Review Article

Prokinetics and ghrelin for the management of cancer cachexia syndrome

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Abstract: Cancer cachexia (CC) is one of the most distressing syndromes for both patients and their families. CC can have an impact on patient reported quality of life and overall survival. It is often associated with symptoms such as fatigue, depressed mood, early satiety, and anorexia. Prokinetic agents have been found to improve chronic nausea and early satiety associated with CC. Among the prokinetic agents, metoclopramide is one of the best studied medications. The role of the other prokinetic agents, such as domperidone, erythromycin, haloperidol, levosulpiride, tegaserod, cisapride, mosapride, renzapride, and prucalopride is unclear for use in cachectic cancer patients due to their side effect profile and limited efficacy studies in cancer patients. There has been an increased interest in the use of ghrelin-receptor agonists for the treatment of CC. Anamorelin HCl is a highly selective, novel ghrelin receptor agonist. A meta-analysis was conducted of the recent randomized trials using anamorelin (daily dose of 50 and 100 mg daily). Results show that both total body weight and lean body mass were significantly increased from baseline in the anamorelin group. Anamorelin did not improve overall survival or hand grip strength, and there were no significant differences between groups for frequency or severity of any adverse events. In this review, the authors discuss the available evidence for the use of prokinetics such as metoclopramide and ghrelin receptor agonists for the treatment of CC.

Keywords: Cancer; cachexia; ghrelin receptor agonists; anamorelin; metoclopramide

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Introduction

Cancer cachexia (CC) is a "multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (1). CC is often associated with symptoms such as fatigue, depressed mood, early satiety, and anorexia. Pathophysiology of CC is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism (1). CC is a frequent syndrome, and it is associated with serious debility in patients with advanced cancer (1). Moreover, it is also associated with a reduction in physical function, tolerance to anticancer therapy, and survival (2,3). The field of cachexia management has seen rapid growth since the definition of cachexia in 2011; however, there is limited published data on the management of debilitating symptoms associated with CC, especially early satiety and anorexia (4-6). In this review, the authors discuss the available evidence for the use of the prokinetic metoclopramide and ghrelin receptor agonists for the treatment of CC.

Prokinetics

CC is associated with secondary symptoms such as anorexia, early satiety, and chronic nausea (7,8). Often, management of the secondary cachexia symptoms will significantly benefit these types of patients (9,10). In regards to anorexia and early satiety, both autonomic dysfunction and gastroparesis can contribute to a worsening of symptoms (11,12). While medications such as opioids can induce chronic constipation leading to nausea (12), prokinetic agents have been found to improve chronic nausea and early satiety related to cachexia (13,14). Among the prokinetic agents, metoclopramide is a well-studied dopamine receptor antagonist (7,10,15) that acts centrally as well as peripherally as an antiemetic and also has gastric emptying properties (10,16). This medication can help treat issues such as autonomic dysfunction related to advanced cancer and impaired gastric emptying due to opioids (10). In patients with chronic nausea and dyspepsia from advanced cancer, the use of metoclopramide can result in the improvement of nausea, vomiting, and bloating (10). Side effects that can be dose-limiting include extrapyramidal symptoms such as akathisia (restlessness and motor agitation) and tremor. These side effects are more severe when co-administered in combination with neuroleptics such as haloperidol (15). Of note, metoclopramide can contribute to prolonging the QTc interval, and in the case of complete bowel obstruction, the drug is contraindicated. *Table 1* shows the mechanism of actions, the starting dose, and the side effects of metoclopramide and other commonly used prokinetic agents.

There are limited studies that evaluate the efficacy of metoclopramide for the treatment of CC symptoms. Metoclopramide was found to be superior to placebo in two of three small controlled studies. In a double-blind, crossover study lasting four days, Bruera *et al.* compared controlled-release metoclopramide with placebo for the chronic nausea and dyspepsia in patients with advanced cancer. The results of this preliminary study were suggestive that metoclopramide may reduce nausea in advanced cancer patients (10). In another trial comparing extended release to immediate release metoclopramide for cancer-related nausea in thirty-four advanced cancer patients, the same investigators found improvement in nausea with both extended release metoclopramide and immediate release metoclopramide, though the extended release was slightly better when nausea was assessed using a visual analogue scale (13). At present, there are no comparative effectiveness studies in advanced cancer patients with CC comparing metoclopramide with other prokinetic agents for the treatment of nausea, anorexia, or early satiety. Additionally, the association of improved motility and symptom relief with prokinetics is poor in functional bowel syndrome and non-existent in cancer. Therefore, further research is needed.

