CLINICAL INVESTIGATION

Cancer cachexia: an unmet need in cancer treatment

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Cachexia is one of the most distressing and devastating experiences for cancer patients. It is now considered a complex, multifactorial metabolic syndrome characterized by anorexia, progressive and uncontrollable weight loss, fatigue, progressive depletion of adipose tissue and skeletal muscle, systemic inflammation, insulin resistance, abnormalities in the metabolism of carbohydrate, protein and lipid, as well as impaired immune function [1–3]. Within recent years substantial progress has been made in unraveling the underlying mechanisms of cancer cachexia [3–6]. Numerous cytokines including TNF-α, IL-1, IL-6 and IFN-γ have been postulated to play an important role in cachexia development [3–6]. These cytokines have been directly or indirectly implicated in cancer-induced muscle wasting by activating the ATP–ubiquitin–proteasome-dependent proteolytic pathway and profound anorexia by mimicking leptin signaling and suppressing orexigenic ghrelin and neuropeptide Y signaling [3–6].

Cachexia significantly impairs quality of life and response to antitumor treatments in cancer patients. Therefore, it strongly influences morbidity and mortality. In addition, cachexia is perceived as a harbinger of death, and therefore it has profound psychological and emotional impact on both patients and their families [7].

In 2011, international expert panel members agreed on the following definition for cancer cachexia: "Cancer cachexia 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. Its pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism" [3]. The panel has also defined the criteria for diagnosing cachexia in cancer patients:

- Weight loss greater than 5% over the past 6 months in the absence of simple starvation;
- BMI less than 20 kg/m^2 and any degree of weight loss greater than 2%;
- Appendicular skeletal muscle index consistent with sarcopenia (males <7.26 kg/m^2; females <5.45 kg/m^2) and any degree of weight loss greater than 2%.

It was also agreed that cachexia syndrome may develop progressively through various stages from precachexia to cachexia, and finally, to refractory cachexia [3].

Patients in the precachectic stage demonstrate early clinical manifestations and metabolic alterations of cachexia, such as loss of appetite, impaired glucose tolerance and elevated C-reactive protein preceding substantial involuntary weight loss. The risk of progression is variable and depends on the stage and type of the underlying cancer, the presence of higher a higher systemic inflammatory status, decreased food intake and lack of response to anticancer therapies [3]. Patients with

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involuntary weight loss of greater than 5% of their pre-illness stable weight over the previous 6 months, or a BMI of less than 20 kg/m² and weight loss of greater than 2%, or sarcopenia (another wasting syndrome) and weight loss of greater than 2%, but that have not entered the refractory stage, are defined as having cachexia. Finally, refractory stage of cachexia is characterized by a low performance status, worsening physical function and a life expectancy of less than 3 months due to progressive and chemorefractory metastatic cancer [3]. In this stage, reversal of weight loss and metabolic disturbances associated with cachexia seems no longer possible. In a preliminary study conducted by Vigano *et al.* [8], a significant correlation was observed between the stages of cancer cachexia and patient-centered indicators, including symptom burden, quality of life, tolerability of chemotherapy, body composition, hospitalization and survival. However, while precachectic and cachectic patients behaved similarly in clinical outcomes, these two groups of patients were significantly different from both noncachectic and refractory cachectic patients. The authors suggested that the data produced support the clinical relevance and applicability of the stages of cancer cachexia. However, more research to validate this staging method is required. Unfortunately, there are presently no robust clinical or molecular biomarkers to identify precachectic patients who are likely to progress further or to predict the rate at which they will progress [3]. Identification of such biomarkers, particularly if directly linked to a mechanism, will likely help determine the most appropriate treatment and estimate prognosis for patients in various stages.

The current treatment of cancer cachexia is very difficult due to its complex and multifactorial nature (particularly in the absence of clear knowledge about mechanism), and requires a multidisciplinary team approach that includes physicians, pharmacists, nurses, dietitians and physiotherapists. All available treatment options and expected outcomes should be discussed with the patients and their families. Treatment decision must take into account the patient's medical status and prognosis [9]. Therefore, the first step in the management of cancer cachexia is to identify the current status of patient's malignancy and the stage of cachexia. Since it takes at least several weeks for patients to respond to anticachectic treatment, patients with limited life expectancy may only be burdened by this treatment without benefit and thus such intervention may not be appropriate [9]. In order to get the best possible outcome, the treatments should be started at the earliest stages of cachexia, possibly at the precachexia with the aim of preventing or delaying the development of overt cachexia [9].

Successful treatment of the underlying malignancy would undoubtedly increase patient's response and tolerance to anticachexia therapies. In addition to this, there are two major components of cancer cachexia treatment: nutritional support and specific pharmacological therapy [4,5]. Although nutrition (parenteral and/or enteral) is a crucial part of a multimodal cachexia treatment, studies have shown that it alone does not improve weight loss or quality of life [10]. Therefore, nutritional interventions should be supported by pharmacological measures that can stimulate appetite and lead to weight gain (by increasing lean body mass [LBM] and with no fluid retention). Such interventions should also improve quality of life, should not interfere with cancer treatment and should have an adequate tolerance profile [4,5].

