a phase 2 study (NCT03496974) for atopic dermatitis. In addition, rapamycin has a therapeutic

potential for sarcopenia by slowing age-related muscle wasting through regulation of mTORC1 (66).

Basic science research has also revealed several factors that are potential therapeutic targets, including fibroblast growth factor inducible 14 (Fn14), muscle RING finger 1 (MuRF1), SPRY domain-containing SOCS box protein 1 (Spsb1), serum amyloid A1 (SAA1), and ZIP14.

Fn14 is a receptor for TNF-related weak inducer of apoptosis (TWEAK), one of the super family of TNF. Anti-Fn14 antibody treatment improved cachexia symptoms, increased body weight, and prolonged survival in mice with carcinoma *in situ* (67). Spsb1 induces destabilization of p21, a CDK inhibitor, and contributes to cancer cell survival (68). SAA1, which is increased in acute phase inflammation, induces activation of TLR2/TLR4/NF-κB signaling and causes muscle cell atrophy (69). ZIP14, a transporter of zinc ions, has been reported to promote cachexia when its levels are elevated in skeletal muscles of advanced cancer mouse models (70). These factors are being investigated as next-generation therapeutic targets for cancer cachexia and are expected to be developed clinically in the future.

Biomarker development for cancer cachexia

Currently, the indicators used in the diagnosis and evaluation of cancer cachexia include body weight and BMI, as well as the diagnostic criteria for cachexia proposed by Evans *et al.* (12). These criteria include serum CRP, hemoglobin, and albumin levels and a QOL questionnaire that is used to score subjective symptoms, such as appetite and fatigue.

The FAACT and its Anorexia-Cachexia subscale (A/Cs) are representative QOL questionnaires. In particular, the A/Cs has been shown to be useful in identifying patients with cancer cachexia (71). The QOL-ACD was used to survey QOL during the development of anamorelin. However, owing to inadequate reimbursement coverage in real-world practice, team-based care for cancer cachexia, such as QOL surveys and patient-family education, is yet to be adequately developed.

For biomarker studies with muscle tissue, blood, and urine samples, various analytical approaches were used, including nuclear resonance spectrometry, gas chromatography-mass spectrometry, and liquid chromatography-mass spectrometry. The levels of metabolites, such as phenylalanine, asymmetric dimethylarginine (ADMA), paraxanthine, 3-hydroxybutyrate, lysoPC 18:2, lysoPC 16:1, hexadecanoic acid (palmitic acid), and octadecanoic acid (stearic acid), were elevated in patients with cachexia and weight loss (72). Among them, ADMA has been identified as a potential therapeutic target for cachexia (73). Although such a comprehensive analysis poses the challenges of procedural complexity and elevated costs, ADMA is expected to develop into a novel biomarker for the diagnosis and disease assessment of cancer cachexia in the future.

Attempts have also been made to evaluate cancer cachexia using imaging data. Although the analysis of skeletal muscle mass using CT images has been widely used to evaluate sarcopenia in the past, most of these methods require labor-intensive manual measurement. Recently, Analyzer using Computed tomography image Segmentation (ABACS), a software that analyzes CT images to quantify skeletal muscle mass and fat mass, was developed in the United States and Canada and was shown to measure with high accuracy (74). Measurement of skeletal muscle mass and fat mass has the potential to assess the pathophysiology of cachexia more accurately than weight loss rate or BMI, and its efficient reproducibility through software is expected to be applied to routine clinical practice similar to estimation of bone density in the diagnosis of osteoporosis.

The clinical biomarkers regarding response to anamorelin therapy remain unclear. Therefore, development of predictive biomarkers for anamorelin therapy remains an issue. In post-marketing surveillance of anamorelin in Japan, gastrointestinal disturbances were the most frequently reported adverse reactions, with nausea reported by half of the patients (75). The action of anamorelin differs from patient to patient, and further clinical investigations are warranted.

Conclusions

The pathogenesis and treatment of cancer cachexia is being established. Patients who are not eligible for conventional supportive care but who have progressive weight loss may have advanced cancer cachexia and require earlier, more aggressive intervention. Beneficial interventions for diseases require an understanding of cancer cachexia by both providers and patients and the development of effective drugs. The Society for Sarcopenia, Cachexia and Wasting Disorder was established in 2008, mainly in Europe and the United States, and is promoting global awareness of cancer cachexia. Cancer cachexia treatment is expected to become the future of drug therapy in advanced lung cancer in conjunction with anticancer therapy.

Acknowledgments

Footnote

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