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What's Next After Anamorelin?

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Abstract

Purpose—In spite of its relevance, treatments for the cancer anorexia and cachexia syndrome (CACS) are not available. One of the agents that recently reached phase III clinical trials is anamorelin. Its development, along with that of other agents for this indication will be reviewed here, with a focus on the gaps in the current knowledge and future directions.

Recent Findings—In spite of several targets showing promising results in early development, their difficulties obtaining regulatory approval underscores the need to reconsider the current strategies in drug development and the challenges in the field of CACS.

Summary—Further research is needed in order to meet the challenges of developing treatments for CACS. Pre-clinical studies should expand our understanding about key regulators of appetite, muscle and energy metabolism in this setting using models that can be translated reliably to humans. Clinical research efforts should focus on validating the entry criteria, endpoints, outcomes and the potential synergistic effects and interaction between different targets, nutrition and exercise interventions. Clinical meaningfulness and significance should be taken into account in the design of clinical trials. It is essential that all key stakeholders are included in the design of future strategies.

Keywords

cachexia; anorexia; cancer; treatment; interventions; wasting

Introduction

Cancer anorexia and cachexia syndrome (CACS) is a complex multifactorial syndrome characterized by a progressive loss of appetite and muscle mass (with or without loss of fat) that cannot be fully reversed by nutritional support alone and that leads to functional impairment [1]. CACS can be present in 40–80% of cancer patients depending on the tumor type, it is linked to poor quality of life (QoL), and is a strong predictor of survival [2–4].

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This syndrome can be due to the cancer itself or, paradoxically, to side effects of the chemo/radiation therapy used for its treatment. Regardless of the specific etiology, CACS usually takes a heavy toll psychologically and physically on the cancer patient. Treatments for CACS are not available. Hence, the development of novel therapeutic agents targeting CACS is desperately needed.

In recent years, our knowledge regarding the pathophysiology of CACS has grown exponentially. Multiple targets have been identified through preclinical studies [5], and proof-of-concept phase I–II clinical studies have validated some of these targets [6–11]. Several agents have already completed phase III clinical trials after seeking regulatory guidance from the U.S. Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for indications related to CACS. Unfortunately, they have failed to gain approval to this date [12–14].

In spite of the great progress made in increasing our understanding of CACS, developing a safe and effective treatment for this condition remains an elusive goal. This highlights the importance of correctly identifying and filling the gaps in the knowledge that could enable the research community to deliver a much-needed treatment for CACS. One of the agents that recently reached phase III clinical trials for CACS is anamorelin, an agonist of the ghrelin receptor GRLN. The development of anamorelin, along with that of other agents for this indication will be reviewed here, with a focus on the current challenges and future directions.

Development of anamorelin for CACS

Ghrelin, a 28-aminoacid hormone, is an important regulator of energy metabolism, food intake and growth hormone (GH) secretion [15–17], increasing lean and fat mass through multiple mechanisms [18,19]. It increases appetite, and food intake by activating GRLN receptor in the hypothalamus and it enhances gastric emptying [20]. It also decreases energy expenditure [21], and activates lipogenesis and decreases lipolysis and lipid oxidation [18,22]. Ghrelin also increases GH and insulin-like growth factor (IGF)-1 which has anabolic effects in muscle and may downregulate inflammation having a positive effect on muscle mass and function [9,23]. Although GRLN is the only identified receptor for ghrelin to this date, mounting evidence suggest the presence of an alternative receptor that may mediate its effect in muscle, fat and liver where the GRLN receptor is not expressed [19,24,25].

In preclinical and small clinical trials in the setting of CACS, ghrelin administration improved food intake, appetite, and chemotherapy-induced nausea with good tolerability [18,19,26–28]. However, its clinical development is limited by its short half-life (~30 minutes) and the need for parenteral administration. Hence, a number of longer-acting, orally bioavailable, synthetic agonists of the GRLN have been the focus of interest in the field. One of these agonists, anamorelin HCl, is the most advanced in its development. In healthy volunteers, anamorelin induces a rapid increase in appetite and food intake compared to placebo. In a randomized, double-blind, placebo-controlled, phase I study,

anamorelin induced a significant dose-related increase in body weight after 6 days of treatment [8]. An increase in IGF-1 was also seen with the higher doses [9].

Anamorelin was tested in a phase II randomized, double-blind, placebo-controlled crossover study showing that 3 days of treatment increased body weight, and patient-reported outcomes (PRO) including appetite in CACS patients [29]. Over 3 months of treatment, anamorelin increased body weight and lean body mass (LBM) measured by x-ray densitometry (DEXA), muscle function as measured by hand grip strength, and quality of life (QOL), particularly in the domains of sense of well-being, sleep, nausea, and drowsiness. Anamorelin also increased IGF-1 and its carrier protein IGF binding protein (IGFBP)-3. It was well-tolerated, with a small but consistent effect on glucose and insulin concentrations [10].

