

The Incidence and Management of Cancer-Related Anorexia During Treatment with Vascular Endothelial Growth Factor Receptor-Tyrosine Kinase Inhibitors

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Abstract: Cancer-related anorexia is a common complication and frequently occurs in cancer patients treated with vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR-TKIs). Anorexia contributes to malnutrition, body weight loss, and cachexia in affected patients. Furthermore, patients who experience anorexia have worse outcomes than those who maintain their appetite, highlighting the importance of managing anorexia and related symptoms. However, as the causes of anorexia are both diverse and interconnected, there have been challenges in evaluating and implementing effective interventions. In this review, we described the contributing factors to cancer-related anorexia and reviewed recent literature for the frequency of anorexia symptoms in patients treated with VEGFR-TKIs. Additionally, we evaluated the evidence for current interventions and the potential benefits of multimodal and multidisciplinary approaches to care. The frequency of anorexia symptoms in patients who received VEGFR-TKIs ranged from 14%–58% for all-grade anorexia and 0%–6% for grade 3 or 4 anorexia. While many of the interventions for cancer-related anorexia have minimal benefit or adverse events, recent advances in our understanding of cancer-related anorexia suggest that multimodal therapy with multidisciplinary care is a promising avenue of investigation. Several studies currently underway are anticipated to further assess the effectiveness of multimodal approaches.

Keywords: appetite, cancer-related anorexia-cachexia syndrome, gastrointestinal symptoms, malnutrition, VEGFR-TKI

Introduction

Cancer-related anorexia (defined as a loss of appetite) is a common complication of cancer and is estimated to affect between 40%–80% of patients with advanced cancer, with considerable impacts on their mood, daily activities, and overall quality of life.^{1,2} Anorexia in these patients contributes to weight loss and cachexia, which leads to sarcopenia in affected patients.^{3,4} There are a wide variety of factors that can contribute to anorexia, including nausea, dysgeusia, dysphagia, mouth ulcers, early satiety, constipation, diarrhea, general malaise, pain, and depression.⁵

Anorexia and the associated weight loss are serious symptoms in patients with cancer, and both are independently associated with poor prognosis and cancer progression.^{5–7} Although there are other known causes of weight loss and cachexia in patients with cancer,^{3,4,8} in this review, we have focused on weight loss associated with cancer-related anorexia. Patients with cancer-related anorexia have a decreased quality of life⁹ and often experience other related effects including weight loss, malnutrition, and a decrease in muscle and fat.¹⁰ Furthermore, patients with anorexia have

a significantly shorter survival than patients who do not experience loss of appetite.¹¹ Given the poor outcomes associated with anorexia, effective management of anorexia and weight loss symptoms is necessary to improve outcomes for patients with cancer. However, there have been challenges in implementing these management strategies in clinical practice: first, a lack of widely accepted methodology for assessing cancer-related anorexia means that the identification of affected patients is inconsistent and the evaluation of interventions is difficult.^{5,6} Second, the multiple causes and pathogenesis of cancer-related anorexia means that a single approach may be unlikely to work for all patients; anorexia can be induced by the tumor, cancer treatment, or both together.¹² Third, pain associated with cancer, depression, nausea, and other symptoms can also contribute to anorexia.¹³ Therefore, a multimodal therapy that addresses both symptoms of anorexia and the associated malnutrition, weight loss, and increased cachexia is desirable and is currently being investigated.¹⁴

Tyrosine kinase inhibitors (TKIs) have recently become important in the treatment of cancer, regardless of the type of carcinoma. Unfortunately, patients treated with TKIs can develop anorexia, sarcopenia, and cachexia, leading to treatment discontinuation. In this paper, we reviewed the mechanisms of cancer-related anorexia and the frequency of anorexia and related symptoms in patients treated with TKIs. Because there is a lack of evidence for managing TKI-related anorexia, we evaluated the evidence for the current interventions for chemotherapy-related anorexia and examined the effectiveness of multidisciplinary care in clinical practice. Furthermore, as anorexia and cachexia are interrelated, cancer-related cachexia is included in this review.

