ANTICANCER RESEARCH *43*: 511-521 (2023)
doi:10.21873/anticanres.16188

Review

The Latest Treatments for Cancer Cachexia: An Overview

HAYATO WATANABE[1,2] and TAKASHI OSHIMA[1]

[1]*Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan;*
[2]*Department of Surgery, Yokohama City University, Yokohama, Japan*

Abstract. *Cancer cachexia demonstrates the same pathology as cachexia found in patients with disease-associated malnutrition presenting with inflammation. In advanced cancer, a decrease in skeletal muscle mass progresses with an increase in cancer cell mass. Moreover, cancer cachexia causes systemic edema and cachexia, reduces the efficacy of chemotherapy, and negatively affects cancer prognosis. Early nutritional intervention and multidisciplinary care are essential to ensure sufficient nutritional requirements and minimize anabolic resistance factors. In addition, preventive care that minimizes deterioration of nutritional status and loss of skeletal muscle mass is required for the effective treatment of cachexia. Therefore, the current review sought to comprehensively describe the available evidence for the effective pharmaceutical treatment of cancer-associated cachexia. Steroids have traditionally been used for cachexia drug therapy. However, their effects are limited, and it is difficult to radically restore the highly reduced muscle mass inherent to cancer-associated cachexia. Recently, anamorelin hydrochloride, an endogenous ligand for the growth hormone release-promoting factor receptor, which has a similar pharmacological action to that of ghrelin, was developed to treat weight loss accompanied by anorexia. This medication also treats cachexia and was the first drug to be approved for this purpose. Anamorelin hydrochloride is expected to bring new advancements into the field of clinical oncology as an effective therapeutic drug for cancer cachexia, a devastating complication that, so far, has no definitive and effective treatment.*

As cancer progresses, many patients develop characteristic symptoms, such as loss of appetite, weight loss, malaise, and poor physical fitness, all of which work synergistically toward increasing the likelihood of malnutrition. Various other factors also contribute to decreased oral nutritional intake and overall energy intake. Malnutrition is associated with absolute nutritional deficiencies (1). Although there are differences in clinical findings depending on the stage of cancer progression, in general, more than half of all cancer patients have moderate to severe anorexia. In addition, weight loss is observed in 30-80% of cancer patients (2).

Hyponutrition in cancer patients impedes daily activity and reduces quality of life (QOL). In addition, malnutrition or hyponutrition decreases tolerability to curative cancer treatments, such as surgery and chemotherapy, leading to significant reductions in therapeutic effects. This adversely and severely affects cancer prognoses (3-5). Even mild nutritional disorders presenting in cancer patients, such as "constant nutritional status due to starvation", a diagnosis that is limited to loss of appetite, cause irreversible nutritional disorders when associated with advanced cancer progression, which involves infiltration into critical organs and metabolic disorders. If not for these cancer-associated complications, recovery from mild nutritional disorders would be easily attainable with appropriate nutritional intake. However, unlike in simple starvation, patients with advanced cancer physiologically and behaviorally resist nutritional management and treatment. Thus, these patients tend to develop metabolic disorders, such as cachexia, that are characterized by marked muscle and weight loss as the cancer progresses (6).

Cachexia is characterized by low nutrition and skeletal muscle mass against the setting of chronic diseases, such as cancer, chronic heart failure, chronic obstructive pulmonary disease (COPD), chronic renal failure, chronic rheumatoid arthritis, and severe burn injuries. The state of malnutrition results in severe weight loss (6, 7). Cancer cachexia is found in approximately 80% of patients with advanced cancer (8-10) and accounts for approximately 30% of cancer-associated deaths (11-14). In contrast to "starvation undernutrition," in which skeletal muscle mass, which is essential for supporting basic life functions, is reversibly preserved and adipose tissue is preferentially reduced, cancer-associated cachexia reduces skeletal muscle mass

Correspondence to: Dr. Takashi Oshima, Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 2-3-2 Nakao, Asahi-ku, Yokohama, Kanagawa 241-8515, Japan. Tel: +81 455202222, Fax: +81 455202202, e-mail: oshimat@kcch.jp

Key Words: Cancer cachexia, anamorelin hydrochloride, review.

starting from an early stage (15). In addition to the typical cachexia symptoms of weight loss and loss of appetite, cancer-associated cachexia also leads to a diminished therapeutic effect of chemotherapy and increased side effects thus, leading to a greater likelihood of discontinuation of treatment and a lower survival rate (16, 17).

Therefore, the current review sought to comprehensively describe the evidence for the effective pharmaceutical treatment of cancer-associated cachexia. In particular, this review discusses the importance of nutritional management in palliative cancer medicine, with a focus on new treatments for cachexia, a topic that has recently gained attention in the fields of medicine and research.

Definition of Cachexia

The term cachexia has long been used to describe a state of weakness caused by malnutrition (18, 19). Cachexia is a terminal stage of malnutrition that occurs not only in cancer but also in various chronic wasting diseases. Physiological and behavioral treatment resistance associated with cachexia worsens the prognosis and QOL of patients.

Cachexia is characterized by the extensive loss of skeletal muscle, termed sarcopenia or myopenia, and adipose tissue. This cancer-associated presentation is opposite to that of the physiological presentation of simple starvation. However, because this cachexia is a complicated condition and can undergo considerable modification due to nutritional and pharmaceutical management, the findings of metabolic analyses are not straightforward. Thus, it is difficult to set a standardized definition that everyone agrees upon. In addition, elucidating the mechanisms underlying this condition and developing effective treatment methods remain to be a challenge.

In 2006, the guidelines published in Europe and the United States defined cachexia as "a syndrome of complex metabolic disorders associated with underlying disease, characterized by a decrease in muscle mass with or without adipose tissue loss". The clinical symptoms of cachexia include weight loss in adults and failure to thrive in children. With regard to differential diagnosis, cachexia was defined as a condition that differs from starvation, age-related muscle loss, depression, malabsorption, hyperthyroidism, anorexia, increased inflammatory response, insulin resistance, and increased protein catabolism (6).

In 2011, the European Palliative Care Research Collaborative (EPCRC) guidelines for cancer cachexia were published, stating that:
"Cancer cachexia is difficult to improve with conventional nutritional support and leads to progressive dysfunction, with or without adipose tissue loss. It is a complex metabolic disorder syndrome characterized by marked loss of muscle tissue. Pathophysiologically, it is characterized by decreased oral intake, decreased protein levels due to metabolic disorders, and a negative energy balance" (20, 21).

In 2017, the classification of malnutrition issued by the European Society for Clinical Nutrition and Metabolism (ESPEN) defined cachexia as a condition synonymous with "chronic disease-related malnutrition with inflammation" (22).

As mentioned above, cancer-associated cachexia is known to differ from both starvation (*i.e.*, a form of malnutrition not caused by a disease) and malabsorption (*i.e.*, a form of malnutrition caused by a disease but not accompanied by inflammation). A state of cachexia presenting as a mild metabolic disorder with the absence of obvious cachexia symptoms is termed "pre-cachexia". The cachexia special interest group (SIG), which is ESPEN's SIG on cachexia-anorexia in chronic wasting diseases, has defined this concept and emphasized the importance of addressing pre-cachexia in clinical management.