Ghrelin and ghrelin receptor agonists

Ghrelin is a natural ligand of the growth hormone (GH) secretagogue receptor (17). It is produced primarily in the stomach (oxyntic mucosa) and its levels increase during anorexia, fasting or starvation (18). Ghrelin stimulates appetite and regulates energy balance by down-regulating thermogenesis (19-22). It modulates pro-inflammatory cytokine synthesis, including IL-6 and TNF-α, by downregulating leptin-induced expression of the cytokines, and expression of cytokines by monocytes and T cells (23). Ghrelin promotes growth of adipose tissue by activation of lipogenic pathways and can influence regulation of skeletal muscle mass (24) by stimulation of insulin-like growth factor 1 (IGF-1) production.

Because of its unique properties, recent research has focused to evaluate how ghrelin can influence inflammatory and metabolic pathways by its effects on the GH receptor, and lead to both improvement of muscle mass and reduction in the rate of muscle atrophy in CC (24). While the data is promising to support the therapeutic use of ghrelin in CC, drawbacks of the treatment that limit clinical use include a short half-life and the need for parenteral administration. These limitations of ghrelin led to the investigation of an orally-available ghrelin agonist for the treatment of CC; ONO-7643, or anamorelin, is one such promising treatment.

Anamorelin

Anamorelin HCl is an orally active ghrelin receptor agonist being investigated as part of the treatment for CC. Two early phase studies were conducted to evaluate the safety and efficacy profile of anamorelin. A phase 1 study by Kumor *et al.* found oral anamorelin (25 and 50 mg daily) to be associated with a significant increase in appetite and food intake (25). In a separate phase 1 study, a significant change in body weight was noted with the use of oral anamorelin (26). The drug was well-tolerated with no dose-limiting adverse effects.

Table 1 Prokinetic agents, their starting doses

Prokinetics	Starting dose, and routes of use	Side-effects and comments
Metoclopramide		
First-line agent. Mechanism of action: dopamine 2 antagonist, $5HT_4$ and weak $5HT_3$ receptor antagonist. Gastric antral contraction, and decreases post prandial fundus relaxation	5–10 mg orally, tablet, liquid or intravenous preparation; Recommended to use 15 minutes prior to meals and bedtime. Short term use, weeks to few months Caution: proactive taper strategies at the earliest such as dose reduction and drug holidays should be considered upon control of symptom	Common side effects include fatigue, anxiety, and depressed mood. Restlessness, hyperprolactinemia, QT- interval prolongation, extrapyramidal symptoms such dystonia and tardive dyskinesia have frequently been reported. Black box warning due these concerns. Acute dystonias frequently reported in children, young adults and females. Parkinson disease like symptoms are more common in older adults. Dosage adjustment specifically in older/pediatric patients and those with renal insufficiency, and concomitant use of CYP2D6 inhibitors
Domperidone		
Second-line agent in patients not responsive to metoclopramide. Mechanism similar to metoclopramide	10 mg orally, tablet or liquid three times a day	Side-effects similar to metoclopramide. Risk of cardiac arrhythmias. Therefore, EKG monitoring recommended. Not available in United States for routine clinical use. Caution with use with other medications with cytochrome P450 (especially CYP3A4) metabolism
Macrolide antibiotics		
Erythromycin & azithromycin: second-line agent in patients not responsive to metoclopramide. It is a motilin agonist, increases gastric emptying by inducing high amplitude gastric contractions	40–250 mg orally, tablet, liquid, or intravenous use three times a day. Erythromycin use should be limited to less than 4 weeks at a time, as the effect of erythromycin decreases due to tachyphylaxis	Abdominal pain, anorexia, diarrhea, nausea, hearing loss, development of resistant bacterial strains, QT-interval prolongation. Caution with use with other medications metabolized via cytochrome P450 (especially CYP3A4) system. Both erythromycin and azithromycin have similar prokinetic activity but azithromycin has a slightly better safety profile
Cisapride		
Second line agent. It is a 5HT4 agonist. It stimulates antral and duodenal motility and accelerates gastric emptying of solids and liquids	10–20 mg oral liquid or tablet preparation	Abdominal cramps, diarrhea, dizziness. Risk of cardiac arrhythmias. Therefore, EKG monitoring recommended. Not available in USA for routine clinical care. Caution with use with other medications metabolized via cytochrome P450 (especially CYP3A4) system

Subsequently, a study by Garcia *et al.* (27) found the use of anamorelin 50 mg orally daily to be associated with a significant increase in body weight and lean body mass (LBM), improvement in the symptom burden, and overall improvement in quality of life (QOL). In another study in patients with stage III/IV non-small cell lung cancer (NSCLC) and cachexia (28), a 100 mg daily dose of anamorelin was associated with significant increase in LBM from baseline when compared to the placebo group at week 12 (P=0.03). In addition to the LBM, individuals treated with 100 mg of anamorelin daily had significant improvement in QOL (P=0.01), performance status (Karnofsky Performance Scale) (P=0.04), and total body weight (P<0.01) at week 12. In this study QOL was assessed using the QOL-ACD scale, a QOL scale validated in Japanese patients receiving chemotherapy (29). It evaluates four domains (functional, physical, mental, and psychosocial) and a global face scale. No significant difference was observed between both arms in terms of handgrip strength. Based on the results of these studies, anamorelin was found to be a well-tolerated medication that can result in significant improvements in LBM and cachexia-related symptoms.

