Cancer cachexia and fatigue

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Clin Med 2006;**6**:140–3

Background

Cachexia is a disease process that develops in numerous chronic, end-stage disease processes (eg cancer, heart failure, AIDS, renal failure). It has no agreed definition but represents the complex metabolic process that occurs in patients with these conditions.[1] Cachectic patients lose lean muscle mass as well as fat, unlike starvation where only fat stores are initially depleted. In addition, the muscle wasting of cachexia cannot be reversed by increased food intake alone.[2,3] Weight loss is the symptom most commonly associated with cachexia but there are numerous other features (Table 1),[1] of which fatigue is an important one (70–100% of cancer patients).[4]

Cancer cachexia is common. Half of all patients with cancer lose some body weight; one-third lose more than 5% of their original body weight and up to 20% of all cancer deaths are caused directly by cachexia (through immobility, cardiac/respiratory failure).[5] Cachexia is particularly prominent in solid tumours of the upper gastrointestinal (GI) tract and lung (Table 2). Weight loss is a prognostic factor in the survival of cancer patients and is associated with a reduced response to chemoradiotherapy.[2]

Pathogenesis

Cancer cachexia is a complex metabolic disturbance involving numerous mechanisms (Fig 1). The cachectic patient is analogous to an accelerating car running out of petrol. The anorexia component of cancer cachexia reduces fuel supply (by ca 300–500 kcal/day) whilst accelerated metabolic cycling drives hypermetabolism (by ca 100–200 kcal/day). There are also the direct catabolic effects of muscle proteolysis and lipolysis. These changes underlie a key paradox of cachexia: whilst metabolic rate may be increased, overall (or total) energy expenditure is decreased due to a fall in physical activity.[7]

Anorexia

The anorexia component of cancer cachexia has both a neurohumoral mechanism due to disturbance of the central physiological mechanisms controlling food intake[8] and a broad raft of clinical causes. Secondary contributory factors include anxiety, depression, intestinal obstruction, nausea, vomiting, constipation, taste alterations and persistent pain.

Cancer-related fatigue

The mechanisms of cancer-related fatigue are unclear. Physiological factors leading to fatigue include anaemia, cancer treatments, tumour bulk and cytokine release. Psychological factors such as depression and anxiety, difficulty sleeping and a low degree of physical functioning also contribute.[4]

Other cachectic factors

Cachexia can occur in the absence of anorexia, suggesting that catabolic mediators produced by tumour or host cells are involved in the cancer cachexia process.[9] Experimental cachexia models suggest pro-inflammatory cytokines, such as tumour necrosis factor-α, interleukin (IL)-6, IL-1 and interferon-γ, can all play a role. Activation of the neuroendocrine stress response is also thought to be important. Potential mediators include increased adrenergic activity, elevated cortisol, low insulin and increased activity of the renin-angiotensin system.[1]

With regard to tumour-specific cachectic factors, proteolysis-inducing factor (PIF) is produced by tumours and excreted in the urine of patients with cancer cachexia. PIF is thought to contribute to increased muscle breakdown and decreased muscle protein synthesis in such patients.[10,11] Cachectic cancer patients can also excrete a lipid-mobilising factor which may contribute to depleted adipose tissue and can be detected in their urine.[12]

Diagnosis

History and examination are the most useful tools in making the diagnosis of cachexia and for assessing response to therapy. Weight loss, anorexia and fatigue are the commonest symptoms reported by advanced cancer patients.

Table 1. Features of cachexia.[1]

- Weight loss
- Anorexia
- Fatigue
- Muscle wasting
- Aesthesia
- Anaemia
- Oedema

Table 2. The commonest malignancies in which cachexia develops as part of the clinical course.[6]

Malignancy	Patients with cachexia (%)
Gastric cancer	85
Pancreatic cancer	83
Non-small cell lung cancer	61
Small cell lung cancer	57
Prostate cancer	56
Colon cancer	54
Unfavourable non-Hodgkin's lymphoma	48
Sarcoma	40
Acute non-lymphocytic leukaemia	39
Breast cancer	36
Favourable non-Hodgkin's lymphoma	31

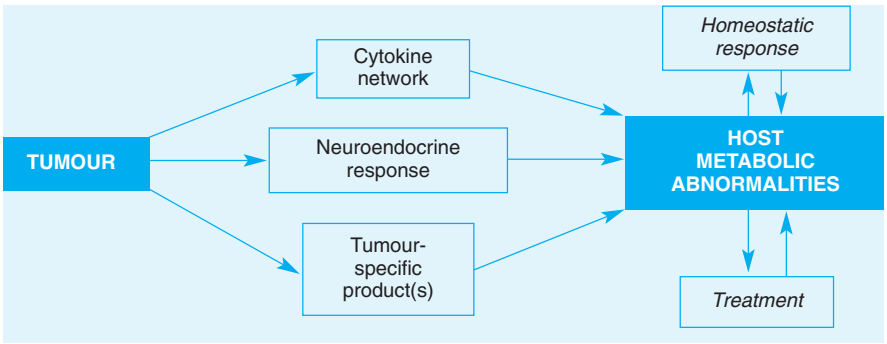

Fig 1. Mediator pathways implicated in cancer cachexia. Different pathways contribute to a variable extent, depending in part on both host and tumour.