The Mechanisms of Cancer-Related Anorexia

The physiological causes of cancer-related anorexia follow several pathways (Figure 1).³ Appetite is controlled by two types of neurons in the central hypothalamus that form two complementary pathways: pro-opiomelanocortin (POMC)/cocaine and amphetamine-regulated transcript (CART) neurons that reduce appetite, and neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons that increase appetite.^{15–17} Tumor cells can influence appetite through the production of inflammatory cytokines; these cytokines modulate neurotransmitter pathways by increasing the activity of the POMC/CART neurons and inhibiting the activity of NPY/AgRP neurons, leading to a suppression of appetite. Additionally, the cytokines are involved in a dysfunction of the melanocortin system, which contributes to anorexia.^{5,12} Increased inflammatory cytokines are also associated with depression in patients with cancer.¹⁸ Tumor cells produce lactate, which can suppress appetite via 5-adenosine monophosphate (AMP) kinase/malonyl-coenzyme A (CoA) signaling in the hypothalamus.^{19–21} Central effects (such as depression and pain) can contribute to anorexia by impacting these neurotransmitter pathways.¹²

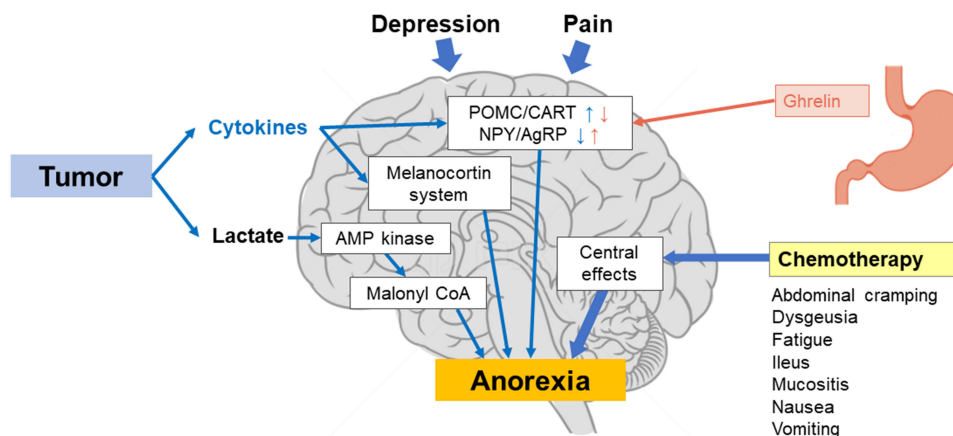


Figure 1 The pathophysiology of cancer-related anorexia. Cytokines increase the activity of POMC/CART and decrease the activity of NPY/AgRP. Ghrelin decreases the activity of POMC/CART and increases the activity NPY/AgRP.

Abbreviations: AgRP, agouti-related peptide neurons; AMP, 5-adenosine monophosphate; CART, cocaine and amphetamine-regulated transcript neurons; CoA, coenzyme A; NPY, neuropeptide Y; POMC, pro-opiomelanocortin.

The hormone ghrelin is secreted by the stomach; it increases the expression of NPY/AgRP and suppresses POMC/CART, thereby increasing appetite.^{22–25} In addition, ghrelin promotes the secretion of gastric acid and emptying of the stomach.²² Patients with cancer tend to have higher ghrelin levels,²⁵ which may function as a compensatory response to weight loss.²⁶ Patients with cachexia may also have increased ghrelin levels yet experience no increase in appetite, which indicates that such patients start developing resistance to ghrelin.²⁶ However, this may not be the case for all patients with cancer, as reports have shown that ghrelin levels are significantly lower in patients with gastric or pancreatic cancer²⁷ and that these levels are further decreased following chemoradiotherapy.²⁸ Patients who receive chemotherapy may also experience dysgeusia and other gastrointestinal symptoms such as vomiting, abdominal cramps, and mucositis.¹² Approximately 39% of patients who receive chemotherapy will experience dysgeusia,²⁹ which can contribute to a decrease in appetite.³⁰

Development of Anorexia Following TKI Treatment

In recent years, vascular endothelial growth factor receptor (VEGFR)-TKIs have played an increasingly important role in the treatment of cancer.^{31,32} Several meta-analyses have shown that patients experience an increased frequency of gastrointestinal side effects, including a decrease in appetite, following VEGFR-TKI therapy.^{33,34} Patients who received TKI therapy had a significantly increased risk of all-grade anorexia compared with those in the control group (36.8% vs 24.3%; $p < 0.00001$).³³ When grouped by the type of carcinoma, the relative risk of all-grade anorexia was significantly higher for patients with colorectal cancer, thyroid cancer, and renal cell carcinoma (RCC), and grade ≥ 3 anorexia was significantly higher for those with thyroid cancer and RCC, which may reflect the relatively longer progression-free survival duration. Furthermore, increases in the incidence of nausea and vomiting were observed following TKI therapy, and for some patients, gastrointestinal adverse events (AEs) prevented the continuation of treatment.