With encouraging results from the preceding studies, two large double-blind, placebo-controlled, randomized phase III trials ensued. The ROMANA 1 and ROMANA 2 trials were conducted, and the results of both studies were recently published (30).

ROMANA 1 and ROMANA 2 were conducted to evaluate the efficacy and safety of anamorelin in patients with advanced NSCLC. Patients received either 100 mg/day of oral anamorelin or placebo for 12 weeks. Primary endpoints of these studies were changes in LBM and handgrip strength over 12 weeks. Secondary endpoints were total body weight, along with anorexia and fatigue. Survival analysis was assessed at one-year survival.

Four hundred eighty-four and four hundred ninety-five patients were enrolled into the ROMANA 1 and ROMANA 2 trials, respectively. LBM was higher in the anamorelin arm compared to the placebo arm (P<0.0001) in both studies. In ROMANA 1, the improvement in LBM was 0.99 kg (95% CI: 0.61 to 1.36 kg) in the study group and –0.47 kg (95% CI: –1.00 to 0.21 kg) in the placebo group. For ROMANA 2, LBM was increased by 0.65 kg (95% CI: 0.38 to 0.91 kg) in the study group and –0.98 kg (95% CI: –1.49 to –0.41) in the placebo group. Hand grip strength did not improve with anamorelin in either trial. The improvements in both body weight and anorexia-cachexia scale score were statistically significant, as the values were higher in the anamorelin group compared to the placebo group (P<0.001).

Long term, a pooled survival analysis at the end of 1 year after the study showed no significant difference between the treatment groups [hazard ratio: 1. 06; 95% CI: 0.89 to 1.26; P=0.47]. The median survival was 8.90 months (95% CI: 8.3 to 9.8 months) and 9.17 months (95% CI: 7.9 to 11.0 months) for the anamorelin and placebo groups, respectively (31). Notably, neither ROMANA 1 nor ROMANA 2 were designed to assess the survival benefits of anamorelin.

A pooled data analysis of the ROMANA trials was conducted to examine the effectiveness of anamorelin in those at risk of malnutrition [body mass index (BMI) ≤20 kg/m^2]. The increase in LBM was comparable in anamorelin-treated patients with either low BMI or normal/high BMI. However, it was found that anamorelin in patients with a low BMI had greater improvement in anorexia-cachexia and fatigue than those with a normal/high BMI. This evidence illustrates that patients with a BMI <20 kg/m^2 benefit to a greater extent from anamorelin than those with normal or increased BMIs (31); Therefore, the patients with a higher risk of malnutrition will experience greater symptom relief when treated with anamorelin.

The results of a meta-analysis of randomized controlled studies using anamorelin for CC found that total body weight and LBM were significantly improved in the anamorelin group versus placebo group, although these effects were modest (mean difference in total body weight for anamorelin compared to placebo was 1.78 kg, 95% CI: 1.28–2.28 kg; for the change in LBM, mean difference was 1.10, 95% CI: 0.35–1.85) (32). Anamorelin was not associated with significant improvement in overall survival or hand grip strength. There were also no significant differences between groups for frequency or severity of adverse events.

Safety of anamorelin

There were no treatment-related deaths in the two ROMANA studies, and the safety profiles were comparable between the anamorelin and placebo groups. The most common adverse events of anamorelin (grade 1 or 2) were hyperglycemia (4%) and nausea (2.5%). The frequency of grade 3 and 4 adverse events was low (~2%) in both studies. The frequency of dropouts for treatment-emerging side effects were not different from placebo in both ROMANA 1 and 2.

The use of ghrelin for the treatment for CC is not yet recommended due to limited evidence. Disadvantages of ghrelin in cancer patients are its short duration of action and lack of oral formulation (33,34). In this regard, selective ghrelin receptor agonists such as anamorelin may be considered as a pragmatic option in treatment of CC as it is available in oral form and has a longer half-life than ghrelin (7 *vs.* 0.5 h). This is based on the ROMANA 1 and ROMANA 2 trials which show efficacy to improve LBM and symptoms and safety of anamorelin in advanced NSCLC patients with CC (30).

Future studies

With limited data on the effectiveness of prokinetics in treatment of symptoms related to CC, further research is needed. Ghrelin and anamorelin are promising drugs that may also play a role in the improvement of symptomatic burden in CC. Because anamorelin is yet to be approved for clinical use by the FDA, further phase 3 studies are imperative to determine the utility of anamorelin in the improvement of the patient experience with anorexia-cachexia syndrome, its effect on different functional outcomes, and safety.

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Footnote

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