In addition, due to the severity of this metabolic disorder, a terminal state known as "late cachexia" or "severe cachexia" may occur, wherein there is no more room for improvement in nutritional status. In the EPCRC guidelines, this state is termed "refractory cachexia" and is defined as "a cachexic condition that causes irreversible nutritional disorders due to highly resistant or rapidly progressing cancer".

The EPCRC guidelines propose three disease stages namely "pre-cachexia", "cachexia", and "refractory cachexia". A set of diagnostic criteria for each stage is also proposed for future implementation within clinical guidelines. Further consideration is necessary before implementing these clinical definitions and diagnostic criteria. However, this development itself is significant in managing the nutrition of cancer patients before and after cachexia (Figure 1).

Mechanisms and Primary Symptoms of Cachexia

The mechanisms underlying the development of cachexia are not well understood. However, these mechanisms are gradually being elucidated through recent progress using biochemical and biological analyses. For example, the involvement of proteolysis-inducing factor (PIF), which is released from tumors and reflects abnormalities of the neuroendocrine system, is gradually being revealed. The activation of inflammatory cytokines resulting from the interactions between the cancer cells and host cells varies. Inflammatory pathways are deeply involved in various metabolic disorders and loss of appetite (23) and play a central role in the mechanisms underlying cachexia (20). In recent years, cachexia has been regarded as a systemic inflammatory reaction mediated by various cytokines (17, 22).

Cancer-associated cachexia is characterized by a unique competitive response in the tumor involving the release of PIF and lipid mobilizing factor (LMF). Disease presentation is largely affected by factors, such as the rate of tumor progression, biological attitudes, and side effects of anticancer treatment, which can include cachexia.

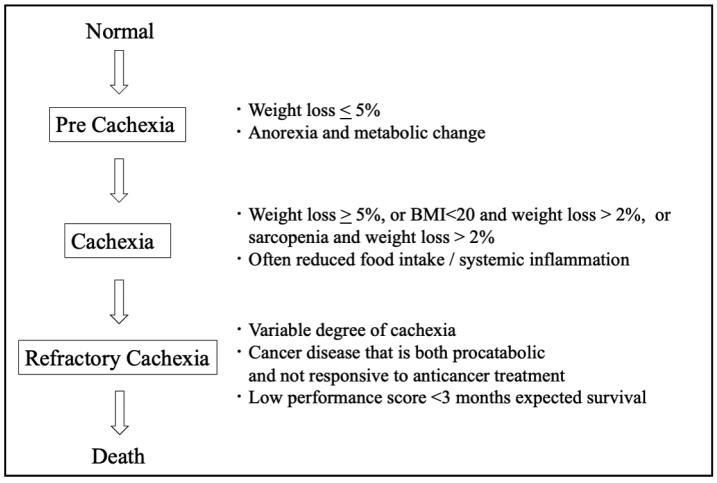

Figure 1. *The spectrum of cachexia. Cancer-related cachexia is known to be distinct from both starvation and malabsorption. The state of cachexia, which presents as a mild metabolic derangement without overt cachectic symptoms, is termed "pre cachexia". As cachexia progresses, a terminal state occurs in which nutritional status cannot be improved. This condition is called refractory cachexia, which is often caused by cancer diseases that have strong catabolic effects and do not respond to anticancer drug treatment, and the expected survival period is less than 3 months.*

As the cancer progresses, cachexia generally develops into irreversible malnutrition that gradually causes death (24, 25). However, some cancer types are less likely to produce cachexia (26, 27), and the rate of progression varies across individuals. The malnutrition caused by cachexia is a metabolic abnormality occurring due to a chronic inflammatory reaction throughout the body as well as increased catabolism. This includes symptoms of increased skeletal muscle decomposition, insulin resistance, and increased lipid decomposition (2, 8). When this metabolic disorder becomes severe, nutritional intake is not effectively utilized and malnutrition gradually becomes irreversible. Therefore, it is extremely important to provide nutritional support early on at the stage where the progress of cachexia is not extensive, that is, wherein the degree of metabolic abnormality is mild.

Loss of appetite. Loss of appetite is observed in approximately 40% of cancer patients and has a prevalence of 80% in patients with advanced-stage cancer (9). Some causes of loss of appetite in cancer patients are nausea, the cancer itself, pain, anxiety, and depression. Recently, it has been suggested that anorexia is caused by an increased inflammatory response. In other words, in the state of cancer cachexia, macrophages, mononuclear cells, and lymphocytes release large amounts of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1β, and interleukin-6 (3, 28). These cytokines, which are peptides present in the hypothalamus, promote feeding behavior and suppress the action of neuropeptide Y as well as the secretion of corticotropin-releasing hormone, which is an antifeedant hormone (3). In advanced cancer, chronic pain caused by nerve compression and bone metastasis results in anorexia (3). For instance, the combined symptomology of gastrointestinal cancer exerting pressure on the ganglia coupled with abdominal pain causes a strong decrease in appetite.

Abnormal energy metabolism. Increased energy expenditure is one of the main factors leading to cancer cachexia. The resting energy expenditure (REE) of cancer patients is approximately 48% higher than that of healthy people (29). According to the current literature, increased REE in cancer patients may be mediated by several mechanisms, such as an increase in uncoupling protein levels, variations in cytokine levels, and release of LMFs (30-32). Changes in intracellular energy production as well as activation of the Cori cycle, involving recycling of lactic acid, are also considered potential mechanisms.

Even in the presence of abundant oxygen, tumor cells also perform anaerobic respiration, that is, respiration that produces energy without the use of oxygen. This is known as the Warburg effect (33, 34). Anaerobic respiration is less efficient than normal aerobic respiration in terms of energy production. Therefore, cancer cells consume more glucose than normal for survival, and thus, energy production is unbalanced. It is believed that this mechanism contributes greatly to the increased energy expenditure observed in cancer patients.

Increased insulin resistance and abnormal metabolism. Cancer patients present with abnormalities in carbohydrate, lipid, and protein metabolism. In particular, glucose

metabolism and gluconeogenesis are enhanced in the liver (35, 36), and decreased sensitivity to insulin or insulin resistance is observed in the skeletal muscles. This impaired glucose tolerance is observed before a decrease in muscle mass becomes apparent (37). With regard to lipid metabolism, lipid mobilization in peripheral tissues is enhanced, and fat accumulation in the body is reduced in cachexia. In addition, fatty acids released from lipid tissues reduce insulin receptor sensitivity, thus leading to insulin resistance. The underlying mechanism of enhanced fatty acid release in cancer patients may be the increased lipoprotein lipase activity, which is involved in the release of fatty acids from adipose tissue. However, several aspects of this mechanism remain unclear (38).

We also note that protein metabolism disorders are changes directly related to the loss of muscle mass. In the muscles, proteolysis is increased while protein synthesis is suppressed in patients with cancer cachexia. In other words, there is an increase in the catabolic reaction and a decrease in the anabolic reaction, thus causing muscle atrophy. On the other hand, in the liver, protein synthesis is increased to counteract the increase in proteolysis in the skeletal muscles (39).