We reviewed the frequency and risk of decreased appetite when treated with VEGFR-TKIs in a variety of carcinomas, focusing on phase III clinical trials (Table 1). The frequency of decreased appetite varied by the specific drug used, with the occurrence of all-grade anorexia ranging from 14%–58%, and between 0%–6% for grade 3 and above. Many treatment-emergent AEs (TEAEs) that occur with VEGFR-TKI treatment can lead to anorexia, including nausea and stomatitis; additionally, diarrhea and mucositis contribute to malnutrition (Figure 2). These AEs can lead to weight loss and contribute to cachexia,^{3,13,30,35,36} necessitating the careful management of these symptoms as well as management of anorexia. A systematic review stated that the incidence of stomatitis is between 20%–35% with TKI treatment (35.2% with sunitinib, 34.21% with cabozantinib, 20.63% with axitinib, and 20.52% with sorafenib), although the majority of these cases were low-grade (grade 1 or 2).³⁷ We reviewed the frequency of both anorexia and other AEs related to malnutrition associated with VEGFR-TKI therapy in patients with RCC for whom the frequency of anorexia and cachexia is relatively high. The incidence of AEs related to anorexia and malnutrition ranged from 20%–62% for nausea, 16%–39% for vomiting, 43%–74% for diarrhea, and 14%–30% for stomatitis (Table 2). Early satiety, a symptom that is highly associated with anorexia, is not included as an AE for VEGFR-TKI therapy. Patients with cancer-related anorexia-cachexia syndrome often experience early satiety,³⁸ which can contribute to weight loss.⁹ Early satiety is reported to be more common in patients with severe anorexia.³⁹ However, standard questionnaires often do not capture information on early satiety, potentially leading to underreporting of this important symptom.⁴⁰ These high rates of anorexia and other AEs highlight the importance of careful monitoring of patients treated with TKIs.

Management of Cancer-Related Anorexia

The development of cancer-related anorexia and cancer-related anorexia-cachexia syndrome can be the result of the tumor, pain, and depression, and can also be a treatment-related AE (Figure 2).^{30,59,60} These factors are interrelated and can occur simultaneously, making it difficult for clinicians to easily identify the cause of anorexia. Importantly, there is currently no effective treatment for cachexia,^{59,60} contributing to the challenge of managing symptoms in these patients. Therefore, it is necessary to understand the patient's experience to ascertain the factors contributing to anorexia and develop a management plan that addresses each factor. For patients who experience anorexia as a TEAE, a reduction in dose or drug withdrawal are the primary measures for those experiencing AEs of grade 3 and above. However, less severe symptoms, such as those below grade 2, may act synergistically and result in an inadequate nutritional intake,

