Asia-Pacific Journal of Oncology Nursing 10 (2023) 100280

Contents lists available at ScienceDirect

Asia-Pacific Journal of Oncology Nursing

journal homepage: www.apjon.org

Review

The role of pharmacists in multimodal cancer cachexia care

Hironori Fujii *, Yunami Yamada, Hirotoshi Iihara, Akio Suzuki

Department of Pharmacy, Gifu University Hospital, Gifu, Japan

ARTICLE INFO

Keywords:
Cancer cachexia
Management
Multidisciplinary
Anamorelin
Pharmacist

ABSTRACT

Cancer cachexia is a complex syndrome, and multidisciplinary management has the potential to improve patient outcomes and efficiency of care. Multidisciplinary management consists primarily of exercise, nutrition, and pharmacotherapy. The pharmacist's role in cancer cachexia is to contribute to appropriate pharmacotherapy practices. For example, anamorelin is an oral drug with ghrelin-like effects that may improve the pathogenesis of cancer cachexia by stimulating appetite and increasing food intake and body weight. Many patients with cancer cachexia are under treatment with anticancer agents, and pharmacists need to determine whether symptoms such as anorexia and nausea are due to cancer cachexia or anticancer agents. Based on that determination, they are then expected to suggest supportive care to the physician. Provision of multidisciplinary care for cancer cachexia requires communication with not only physicians but also with nurses, dietitians, and other professionals so that nutritional therapy can be provided at the time cachexia is detected. However, the role of pharmacists in the management of cancer cachexia is not well established, and there is no evidence that pharmacist interventions are of benefit to patients. In this article, to contribute to the treatment of cancer cachexia by multidisciplinary care, we describe the role of pharmacists in cancer cachexia as currently practiced at our hospital. We also consider future challenges to this type of multidisciplinary care. Evidence concerning multidisciplinary treatment of cancer cachexia is scarce, including therapeutic agents, and there is a current lack of collaboration among medical professionals and education in cancer cachexia. Solving these problems will require efforts in the practice and evaluation of treatment for cancer cachexia.

Introduction

Cancer cachexia is defined as "a multifactorial syndrome characterized by a persistent loss of skeletal muscle mass (with or without fat loss) that cannot be completely reversed by normal nutritional support and leads to progressive functional disability".[1] Cancer cachexia not only leads to decreased quality of life (QOL) due to weight loss and anorexia but also decreases the therapeutic efficacy of cancer chemotherapy.[2–7] Recent retrospective observational studies of patients with lung[5,6] and gastric cancer[7] treated with immune chuck point inhibitors reported that patients with cachexia had shorter overall survival than those without.

According to the European Palliative Care Research Collaborative definition,[1] cancer cachexia is classified into three categories: "pre-cachexia phase", "cachexia phase", and "refractory cachexia phase". In pre-cachexia, early clinical manifestations include anorexia and glucose intolerance and involuntary weight loss (< 5%). In cachexia, significant weight loss (more than 5% loss of stable body weight over the past 6 months; a body mass index less than 20 kg/m^2 and ongoing weight loss of more than 2%, or sarcopenia and ongoing weight loss of more than 2%) is seen, as well as decreased food intake, fatigue, and muscle weakness due to systemic inflammation. In refractory cachexia, active catabolism by the tumor occurs, with little response to nutritional therapy or anticancer agents.[8,9] Refractory cachexia is characterized by low performance status (World Health Organization score 3 or 4) and a life expectancy of less than 3 months. Accordingly, multidisciplinary early intervention (e.g., drugs, exercise, nutrition, and psychotherapy) is required to treat cancer cachexia before it becomes refractory cachexia.

The role of the pharmacist in clinical practice is not only to dispense drugs as prescribed. A second important role is to estimate the patient's renal and hepatic function based on the results of biochemical tests and to suggest to the physician the appropriate dosage or change to an appropriate drug. Pharmacists should evaluate the efficacy and safety of drugs and suggest additional supportive care when side effects occur (especially with anticancer drugs).[10] However, the role of pharmacists in the management of cancer cachexia is not well established, and there is no evidence that pharmacist interventions are of benefit in these patients.