Changes in the neuroendocrine system. In cancer cachexia, blood levels of the anabolic hormone insulin-like growth factor-1 (IGF-1) may decrease, thereby causing muscle atrophy (40). It has also been reported that leptin concentrations, which regulate appetite, are decreased in cachexia, while blood concentrations of ghrelin are increased (41). Since leptin is mainly produced in the adipose tissue, the decrease in leptin concentration reflects a decrease in fat mass occurring due to cancer cachexia. However, in cancer cachexia, the assimilation of protein is decreased, and it is hypothesized that blood ghrelin concentrations increase as a compensatory reaction. Ghrelin, a hormone mainly produced in the stomach, is involved in the promotion of anabolic and growth factor secretion as well as in the enhancement of appetite. Its clinical application to cancer cachexia has previously been determined (42-44).

Diagnostic Criteria for Cancer Cachexia

The diagnostic criteria for cachexia were described in the guidelines published in both the United States and Europe in 2008 (Figure 2). When cachexia occurs due to underlying diseases, including cancer, chronic heart failure, COPD, chronic renal failure, chronic inflammation, septicemia, anorexia, inflammation, insulin resistance, sexual dysfunction, and anemia are frequently observed in the disease presentation. Moreover, tissue loss and muscle exhaustion can lead to weight loss, weakness, and fatigue. The diagnostic criteria for cachexia are defined as the presence of three or more of the following five items: 1) muscle weakness, 2) fatigue, 3) decreased appetite, 4) low lean body mass, and 5) abnormal biochemical data [*e.g.*, C-reactive protein (CRP), Hb (hemoglobin), and albumin (Alb) levels] (5) (Figure 2).

Non-pharmaceutical Therapies for Cancer Cachexia

Current medical guidelines recommend monitoring and performing preventive nutritional interventions in the case of pre-cachexia, in which weight loss is significant due to loss of appetite (45, 46).

Nourishment route. Even for cancer patients, oral and enteral nutrition is recommended, whichever is possible. Enteral nutrition is considered an auxiliary means of treatment based on the principles of nutritional management. The ESPEN guidelines, which mention nutritional pathways, designate oral and enteral nutrition as the first choice in the nutritional treatment of cancer patients. If oral intake is difficult, for example, due to the presence of head and neck or esophageal cancer, tube feeding from a gastric fistula *via* a nasogastric tube or percutaneous endoscopic gastrostomy is recommended (47). Enteral nutrition is recommended only when oral intake or dietary supplementation is not possible (20).

Energy dosing. The optimal energy dose for cancer patients is set to a normal nutritional level when the metabolic disorder is mild, and the dose is reduced when the metabolic disorder becomes severe. The REE of cancer patients varies depending on the type of cancer and the degree of progression (48, 49). According to the ESPEN guidelines, REE increases in cases with a high inflammatory response. In general, the total energy expenditure (TEE) of cancer patients decreases due to a decrease in physical activity. This decrease in TEE is translated into changes in weight. A TEE of 25 kcal/kg/day is recommended. In addition, patients should actively refrain from nutritional administration at the end of cancer treatment.

Refractory cachexia is defined as a stage that does not respond to nutritional administration. It is considered appropriate to reduce the nutritional dose towards the terminal stage of cancer when metabolic disorders become severe. In the terminal stage of cancer, even if active nutrition is administered, nutrition is not used effectively and instead becomes an excess metabolic load that may be harmful to the body.

Infusion management at the end of life. In Japan, infusion is often performed for patients with decreased oral intake at the end of life. However, various metabolic disorders occur at the terminal stage of cancer, and infusion often leads to an increase in edema, pleural effusion, ascites, and airway secretions. When infusing at the end of life, it is important to comply with clinical recommendations regarding treatment indications and to take careful measures based on

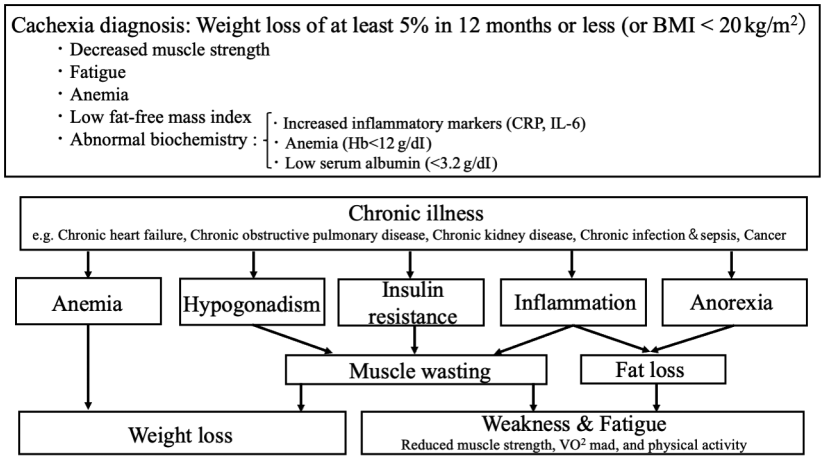

Figure 2. *Diagnostic criteria for cachexia. This figure is a conceptual representation of the definition of cachexia. In particular, cachexia results from an adaptation to an underlying illness, such as cancer. The illness creates an environment that may be characterized by inflammation, loss of appetite or anorexia, low levels of testosterone and other anabolic hormones, and anemia. Decreased food intake and anorexia result in the loss of body and muscle mass. In addition, inflammation, insulin resistance, and low levels of anabolic hormones result in muscle wasting.*

the patient's and family's intentions. Infusion is generally judged to be beneficial to the patient at the end of life and is indicated if the patient or his/her family approves. Careful follow-up is required to maximize the benefits and minimize the risks of this intervention.

Nutrition therapy. Providing nutritional guidance, counseling, and health education to patients is thought to have a positive effect on their nutritional status and QOL (50-52). Because the patients and families are not aware of the importance of nutritional management, patients often have inadequate nutritional intake, which worsens their nutritional status. Thus, appropriate nutritional guidance from a doctor or a registered dietitian regarding dietary content, intake methods, and the use of dietary supplements is necessary (53, 54).

Exercise therapy. Patients with cancer are less physically active due to the confluence of various factors. Consequently, they are more likely to develop skeletal muscle atrophy due to the lack of exercise. Loss of muscle mass causes fatigue and creates a vicious cycle of reduced activity and further muscle atrophy. Moreover, anabolic stimulation by muscle contraction is required to maintain the body's protein at acceptable levels (55, 56). Thus, it is important for clinicians to recommend light exercises, such as walking, to prevent loss of muscle mass (50, 51). However, the effectiveness of exercise therapy has not been verified at the advanced stage of cachexia, and excessive exercise may lead to exhaustion when sufficient nutritional intake cannot be secured or when metabolic disorders are severe. This is burdensome for the patient and necessitates the administration of extra medical care (57-59).

Patients who can complete an exercise program can obtain complete physical function and a greatly improved QOL. Unfortunately, a high dropout rate is a substantial limitation of exercise therapy for cancer patients. Additionally, attending group interventions and/or high-intensity exercise prescriptions using recommended training equipment increases the number of hospital visits and causes a heavy burden on patients.

At present, there have been a few randomized controlled trials of non-pharmaceutical treatments, such as nutrition therapy and exercise therapy, in patients with cancer cachexia (60, 61). In one randomized controlled trial of patients with advanced cancer, nutritional therapy alone did not prove to be consistently effective in terms of the effects on body weight, survival, and other outcomes (62, 63). As mentioned above, nutritional support for cancer patients includes not only dietary interventions and infusions but also nutritional guidance and exercise therapy. Currently, it is difficult to address cachexia, which is a complex metabolic disorder syndrome. However, an effective multidisciplinary approach administered by the medical care team has been shown to delay the progression of this disorder and ultimately, improve the QOL and prognosis of cancer patients (64, 65).

