

Module 26.4

Pharmacological and Multimodal Therapy for Cancer Cachexia

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Learning Objectives

- Comprehend the importance of a multidisciplinary approach to treatment of cancer cachexia;
- Understand the varied actions of drugs used in the treatment of cancer cachexia;
- Understand that there are non-pharmacological approaches to the management of patients with cancer cachexia, such as nutrition and exercise regimens.

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5. Self Assessment Test

Key Messages

- The management of cachexia requires a dedicated multi-disciplinary team and is best commenced earlier rather than later. Prevention is the key;
- Once a patient with advanced cancer is severely wasted it is neither practical nor ethical to intervene with anything other than supportive care;
- Drug treatments for cancer cachexia may interrupt the muscle wasting process by: reducing anorexia/stimulating appetite, attenuating skeletal muscle catabolism or stimulating muscle protein anabolism;
- Exercise regimens are methods of increasing muscle mass and decreasing patient fatigue;
- An improvement in the condition of all patients with cachexia may not be possible, however the goal must be to stabilise cachexia and prevent or delay further decline;
- There is currently no single or combined treatment strategy which is successful in all patients. However, reversible symptoms should always be treated and nutrition optimised.

1. Principals of the Treatment of Cachexia

The management of cachexia should always involve repeated re-evaluation of the at-risk patient by a dedicated multi-disciplinary team, including oncologist, family physician, clinical nurse specialist, occupational therapist and dietician (1). The purpose of this team is to identify the cachectic process as soon as it emerges and take prophylactic measures to attenuate its progression. Unfortunately, once a patient has become severely wasted, the primary initiating events are frequently compounded by secondary factors (e.g. prolonged bed rest), and it is often impossible to make any realistic form of therapeutic intervention, treatment is neither practical or (given the patient's almost imminent demise) ethically advisable. This systematic approach to the management of cachexia is currently complicated by the fact that there are no agreed early markers (clinical or biochemical) of cachexia.

Conventional entry criteria for randomised trials in the treatment of cachexia have suggested initiation of therapy with weight loss $\geq 5\%$ of normal body weight (2). Recent evidence has suggested a refinement of such criteria to reflect the multifaceted nature of cachexia (3). Patients with weight loss, reduced food intake and evidence of systemic inflammation (raised serum C-reactive protein concentration) are particularly at risk in terms of adverse functional status and prognosis. Such patients should be targeted for multimodal intervention as soon as identified (Fig. 1).

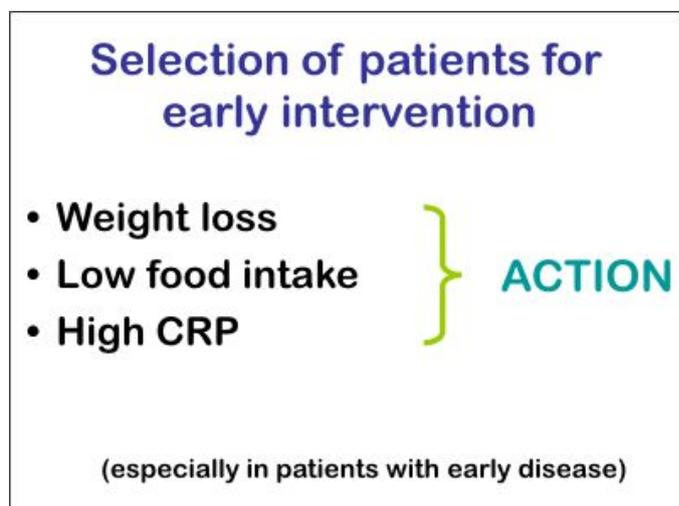


Figure 1 Selection of patients for early intervention

The current therapeutic options are limited both in scope and efficacy. However, the limited benefits of active management are no justification to ignore or fail to treat reversible factors associated with the cachexia journey (Fig. 2).