* *Corresponding author.*
E-mail address: h_fujii@gifu-u.ac.jp (H. Fujii).

https://doi.org/10.1016/j.apjon.2023.100280
Received 24 April 2023; Accepted 27 July 2023

In our hospital (Gifu University Hospital in Japan), pharmacists manage chemotherapy for patients having cancer in the outpatient chemotherapy unit and focus on the management of cancer cachexia in collaboration with physicians, nurses, and other medical staff. In this article, we describe the role of pharmacists in cancer cachexia (Table 1) as currently practiced as well as future challenges, with the aim of contributing to the treatment of cancer cachexia by multidisciplinary care.

The role of pharmacists for patients with cancer cachexia

First, we describe the role of pharmacists in outpatient cancer chemotherapy at our hospital. The pharmacist provides pharmaceutical care services (PCSs) for all patients having cancer and receiving outpatient chemotherapy. In the PCSs, the pharmacists check regimen contents, including anticancer drug dosages and administration, and adverse events experienced by patients during chemotherapy. When any adverse events happen, we propose prescriptions for countermeasures against them to physicians. Moreover, the pharmacists explain precautions in daily life for preventing adverse events and support patients in coping with anxiety and completing their treatment. The PCSs are performed before or after medical examination by an attending physician. In the case of post-medical examination PCSs, the pharmacists perform these with nurses as needed at the patient's bedside. The collaborative assessment of adverse events between pharmacists and nurses can reliably detect adverse events, such as skin disorders that improve and worsen repeatedly. Furthermore, with the advent of anamorelin, as discussed below, we have established a multidisciplinary team to promote the appropriate use of this agent as part of the management of cancer cachexia.

Monitoring of symptoms associated with cancer cachexia

Screening for cancer cachexia in the pre-cachexia phase is important for early intervention. In the pre-cachexia phase, mild anorexia and weight loss ($< 5\%$) are seen. In cachexia, there is $> 5\%$ weight loss, or $> 2\%$ weight loss in patients with a body mass index < 20, or $> 2\%$ weight loss in patients with sarcopenia, often with reduced food intake and systemic inflammation. Accordingly, weight should be measured routinely to monitor changes. Lean body mass (LBM) is the total amount of muscle, bone, and visceral organs, excluding body fat, in the total body weight. It is often used in clinical trials as an indicator in the management of cancer cachexia because it fluctuates under the influence of nutritional disorders and muscle weakness.[11–17] In real-world clinical practice, monitoring of LBM is preferred, if possible, but is not considered essential. In conjunction with weight measurement, it is also useful to monitor changes in food intake. In our outpatient chemotherapy unit, the nurses measure patients' weights and record them in the electronic medical record at each visit for anticancer drug administration. Based on these data, the pharmacists evaluate the occurrence of adverse events and the progression of cancer cachexia. Many patients with cancer cachexia are treated with chemotherapy using anticancer drugs, but the side effects of these drugs (nausea, oral mucositis, etc.) may also cause a decrease in food intake. Although symptoms of the adverse effects of anticancer drugs are temporary, the loss of appetite due to cachexia is persistent. This difference in the pattern of onset of decreased appetite is important in evaluating whether the symptom has an anticancer drug origin or a tumor origin. If persistent anorexia and weight loss occur regardless of anticancer drug administration, we should consider the possibility of a shift to cancer cachexia, even if the weight loss is less than 5%. As one role of pharmacists, it is also important to share information about changes in food intake and weight loss with the dietitian and consult about the initiation of nutritional therapy to prevent cachexia when necessary.

Table 1
The role of pharmacists in the treatment of cancer cachexia.

Treatment with anamorelin	Selection of indicated patients (early initiation of treatment)
	Check for drug interactions with strong CYP3A4 inhibitors
	Check for medical history and comorbidities
	congestive heart failure
	myocardial infarction
	angina pectoris
	severe conduction system failure
	Efficacy monitoring
	lean body mass
	muscle mass
	appetite
	motor activity
	Safety monitoring
	electrocardiography
	glycemic control
Assessment of the adverse events of cancer chemotherapy	Nausea and vomiting
	Stomatitis/taste disorder
	Malaise
	Peripheral neuropathy
Intervention for concomitant symptoms of cancer cachexia	Pain management
	Psychopharmacological treatment
	Support in appearance
Collaboration with multiple professions	