Drug Treatment

Non-steroidal anti-inflammatory drugs. Although non-steroidal anti-inflammatory drugs are useful analgesic aids to medical narcotics, their single-agent administration-based anti-inflammatory effects have not been shown to improve

metabolism and nutritional status. However, these drugs may prevent the development of cachexia when used as a part of a multimodal treatment. Unfortunately, at present, these drugs are known to cause adverse events in cases of severe cachexia. Unnecessary administration should therefore be avoided.

Corticosteroids. Corticosteroids are powerful anti-inflammatory drugs that are often used together with progesterone preparations in the treatment of anorexia in cachexic patients in Europe and the United States. Corticosteroids demonstrated efficacious results with regard to maintaining body weight and QOL. However, because side effects occur at a high rate with long-term use, their indicated use is limited to end-of-life care (66, 67).

Anti-cytokine therapy. As the mechanism of cachexia has been gradually elucidated, attempts have been made to improve malnutrition caused by cachexia through the use of drugs and specialized nutrients. Because inflammatory cytokines play an important role in metabolic disorders and anorexia occurring within cachexia, treatments, such as anti-cytokine therapy, have been attempted in previous researches.

Eicosapentaenoic acid. In addition to its anti-inflammatory effects, eicosapentaenoic acid has been reported to reduce PIF production, inhibit skeletal muscle decomposition, and improve QOL in cachexia patients. In Japan, eicosapentaenoic acid is widely used to treat cancer patients with favorable results (68).

Branched-chain amino acids, L-carnitine, CoQ10. Branched-chain amino acids suppress protein breakdown and promote protein synthesis in the brain. Moreover, they also control the metabolism of pseudoneurotransmitters *in vivo* to improve "greed". It has been reported that L-carnitine promotes fatty acid metabolism at the cellular level when used in combination with coenzyme Q10 (CoQ10) and also improves the symptoms of anorexia (69). However, additional detailed studies on the effects of these various nutrients are necessary.

Gastrointestinal hypermotility drugs. Gastrointestinal hypermotility drugs, such as metoclopramide, are effective in treating appetite loss and gastrointestinal peristalsis in cancer patients, and their use is recommended within current medical guidelines. However, side effects and serious complications associated with these medications have been reported. Thus, these drugs should be used in compliance with the relevant indications.

Oral supplements. The use of oral supplements (ONS) is currently the first nutritional care strategy that is recommended for increasing oral nutritional intake (51, 70).

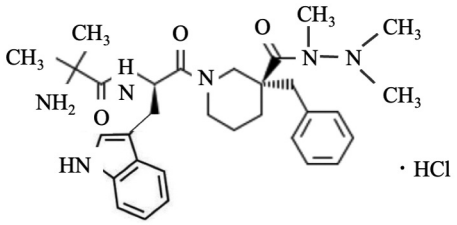

Figure 3. *The chemical structure of anamorelin hydrochloride*.

There has been an increase in the number of ONS listed in the National Health Insurance (NHI) price list. In addition, many nutritional supplements, which are treated as food according to national regulations, are sold over the counter. The wide variety of ONS available as prescriptions or in the general market includes 1) supplements with different flavors, 2) supplements with fortified nutrients, high nutrient concentrations, and/or high protein levels, and 3) supplements with different textures. To improve compliance with and effective administration of ONS, it is necessary to educate patients regarding the appropriate method of intake and to provide a sufficient explanation of the significance of these supplements.

Anamorelin hydrochloride. Anamorelin hydrochloride is an orally administered low molecular weight drug that exhibits ghrelin-like action *via* growth hormone secretagogue receptor 1a (GHS-R1a), which is a G-protein coupled receptor that is distributed in many tissues including the pituitary gland, hypothalamus, stomach, pancreas, and myocardium (Figure 3) (71-75). In transgenic rats over-expressing the antisense GHS receptor gene and with attenuated expression of the GHS receptor in the arcuate nucleus, GHS-R1a secretes growth hormone (GH) from the pituitary gland and hypothalamus. This mechanism is involved in increasing appetite (76).

Ghrelin is a peptide hormone identified as an endogenous agonist of GHS-R1a. In addition to promoting GH secretion and appetite, ghrelin also promotes weight gain, fat production, glucose metabolism suppression, gastrointestinal motility regulation, and cytokine production. Ghrelin is thought to play an important role in maintaining the homeostasis of *in vivo* energy metabolism by antagonizing leptin-like signals that suppress appetite (72, 77-81). However, the elimination half-life of ghrelin in human plasma is as short as 10 minutes, and the route of administration is limited to intravenous or subcutaneous routes (82).

In contrast, anamorelin hydrochloride is a ghrelin-like agent that has an elimination half-life of approximately nine hours and can be administered orally. Anamorelin hydrochloride promotes GH secretion in the pituitary gland

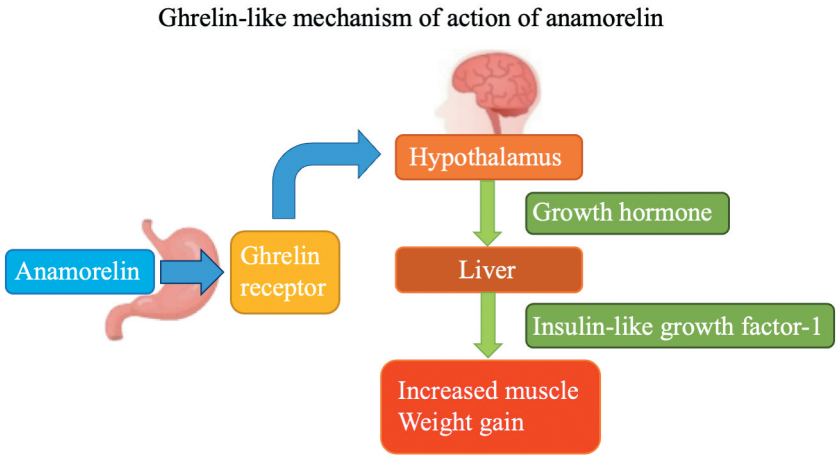

Figure 4. *A depiction of anamorelin's ghrelin-like mechanism of action. Anamorelin activates growth hormone secretagogue receptor 1a (GHS-R1a), which in turn promotes growth hormone (GH) secretion in the pituitary gland and increases appetite in the hypothalamus. GH secreted by the pituitary gland leads to insulin-like growth factor-1 (IGF-1) secretion from the liver and promotes muscle protein synthesis, thereby leading to increased muscle mass and weight.*

and increases appetite in the hypothalamus. GH secreted from the pituitary gland secretes insulin-like growth factor-1 (IGF-1) from the liver and promotes muscle protein synthesis thus leading to an increase in muscle mass and weight in humans (Figure 4) (83).

Anamorelin hydrochloride was introduced in Japan in January 2021 after undergoing three domestic and international trials (ONO-7643-04, ONO-7643-05, HT-ANAM-301/302) (84-87). After its introduction, manufacturing and marketing approval for cancer cachexia was obtained from regulatory bodies. Anamorelin hydrochloride is the only approved therapeutic agent that can renew appetite *via* oral administration.