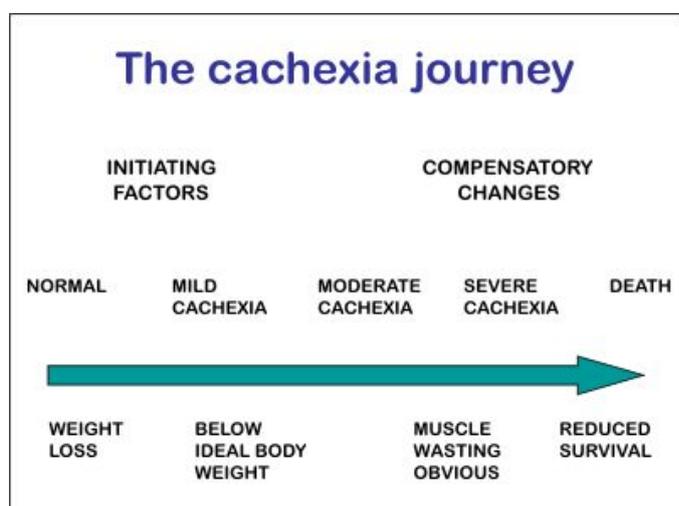


Figure 2 The cachexia journey

2. Pharmacological Treatment of Cachexia

In recent years, there have been a great number of clinical trials assessing a wide variety of pharmacological and non-pharmacological treatments for the amelioration of cachexia. All current approved therapies and experimental treatments for cachexia interrupt the wasting process by either reducing anorexia/stimulating appetite, attenuating skeletal muscle catabolism or stimulating muscle protein anabolism.

Appetite Stimulants

In patients complaining of severe anorexia or early satiety, an appetite stimulant may provide symptomatic improvement. Progestational agents (e.g. megestrol acetate (4) or medroxyprogesterone (5)) at high doses can improve appetite in approximately 70% of patients and may act by down-regulating pro-inflammatory cytokines. However, despite subjective improvement in appetite, increased food intake and induced weight gain may only be observed in approximately 20% of patients. There are three further problems with this strategy. Firstly, any observed weight gain is often due to oedema or increased fat deposition. Furthermore, by reducing circulating androgen levels, progestagens may actually decrease skeletal muscle mass. This may be one reason why no definite improvement in global quality of life (QoL) scores was observed in most clinical trials of progestagens. Secondly, the exact dose of progestagens required is unknown. Thirdly, there are a significant number of potential side-effects.

Agents which attenuate skeletal muscle catabolism

The attenuation of muscle loss has long been attempted through an upstream approach, which was mainly based on the knowledge that pro-inflammatory cytokines are important humoral mediators of muscle catabolism in both human and experimental cachexia. Thus, drugs which are capable of inhibiting the synthesis and/or release of cytokines (e.g. COX inhibitors, pentoxifylline, thalidomide, melatonin, statins, ACE inhibitors); cytokine antagonists (e.g. anti-cytokine antibodies, suramin); anti-inflammatory cytokines (IL-12, IL-15); and anti-inflammatory nutraceuticals have been extensively tested in experimental cachexia, with substantially positive results. Unfortunately, clinical trials testing the efficacy of this approach in human beings are extremely limited and only COX inhibitors and certain nutraceuticals (e.g. eicosapentaenoic acid (EPA)) represent current standard therapy. Non-steroidal anti-inflammatory drugs (NSAIDs) (in conjunction with peptic ulcer prevention) had been shown in several studies to prolong survival of cancer patients (6) (Fig. 3), reduce systemic inflammation and preserve body fat (7). In combination with megestrol acetate, ibuprofen has been shown to promote weight gain better than megestrol acetate alone when given to weight-losing patients with advanced GI malignancy (8).