Subsequently, two large, international, randomized, double-blind, placebo controlled phase III studies in patients with advanced NSCLC and CACS were conducted in the US and Europe (ROMANA 1 and 2) [13]. Two co-primary endpoints of change in LBM and handgrip strength as well as secondary endpoints of survival, body weight, fat mass and symptoms of CACS and fatigue were measured throughout the study. Although anamorelin increased LBM, fat mass, body weight and appetite-related QoL compared to placebo, there was no difference in HGS between groups. One-year survival was similar between groups and anamorelin was well-tolerated with mild hyperglycemia again noted. The EMA recently refused to authorize the marketing of anamorelin arguing that the studies show a marginal effect on LBM and no proven effect on hand grip strength or patients' QOL [30]. Further regulatory review is pending in Europe and in the US.

Development of other drugs for CACS

Besides anamorelin, other pharmaceutical targets have also reached phase III clinical development. The selective androgen receptor modulator (SARM) enobosarm was well-tolerated and increased LBM by DEXA and muscle function assessed by stair climbing power (SCP) in a phase II, double-blinded, multicentric, placebo-controlled trial that included patients with cancer-induced pre-cachexia [6]. Subsequently, two unpublished phase III studies (not using CACS as an entry criteria) in NSCLC patients failed to meet the two co-primary endpoints of LBM and SCP (NCT01355497, NCT01355484) [31].

The novel drug MABp1, a human antibody targeting interleukin-1 α with anti-tumor activity, is also under development for the treatment of CACS. In an open-label, phase I dose-escalation study of refractory cancer patients, this drug was well-tolerated and improved LBM during an 8-week period [11]. A recently completed double-blinded, placebo-controlled phase III study in patients with refractory, metastatic colorectal cancer and CACS-related symptoms (fatigue, pain, elevated inflammatory markers, weight loss and reduced physical ability) evaluated the effect of MABp1 versus placebo. X-ray imaging was used to quantify change in LBM and health status was assessed based on patient reported outcomes (PRO) using the European Organization of Research and Evaluation of Cancer instrument (EORTC-QLQ-C30). Although more patients met the responder criteria in the treatment group than in placebo [14], a recent EMA opinion refused to authorize its

marketing due to concerns about the lack of clear improvements in LBM or QOL. Secondly, there was an increased risk of infection, which was not considered acceptable [32]. Further regulatory review is pending in Europe. A different clinical trial in the U.S. using survival as the primary endpoint was terminated early because the study crossed the prospective futility boundary of the primary endpoint (NCT01767857).

Other drugs targeting inflammation, myostatin/activins, cannabinoids, and beta-blockers have either failed or are still early in their development [12].

Challenges in clinical trials design

In spite of several targets showing promising results in early development, their difficulties obtaining regulatory approval after completing phase III trials underscores the need for the scientific community to reconsider the current strategies in drug development and the challenges moving forward in the field of CACS.

Unclear entry criteria for clinical trials

One of the areas where there is no consensus is on what the entry criteria for such trials should be. Recent definitions of cachexia have incorporated an earlier “pre-cachexia” stage and a late “refractory cachexia” stage. It seems clear that entering patients into clinical trials when they are in a late “refractory” stage will likely decrease the chance for any intervention to be successful. There is insufficient evidence to support the idea of including patients with “pre-cachexia” in clinical trials. Also, a validated definition of such state is not available and a number of “pre-cachexia” patients may improve or stabilize even without intervention, potentially decreasing the effect size of an intervention in a placebo-controlled trial.

The use of a biomarker that can identify individuals likely to progress or to respond to a specific intervention has been proposed but it has not been thoroughly tested. Inflammatory markers such as interleukin (IL)-6 or tumor necrosis factor (TNF)- α are elevated in CACS but attempts to target them specifically have failed [33,34]. This is an area of great interest but further research is needed before it can be implemented.

Another unanswered question is whether symptom burden, as measured by different PRO, should be part of the entry criteria for a trial. Although these are usually used as secondary outcomes, most trials do not include them as entry criteria. Given that recruiting patients for these studies is challenging, the argument often is that patients should not be excluded for lacking symptoms. On the other hand, including patients with low symptom burden may decrease the chance of finding a difference with any intervention on these PRO due to a “ceiling” effect.

Lack of regulatory precedent/guidance

Unlike in the development of treatments for other conditions (i.e. diabetes) where a regulatory pathway is well-established, there are no clear parameters by EMA or the FDA regarding the outcomes, effect size or other standard of care measures to be used in a trial. This forces each clinical program to test different strategies early in their development, increasing the costs of the trials. Given that each program adopts a different design, it is very

challenging to compare effects across different trials or to build upon the results of previous studies. Increased clarity in this regard has been recommended by an expert panel recently [35]. It is also unclear what specific indications these regulatory agencies would consider as “approvable” (i.e. anorexia, fatigue, cachexia, pre-cachexia, etc.) and so different companies have targeted different populations. This adds to the challenges of comparing trial results.