Drug therapy for cancer cachexia

The cachexia phase is defined as significant weight loss and persistent anorexia and is characterized by fatigue and muscle weakness due to systemic inflammation. Expected pharmacological actions against cancer cachexia are mainly anti-inflammatory, metabolism-improving, and appetite-improving. Although a number of drugs aimed at improving cancer cachexia have been investigated in clinical trials, many have shown limited therapeutic effects, and only a few have entered clinical use. A systematic review of clinical trials on the pharmacological management of patients with cancer cachexia identified enobosarm and anamorelin as promising agents.[18] Enobosarm, an osteoporosis drug, acts on muscle and bone as a selective androgen receptor modulator.[19] Anamorelin is an oral drug which offers ghrelin-like effects, marked appetite stimulation, food and weight gain, and growth hormone secretion.[20] Neither of these drugs has proved consistently effective in improving physical function (for example, hand grip strength and stair climbing), however, and their more effective utilization requires investigation.[11–14,21] At present, anamorelin is the only drug officially approved for the treatment of cancer cachexia and in a limited number of regions.

In the ONO-7643-04 study,[11] the efficacy of anamorelin 100 mg vs. placebo was evaluated in Japanese patients with non-small cell lung cancer (NSCLC). The 12-week change in LBM of 1.38 ± 0.18 kg in the anamorelin 100 mg group was significantly better than the -0.17 ± 0.17 kg change in the placebo group ($P < 0.0001$). Subsequently, a single-arm ONO-7643-05 study was conducted in Japanese patients with gastrointestinal (colon, stomach, pancreas) cancer, after which anamorelin was covered by insurance in Japan for use in NSCLC, colon cancer, gastric cancer, and pancreatic cancer.[12] The ROMANA1 and ROMANA2 trials are randomized, double-blind, placebo-controlled, phase III trials conducted in 15 and 7 countries, respectively, in patients with NSCLC.[13] Mean change in LBM was +0.99 kg (95% CI, 0.61–1.36) in the anamorelin 100 mg group and −0.47 kg (95% CI, −1.00 to 0.21) ($P < 0.0001$) in the placebo group in Study 1 and +0.65 kg (95% CI, 0.38–0.91) and −0.98 kg (95% CI, −1.49 to −0.41) ($P < 0.0001$) in Study 2.

In our hospital, we undertake the following collaborative efforts before starting anamorelin to ensure its effective and safe use. If

physicians diagnose cancer cachexia, dietitians provide nutritional guidance and body composition evaluation (LBM, skeletal muscle mass). Nurses collect information from patients on changes in eating habits, and pharmacists evaluate adverse events of chemotherapy that may affect eating habits (nausea, etc.) and plan measures to address them. The physicians evaluate blood glucose level, liver function markers and, in patients at risk of arrhythmia, the electrocardiogram in preparation for the possible adverse events of anamorelin. The pharmacists confirm whether all of the above measures are implemented, and if not, collaborate with the relevant discipline. After the initiation of anamorelin, relevant ongoing support is provided by the respective providers, who discuss the advisability of continuing anamorelin in terms of efficacy and safety, or other therapeutic interventions, as appropriate. The studies mentioned above[11,13] reported a significant increase in mean LBM compared to placebo at the third week of initiation, which was then maintained for 12 weeks. Therefore, at 3 weeks after anamorelin initiation, changes in LBM and food intake should be evaluated and the results used to confirm whether anamorelin should be continued. At that time, it is necessary to evaluate whether the effects of anamorelin are masked by chemotherapy adverse events or other factors.

In the refractory cachexia phase, medical interventions that provide patients with more nutrition may be futile or inappropriately intrusive.[8,9] The inclusion criteria for anamorelin in clinical trials also dictated that a survival prognosis of at least 3 months should be expected or that the performance status should be less than 3. In addition, Garcia reported that active ghrelin levels and the active to total ghrelin ratio were significantly increased in subjects with cancer-induced cachexia compared with cancer and non-cancer controls.[22] This explains why an increase in active ghrelin levels is likely to be a compensatory response to weight loss, and that patients with late-phase cancer cachexia may be in a state of ghrelin resistance. Anamorelin is not fully effective in patients with advanced cachexia, such as those with high levels of active ghrelin. The pharmacists should communicate with the physicians and nurses regarding the patient's prognosis, and if it is determined that the patient has refractory cachexia, discontinuation of anamorelin, and a reduction of nutritional therapy should be considered. On the other hand, for malaise in patients with refractory cachexia, the use of steroids may be effective.[23–25] Cancer cachexia treatment should be implemented with consideration of the expected benefits of weight gain relative to its risks, burdens, and costs, with the knowledge and consent of the patient.