Symptoms associated with declining food intake are key warning signals (eg loss of appetite, early satiety, nausea/vomiting and taste/smell alterations). Weight and height should be recorded. Weight loss greater than 5% suggests developing cachexia, while above 15% suggests the patient is well advanced into the cachectic state. Body mass index (BMI) should be calculated (BMI <18 indicates significant undernutrition). Oedema and ascites are common, and this fluid retention may mask the severity of underlying weight loss. Plasma albumin concentration may be low and, if accompanied by an elevated C-reactive protein or erythrocyte sedimentation rate, reflects an underlying systemic inflammatory response that occurs in many malignancies and which contributes to the weight-losing process.[13]

Management

The management of cachexia requires a dedicated multidisciplinary team approach: physician, surgeon, general practitioner, nurse specialist and dietitian. Cachexia is a chronic problem requiring repeated re-evaluation as the clinical condition of the patient changes (Fig 2). Intervention is not usually beneficial for a patient who has become severely wasted, is bedridden and within weeks of dying, but such patients may be helped by a course of steroids to improve mood and appetite. Early recognition and prophylactic measures are better than trying to reverse an advanced situation. Control of the following symptoms will provide the ideal background for optimisation of appetite, function of the GI tract and treatment of the metabolic disorder:[1]

- *nausea/vomiting* can be controlled with regular anti-emetics (or surgery for mechanical obstruction)
- *early satiety* is eased by gastric stimulants
- *malabsorption* is treated with pancreatic enzyme supplements
- *constipation* is relieved with laxatives
- *pain* should be controlled with the minimum of sedation
- *depression* may be treated with antidepressants and counselling.

Diet

Food intake can be improved by providing small, frequent energy-dense meals that are easy to eat (eg dairy products, ice cream). Patients should eat in pleasant surroundings and attention be given to the presentation of food. Extremes of taste/smell should be avoided, as should meals with very high fat contents (which delay gastric emptying and worsen anorexia). Formal nutritional counselling should be sought from a dietitian.[8] Provision of energy and protein-dense oral feeds (1.5 kcal/ml) can be useful, but these must not replace normal food.

One way of optimising nutritional input is for the patient to take a fixed dose of supplements at regular times (as with a prescription medication). Patients should aim to take 200–400 ml of supplements daily (300–600 kcal), accepting that this will suppress some normal food intake but providing an overall gain of 200–400 kcal/day.

Artificial nutritional support

It is sometimes justified to provide artificial nutritional support (either enteral or parenteral) in advanced cancer patients when the main cause of cachexia is reduced food intake and where limited tumour burden and good performance status justify such invasive forms of supportive therapy. It is at all times important to balance the benefits to a patient's quality of life with the problems of artificial nutritional support (eg time in hospital, complications of central venous access for total parenteral nutrition).

Severe anorexia

In patients complaining of severe anorexia or early satiety an appetite stimulant may provide symptomatic improvement. Moderate alcohol consumption before and during a meal can help. Early satiety will respond temporarily to the use of prokinetic agents (eg metoclopramide). High doses of progesterones (eg megestrol acetate or

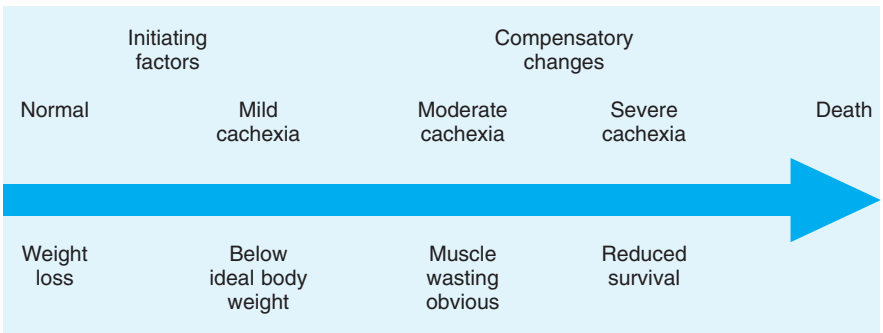

Fig 2. The cancer cachexia journey.

medroxyprogesterone) improve appetite in about 70% of patients and can result in increased food intake and weight gain in approximately 20%.[14] However, this weight gain is often due to oedema or increased fat deposition rather than skeletal muscle. Together with progestagens, corticosteroids induce a temporary effect on appetite, performance status and the patient's feeling of physical well-being. These changes are limited to a few weeks. Due to the greater toxic side effects associated with corticosteroids, progestagens are the current front-line agents used to treat anorexia in patients with cancer.