Numerous pharmacologic agents (megestrol acetate [MA], corticosteroids, cyproheptadine, dronabinol, mirtazapine, and so forth) have been used as appetite stimulants to treat unintentional weight loss in patients with cancer. Among these agents, MA, a synthetic progestin, is currently widely used as the first choice in clinical practice, which may stimulate appetite via neuropeptide Y in the ventromedial hypothalamus or by downregulating the synthesis and release of proinflammatory cytokines [11]. Recently published systematic reviews and meta-analysis investigating the efficacy and safety of MA in anorexia–cachexia syndrome demonstrated that MA significantly increases appetite and weight gain in cancer patients [12]. However, it has relatively short-term effect on appetite and does not lead to an improvement in patients' quality of life and survival [12].

Growing evidence points to an important role for a systemic chronic inflammatory response in the pathophysiology of cancer cachexia. Therefore, the use of anti-inflammatory agents (nonsteroidal anti-inflammatory drugs or COX-2 inhibitors), alone or combined with MA, may be able to break the cycle of cachexia. Eicosapentaenoic acid (EPA; an omega-3 fatty acid from fish oils) has also been shown to have anti-inflammatory properties including downregulation of both proinflammatory cytokine production and the acute phase protein response in both healthy individuals and cancer patients [13]. EPA may also decrease muscle breakdown by decreasing the expression of proteasome subunits, which are elevated in cancer cachexia [13]. These significant pharmacological properties of EPA make it a good candidate for the treatment of cachexia. Initial

results of EPA-enriched supplementation in cachectic cancer patients were promising with improvements in LBM, appetite and quality of life [13]. However, subsequent larger Phase III clinical trials reported minimal benefits of supplementation [13,14].

It is clear that one single treatment may not be completely successful in the management of cachexia because of the complexity of the pathogenesis and symptoms of this syndrome. Currently, multimodal therapeutic approaches would target more than one of the factors contributing to the development of cachexia is strongly recommended. According to Mantovani *et al.* [15], appropriate treatment of cancer cachexia should include drugs that address the following conditions: inflammatory state, nutritional disorder, metabolic derangements, immunological defects, poor quality of life and, in particular, fatigue. Accordingly, therapeutic approaches for cancer cachexia (and clinical trials) should include as primary end points the following variables: an increase in LBM and physical functional performance; a decrease in resting energy expenditure; an improvement in fatigue [4,15]. Moreover, the following variables should be included as secondary end points: increased appetite, improved quality of life and a decrease in proinflammatory cytokine levels [4,15].

The effectiveness and tolerability of a combination therapy targeting different mechanisms contributing to cancer cachexia was investigated by Mantovani *et al.* [16]. They carried out a randomized Phase III study comparing the efficacy and safety of MA, oral supplementation with EPA, L-carnitine and thalidomide in 332 patients with cancer cachexia and found that the combination of all drugs was superior to the drugs used alone in terms of primary end points (LBM, RRE and fatigue) as well as inflammation. Another Phase III study conducted by Macciò *et al.* [17] assessed the safety and efficacy of a multitargeted anticachectic therapy including MA, celecoxib, antioxidants (carboxycysteine and lipoic acid) and L-carnitine versus MA alone in patients with advanced-stage gynecological cancer. The combination treatment was found to be more effective than MA alone in improving LBM, resting energy expenditure, fatigue and global quality of life. Moreover, the serum inflammatory and oxidative stress markers IL-6, TNF-α, C-reactive protein, and reactive oxygen species decreased significantly in the combination arm, but did not change in the arm receiving MA alone.

Two-drug combination therapies may be more feasible in terms of reducing cost and overall treatment's complexity. In a small pilot study conducted by Kanat *et al.* [18], 62 patients with cancer cachexia were randomized into one of the three treatment arms:

- MA plus meloxicam, a selective COX-2 inhibitor;
- MA plus meloxicam plus oral EPA-enriched nutritional supplement;
- Meloxicam plus oral EPA-enriched supplement.

Treatment duration was 3 months. The results of the study did not show a significant difference between the treatment arms in both primary (bodyweight and LBM) and secondary (BMI, quality of life and serum cytokine levels) end points. In addition, results from a Phase III study conducted by Madeddu *et al.* [19] also showed a noninferiority of two-drug combination (L-carnitin + celecoxib) versus three-drug combination (L-carnitin + celecoxib + MA) in the treatment of patients with cancer-related anorexia/cachexia syndrome.

Promising initial results have also been obtained in current clinical studies evaluating several new classes of drugs for cancer cachexia treatment, such as melanocortin antagonists, β2 antagonists (formoterol and clenbuterol), anti-IL-6 monoclonal antibodies and nonsteroidal selective androgen receptor modulators [3–5]. Results from a recent Phase II trial by Dobs and colleagues have demonstrated for the first time that the use of enobosarm, a selective androgen receptor modulator, resulted in a significant gain of LBM and improvement in physical function in patients with cancer [20]. The results of this study may open a new era for therapeutic strategy for the management of muscle loss in patients with cancer.

Despite scientific advances in our understanding of the pathophysiology and management of cancer cachexia, there still remains a significant unmet medical need for effective treatments. The identification of novel targets and the integration of new drugs into various combinations will hopefully lead toward successful strategies to treat patients suffering from cachexia and/or its associated or related disorders.

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