Table 1 Frequency of Anorexia^a with TKI Treatment

TKI	Phase	Cancer Type	Control Group	Number of Patients, TKI/Control	TKI Group Frequency of Anorexia, %		Control Group Frequency of Anorexia, %		Reference
					All Grade	Grade 3 or 4	All Grade	Grade 3 or 4	
Sunitinib	3	RCC	Nivolumab plus ipilimumab	535/547	25	<1	14	1	Motzer et al ⁴¹
	3	RCC	INF- α	375/360	44	2	39	2	Motzer et al ⁴²
	3	pNET	Placebo	83/82	22	2	21	1	Raymond et al ⁴³
	3	GIST	Placebo	202/102	19	0	6	1	Demetri et al ⁴⁴
Sorafenib	3	RCC	Placebo	451/451	16	<1	13	1	Escudier et al ⁴⁵
	3	HCC	Placebo	297/302	14	<1	3	1	Llovet et al ⁴⁶
	3	DTC	Placebo	207/209	31.9	2.4	4.8	0	Brose et al ⁴⁷
Pazopanib	3	RCC	Sunitinib	554/548	37	1	37	3	Motzer et al ⁴⁸
Axitinib	3	RCC	Sorafenib	189/96	29	2	19	0	Hutson et al ⁴⁹
Regorafenib	3	GIST	Placebo	132/66	20.5	0	7.6	0	Demetri et al ⁵⁰
	3	CRC	Placebo	500/253	30	3	15	3	Grothey et al ⁵¹
	3	HCC	Placebo	374/193	31	3	15	2	Bruix et al ⁵²
Cabozantinib	3	RCC	Everolimus	331/322	46	2	34	<1	Choueiri et al ⁵³
	3	MTC	Placebo	214/109	45.8	4.7	15.6	0.9	Elisei et al ⁵⁴
	3	HCC	Placebo	467/237	48	6	18	<1	Abou-Alfa et al ⁵⁵
Lenvatinib	3	DTC	Placebo	261/131	50.2	5.4	11.5	0	Schlumberger et al ⁵⁶
	3	HCC	Sorafenib	476/475	34	5	27	1	Kudo et al ⁵⁷
	2	RCC	Everolimus	52/50	58	4	18	0	Motzer et al ⁵⁸

Notes: ^aIncludes decreased appetite.
Abbreviations: CRC, colorectal cancer; DTC, differentiated thyroid carcinoma; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; INF- α , interferon alpha; MTC, medullary thyroid cancer; pNET, pancreatic neuroendocrine tumor; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.

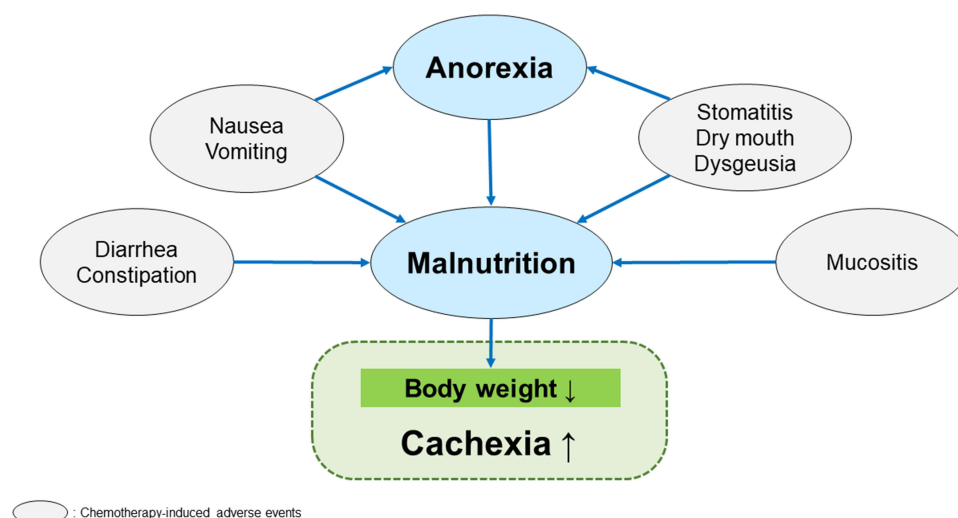


Figure 2 Chemotherapy-induced adverse events contributing to malnutrition.

weight loss, and cachexia. Therefore, interventions such as medication and nutritional therapy should be considered to improve the patient's appetite and prevent malnutrition.⁶¹ Other suggested approaches include exercise therapy, dietary counseling, progesterone analogs, and corticosteroids (Table 3).⁶² As there is a high frequency of AEs associated with TKI therapy that are directly related to appetite and eating, such as nausea, vomiting, and stomatitis, a comprehensive response that considers these symptoms is likely to improve the appetite of affected patients and support a healthy nutritional intake.