Metabolic management

The metabolic management of patients with cachexia should focus on downregulating the systemic inflammatory response to malignancy. Non-steroidal anti-inflammatory drugs together with peptic ulcer prophylaxis have been shown to prolong survival of cancer patients, reduce systemic inflammation and preserve body fat.[13] Eicosapentaenoic acid (EPA), a natural component of fish oil, is known both to downregulate pro-inflammatory cytokines and to block the effects of tumour-specific cachectic factors (eg PIF). EPA can be provided either as fish oil capsules or as a combination therapy by being incorporated in a high protein and calorie oral feed (eg Prosure®). This combination has been shown to arrest nutritional decline and improve physical activity levels but not to cause weight gain.[7,15]

Drugs with a direct anabolic effect (eg testosterone) have been suggested for the treatment of cachexia, and anabolic steroids have been shown to improve patients' weight without any apparent adverse effect.[1]

Fatigue

Management of cachexia as outlined above can improve fatigue.[4] Decreased activity in order to conserve energy may lead to deconditioning and decreased exercise tolerance. Exercise regimens, such as walking programmes, can reduce the level of fatigue experienced by patients.[4] Fatigue can also be lessened by attempting to reduce stress and increase psychosocial support.[4] If fatigue proves a problem or occurs in tandem with anaemia, there is evidence to suggest that recombinant erythropoietin (EPO) may be beneficial.[16] However, recent evidence has also raised the issue of stimulation of tumour progression with EPO in patients with head and neck cancer.[17]

Finally, it is important to recognise that, although some patients with cachexia can be improved, the goals of intervention are often to stabilise the situation or attenuate decline. Patients should be encouraged to keep active to prevent muscle wasting due to immobilisation. Patients with limited energy reserves/physical activity capacity should be advised to make most efficient use of the energy they have (focusing on meal times and social interaction). Advice from occupational therapy and provision of physical aids in the home may enhance quality of life.

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 and possible translation into stable or improved physical

Key Points

- **Cancer cachexia has no agreed definition but represents a wasting syndrome involving loss of muscle and fat caused directly by tumour factors and/or indirectly by abnormal host response to tumour presence**
- **Patients with cancer cachexia develop chronic negative energy and protein balance driven by a combination of reduced food intake (secondary to anorexia) and metabolic change**
- **The management of cachexia requires a dedicated multidisciplinary team and is best commenced earlier rather than later**
- **No single or combined treatment strategy will be successful in all patients**

KEY WORDS: anorexia, cachexia, cytokines, fatigue

Table 3. Possible future therapies for cancer cachexia.

Therapy	Details
Cannabinoids (eg dronabinol)	Affect cytokine production
Thalidomide	Stops weight loss in unresectable pancreatic cancer by downregulating pro-inflammatory cytokines
Suramin	Inhibits cachexia by inhibition of TNF-α and IL-6
ATP infusion	Modestly increases strength and slows decline in quality of life
Cytokine traps	Block cytokines (no clinical data yet)
Ghrelin	Appetite stimulant which increases food intake and stops weight loss in animal models
Branched chain amino acids	Improve energy levels
Dopamine	Increases food intake and mood
Melatonin	In combination with fish oils stabilises weight
Nitric oxide and eicosanoids	Reduce tumour growth and improve anorexia
β-blockers	Reduce resting energy expenditure and potentially reduce weight loss
ACEIs	Angiotensin II can stimulate muscle breakdown; hence ACEIs can potentially attenuate this weight loss
β-hydroxy-β-methylbutyrate plus arginine and glutamine	Increases lean body mass

ACEI = angiotensin-converting enzyme inhibitor; ATP = adenosine 5'-triphosphate; IL = interleukin; TNF = tumour necrosis factor.

function/quality of life. However, the limited benefits of active management are no justification to ignore or fail to treat reversible factors associated with cachexia.

The future

Over the last decade there has been an explosion of research into the mechanisms of cancer cachexia and potential targets for treatment. Table 3 outlines possible future therapies currently being evaluated. Clinical trials evaluating therapies for cancer cachexia patients are hampered by patient heterogeneity, difficulty in defining end-points, mild to moderate activity of combination regimens, patient attrition and cost. Such problems need to be addressed actively by major research initiatives if there is to be progress in management of this distressing syndrome.

Conflicts of interest

None.

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