Perspective

Pharmacological management update: clinical significance of anamorelin clinical trials for the treatment of cancer cachexia in advanced cancer patients

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Abstract: Cancer cachexia is a debilitating and multifactorial metabolic condition that is highly prevalent among advanced cancer patients. Currently there are limited effective pharmacological treatment options for the management of cancer cachexia. In recent years, there is an increasing attention on the use of ghrelin-receptor agonists in the treatment of cancer cachexia. In this perspective, we discuss recent clinical trials that have evaluated the efficacy and safety of ghrelin-receptor agonist, anamorelin for the treatment of anorexia cancer cachexia syndrome and its potential role of anamorelin in clinical care in advanced cancer patients.

Keywords: Cancer cachexia; anamorelin; ghrelin receptor agonists; cancer related fatigue; anorexia

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Introduction: cancer cachexia

Cancer cachexia is a debilitating and multifactorial metabolic condition that is highly prevalent among cancer patients with advanced disease. The incidence of cancer cachexia ranges between 50% to 80%, and varies according to the tumor type (1). Clinical presentations of cancer cachexia include disproportionate and excessive weight loss (primarily the skeletal muscle and body fat), asthenia, anemia and fatigue (2). This is a particular issue of concern to cancer patients, as evidence has shown that the presence of cachexia is strongly associated with poor survival and outcomes (3-5). Furthermore, cancer cachexia can directly impair patients' functional capacity and quality of life, and also cause undesirable psychosocial distress to both patients and their caregivers (6-8).

In this review, recent clinical trials that have evaluated the efficacy and safety of anamorelin (ANAM) were identified from PubMed. The following search terms were used: "cancer", "cancer cachexia", "anamorelin", "ONO-7643" and "RC-1291".

Current pharmacological treatment options

Currently, orexigenic agents remain a major cornerstone in the treatment of cachexia by stimulating appetite to increase energy intake. Among the various orexigenic agents, dexamethasone and progesterone analogs, such as megestrol acetate, are the only agents with proven clinical benefits (9-13). Although these orexigenic agents can help to increase food intake, none of these drugs are able to substantially improve lean body mass (LBM), survival and quality of life (9-13). Besides the orexigenic agents, there are limited evidence to support the use of other agents of different therapeutic classes, such as the anabolic agents and cytokine and metabolic inhibitors (eicosapentaenoic acid and thalidomide), in the treatment of cancer cachexia. Since the mechanisms underlying cancer cachexia are highly complex, and implicate multiple organs and metabolic pathways, it has been widely recognized that the treatment of cancer cachexia should be a multimodal approach involving various targeted interventions (2,14). Hence, combination therapy involving various agents, such

as L-carnitine, NSAIDs and megestrol acetate, has been evaluated for the treatment of cancer cachexia (15-18). Even though the results are promising, the effectiveness of these combination therapies remains inconclusive due to a lack of replication. Evidently, there are limited effective pharmacological therapies available for the treatment of cancer cachexia.

In recent years, there is an increasing attention on the use of ghrelin-receptor agonists in the treatment of cancer cachexia. Ghrelin is a short chain amino acid that is a natural ligand of the growth hormone (GH) secretagogue receptor (19). It is produced primarily by the oxyntic mucosa in the stomach and increases during periods of fasting or under conditions associated with negative energy balance, such as starvation or anorexia (20). Physiological functions of ghrelin include stimulation of appetite and GH secretion, and regulation of energy balance by down-regulating thermogenesis (21-24). Most importantly, ghrelin also possesses anti-inflammatory property by acting as a counter-regulating signal. It inhibits the production of pro-inflammatory cytokines, such as IL-6 and TNF-α, by downregulating leptin-induced expression of the cytokines, as well as the expression of cytokines by monocytes and T cells (25). Since systemic inflammation is a hallmark of cancer cachexia, the anti-inflammatory property of ghrelin would prove to be beneficial in the treatment of cachexia (25). In addition, ghrelin can promote adipose tissue growth through the activation of lipogenic pathways and stimulate insulin-like growth factor 1 (IGF-1) production, which is essential for the regulation of skeletal muscle mass (26). There is also evidence to suggest that ghrelin could prevent muscle atrophy (27).