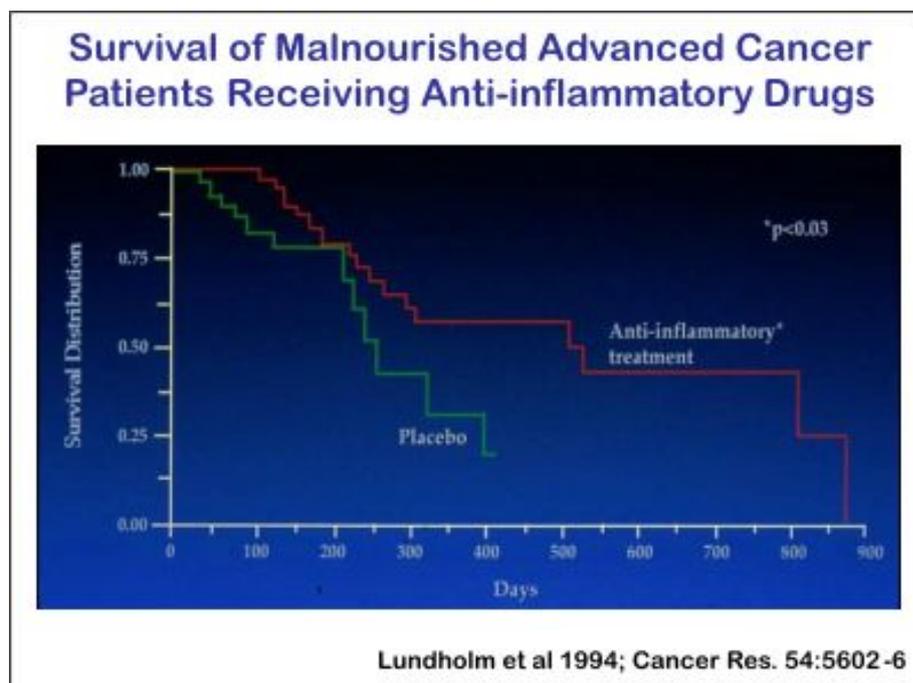


Figure 3 Survival of malnourished advanced cancer patients receiving anti-inflammatory drugs (6)

EPA, a natural omega-3 fatty acid component of fish oil, is known to down-regulate pro-inflammatory cytokines, block the effects of tumour-specific cachectic factors (e.g. PIF), and interact synergistically with current cancer chemotherapeutic agents. EPA can be provided either as fish oil capsules or as a constituent part of a high protein and calorie oral feed (e.g. Prosure®). This combination has been shown to arrest nutritional decline (9) and improve physical activity levels (10). Unfortunately, a large randomised EPA trial (n=200) of patients with pancreatic cancer was complicated by problems of patient compliance, but post-hoc dose-response analysis demonstrated a linear relationship between plasma EPA levels and gain in patient LBM (2) (Fig. 4).

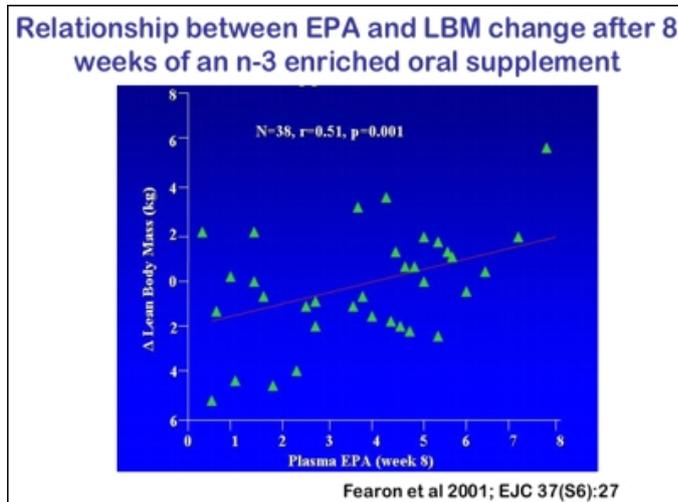


Figure 4 Relationship between EPA and Δ LBM after 8 weeks of an n-3 enriched oral supplement (2)

When considering the efficacy of this upstream approach to preventing muscle catabolism, it should be remembered that the consequences of chronic impairment of the systemic inflammatory (and immune response) in patients with underlying chronic disease (e.g. cancer) are currently unknown. Trials of IL-1 receptor antagonists (e.g. anakinra) and TNF inhibitors (e.g. infliximab, etanercept) in rheumatoid arthritis have been complicated by increased rates of opportunistic infections (particularly tuberculosis in the case of infliximab). Therefore, a more selective downstream approach might be safer and more effective at attenuating muscle loss. In this respect, direct proteasome inhibition could prove an effective strategy. Proteasome inhibition can also be achieved by pharmacological or nutritional manipulation. Experimental pharmacological agents include peptide aldehydes, lactacystin/ β -lactone, vinyl sulfones and dipeptide boronic acid analogues e.g. bortezomib (11). Again, EPA is the most widely researched nutritional proteasome inhibitor. It has been suggested that EPA can block the U-P pathway by inhibiting the formation of certain mediators in skeletal muscle (12).