Intervention for concomitant symptoms of cancer cachexia

The concomitant symptoms of cancer cachexia are diverse and affect the patient's QOL. Not only eating habits but also pain, psychiatric symptoms, and changes in appearance can become barriers to the patient's life, both physically and socially. The introduction of opioids and other analgesics for pain management should be considered after assessing the cause of the pain, and appropriate antidepressants and sleeping pills should be considered for psychiatric symptoms, in consultation with a medical specialist. Pharmacists have a great deal of knowledge and experience regarding the potential for symptom improvement through pharmacological intervention or drug options. We, therefore, recommend that nurses who receive patient complaints regarding certain symptoms share this information with pharmacists. Pharmacists can suggest appropriate medications to the physician, taking into account the characteristics of the current chemotherapy regimen and other patient background factors. Cooperation with specialized palliative care teams and liaison teams is also important.

Management of chemotherapy-induced adverse events

A close association exists between cancer chemotherapy and cancer cachexia. Cancer cachexia, skeletal muscle loss, and sarcopenia affect the efficacy and continuation of chemotherapy.[26–32] Conversely, chemotherapy reportedly exacerbates skeletal muscle wasting in patients having cancer.[33] This association accordingly points to the need for simultaneous monitoring and intervention in the management of chemotherapy-induced adverse events and cancer cachexia.

Patients having cancer often receive some form of cancer chemotherapy.[34] Factors contributing to weight loss in patients having cancer include cancer cachexia and starvation, the latter of which can result from adverse events of cancer chemotherapy and may be treatable. The balance between cancer cachexia and starvation is altered by the patient's stage and disease progression, but the impact of cancer chemotherapy adverse events in any patient should be considered appropriately for each treatment regimen (Table 2). Patients with cancer cachexia may experience severe side effects of cancer chemotherapy due to their poor nutritional status (e.g., increased blood levels of active anticancer drugs due to decreased blood albumin). In several reports, cancer cachexia was associated with the occurrence of chemotherapy adverse events.[35,36] Therefore, management of the side effects of cancer chemotherapy is also important in the proper management of cancer cachexia. We previously reported that pharmacist intervention reduces adverse events in patients receiving chemotherapy in the outpatient setting.[37] This reduction in the adverse events of chemotherapy through pharmacist intervention is expected to improve the QOL of patients with cancer cachexia.[37]

Nausea and vomiting

When anticancer agents with high emetic risk are used, symptom relief should be achieved through the administration of appropriate antiemetic agents. Anticancer agents are classified into four emetic risk categories based on the incidence of emesis within 24 h of administration (acute phase) in the absence of prophylactic administration of antiemetic agents (high: $>$ 90%, moderate: 30%–90%, low: 10%–30%, minimal: $<$ 10%).[38] Antiemetic prophylaxis is recommended by guidelines for each emetic risk and should be adhered to. For prominent nausea and vomiting, antiemetic agents with different mechanisms of action should be added. Olanzapine, a multiple receptor-targeting antipsychotic, is particularly effective for chemotherapy-induced nausea and vomiting and also has an appetite-stimulating effect.[39] However, olanzapine is contraindicated in patients with diabetes because it causes hyperglycemia.[40,41] In a recent report, a randomized, double-blind, placebo-controlled trial found that daily olanzapine administration significantly improved appetite and weight gain in patients undergoing cancer chemotherapy.[42] Although the efficacy of olanzapine for cancer cachexia has not yet been established, it is clearly a useful drug for patients having cancer.

Table 2
Adverse events of cancer chemotherapy that can affect the symptoms of cancer cachexia and the main causative anticancer agents.

Adverse event	Main causative anticancer agents
Nausea and vomiting	Anthracycline/Cyclophosphamide
	Cyclophosphamide ($\geq$ 1500 mg/m^2)
	Cisplatin
	Streptozocin
	Dacarbazine
	Procarbazine
Oral mucositis	Anticancer antibiotics such as bleomycin
	Plant alkaloids such as irinotecan
	Alkylating agents
	Platinum drugs
	Taxanes
	Molecular targeted drugs such as cetuximab
Taste disorder	Platinum drugs
	Taxanes
	Pyrimidine fluoride
	Molecular targeted drugs
Peripheral neuropathy	Oxaliplatin
	Cisplatin
	Carboplatin
	Paclitaxel
	Docetaxel
	Vincristine
	Bortezomib

Oral mucositis/taste disorder

The development of oral mucositis is a significant factor affecting feeding. There are no established preventive measures, and oral care and symptomatic treatment are recommended. If pain is present, anti-inflammatory analgesics such as acetaminophen and Nonsteroidal anti-inflammatory agents (NSAIDs), steroid ointments, and Chinese herbal medicine (Hanxia Shashinto) can be suggested.[43] When using steroid ointments, care should be taken to avoid serious oral infections such as oral candida.