In view of ghrelin's ability to target the multiple inflammatory and metabolic pathways associated with cancer cachexia, it is evident that ghrelin is a promising therapeutic agent, and studies have investigated the use of ghrelin infusion in the treatment of cancer cachexia. While there are promising data to support the therapeutic role of ghrelin in cachexia, the short half-life and the need for intravenous infusion have limited its role in the clinical setting. As such, researchers have switched to the development of orally-available ghrelin agonists.

Anamorelin: clinical efficacy in phase I and II trials

Anamorelin HCL (ANAM) (ONO-7643; RC-1291) is a potent and highly selective novel ghrelin receptor agonist. ANAM has a much longer half-life than ghrelin (7 hours *vs.* 15 minutes), and hence it is suitable for development as an oral agent.

Two phase I studies were conducted to establish the maximum tolerable dose, as well as to evaluate the efficacy and safety profile of ANAM. In the study conducted by Kumor *et al.*, ANAM was shown to induce a significant increase in appetite and food intake at doses of 25 and 50 mg than the placebo (28). In a separate phase I trial, it was observed that the change in body weight from baseline increased significantly at daily doses of 50 and 75 mg when compared with the placebo-treated group (29). For both studies, ANAM was generally well-tolerated with no dose-limiting adverse effects.

The clinical efficacy of ANAM was further evaluated in a number of phase II trials. Details on these studies have been extensively discussed in a recent review by Garcia *et al.* (30). In general, ANAM is shown to significantly increase body weight, LBM, and improve symptom burden and overall quality of life. Marked improvement in the levels of biomarkers, such as GH and insulin-growth factor 1, was observed. An update to the review by Garcia *et al.* is a recent phase II study conducted in Japanese patients with stage III/IV non-small cell lung cancer (NSCLC) and cachexia (31). Consistent with the data of previous phase II trials, Japanese patients on 100 mg daily dose of ANAM exhibited significant improvement in LBM from baseline than the placebo group at week 12 ($P=0.03$). The least square mean change in LBM were 1.15 kg (SE: 0.31) and 0.55 kg (SE: 0.29) in the 100 mg ANAM and placebo arms respectively. However, no significant difference in handgrip strength test result was observed between both arms. In addition to the LBM, patients treated with 100 mg ANAM showed substantial improvement in the quality of life ($P=0.01$), performance status ($P=0.04$) and total body weight ($P<0.01$) at week 12. With regards to the serum biomarkers, levels of IGF1 ($P<0.01$), IGF binding protein 3 ($P<0.01$) and prealbumin ($P=0.02$) increased significantly in patients taking 100 mg ANAM than placebo. Findings of these phase II trials suggest that ANAM has similar efficacy in both Caucasian and Asian cancer patients with cachexia. Across all the phase II trials, conflicting data exists regarding the efficacy of ANAM in the handgrip strength test. Overall, ANAM was well-tolerated with most adverse effects being mild in nature.

Phase III trials: ROMANA 1 and ROMANA 2

Based on the promising results from the phase II trials, two pivotal phase III trials, namely ROMANA 1 and ROMANA

2 were conducted and the results of both trials were published recently (32).

ROMANA 1 (NCT01387269) and ROMANA 2 (NCT01387282) were two international, double-blind, placebo-controlled, randomized phase III trials to evaluate the efficacy and safety of ANAM in patients with advanced NSCLC. Patients were randomized (2:1) to either 100 mg ANAM or placebo, given once daily orally for 12 weeks. Co-primary endpoints were changes in LBM and handgrip strength over 12 weeks from baseline. Secondary endpoints included the change from baseline over 12 weeks in total body weight and symptoms of anorexia and fatigue as assessed using the functional assessment of cancer therapy (FACT) measurement system anorexia-cachexia and fatigue scales. Survival analysis was also performed to evaluate the overall 1 year survival between the two arms. Treatment-related adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.