Conclusion

This review details the current state of knowledge regarding cancer cachexia and its latest treatments. Anamorelin hydrochloride, which is an endogenous ligand for GHS-R1a that has the same pharmacological action as ghrelin, was developed for the treatment of weight loss accompanied by a loss of appetite. It is also approved for treating cancer-associated cachexia. Since this medication has emerged as a therapeutic agent, cancer cachexia treatment has entered a new era. It is strongly believed that this new treatment method will continue to improve cancer cachexia symptomology as well as enhance treatment results in cancer patients.

Conflicts of Interest

The Authors have no actual or potential conflicts of interest to declare in relation to this study.

Authors' Contributions

Conceptualization and design: H.W. and T.O. Literature review/writing/revision: H.W. and T.O. All Authors have read and agreed to the published version of the manuscript.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Number JP20K08997 and JP22H04990.

References

1 Wigmore SJ, Plester CE, Ross JA and Fearon KC: Contribution of anorexia and hypermetabolism to weight loss in anicteric patients with pancreatic cancer. Br J Surg *84(2)*: 196-197, 1997. PMID: 9052431.

2 Argilés JM, Busquets S, Felipe A and López-Soriano FJ: Molecular mechanisms involved in muscle wasting in cancer and ageing: cachexia *versus* sarcopenia. Int J Biochem Cell Biol *37(5)*: 1084-1104, 2005. PMID: 15743680. DOI: 10.1016/j.biocel.2004.10.003

3 Esper DH and Harb WA: The cancer cachexia syndrome: a review of metabolic and clinical manifestations. Nutr Clin Pract *20(4)*: 369-376, 2005. PMID: 16207677. DOI: 10.1177/011542650 5020004369

4 Hankin JH: Development of a diet history questionnaire for studies of older persons. Am J Clin Nutr *50(5 Suppl)*: 1121-7; discussion 1231-5, 1989. PMID: 2683719. DOI: 10.1093/ajcn/50.5.1121

5 Fujii H, Makiyama A, Iihara H, Okumura N, Yamamoto S, Imai T, Arakawa S, Kobayashi R, Tanaka Y, Yoshida K and Suzuki A: Cancer cachexia reduces the efficacy of nivolumab treatment in patients with advanced gastric cancer. Anticancer Res *40(12)*: 7067-7075, 2020. PMID: 33288604. DOI: 10.21873/anticanres. 14734

6 Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, Jatoi A, Kalantar-Zadeh K, Lochs H, Mantovani G, Marks D, Mitch WE, Muscaritoli M, Najand A, Ponikowski P, Rossi Fanelli F, Schambelan M, Schols A, Schuster M, Thomas D, Wolfe R and Anker SD: Cachexia: a new definition. Clin Nutr *27(6)*: 793-799, 2008. PMID: 18718696. DOI: 10.1016/j.clnu.2008.06.013

7 Argilés JM, Busquets S, Stemmler B and López-Soriano FJ: Cachexia and sarcopenia: mechanisms and potential targets for intervention. Curr Opin Pharmacol *22*: 100-106, 2015. PMID: 25974750. DOI: 10.1016/j.coph.2015.04.003

8 Argilés JM, Busquets S, Stemmler B and López-Soriano FJ: Cancer cachexia: understanding the molecular basis. Nat Rev Cancer *14(11)*: 754-762, 2014. PMID: 25291291. DOI: 10.1038/nrc3829

9 Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, Cohen MH, Douglass HO Jr, Engstrom PF, Ezdinli EZ, Horton J, Johnson GJ, Moertel CG, Oken MM, Perlia C, Rosenbaum C, Silverstein MN, Skeel RT, Sponzo RW and Tormey DC: Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med *69(4)*: 491-497, 1980. PMID: 7424938. DOI: 10.1016/s0149-2918(05)80001-3

10 Farkas J, von Haehling S, Kalantar-Zadeh K, Morley JE, Anker SD and Lainscak M: Cachexia as a major public health problem: frequent, costly, and deadly. J Cachexia Sarcopenia Muscle *4(3)*: 173-178, 2013. PMID: 23539127. DOI: 10.1007/s13539-013-0105-y

11 Tisdale MJ: Pathogenesis of cancer cachexia. J Support Oncol *1(3)*: 159-168, 2003. PMID: 15334872.

12 Acharyya S, Butchbach ME, Sahenk Z, Wang H, Saji M, Carathers M, Ringel MD, Skipworth RJ, Fearon KC, Hollingsworth MA, Muscarella P, Burghes AH, Rafael-Fortney JA and Guttridge DC: Dystrophin glycoprotein complex dysfunction: a regulatory link between muscular dystrophy and cancer cachexia. Cancer Cell *8(5)*: 421-432, 2005. PMID: 16286249. DOI: 10.1016/j.ccr.2005.10.004

13 Fearon KC: Cancer cachexia: developing multimodal therapy for a multidimensional problem. Eur J Cancer *44(8)*: 1124-1132, 2008. PMID: 18375115. DOI: 10.1016/j.ejca.2008.02.033

14 Tisdale MJ: Mechanisms of cancer cachexia. Physiol Rev *89(2)*: 381-410, 2009. PMID: 19342610. DOI: 10.1152/physrev.00016.2008

15 Brennan MF: Uncomplicated starvation versus cancer cachexia. Cancer Res *37(7 Pt 2)*: 2359-2364, 1977. PMID: 861953.

16 Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, Strasser F, Thoresen L, Jagoe RT, Chasen M, Lundholm K, Bosaeus I, Fearon KH and Baracos VE: Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol *33(1)*: 90-99, 2015. PMID: 25422490. DOI: 10.1200/JCO.2014.56.1894

17 Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, Boirie Y, Bosaeus I, Cederholm T, Costelli P, Fearon KC, Laviano A, Maggio M, Rossi Fanelli F, Schneider SM, Schols A and Sieber CC: Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr *29(2)*: 154-159, 2010. PMID: 20060626. DOI: 10.1016/j.clnu.2009.12.004

18 Bozzetti F and Mariani L: Defining and classifying cancer cachexia: a proposal by the SCRINIO Working Group. JPEN J Parenter Enteral Nutr *33(4)*: 361-367, 2009. PMID: 19109514. DOI: 10.1177/0148607108325076

19 Bennani-Baiti N and Walsh D: What is cancer anorexia-cachexia syndrome? A historical perspective. J R Coll Physicians Edinb *39(3)*: 257-262, 2009. PMID: 20608345.

20 Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S and Baracos VE: Definition and classification of cancer cachexia: an international consensus. Lancet Oncol *12(5)*: 489-495, 2011. PMID: 21296615. DOI: 10.1016/S1470-2045(10)70218-7

21 Radbruch L, Elsner F, Trottenberg P, Strasser F, Baracos V and Fearon K: Clinical practice guidelines on cancer cachexia in advanced cancer patients with a focus on refractory cachexia: European Clinical Guidelines. Department of Palliative Medicine/European Palliative Care Research Collaborative, 2010.