Treatment of Associated Symptoms

As anorexia often occurs with other symptoms such as stomatitis, nausea, and vomiting, management of these related symptoms is crucial when treating patients with cancer-related anorexia. Stomatitis is common in patients with metastatic breast cancer who are treated with mammalian target of rapamycin inhibitors; however, treatment options are limited to educating patients about good oral health care and prophylactic use of a dexamethasone mouth rinse.⁶³ Although stomatitis experienced by patients treated with TKI therapy is often mild (grade 1 or 2),³⁷ the use of appropriate prophylaxis is recommended because untreated stomatitis can lead to a loss of appetite. Similarly, dysgeusia can also alter appetite by making normally appetizing foods unappealing. Treatment with monosodium glutamate has been recently shown to increase the expression of the taste receptor subunit T1R3 and increase energy intake in patients with advanced head and neck cancer.⁶⁴

Oral mucositis is a common side effect of both chemotherapy and radiotherapy.⁶⁵ Glutamine has been studied as a treatment for chemotherapy- and radiotherapy-induced oral mucositis: a recent systematic review of several clinical trials showed that patients treated with glutamine had a significantly reduced incidence of severe (grade 3 or 4) oral mucositis.^{66,67} Conversely, an earlier systematic review reported that glutamine had no effect on the incidence and severity of radiotherapy-induced oral mucositis in patients with head and neck cancer.⁶⁸ As stomatitis and oral mucositis experienced by patients treated with TKIs is often mild, the use of glutamine for these patients requires further investigation.

Pharmacologic Approaches to Cancer-Related Anorexia

The progesterone analog megestrol acetate has been shown to improve appetite, weight gain, and quality of life in patients with anorexia in a Cochrane review,⁶⁹ and is recommended for the treatment of cancer-related anorexia in the American Society of Clinical Oncology (ASCO) guidelines.⁶² However, as this drug has not been approved for the treatment of anorexia in Japan (Table 3), pharmacologic approaches to managing cancer-related anorexia in Japan rely on corticosteroids and the recently approved ghrelin receptor agonist anamorelin. Here, we describe the evidence for these

Table 2 The Frequency of Anorexia and Related Adverse Events in Patients with Renal Cell Carcinoma Treated with VEGF/VEGFR TKIs

TKI	Phase	Arm	n	Anorexia ^a	Weight Loss	Nausea	Vomiting	Diarrhea	Constipation	Stomatitis	Fatigue, Asthenia ^b	Dysgeusia	Ref.
Sunitinib	3	TKI	535	25	NA	38	21	52	NA	28	66	33	Motzer et al ⁴¹
		Control	547	14	NA	20	11	27	NA	4	50	6	
Sunitinib	3	TKI	375	44	12	52	31	61	12	30	74	46	Motzer et al ⁴²
		Control	360	39	14	35	12	15	4	4	71	15	
Sorafenib	3	TKI	451	16	10	23	16	43	15	NA	37	NA	Escudier et al ⁴⁵
		Control	451	13	6	19	12	13	11	NA	28	NA	
Pazopanib	3	TKI	554	37	15	45	28	63	17	14	64	26	Motzer et al ⁴⁸
		Control	548	37	6	46	27	57	24	27	73	36	
Axitinib	3	TKI	189	29	37	20	NA	50	NA	NA	54	NA	Hutson et al ⁴⁹
		Control	96	19	24	15	NA	40	NA	NA	42	NA	
Cabozantinib	3	TKI	331	46	31	50	32	74	25	22	75	24	Choueiri et al ⁵³
		Control	322	34	12	28	14	27	19	24	62	9	
Lenvatinib	2	TKI	52	58	48	62	39	72	37	25	50	NA	Motzer et al ⁵⁸
		Control	50	18	8	16	10	34	18	42	38	NA	

Notes: ^aIncludes decreased appetite. ^bFatigue and asthenia are shown as a combined frequency. Adverse events are all shown as percentages.
Abbreviations: n, number of cases; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Table 3 The Currently Approved Treatments for Cancer Anorexia-Cachexia Syndrome in Japan and the American Society of Clinical Oncology Guideline Recommendations⁶²

Intervention	Strength of the Recommendation		
	Recommend in Favor	No Recommendation	Recommend Against
Pharmacologic interventions			
Corticosteroids	✓		
Anamorelin		✓	
Nutritional interventions			
Dietary counseling	✓		
Omega-3 fatty acids		✓	
Supplements		✓	
Other interventions			
Exercise		✓	

Note: Progesterone analogs, thalidomide, and olanzapine are not approved for the treatment of anorexia-cachexia syndrome in Japan.

two classes of drugs for the management of cancer-related anorexia. Other pharmacologic approaches are expected to be available in the future: for example, olanzapine has recently shown promising results in patients with locally advanced or metastatic gastric, hepatopancreatobiliary, and lung cancers.⁷⁰ However, these newer treatments are outside of the scope of this review.