A total of 484 and 495 patients were enrolled into the ROMANA 1 and ROMANA 2 trials respectively, with majority of the patients being Caucasians. In both trials, LBM was significantly increased in the ANAM arm as compared to the placebo arm (P<0.0001). In ROMANA 1, the median change in LBM was 0.99 kg (95% CI: 0.61 to 1.36) in the ANAM arm and –0.47 kg (95% CI: –1.00 to 0.21) in the placebo arm. For ROMANA 2, the median change in LBM was 0.65 kg (95% CI: 0.38 to 0.91) in the ANAM arm and –0.98 (95% CI: –1.49 to –0.41) in the placebo arm. With regards to the handgrip strength test, no statistical differences were observed between the study arms in both trials.

For the secondary endpoints, the change in mean body weight and mean anorexia-cachexia scale score over 12 weeks from baseline were statistically significantly higher in the ANAM arm than the placebo arm (P<0.001). Although there was a substantial improvement in the mean change fatigue score in the ANAM arm as compared to the placebo arm at week 9 (P=0.033) and week 12 (P=0.024) of the ROMANA 1 trial, the change in fatigue scores from baseline did not differ significantly between the treatment arms over the entire study period in both trials (P>0.05).

A pooled overall survival analysis at 1 year showed no significant difference between the two treatment arms (hazard ratio: 1.06; 95% CI: 0.89 to 1.26; P=0.47). Median survival over 1 year was 8.90 months (95% CI: 8.3 to 9.8) and 9.17 months (95% CI: 7.9 to 11.0) for the ANAM and placebo arms respectively. It must be emphasized that both trials were not designed and powered to establish the survival benefits of ANAM.

Overall, ANAM was well tolerated in both trials with no treatment-related deaths, and safety profiles were comparable between the treatment arms. The most common grade 1 or 2 adverse events were hyperglycemia (4%) and nausea (2.5%). Incidence of grade 3 and 4 adverse events was low (~2%) in each trial. The number of patients who discontinued for ANAM-related treatment emergent adverse events was 21/320 (7%) and 13/330 (4%) in ROMANA 1 and ROMANA 2, respectively. No dose reductions were observed for patients in both trials.

Potential role of anamorelin in clinical care in advanced cancer patients

In cancer patients with advanced disease, the main treatment goals are to reduce suffering and to improve the quality of life for both patients and their family, as well as to help patients to live longer and well for as long as they can. Cancer cachexia is an undesirable syndrome that severely compromises patients' quality of life and daily functioning. It is associated with poor performance status and reduced survival, all of which contribute to worsen the quality of life and functional status of cancer patients.

The ROMANA 1 and ROMANA 2 trials have successfully demonstrated the clinical efficacy and short term safety of ANAM in stage III/IV NSCLC patients with cachexia (32). Indubitably, the compelling results confirm that ANAM is an effective class of drugs for the treatment of cancer cachexia, and the study has the potential to be practice changing, particularly in the absence of an effective intervention. However, there are some considerations to be taken into account when assessing the clinical impact of the ROMANA trials.

Both trials have established the effectiveness of ANAM in terms of increasing LBM, fat mass and total body weight, however there are limited studies to suggest whether the improvement in body compositions would translate to better functional status and quality of life. Although the FACT anorexia-cachexia and fatigue scales were incorporated in both trials as secondary endpoints, the quality of life outcomes, such as the physical and social well-being domains, were not explicitly reported. Information gleaned from these quality of life domains is necessary for evaluating the impact of ANAM on patients' emotional, functional, physical and social well-being. This information would give us a deeper insight into the impact of ANAM on patients' functional status and quality of life. Traditional

clinical studies focus solely on the clinical indicators and outcomes of new therapeutics, and the humanistic outcomes (functional status and quality of life) are either neglected or treated as secondary endpoints (in which studies may not be sufficiently powered for these secondary endpoints). Therefore, it is imperative that humanistic outcomes should be coupled with clinical outcomes as co-primary endpoints when evaluating the efficacy of ANAM, particularly when the current trials failed to demonstrate any direct benefits to patients on palliative care.