22 Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, Compher C, Correia I, Higashiguchi T, Holst M, Jensen GL, Malone A, Muscaritoli M, Nyulasi I, Pirlich M, Rothenberg E, Schindler K, Schneider SM, de van der Schueren MA, Sieber C, Valentini L, Yu JC, Van Gossum A and Singer P: ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr *36(1)*: 49-64, 2017. PMID: 27642056. DOI: 10.1016/j.clnu.2016.09.004

23 Aoyagi T, Terracina KP, Raza A, Matsubara H and Takabe K: Cancer cachexia, mechanism and treatment. World J Gastrointest Oncol *7(4)*: 17-29, 2015. PMID: 25897346. DOI: 10.4251/wjgo.v7.i4.17

24 Aapro M, Arends J, Bozzetti F, Fearon K, Grunberg SM, Herrstedt J, Hopkinson J, Jacquelin-Ravel N, Jatoi A, Kaasa S, Strasser F and ESMO (European School of Medical Oncology): Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force. Ann Oncol *25(8)*: 1492-1499, 2014. PMID: 24569913. DOI: 10.1093/annonc/mdu085

25 Blauwhoff-Buskermolen S, de van der Schueren MA, Verheul HM and Langius JA: 'Pre-cachexia': a non-existing phenomenon in cancer? Ann Oncol *25(8)*: 1668-1669, 2014. PMID: 24827129. DOI: 10.1093/annonc/mdu178

26 Kubo Y, Naito T, Mori K, Osawa G and Aruga E: Skeletal muscle loss and prognosis of breast cancer patients. Support Care Cancer *25(7)*: 2221-2227, 2017. PMID: 28204990. DOI: 10.1007/s00520-017-3628-5

27 Baracos VE, Martin L, Korc M, Guttridge DC and Fearon KCH: Cancer-associated cachexia. Nat Rev Dis Primers *4*: 17105, 2018. PMID: 29345251. DOI: 10.1038/nrdp.2017.105

28 Bonetto A, Aydogdu T, Kunzevitzky N, Guttridge DC, Khuri S, Koniaris LG and Zimmers TA: STAT3 activation in skeletal muscle links muscle wasting and the acute phase response in cancer cachexia. PLoS One *6(7)*: e22538, 2011. PMID: 21799891. DOI: 10.1371/journal.pone.0022538

29 Bosaeus I, Daneryd P and Lundholm K: Dietary intake, resting energy expenditure, weight loss and survival in cancer patients. J Nutr *132(11 Suppl)*: 3465S-3466S, 2002. PMID: 12421871. DOI: 10.1093/jn/132.11.3465S

30 Skipworth RJ, Stewart GD, Dejong CH, Preston T and Fearon KC: Pathophysiology of cancer cachexia: much more than host-tumour interaction? Clin Nutr *26(6)*: 667-676, 2007. PMID: 17507116. DOI: 10.1016/j.clnu.2007.03.011

31 Bianchi A, Bruce J, Cooper AL, Childs C, Kohli M, Morris ID, Morris-Jones P and Rothwell NJ: Increased brown adipose tissue

activity in children with malignant disease. Horm Metab Res *21(11)*: 640-641, 1989. PMID: 2591881. DOI: 10.1055/s-2007-1009308

32 Collins P, Bing C, McCulloch P and Williams G: Muscle UCP-3 mRNA levels are elevated in weight loss associated with gastrointestinal adenocarcinoma in humans. Br J Cancer *86(3)*: 372-375, 2002. PMID: 11875702. DOI: 10.1038/sj.bjc.6600074

33 Warburg O, Posener K and Negelein E: The metabolism of cancer cells. Biochem Z *152*: 319-344, 1924.

34 Warburg O: On the origin of cancer cells. Science *123(3191)*: 309-314, 1956. PMID: 13298683. DOI: 10.1126/science.123.3191.309

35 Cersosimo E, Pisters PW, Pesola G, Rogatko A, Vydelingum NA, Bajorunas D and Brennan MF: The effect of graded doses of insulin on peripheral glucose uptake and lactate release in cancer cachexia. Surgery *109(4)*: 459-467, 1991. PMID: 2008651.

36 Dodesini AR, Benedini S, Terruzzi I, Sereni LP and Luzi L: Protein, glucose and lipid metabolism in the cancer cachexia: A preliminary report. Acta Oncol *46(1)*: 118-120, 2007. PMID: 17438714. DOI: 10.1080/02841860600791491

37 Rofe AM, Bourgeois CS, Coyle P, Taylor A and Abdi EA: Altered insulin response to glucose in weight-losing cancer patients. Anticancer Res *14(2B)*: 647-650, 1994. PMID: 8010722.

38 Vlassara H, Spiegel RJ, San Doval D and Cerami A: Reduced plasma lipoprotein lipase activity in patients with malignancy-associated weight loss. Horm Metab Res *18(10)*: 698-703, 1986. PMID: 3781475. DOI: 10.1055/s-2007-1012410

39 Pisters PW and Pearlstone DB: Protein and amino acid metabolism in cancer cachexia: investigative techniques and therapeutic interventions. Crit Rev Clin Lab Sci *30(3)*: 223-272, 1993. PMID: 8260072. DOI: 10.3109/10408369309084669

40 Biolo G, Cederholm T and Muscaritoli M: Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: from sarcopenic obesity to cachexia. Clin Nutr *33(5)*: 737-748, 2014. PMID: 24785098. DOI: 10.1016/j.clnu.2014.03.007

41 Garcia JM, Garcia-Touza M, Hijazi RA, Taffet G, Epner D, Mann D, Smith RG, Cunningham GR and Marcelli M: Active ghrelin levels and active to total ghrelin ratio in cancer-induced cachexia. J Clin Endocrinol Metab *90(5)*: 2920-2926, 2005. PMID: 15713718. DOI: 10.1210/jc.2004-1788

42 Shioda S, Takenoya F, Yagi M, Wang L, Hori Y and Kageyama H: Neural networks of several novel neuropeptides involved in feeding regulation. Nutrition *24(9)*: 848-853, 2008. PMID: 18725082. DOI: 10.1016/j.nut.2008.06.016

43 Molfino A, Formiconi A, Rossi Fanelli F and Muscaritoli M: Ghrelin: from discovery to cancer cachexia therapy. Curr Opin Clin Nutr Metab Care *17(5)*: 471-476, 2014. PMID: 24905862. DOI: 10.1097/MCO.0000000000000075

44 Akamizu T and Kangawa K: Emerging results of anticatabolic therapy with ghrelin. Curr Opin Clin Nutr Metab Care *10(3)*: 278-283, 2007. PMID: 17414495. DOI: 10.1097/MCO.0b013e3280fa8208

45 Bozzetti F, Arends J, Lundholm K, Micklewright A, Zurcher G, Muscaritoli M and ESPEN: ESPEN Guidelines on Parenteral Nutrition: non-surgical oncology. Clin Nutr *28(4)*: 445-454, 2009. PMID: 19477052. DOI: 10.1016/j.clnu.2009.04.011

46 Arends J, Bodoky G, Bozzetti F, Fearon K, Muscaritoli M, Selga G, van Bokhorst-de van der Schueren MA, von Meyenfeldt M, DGEM (German Society for Nutritional Medicine), Zürcher G, Fietkau R, Aulbert E, Frick B, Holm M, Kneba M, Mestrom HJ, Zander A and ESPEN (European Society for Parenteral and Enteral Nutrition): ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology. Clin Nutr *25(2)*: 245-259, 2006. PMID: 16697500. DOI: 10.1016/j.clnu.2006.01.020