Taste disorder is one adverse event that may decrease the patient's QOL[44] and zinc deficiency may be indicated as the cause. Severe taste disorders are associated with decreased food intake and cachexia-related decreases in QOL.[45] Zinc supplementation with zinc acetate hydrate is used to treat hypozincemia, but attention should be paid to copper deficiency because of the inhibition of copper absorption.

Malaise

It is difficult to clearly distinguish malaise as an adverse event of cancer chemotherapy from malaise caused by cancer cachexia, which may also be influenced by other factors such as anemia and electrolyte abnormalities. Furthermore, there is no established treatment for malaise, and improvement is encouraged through reasonable rest and exercise. If symptoms seem to change with the cancer chemotherapy regimen cycle, it may be inferred that the malaise is due to the adverse effects of anticancer agents rather than cancer cachexia.

Peripheral neuropathy

Anticancer agents that cause peripheral neuropathy can affect various activities of daily living, such as abnormal sensation in the fingertips, and in movement and walking. Oxaliplatin, vincristine, and paclitaxel cause dose-limiting toxicity, and a reduction or discontinuation of anticancer agents should be considered before irreversible symptoms develop. Symptomatic treatment with pregabalin or duloxetine can be suggested.[46,47] The measures against cold exposure are effective in the acute phase of peripheral neuropathy caused by oxaliplatin.

Future challenges in the treatment of cancer cachexia by multidisciplinary care

Early intervention is recommended for cancer cachexia, and once it reaches an irreversible stage, any treatment is unlikely to be effective.[4,48] However, there are no adequate evidence-based recommendations on what stage of cancer cachexia to start complex therapeutic interventions, or indeed, which interventions should be selected. Furthermore, a system for smooth collaboration in the treatment setting among multiple professions, including those other than physicians and nurses, may not always be place. For example, our team lacks the ability to implement exercise therapist intervention. Appropriate exercise therapy may improve the physical function and QOL of patients with cancer cachexia.[49] It is reported that knowledge and education related to cancer cachexia is lacking among medical professionals; that multidisciplinary cooperation cannot be practiced; that the roles and responsibilities of each team member are not clearly defined.[50–53] Clinical trials of multidisciplinary interventions which combine drug therapy, nutritional therapy, and exercise therapy are currently underway, and it is hoped that the results will lead to the broad development and implementation of multidisciplinary patient support systems across medical institutions.

As mentioned above, our team administers anamorelin according to patient inclusion criteria that follow clinical trial protocols and practices multidisciplinary collaboration. However, anamorelin is not effective in all patients with cachexia. In previous findings, anamorelin induced a significantly greater increase in LBM in patients with a short history of chemotherapy than in those with a long history.[54] In their retrospective study, Takeda et al. reported the results of a comparative study of changes in body weight and appetite after anamorelin treatment in pancreatic cancer patients with cachexia, divided into a moderate weight loss group (5%–10%) and a severe weight loss group (> 10%).[55] Results showed that the moderate weight loss group gained significantly more weight than the severe weight loss group. These results may suggest that early initiation of anamorelin is associated with the efficacy of this agent. The accumulation of such evidence has the potential to realize optimal interventions for individual patients, and analyzing outcomes in actual clinical practice is an important future task.

Furthermore, the impact of the active management of adverse events on the progression of cancer cachexia in patients receiving chemotherapy is not clear. Patients with cancer cachexia have metabolic abnormalities that may affect the excretion of anticancer drugs, which may be strongly reflected in adverse effects. Studies are needed to identify adverse event symptoms that are strongly associated with cancer cachexia and to determine whether reducing adverse event symptoms through appropriate management can contribute to the improvement of cancer cachexia.

Conclusions

Cancer cachexia is associated with decreased food intake and increased inflammation, resulting in decreased muscle strength and reduced QOL for the patient.[2–4] Pharmacists, along with physicians, nurses, dietitians, and physical therapists, should share information with the team and actively participate in the establishment of multidisciplinary treatment for cancer cachexia as members of a professional team, through monitoring cancer cachexia, supporting appropriate drug therapy, managing chemotherapy-induced adverse events, and resolving clinical problems.