Corticosteroids

Corticosteroids are widely used to manage cancer-related anorexia as they inhibit the release of inflammatory cytokines such as tumor necrosis factor (TNF)- α and interleukin-1, thereby increasing appetite and weight in patients with cachexia.⁷¹ However, the benefits are transient and corticosteroids are not suitable for long-term use because of potential AEs such as hyperglycemia, hypertension, infection, bone fractures, and gastrointestinal bleeding.^{72,73} Furthermore, steroids used in combination with immune checkpoint inhibitors (ICIs) may decrease the efficacy of ICIs and lead to worse patient outcomes, though this has not been conclusively shown.^{74–76} Thus, corticosteroids may not be appropriate for all patients, and the dose must be carefully managed to maximize the benefits while preventing unwanted side effects.

Anamorelin

The ghrelin receptor agonist anamorelin was recently approved in Japan for the treatment of cachexia in patients with colorectal cancer, gastric cancer, non-small-cell lung cancer, and pancreatic cancer.⁷⁷ In a meta-analysis of patients with cancer, those treated with anamorelin had an increased appetite as measured by the Anderson Symptom Assessment Scale score of 8.05 (95% confidence interval [CI]: 5.97–10.12, $p < 0.00001$) and improved symptom relief and quality of life.⁷⁸ Another meta-analysis also reported that treatment with anamorelin increases lean body mass and quality of life compared with placebo (mean difference: 1.10; 95% CI: 0.35–1.85, $p = 0.004$; and mean difference: 0.19; 95% CI: 0.08–0.30, $p = 0.0006$, respectively).⁷⁹ The largest phase III clinical trials included in the meta-analysis, the ROMANA 1 and ROMANA 2 trials, found an increase in lean body mass following anamorelin treatment compared with placebo.⁸⁰ However, no improvement in hand grip strength was obtained with anamorelin treatment. When treatment was extended for a further 12 weeks (the ROMANA 3 trial), patients showed improvement in anorexia-cachexia symptoms compared with placebo, but no improvement in hand grip strength.⁸¹ Thus, anamorelin has not been approved for use in the United States for the treatment of cancer cachexia and is not recommended by the ASCO guidelines.⁶²

In Japan, anamorelin at a dose of 100 mg was approved based on the results of two studies: a study of 174 patients with advanced non-small-cell lung cancer and cachexia, who showed improvements in lean body mass, performance status, and quality of life with anamorelin treatment;⁸² and a study in patients with advanced gastrointestinal cancer, who

showed improvements in anorexia symptoms, nutritional status, lean body mass, and body weight following anamorelin treatment.⁸³ Thus, anamorelin is often used in Japanese clinical practice. However, some patients may not benefit from anamorelin treatment, such as those with low performance status, and more evidence is needed to assess potential biomarkers and identify which patients will benefit the most. Newer multimodal interventions, that combine nutritional and exercise therapy, may work synergistically with anamorelin and lead to better outcomes when anamorelin alone is not sufficient, and are currently being explored.⁸⁴ Other pharmacologic options (including thalidomide, olanzapine, and mirtazapine) are not currently indicated for the treatment of cachexia and anorexia (Table 3).

Multimodal Therapy

As noted throughout the previous sections of this review, each individual therapy for cancer-related anorexia on its own often shows either inconsistent benefits or potential unwanted side effects. This is also true for exercise therapy: the ASCO Exercise, Diet, and Weight management guidelines state that exercise therapy during cancer treatment led to improvements in fatigue, muscle strength, and quality of life of patients and recommend both aerobic and resistance exercise.⁸⁵ However, the ASCO guidelines for cachexia state that there is no evidence for the benefit of exercise therapy,⁶² and a Cochrane review also found no evidence for the use of nutritional therapy to treat cachexia.⁸⁶ As anorexia and cachexia often involve interrelated symptoms and diverse causes, a combined approach that brings together different treatments may offer an effective management of anorexia. While either nutritional or exercise therapy alone may have limited efficacy, combinations of these therapies should be considered.^{14,36} Combined approaches that address the multiple factors contributing to the condition are termed multimodal therapy and are likely to be the next step in cancer-related anorexia therapy. Taking a multimodal approach involves identifying the treatable causes and symptoms for each individual patient and developing a personalized plan involving a combination of therapies for reducing inflammation, improving metabolism, and restoring appetite, with the aim to increase skeletal muscle mass and physical function.^{40,85}