47 Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, Garry PJ and Lindeman RD: Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol *147(8)*: 755-763, 1998. PMID: 9554417. DOI: 10.1093/oxfordjournals.aje.a009520

48 Jatoi A: Weight loss in patients with advanced cancer: effects, causes, and potential management. Curr Opin Support Palliat Care *2(1)*: 45-48, 2008. PMID: 18685394. DOI: 10.1097/SPC.0b013e3282f4b734

49 Ravasco P, Monteiro-Grillo I and Camilo M: Colorectal cancer: intrinsic characteristics modulate cancer energy expenditure and the risk of cachexia. Cancer Invest *25(5)*: 308-314, 2007. PMID: 17661205. DOI: 10.1080/07357900701208873

50 Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, Cederholm T, Cruz-Jentoft A, Krznariç Z, Nair KS, Singer P, Teta D, Tipton K and Calder PC: Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr *33(6)*: 929-936, 2014. PMID: 24814383. DOI: 10.1016/j.clnu.2014.04.007

51 Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, Erickson N, Laviano A, Lisanti MP, Lobo DN, McMillan DC, Muscaritoli M, Ockenga J, Pirlich M, Strasser F, de van der Schueren M, Van Gossum A, Vaupel P and Weimann A: ESPEN expert group recommendations for action against cancer-related malnutrition. Clin Nutr *36(5)*: 1187-1196, 2017. PMID: 28689670. DOI: 10.1016/j.clnu.2017.06.017

52 Lee JLC, Leong LP and Lim SL: Nutrition intervention approaches to reduce malnutrition in oncology patients: a systematic review. Support Care Cancer *24(1)*: 469-480, 2016. PMID: 26404858. DOI: 10.1007/s00520-015-2958-4

53 Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley JE, Phillips S, Sieber C, Stehle P, Teta D, Visvanathan R, Volpi E and Boirie Y: Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. J Am Med Dir Assoc *14(8)*: 542-559, 2013. PMID: 23867520. DOI: 10.1016/j.jamda.2013.05.021

54 Hanna RM, Ghobry L, Wassef O, Rhee CM and Kalantar-Zadeh K: A practical approach to nutrition, protein-energy wasting, sarcopenia, and cachexia in patients with chronic kidney disease. Blood Purif *49(1-2)*: 202-211, 2020. PMID: 31851983. DOI: 10.1159/000504240

55 Biolo G, Ciocchi B, Lebenstedt M, Barazzoni R, Zanetti M, Platen P, Heer M and Guarnieri G: Short-term bed rest impairs amino acid-induced protein anabolism in humans. J Physiol *558(Pt 2)*: 381-388, 2004. PMID: 15131238. DOI: 10.1113/jphysiol.2004.066365

56 Wood NR, Garritson J, Mathias A, Haughian JM and Hayward R: Moderate intensity endurance and resistance exercise attenuates cachexia in tumor-bearing mice. Anticancer Res *42(1)*: 397-405, 2022. PMID: 34969750. DOI: 10.21873/anticanres.15498

57 Oldervoll LM, Loge JH, Lydersen S, Paltiel H, Asp MB, Nygaard UV, Oredalen E, Frantzen TL, Lesteberg I, Amundsen L, Hjermstad MJ, Haugen DF, Paulsen Ø and Kaasa S: Physical exercise for cancer patients with advanced disease: a randomized

controlled trial. Oncologist *16(11)*: 1649-1657, 2011. PMID: 21948693. DOI: 10.1634/theoncologist.2011-0133

58 Adamsen L, Quist M, Andersen C, Møller T, Herrstedt J, Kronborg D, Baadsgaard MT, Vistisen K, Midtgaard J, Christiansen B, Stage M, Kronborg MT and Rørth M: Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. BMJ *339*: b3410, 2009. PMID: 19826172. DOI: 10.1136/bmj.b3410

59 Rummans TA, Clark MM, Sloan JA, Frost MH, Bostwick JM, Atherton PJ, Johnson ME, Gamble G, Richardson J, Brown P, Martensen J, Miller J, Piderman K, Huschka M, Girardi J and Hanson J: Impacting quality of life for patients with advanced cancer with a structured multidisciplinary intervention: a randomized controlled trial. J Clin Oncol *24(4)*: 635-642, 2006. PMID: 16446335. DOI: 10.1200/JCO.2006.06.209

60 Balstad TR, Solheim TS, Strasser F, Kaasa S and Bye A: Dietary treatment of weight loss in patients with advanced cancer and cachexia: a systematic literature review. Crit Rev Oncol Hematol *91(2)*: 210-221, 2014. PMID: 24703549. DOI: 10.1016/j.critrevonc.2014.02.005

61 Grande AJ, Silva V and Maddocks M: Exercise for cancer cachexia in adults: Executive summary of a Cochrane Collaboration systematic review. J Cachexia Sarcopenia Muscle *6(3)*: 208-211, 2015. PMID: 26401466. DOI: 10.1002/jcsm.12055

62 Baldwin C, Spiro A, McGough C, Norman AR, Gillbanks A, Thomas K, Cunningham D, O'Brien M and Andreyev HJ: Simple nutritional intervention in patients with advanced cancers of the gastrointestinal tract, non-small cell lung cancers or mesothelioma and weight loss receiving chemotherapy: a randomised controlled trial. J Hum Nutr Diet *24(5)*: 431-440, 2011. PMID: 21733143. DOI: 10.1111/j.1365-277X.2011.01189.x

63 Bourdel-Marchasson I, Blanc-Bisson C, Doussau A, Germain C, Blanc JF, Dauba J, Lahmar C, Terrebonne E, Lecaille C, Ceccaldi J, Cany L, Lavau-Denes S, Houede N, Chomy F, Durrieu J, Soubeyran P, Senesse P, Chene G and Fonck M: Nutritional advice in older patients at risk of malnutrition during treatment for chemotherapy: a two-year randomized controlled trial. PLoS One *9(9)*: e108687, 2014. PMID: 25265392. DOI: 10.1371/journal.pone.0108687

64 Del Fabbro E: More is better: a multimodality approach to cancer cachexia. Oncologist *15(2)*: 119-121, 2010. PMID: 20133501. DOI: 10.1634/theoncologist.2010-0019

65 Mantovani G, Macciò A, Madeddu C, Serpe R, Massa E, Dessì M, Panzone F and Contu P: Randomized phase III clinical trial of five different arms of treatment in 332 patients with cancer cachexia. Oncologist *15(2)*: 200-211, 2010. PMID: 20156909. DOI: 10.1634/theoncologist.2009-0153

66 Mantovani G, Macciò A, Esu S, Lai P, Santona MC, Massa E, Dessì D, Melis GB and Del Giacco GS: Medroxyprogesterone acetate reduces the *in vitro* production of cytokines and serotonin involved in anorexia/cachexia and emesis by peripheral blood mononuclear cells of cancer patients. Eur J Cancer *33(4)*: 602-607, 1997. PMID: 9274442. DOI: 10.1016/s0959-8049(96)00486-8

67 Lundholm K, Körner U, Gunnebo L, Sixt-Ammilon P, Fouladiun M, Daneryd P and Bosaeus I: Insulin treatment in cancer cachexia: effects on survival, metabolism, and physical functioning. Clin Cancer Res *13(9)*: 2699-2706, 2007. PMID: 17473202. DOI: 10.1158/1078-0432.CCR-06-2720