Among the complex treatment now available for cancer cachexia, pharmacists should contribute mainly pharmacologically. The role of pharmacists is not only to intervene by checking compliance, concomitant medications, and adverse events in patients with cancer cachexia; pharmacists should also seek effective methods of medication, as well as identify pharmacological factors that influence patients' anorexia and weight loss, and work on interventions to improve them. For this purpose, pharmacists need to collect information for patients which provide a rationale for the timing of drug treatment recommendations for cancer cachexia to physicians. Attention should be paid not only to numerical data such as body weight, inflammatory response, albumin, and other indicators of nutritional status but also to changes related to the patient's QOL, such as activities of daily living, motivation, sociability, and appearance. In particular, it is markedly valuable for nurses, who have many opportunities to directly care for patients, to collect information on changes in QOL. This information should be shared among the team, including pharmacists, to identify the next point of intervention.

CRediT author statement

Hironori Fujii: Conceptualization, Methodology, Writing – Original draft preparation. **Yunami Yamada**: Investigation, Writing – Original draft preparation. **Hirotoshi Iihara**: Writing – Reviewing and Editing, Supervision. **Akio Suzuki**: Writing – Reviewing and Editing, Supervision. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of competing interest

The authors declare no conflict of interest.

Funding

This study received no external funding.

Ethics statement

Not required.

Disclosure

Publication of this paper is supported by Helsinn Healthcare SA. Helsinn does not have any influence on the content and all items are subject to independent peer and editorial review.