The discordance between LBM and handgrip strength in the ROMANA trials is congruous with findings of earlier phase II studies (30,31). Since sarcopenia is an important prognostic factor in oncology, the improvement in LBM is a desired therapeutic outcome (33). However, the increase in skeletal muscle mass does not translate to improvement in physical function, and this cast doubts on the suitability of handgrip strength test as a measure of functional strength among patients with cancer cachexia. It must be highlighted that muscles mass is not the major determinant of muscle strength and other factors, such as muscle composition and fatty infiltration of muscle, are important considerations as well (34). Taken together, the poor correlation between muscle mass and handgrip strength test underscores the need for alternative measures of muscle strength in clinical trials of cancer cachexia. Future trials could consider the use of a combination of muscle strength tests, such as the elbow flexor strength testing and 30-second chair stand test, or utilize the 6-minute walk test to assess patients' physical functional capacity (35,36).

While the short-term safety profile of ANAM is remarkable based on the results of the preliminary and phase 3 trials, the long-term effects could not be ascertained due to a lack of extended follow up in the ROMANA trials. Evidently, clinical trials with longer follow-up period are required to examine the long term benefits and risks of ANAM (37).

Identifying a subset of cancer patients who will derive the most benefit from the use of ANAM would be clinically useful. A pooled efficacy data analysis of the ROMANA trials was conducted to investigate the effectiveness of ANAM in patients at risk of malnutrition (body mass index ≤20 kg/m^2). Comparing to the placebo, the increase in LBM was comparable in ANAM-treated patients with low BMI and those with normal/high BMI. However, ANAM-treated patients with low BMI had a significant improvement in their anorexia-cachexia and fatigue symptom burden. Findings of this study suggest that patients who are at higher risk of malnutrition experience greater symptom relief when treated with ANAM. This evidence supports the use of ANAM in cancer patients with BMI less than 20 kg/m^2.

Another symptom significantly associated with cancer cachexia is cancer related fatigue (38). As such, the treatment of cancer cachexia with ANAM is expected to result in an improvement in fatigue status. In addition, given the strong causal link between inflammation and cancer-related fatigue, ANAM is a potential therapeutic agent for fatigue by inhibiting the production of pro-inflammatory cytokines (39,40). Interestingly, fatigue status did not improve significantly over the entire study period in both trials, but ANAM was found to improve fatigue level at week 9 and 12 of the study period in ROMANA I but not in ROMANA II. Since fatigue is a complex symptom that could be influenced by numerous intrinsic and extrinsic factors, such as disease burden and the use of chemotherapy, the failure to account for these factors may confound the results (41). Regardless, the negative results should not undermine the efficacy of ANAM in improving fatigue symptom, as the ROMANA trials may not be sufficiently powered to detect changes in fatigue status. Furthermore, symptom cluster of fatigue, depression and pain have been established in advanced cancer patients with cachexia, hence accentuating the therapeutic potential of ANAM in the treatment of fatigue and its associated symptoms (42). As such, future studies should be conducted in a well-characterized population to investigate the efficacy of ANAM in the treatment of fatigue.

In conclusion, among NSCLC patients with cachexia, ANAM is proven to be an effective therapeutic agent in the treatment of cancer cachexia. The improvement in LBM and anorexia-cachexia symptom burden is compelling, however more work is required to firmly ascertain the therapeutic role of ANAM in the clinical setting. Future research should investigate the survival benefits of ANAM, as well as its impact on patients' quality of life and daily functioning. A head to head comparision between ANAM and the orexigenic agents would further clarify the therapeutic position of ANAM in the management of cancer cachexia in advanced cancer patients. Nevertheless, based on existing evidence, ANAM represents a safe and effective option for advanced cancer patients with cancer cachexia.

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Footnote

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