68 Tisdale MJ and Beck SA: Inhibition of tumour-induced lipolysis *in vitro* and cachexia and tumour growth *in vivo* by eicosapentaenoic acid. Biochem Pharmacol *41(1)*: 103-107, 1991. PMID: 1846070. DOI: 10.1016/0006-2952(91)90016-x

69 Gramignano G, Lusso MR, Madeddu C, Massa E, Serpe R, Deiana L, Lamonica G, Dessì M, Spiga C, Astara G, Macciò A and Mantovani G: Efficacy of l-carnitine administration on fatigue, nutritional status, oxidative stress, and related quality of life in 12 advanced cancer patients undergoing anticancer therapy. Nutrition *22(2)*: 136-145, 2006. PMID: 16459226. DOI: 10.1016/j.nut.2005.06.003

70 Rozentryt P, von Haehling S, Lainscak M, Nowak JU, Kalantar-Zadeh K, Polonski L and Anker SD: The effects of a high-caloric protein-rich oral nutritional supplement in patients with chronic heart failure and cachexia on quality of life, body composition, and inflammation markers: a randomized, double-blind pilot study. J Cachexia Sarcopenia Muscle *1(1)*: 35-42, 2010. PMID: 21475692. DOI: 10.1007/s13539-010-0008-0

71 Gnanapavan S, Kola B, Bustin SA, Morris DG, McGee P, Fairclough P, Bhattacharya S, Carpenter R, Grossman AB and Korbonits M: The tissue distribution of the mRNA of ghrelin and subtypes of its receptor, GHS-R, in humans. J Clin Endocrinol Metab *87(6)*: 2988, 2002. PMID: 12050285. DOI: 10.1210/jcem.87.6.8739

72 Nogueiras R, Perez-Tilve D, Wortley KE and Tschöp M: Growth hormone secretagogue (ghrelin-) receptors – a complex drug target for the regulation of body weight. CNS Neurol Disord Drug Targets *5(3)*: 335-343, 2006. PMID: 16787234. DOI: 10.2174/187152706777452227

73 Wellman M and Abizaid A: Growth hormone secretagogue receptor dimers: a new pharmacological target. eNeuro *2(2)*: ENEURO.0053-14.2015, 2015. PMID: 26464979. DOI: 10.1523/ENEURO.0053-14.2015

74 Ueberberg B, Unger N, Saeger W, Mann K and Petersenn S: Expression of ghrelin and its receptor in human tissues. Horm Metab Res *41(11)*: 814-821, 2009. PMID: 19670151. DOI: 10.1055/s-0029-1233462

75 Shuto Y, Shibasaki T, Otagiri A, Kuriyama H, Ohata H, Tamura H, Kamegai J, Sugihara H, Oikawa S and Wakabayashi I: Hypothalamic growth hormone secretagogue receptor regulates growth hormone secretion, feeding, and adiposity. J Clin Invest *109(11)*: 1429-1436, 2002. PMID: 12045256. DOI: 10.1172/JCI13300

76 Smith RG, Cheng K, Schoen WR, Pong SS, Hickey G, Jacks T, Butler B, Chan WW, Chaung LY and Judith F: A nonpeptidyl growth hormone secretagogue. Science *260(5114)*: 1640-1643, 1993. PMID: 8503009. DOI: 10.1126/science.8503009

77 Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H and Kangawa K: Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature *402(6762)*: 656-660, 1999. PMID: 10604470. DOI: 10.1038/45230

78 Inui A: Ghrelin: an orexigenic and somatotrophic signal from the stomach. Nat Rev Neurosci *2(8)*: 551-560, 2001. PMID: 11483998. DOI: 10.1038/35086018

79 Dixit VD, Schaffer EM, Pyle RS, Collins GD, Sakthivel SK, Palaniappan R, Lillard JW Jr and Taub DD: Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. J Clin Invest *114(1)*: 57-66, 2004. PMID: 15232612. DOI: 10.1172/JCI21134

80 Nagaya N, Uematsu M, Kojima M, Ikeda Y, Yoshihara F, Shimizu W, Hosoda H, Hirota Y, Ishida H, Mori H and Kangawa K:

Chronic administration of ghrelin improves left ventricular dysfunction and attenuates development of cardiac cachexia in rats with heart failure. Circulation *104(12)*: 1430-1435, 2001. PMID: 11560861. DOI: 10.1161/hc3601.095575

81 Yanagi S, Sato T, Kangawa K and Nakazato M: The homeostatic force of ghrelin. Cell Metab *27(4)*: 786-804, 2018. PMID: 29576534. DOI: 10.1016/j.cmet.2018.02.008

82 Akamizu T, Takaya K, Irako T, Hosoda H, Teramukai S, Matsuyama A, Tada H, Miura K, Shimizu A, Fukushima M, Yokode M, Tanaka K and Kangawa K: Pharmacokinetics, safety, and endocrine and appetite effects of ghrelin administration in young healthy subjects. Eur J Endocrinol *150(4)*: 447-455, 2004. PMID: 15080773. DOI: 10.1530/eje.0.1500447

83 Katakami N, Uchino J, Yokoyama T, Naito T, Kondo M, Yamada K, Kitajima H, Yoshimori K, Sato K, Saito H, Aoe K, Tsuji T, Takiguchi Y, Takayama K, Komura N, Takiguchi T and Eguchi K: Anamorelin (ONO-7643) for the treatment of patients with non-small cell lung cancer and cachexia: Results from a randomized, double-blind, placebo-controlled, multicenter study of Japanese patients (ONO-7643-04). Cancer *124(3)*: 606-616, 2018. PMID: 29205286. DOI: 10.1002/cncr.31128

84 Pietra C, Takeda Y, Tazawa-Ogata N, Minami M, Yuanfeng X, Duus EM and Northrup R: Anamorelin HCl (ONO-7643), a novel ghrelin receptor agonist, for the treatment of cancer anorexia-cachexia syndrome: preclinical profile. J Cachexia Sarcopenia Muscle *5(4)*: 329-337, 2014. PMID: 25267366. DOI: 10.1007/s13539-014-0159-5

85 Hamauchi S, Furuse J, Takano T, Munemoto Y, Furuya K, Baba H, Takeuchi M, Choda Y, Higashiguchi T, Naito T, Muro K, Takayama K, Oyama S, Takiguchi T, Komura N and Tamura K: A multicenter, open-label, single-arm study of anamorelin (ONO-7643) in advanced gastrointestinal cancer patients with cancer cachexia. Cancer *125(23)*: 4294-4302, 2019. PMID: 31415709. DOI: 10.1002/cncr.32406

86 Temel JS, Abernethy AP, Currow DC, Friend J, Duus EM, Yan Y and Fearon KC: Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. Lancet Oncol *17(4)*: 519-531, 2016. PMID: 26906526. DOI: 10.1016/S1470-2045(15)00558-6

87 Currow D, Temel JS, Abernethy A, Milanowski J, Friend J and Fearon KC: ROMANA 3: a phase 3 safety extension study of anamorelin in advanced non-small-cell lung cancer (NSCLC) patients with cachexia. Ann Oncol *28(8)*: 1949-1956, 2017. PMID: 28472437. DOI: 10.1093/annonc/mdx192

Received November 23, 2022
Revised December 5, 2022
Accepted December 6, 2022