In studies of cardiac cachexia, both angiotensin-converting enzyme (ACE) inhibitors (e.g. enalapril) and β -blockers (e.g. carvedilol and bisoprolol) (on top of existing ACE-inhibitor therapy) have been shown to prevent (or delay) the development of weight loss in patients with congestive heart failure (CHF). However, the beneficial effect of β -blockers may only be selective to cases of cardiac cachexia, as β -agonists (e.g. albuterol) have been shown to promote muscle anabolism in other forms of muscle atrophy. β -blockers cause a fall in the basal metabolic rate an effect which may underlie the increase in weight seen in some patients on long-term β -blocker therapy (13).

Agents which promote skeletal muscle anabolism

Anabolic androgenic steroid (AAS) administration increases mRNA expression of skeletal muscle androgen receptor, increases the intracellular utilisation of amino acids derived from protein degradation, and stimulates net muscle protein synthesis, resulting in net gain of skeletal muscle mass. Testosterone, nandrolone decanoate and oxandrolone have all been shown to be beneficial in a number of catabolic conditions, including severe burns (14), human immunodeficiency virus (HIV) infection (15), chronic obstructive pulmonary disease (COPD) (16), and sarcopenia associated with hypogonadism (17).

In recent years, much interest has focused on the importance of the growth hormone (GH)/insulin-like growth factor (IGF)-1 axis on the anabolic regulation of skeletal muscle mass. However, despite initially promising results, large, randomised, placebo-controlled, multi-centre trials have revealed

an increase in morbidity and mortality in critically ill intensive care patients receiving GH treatment (18). These negative results may have dampened initial enthusiasm from GH therapy, but the exact causes of the observed increased morbidity and mortality have never been elucidated. Indeed, experimental data from catabolic patients with sepsis, trauma, burns, cardiac failure and even anorexia nervosa indicate that heterogeneous alterations in the somatotroph axis remain an integral part of the wasting process. In cancer patients there remains the ongoing worry that growth factors may stimulate tumour growth, and these concerns have inhibited trials in this area.

3. Multimodal Therapy for Cachexia

Nutritional support of patients with cancer cachexia is an important part of the global management. Weight loss reflects a negative energy balance, which can be due to changes in energy intake, energy expenditure, or both (Fig. 5).

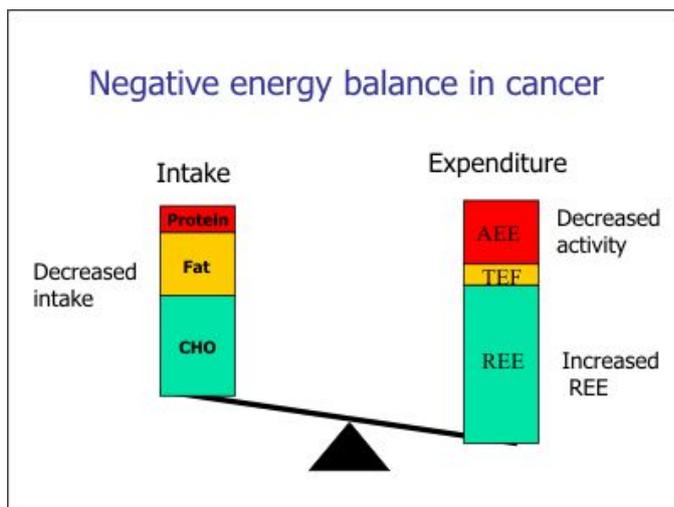


Figure 5 Negative energy balance in cancer

Several factors may contribute to the decreased intake of food in cancer patients. Anorexia, gastrointestinal symptoms, and effects of treatment with opiates, radio- or chemotherapy may all contribute to decreased food intake. The best way to improve energy balance would be to attenuate the metabolic abnormalities induced by the tumour and/or tumour-host interactions by controlling tumor progression. When this cannot be achieved, the next option is to try to increase nutritional intake by oral nutritional support or artificial nutrition. Artificial (enteral and parenteral) nutrition alone does not appear to affect overall survival in advanced cancer and is not superior to oral nutrition if a patient's gut is functioning normally (19, 20). Parenteral nutrition is difficult to maintain over extended periods of time and is associated with a number of complications. A number of parenteral nutrition trials were carried out in the 1980s in cancer patients. They showed little benefit but significant problems with infectious complications. Such findings further demonstrate the need for multimodal treatment of cancer cachexia. At present, early-intervention therapeutic strategies aimed at modulating mediators of the catabolic response, in combination with maintaining an adequate supply of nutrients, if possible by the oral/enteral route seem to be the best option. Nutritional support is discussed in detail in module 26.3.