Current multimodal therapies that combine exercise and nutritional therapy have shown promising results for the treatment of cachexia, anorexia, and weight loss. A systematic review that evaluated the use of combined exercise and nutritional therapy for the rehabilitation of patients with refractory cancer found that this type of multimodal therapy improved physical endurance and reduced depression scores.⁸⁷ A study of patients with advanced tumors ($n = 58$) showed that nutrition counseling with an exercise program resulted in reduced nausea and vomiting, and improved protein intake compared to standard care.⁸⁸ A phase II study of patients with refractory lung or pancreatic cancer found that the multimodal therapy (including omega-3 fatty acid nutritional supplements, exercise, and the anti-inflammatory drug celecoxib) cohort tended to maintain their body weight while the standard care cohort did not; however, this study had a small sample size, and no further effects were identified.⁸⁹ A larger phase III clinical trial is currently underway to investigate the multimodal therapy described above for cachexia.⁹⁰ Another study found that patients who received multimodal therapy (involving fish oil supplements, nutritional counseling, and exercise therapy) had increased skeletal muscle compared with the control group.⁹¹ Although the evidence for these multimodal therapies is so far limited to small clinical trials, the results are promising and warrant further investigation. The Japanese phase II NEXTAC-TWO clinical trial of multimodal therapy has been planned,⁹² which will further contribute to our knowledge regarding multimodal therapy.

Multidisciplinary Care

Coordination and collaboration among multiple disciplines, including nurses, pharmacists, dietitians, physical therapists, and psychotherapists, is important for successful implementation of multimodal therapy.⁹³ It is also important to collect information from multiple perspectives to best understand the patient's experience, and difficulties, and to provide an appropriate diagnosis and treatment.⁶¹ Several studies reported that the use of multimodal therapy based on a multidisciplinary program leads to improvements in quality-of-life measures.^{94,95} Additionally, a study that investigated multimodal therapy in an interdisciplinary clinic reported that the therapy contributed to both weight gain and increased functional strength in patients with cancer.⁹⁶ A phase II clinical trial that examined the efficacy of multimodal treatment from a multidisciplinary team (an oncologist, a nutritionist, and a psychotherapist) for treating patients with metastatic

esophagogastric cancer showed that patients treated with multimodal therapy had significantly increased median overall survival compared with the standard care cohort (14.8 months vs 11.9 months, $p = 0.021$).⁹⁷ Patients treated with multimodal therapy also showed improvements in their emotional and cognitive functions, but no significant difference in anorexia was measured between the two cohorts. Similar results were reported from a feasibility study of a multidisciplinary care program including nutrition counseling, exercise therapy, and psychological support; the study reported high patient satisfaction, although non-attendance rates increased as the study progressed.⁹⁸

Early detection of cachexia is important for improving outcomes in affected patients, as cachexia is interrelated with anorexia. Nurses are important for the identification of cachexia and assessment of a patient's nutritional state.⁹⁹ However, a survey of Japanese nurses showed that while nurses were aware of the importance of identifying cachexia, they were often not confident in their abilities to assess cachexia.¹⁰⁰ Thus, further training and education of nurses in assessing cachexia is important for the early identification and treatment of affected patients.¹⁰¹ Other key roles include dietitians, who work with the wider clinical team to understand the patient's condition, symptoms, quality of life, and needs, to safely incorporate a nutrition plan that will improve anorexia and cachexia.¹⁰² In addition, the dietitian can play an integral role in the identification and management of cancer cachexia, focusing on aspects of nutrition screening and intervention.¹⁰³

The use of complementary supplements and alternative medicine has been met with concern, as they are often accompanied by reduced adherence to standard therapy, significant reduction in 5-year overall survival, and increased risk of death.¹⁰⁴ Similarly, the use of alternative medicines by patients with nonmetastatic breast, prostate, lung, and colorectal cancer is associated with an increased risk of death compared with standard care.¹⁰⁵ A multicenter prospective cohort study of patients with early-stage breast cancer revealed that patients who used complementary medicines were less likely to start chemotherapy than those who did not use complementary medicines.¹⁰⁶ It is important for the wider team, including dietitians and pharmacists, to build a trusting relationship with the patient to ensure that appropriate education is available and that effective treatments are provided.