Data availability statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

Declaration of Generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

References

1. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. 2011;12:489–495.
2. Vaughan VC, Martin P, Lewandowski PA. Cancer cachexia: impact, mechanisms and emerging treatments. *J Cachexia Sarcopenia Muscle*. 2013;4:95–109.
3. Oberholzer R, Hopkinson JB, Baumann K, et al. Psychosocial effects of cancer cachexia: a systematic literature search and qualitative analysis. *J Pain Symptom Manag*. 2013;46:77–95.
4. Watanabe H, Oshima T. The latest treatments for cancer cachexia: an Overview. *Anticancer Res*. 2023;43:511–521.
5. Roch B, Coffy A, Jean-Baptiste S, et al. Cachexia - sarcopenia as a determinant of disease control rate and survival in non-small lung cancer patients receiving immune-checkpoint inhibitors. *Lung Cancer*. 2020;143:19–26.
6. Fujii H, Araki A, Iihara H, et al. Cancer cachexia as a determinant of efficacy of first-line pembrolizumab in patients with advanced non-small cell lung cancer. *Mol Clin Oncol*. 2022;16:91.
7. Fujii H, Makiyama A, Iihara H, et al. Cancer cachexia reduces the efficacy of nivolumab treatment in patients with advanced gastric cancer. *Anticancer Res*. 2020;40:7067–7075.
8. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr*. 2017;36:11–48.
9. Bozzetti F. ESPEN guideline on ethical aspects of artificial nutrition and hydration. *Clin Nutr*. 2016;35:1577.
10. Iihara H, Ishihara M, Matsuura K, et al. Pharmacists contribute to the improved efficiency of medical practices in the outpatient cancer chemotherapy clinic. *J Eval Clin Pract*. 2012;18:753–760.
11. Katakami N, Uchino J, Yokoyama T, et al. 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*. 2018;124:606–616.
12. Hamauchi S, Furuse J, Takano T, et al. A multicenter, open-label, single-arm study of anamorelin (ONO-7643) in advanced gastrointestinal cancer patients with cancer cachexia. *Cancer*. 2019;125:4294–4302.
13. Temel JS, Abernethy AP, Currow DC, et al. 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*. 2016;17:519–531.
14. Dobs AS, Boccia RV, Croot CC, et al. Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. *Lancet Oncol*. 2013;14:335–345.
15. Kanat O, Cubukcu E, Avci N, et al. Comparison of three different treatment modalities in the management of cancer cachexia. *Tumori*. 2013;99:229–233.
16. Mantovani G, Macciò A, Madeddu C, et al. Randomized phase III clinical trial of five different arms of treatment in 332 patients with cancer cachexia. *Oncol*. 2010;15:200–211.
17. Madeddu C, Dessì M, Panzone F, et al. Randomized phase III clinical trial of a combined treatment with carnitine+ celecoxib±megestrol acetate for patients with cancer-related anorexia/cachexia syndrome. *Clin Nutr*. 2012;31:176–182.
18. Advani SM, Advani PG, VonVille HM, Jafri SH. Pharmacological management of cachexia in adult cancer patients: a systematic review of clinical trials. *BMC Cancer*. 2018;18:1174.
19. Narayanan R, Coss CC, Yepuru M, Kearbey JD, Miller DD, Dalton JT. Steroidal androgens and nonsteroidal, tissue-selective androgen receptor modulator, S-22, regulate androgen receptor function through distinct genomic and nongenomic signaling pathways. *Mol Endocrinol*. 2008;22:2448–2465.
20. Pietra C, Takeda Y, Tazawa-Ogata N, et al. Anamorelin HCl (ONO-7643), a novel ghrelin receptor agonist, for the treatment of cancer anorexia-cachexia syndrome: preclinical profile. *J Cachexia Sarcopenia Muscle*. 2014;5:329–337.
21. Crawford J. Clinical results in cachexia therapeutics. *Curr Opin Clin Nutr Metab Care*. 2016;19:199–204.
22. Garcia JM, Garcia-Touza M, Hijazi RA, et al. Active ghrelin levels and active to total ghrelin ratio in cancer-induced cachexia. *J Clin Endocrinol Metab*. 2005;90:2920–2926.
23. Yennurajalingam S, Frisbee-Hume S, Palmer JL, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. *J Clin Oncol*. 2013;31:3076–3082.
24. Paulsen O, Klepstad P, Rosland JH, et al. Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. *J Clin Oncol*. 2014;32:3221–3228.
25. Matsuo N, Morita T, Matsuda Y, et al. Predictors of responses to corticosteroids for cancer-related fatigue in advanced cancer patients: a multicenter, prospective, observational study. *J Pain Symptom Manag*. 2016;52:64–72.
26. Salinas-Miranda E, Deniffel D, Dong X, et al. Prognostic value of early changes in CT-measured body composition in patients receiving chemotherapy for unresectable pancreatic cancer. *Eur Radiol*. 2021;31:8662–8670.
27. Suzuki Y, Saito K, Nakai Y, et al. Early skeletal muscle mass decline is a prognostic factor in patients receiving gemcitabine plus nab-paclitaxel for unresectable pancreatic cancer: a retrospective observational study. *Support Care Cancer*. 2023;31:197.
28. Matsuo N, Azuma K, Murotani K, et al. Prognostic effect of cachexia in patients with non-small cell lung cancer receiving immune checkpoint inhibitors. *Thorac Cancer*. 2023;14:1362–1367.
29. Madeddu C, Busquets S, Donisi C, et al. Effect of cancer-related cachexia and associated changes in nutritional status, inflammatory status, and muscle mass on immunotherapy efficacy and survival in patients with advanced non-small cell lung cancer. *Cancers*. 2023;15:1076.
30. Aslan V, Kılıç ACK, Sütcüoğlu O, et al. Cachexia index in predicting outcomes among patients receiving immune checkpoint inhibitor treatment for metastatic renal cell carcinoma. *Urol Oncol*. 2022;40:494. e1–10.
31. Goh MJ, Kang W, Jeong WK, et al. Prognostic significance of cachexia index in patients with advanced hepatocellular carcinoma treated with systemic chemotherapy. *Sci Rep*. 2022;12:7647.
32. White R, Weekes CE, Grant R, Baldwin C, Ahmed H. Determining the prevalence and severity of cancer cachexia in advanced non-small cell lung cancer and its relationship with chemotherapy outcomes. *Support Care Cancer*. 2020;28:4373–4380.
33. Pedrosa MB, Barbosa S, Vitorino R, Ferreira R, Moreira-Gonçalves D, Santos LL. Chemotherapy-induced molecular changes in skeletal muscle. *Biomedicines*. 2023;11:905.
34. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cancer cachexia: understanding the molecular basis. *Nat Rev Cancer*. 2014;14:754–762.
35. da Rocha IMG, Marcadenti A, de Medeiros GOC, et al. Is cachexia associated with chemotherapy toxicities in gastrointestinal cancer patients? A prospective study. *J Cachexia Sarcopenia Muscle*. 2019;10:445–454.
36. Mitsunaga S, Kasamatsu E, Machii K. Incidence and frequency of cancer cachexia during chemotherapy for advanced pancreatic ductal adenocarcinoma. *Support Care Cancer*. 2020;28:5271–5279.
37. Fujii H, Ueda Y, Hirose C, et al. Pharmaceutical intervention for adverse events improves quality of life in patients with cancer undergoing outpatient chemotherapy. *J Pharm Health Care Sci*. 2022;8:8.
38. Aogi K, Takeuchi H, Saeki T, et al. Optimizing antiemetic treatment for chemotherapy-induced nausea and vomiting in Japan: update summary of the 2015 Japan society of clinical oncology clinical practice guidelines for antiemesis. *Int J Clin Oncol*. 2021;26:1–17.
39. Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. *N Engl J Med*. 2016;375:134–142.
40. Koller EA, Doraiswamy PM. Olanzapine-associated diabetes mellitus. *Pharmacotherapy*. 2002;22:841–852.
41. Ebenbichler CF, Laimer M, Eder U, et al. Olanzapine induces insulin resistance: results from a prospective study. *J Clin Psychiatry*. 2003;64:1436–1439.
42. Sandhya L, Sreenivasan ND, Goenka L, et al. Randomized double-blind placebo-controlled study of olanzapine for chemotherapy-related anorexia in patients with locally advanced or metastatic gastric, hepatopancreaticobiliary, and lung cancer. *J Clin Oncol*. 2023;41:2617–2627.
43. Matsuda C, Munemoto Y, Mishima H, et al. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (Hangeshashinto) for infusional fluorinated-pyrimidine-based colorectal cancer chemotherapy-induced oral mucositis. *Cancer Chemother Pharmacol*. 2015;76:97–103.
44. Fujii H, Hirose C, Ishihara M, et al. Improvement of dysgeusia by polaprezinc, a zinc-L-carnosine, in outpatients receiving cancer chemotherapy. *Anticancer Res*. 2018;38:6367–6373.
45. Hiroyuki O, Amano K, Morita T, et al. Impact of taste/smell disturbances on dietary intakes and cachexia-related quality of life in patients with advanced cancer. *Support Care Cancer*. 2023;31:141.