Lack of consensus on outcomes

Another area of uncertainty at the time of designing clinical trials includes the selection of primary and secondary outcomes. Traditionally, most studies have included a measure of muscle mass and another measure of function as co-primary endpoints given that mass alone is considered insufficient for regulatory approval. Although mortality has been shown to decrease in preclinical studies targeting cachexia [19], survival is not typically used as a sole primary endpoint in clinical studies given that most interventions are not expected to alter the natural course of the disease to a degree that would change mortality. An exception may be a recent MABp1 trial (NCT01767857). Although this trial was recently stopped due to futility, it is an interesting concept to use a drug that prevents tumor progression (more often considered a chemotherapeutic agent) as a way to ameliorate CACS. PROs have usually been included as secondary endpoints. It remains to be tested whether they can be used as primary endpoints for an indication. There is precedent for this in the U.S. in other settings such as HIV-induced anorexia [36], or in chemotherapy-induced nausea and vomiting [37]; but it is unclear if this regulatory pathway can be followed in CACS. Although the EMA may consider these type of outcomes for palliative care indications, their recent opinion in the case of MABp1 suggest that they may require a higher level of evidence to grant approval [32].

Lack of consensus on standardized methods

There is also lack of consensus on the validity of specific methods to assess these outcomes. For assessing muscle mass, DEXA has been the most common tool used although more recently computer tomography (CT) or MRI are emerging as the preferred methods due to their higher accuracy. Other methods including ultrasound and bioimpedance are usually seen as less accurate and not sufficient as primary or secondary outcomes in a clinical trial. The assessment of muscle function has also been challenging and different studies have used handgrip strength, stair climbing power, and actigraphy among others [13,31,38]. Further research is needed as this area is considered critical as an objective way to assess clinical relevance. Several questionnaires have been used to assess PROs but they are typically not used as primary endpoints. Some of the more well-validated questionnaires have a very broad scope and include symptoms that are unlikely to be affected by CACS treatments, whereas some of the more CACS-specific questionnaires have been criticized for being too focused and not representing overall QOL in a meaningful way. More research is needed in this area as well.

Lack of consensus on standard of care interventions

Although nutritional and exercise recommendations have been recently issued [39–41], they are not consistently implemented across institutions [42]. This represents a significant barrier to the development of large clinical trials as the standard of care treatments for CACS

(i.e. visits with dietitians, administration of caloric/protein/vitamin supplementation, exercise therapies) may vary widely among sites. Moreover, most large clinical trials testing the effects of pharmacological agents have not included specific nutritional or exercise interventions. This could explain why the results found in small, single-center clinical trials are often not reproduced once they are implemented in larger studies. This could also be a factor accounting for the lack of effect of certain anabolic interventions known to be effective in other settings where nutritional deficiencies or severe sedentarism are not as prevalent as in CACS.

Future Directions

Several groups have recently recommended that CACS patients be treated using a multimodal approach aiming at reversing weight and muscle loss [Arends, 2017 #21381; Anderson, 2017 #21298] including detailed assessments and repeated monitoring, nutritional support, anti-inflammatory treatment, treatment of secondary gastrointestinal symptoms and other causes for decreased oral intake as well as evaluation of anti-neoplastic options to reduce catabolism induced by the tumor or its treatments.

It is clear that further research is needed to fill the gaps in the current knowledge. More pre-clinical studies are needed to expand our understanding about key regulators of appetite, muscle mass and function, fat mass and energy metabolism in this setting. Moreover, suitable models that can be translated reliably to humans are desperately needed. Translational and clinical research efforts should focus on validating entry criteria, endpoints/outcomes and the different methods to assess these outcomes, and the potential synergistic effects and interaction between different targets, nutrition and exercise interventions. Clinical meaningfulness and significance should be taken into account in the design of clinical trials. Lastly, implementation research will be needed to assess the impact of the different guidelines and future therapies on these patients.

In order to effectively design successful research strategies, it is essential that all key stakeholders are included in the decision process. These should encompass: researchers, funding agencies, patients, regulatory bodies, health care providers (including physicians, nurses, dietitians, physical therapies, etc.) and payers.

Conclusions

Several pharmaceutical agents, including anamorelin, enobosarm, and MABp1 have recently completed phase III clinical trials for CACS or related indications and although no drug treatment has gained approval for these indications at this point, there are important lessons to be learned. CACS is a multifactorial/multidimensional syndrome and therefore a single agent/drug may be unlikely to treat/prevent all aspects of the disease. Nevertheless, most therapeutic strategies in development are single agents and do not include non-pharmacological interventions. It is possible that multiple agents addressing various symptoms or in combination with other interventions (nutrition/exercise) will eventually become the mainstay and have the greatest impact on patients' well-being. Further research

is needed in order to meet the challenges of bringing treatments into the clinic for patients suffering from CACS.

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Key points

- Cancer anorexia and cachexia syndrome remains an unmet medical need given that treatments for this condition are not currently available.
- Several programs including anamorelin, enobosarm and MABp1 have shown promising results in early development but have not obtained regulatory approval to this date.
- More research is needed including pre-clinical studies in models that translate reliably to humans and clinical studies validating the entry criteria, outcomes and interactions between drug, nutrition and exercise interventions.
- Clinical meaningfulness including input from all key stakeholders should be part of future study designs.