Future Research: Nutritional Therapy

There have been several studies that have examined the potential use of nutritional therapy for treating anorexia. However, the lack of established evaluation methods and the differences within and between study populations has resulted in inconsistent evidence for the use of vitamins, minerals, and other dietary supplements. Therefore, the ASCO guidelines do not recommend their use by patients with cancer experiencing anorexia.⁶² However, nutrition counseling by a registered dietitian for advanced cancer patients with decreased appetite and weight loss has a moderate recommendation in the ASCO guidelines.⁶² The European Society for Clinical Nutrition and Metabolism guidelines also recommend that appropriately trained professionals provide nutritional guidance.¹⁰⁷ As noted earlier in this review, nutritional therapy may play an important role in multimodal therapies, working synergistically with other therapies.^{14,36} Here, we discuss the emerging evidence for the use of omega-3 fatty acids and royal jelly for the management of cancer-related anorexia.

Eicosapentaenoic (EPA) and docosapentaenoic acid are both omega-3 fatty acids that have been extensively studied in nutritional therapy for cachexia, and have been shown to improve cachexia, promote weight gain, reduce inflammation, improve neuropathy, and improve quality of life measures.¹⁰⁸ The ASCO guidelines evaluated three systematic reviews and meta-analyses in 2011, 2015, and 2018, and found an effect of omega-3 fatty acids on improving weight gain,^{62,109} but found insufficient evidence for treating cachexia, and thus the ASCO guidelines do not recommend their use for managing cachexia. Similarly, the European Society for Medical Oncology guidelines state that reports of omega-3 fatty acids have shown some benefits on body weight, lean body mass, and quality of life measures, but lacked sufficient evidence for their benefit.¹⁴ In a 2022 systematic review, EPA treatment did not show any clear effect on weight gain.¹¹⁰ Another recent systematic review of the use of omega-3 fatty acids found that patients gained weight in some trials, but the sample sizes were small and not supported by sufficient evidence.¹¹¹ In contrast, an earlier systematic review that examined the effectiveness of nutritional interventions for anorexia reported that increased EPA from oral nutritional supplements, dietary counseling, and fish oil supplements, improved appetite and nutrition outcomes in patients with cancer.¹¹² Thus, there is inconsistent evidence for the use of omega-3 fatty acids for the treatment of anorexia or cachexia.

Royal jelly, a substance collected from honeybees, has been investigated for interactions with chemotherapeutic agents and potential anti-inflammatory effects,^{113–115} and a previous study examining royal jelly revealed insights into the mechanism of TKI-induced anorexia.¹¹⁶ Royal jelly affects the regulation of cytokines such as TNF- α and TGF- β ;^{117,118} and it has recently been

considered for its potential to prevent TKI-induced anorexia.^{116,118} Patients with RCC who received pre-treatment with royal jelly before TKIs had a reduction in TNF- α levels and an increase in TGF- β and macrophage colony-stimulating factor levels; however, the effect was transient and did not last beyond 12 weeks.¹¹⁶ In another study, patients with RCC who received royal jelly had significantly lower rates of TKI-induced anorexia compared with those receiving placebo,¹¹⁸ and fewer patients who received royal jelly required TKI dose reductions. Considering these findings, royal jelly is a promising candidate for its potential in preventing anorexia in patients with cancer.

Conclusion

In this review, we have discussed the causes and mechanisms of cancer-related anorexia, including the interconnected symptoms experienced by affected patients. In addition, we have described the current management approaches, ranging from pharmacologic therapies to the recent advances in multimodal and multidisciplinary care and the emerging evidence for nutritional therapy. The frequency of all-grade anorexia was evaluated in clinical trials of patients treated with VEGFR-TKIs and was found to be between 14%–58%. Anorexia can severely impact quality of life, resulting in weight loss and contributing to cachexia, which can lead to treatment discontinuations. Therefore, early detection and effective management of anorexia are crucial in patients with cancer. A comprehensive approach, encompassing not only pharmacotherapy but also exercise and nutritional therapy, may be necessary to effectively treat anorexia. Effective collaboration among healthcare professionals is essential to ensure successful multidisciplinary management.

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