46. Smith EM, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *JAMA*. 2013;309:1359–1367.
47. Salehifar E, Janbabaei G, Hendouei N, Alipour A, Tabrizi N, Avan R. Comparison of the efficacy and safety of pregabalin and duloxetine in taxane-induced sensory neuropathy: a randomized controlled trial. *Clin Drug Invest*. 2020;40:249–257.
48. Aapro M, Arends J, Bozzetti F, et al. Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force. *Ann Oncol*. 2014;25:1492–1499.
49. Storck LJ, Uster A, Gafner L, et al. Effect of combined therapies including nutrition and physical exercise in advanced cancer patients: a pooled analysis. *Front Nutr*. 2023;10:1063279.
50. Ellis J, Petersen M, Chang S, et al. Health care professionals' experiences of dealing with cancer cachexia. *Int J Clin Oncol*. 2023;28:592–602.
51. Baracos VE, Coats AJ, Anker SD, Sherman L, Klompenhouwer T. Identification and management of cancer cachexia in patients: assessment of healthcare providers' knowledge and practice gaps. *J Cachexia Sarcopenia Muscle*. 2022;13:2683–2696.
52. Sato R, Hayashi N, Nakayama N, Okimura A. Factors affecting the assessment of cancer cachexia by nurses caring for patients with advanced cancer undergoing chemotherapy: a cross-sectional survey. *Asia Pac J Oncol Nurs*. 2022;9:100075.
53. Socratous G, Cloconi C, Tsatsou I, Charalambous A. Nurses' knowledge in relation to the anorexia-cachexia syndrome in cancer patients: a cross-national comparison in two European countries. *SAGE Open Nurs*. 2021;7:23779608211035208.
54. Takayama K, Takiguchi T, Komura N, Naito T. Efficacy and safety of anamorelin in patients with cancer cachexia: post-hoc subgroup analyses of a placebo-controlled study. *Cancer Med*. 2023;12:2918–2928.
55. Takeda T, Sasaki T, Okamoto T, et al. Impact of the extent of weight loss before administration on the efficacy of anamorelin in advanced pancreatic cancer patients with cachexia. *Intern Med*. 2022. https://doi.org/10.2169/internalmedicine.0730-22 [Online ahead of print].