Exercise Regimen

Physical activity is reduced in cachectic individuals for two different reasons. Firstly, wasted, cachectic muscle has reduced power output and fatigue earlier than healthy muscle. Secondly, it has been postulated that reduced physical activity is a result of modulation of energy demand by the cachectic individual, in order to reduce total energy expenditure (TEE) in the face of increased resting energy expenditure (REE) (10). Recent studies have confirmed significantly lower levels of physical activity in cachectic cancer patients compared with healthy controls (10). The levels observed in these cachectic patients are comparable to those seen in spinal cord injury patients living at home or in patients with cerebral palsy. It is entirely plausible that levels of activity as low as this will exacerbate the muscle wasting seen in cachexia through a process of deconditioning. Therefore, exercise regimes, such as walking programs, have been proposed as one method of

improving muscle mass and reducing subjective patient fatigue (21). General management of cachexia as outlined in this and other modules can improve fatigue (21). Fatigue can be further reduced by increasing psychosocial support and limiting patient stress levels (21). Patients with significantly reduced energy reserves should be advised to make most efficient use of the energy they do have by focusing on meal times and social interaction. Input from occupational therapists and the provision of physical aids in the home may also enhance QoL. If fatigue occurs in the presence of anaemia, recombinant human erythropoietin (rhEPO) treatment may be beneficial (22), although the benefit derived may not solely arise from its haematopoietic effects. There is increasing evidence for a protective role in EPO in experimental models of both myocardial infarction and ischaemia/reperfusion injury through anti-apoptotic effects within the myocardium. However, there are still undefined effects of EPO treatment on the progression of neoplastic progresses. Recent studies in patients with anaemia in the course of head and neck cancer have reported that long term rhEPO therapy significantly impaired disease control and decreased survival (23).

Further evidence of the need for a multimodal approach to cancer cachexia has been provided by studies demonstrating that nutritional support combined with a COX inhibitor and EPO, prolonged survival and increased both exercise capacity and body fat. However, careful attention to nutritional needs was found to be essential for these benefits to be obtained (24).

In the past, nutritional parameters (e.g. gain in weight or LBM) have been used as surrogate outcome measures in trials of anti-cachexia intervention. As physical activity is a function of patient wellbeing and appears to be linked to QoL, it has been suggested that it should be used as a primary outcome measure in intervention studies (25). However, methods of assessing patient physical activity levels in a simple, accurate and inexpensive fashion still remain elusive.

It is important to recognise that although some patients with cachexia can be improved, often the goals of intervention are limited to stabilising the situation or attenuate decline. Unfortunately no single therapy is effective in all patients. Even with optimal management only a proportion of patients will respond to therapy with weight stabilisation or improved physical function/quality of life. However, the limited benefits of active management are no justification for ignoring or failing to treat reversible factors associated with cachexia.

Supportive Care

Cachexia can be associated with a wide range of distressing, yet reversible, symptoms. Efforts should be made to ameliorate these symptoms wherever possible, in order to maximise patient QoL and to improve appetite and to reverse the underlying metabolic disorder. Nausea and vomiting should be controlled with regular anti-emetics (or surgery for mechanical obstruction); early satiety can be eased by gastric prokinetic agents; malabsorption is treated with pancreatic enzyme supplements; and constipation is relieved by laxatives. Whenever pain is a significant issue, attempts should be made to control it with the minimum of sedation. The treatment of depression in cachectic patients with either anti-depressant medication and/or and counselling improves dysphoria and QoL, and may also improve immune function and survival time. However, the diagnosis of major depression in these individuals is often clouded by neurovegetative symptoms that may be secondary to either cancer or depression (Fig. 6).



Figure 6 What is standard of care in cancer cahexia?

Summary

The optimal management of cancer cachexia requires a well coordinated multimodal and multidisciplinary approach. Adequate nutritional intake is fundamental, supported by an exercise programme where appropriate and by pharmacological intervention to improve appetite (e.g. megestrol acetate) or to moderate catabolism (e.g. EPA, or cox-inhibitors). These measures should be part of full supportive care for advanced cancer.

Currently, the best option seems to be early intervention combining modulation of catabolic mediators with adequate nutrient intake, preferably by the oral or enteral route.

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