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Cancer cachexia: Developing multimodal therapy for a multidimensional problem

*K.C.H. Fearon**

Clinical and Surgical Sciences (Surgery), School of Clinical Sciences and Community Health, University of Edinburgh, Royal Infirmary, 51 Little France Crescent, Edinburgh EH16 4SA, United Kingdom

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ABSTRACT

Cancer cachexia is a multi-factorial syndrome that encompasses a spectrum from early weight loss (pre-cachexia) to a state of severe incapacity incompatible with life. The molecular basis of the syndrome in animal models (based on host–tumour cell interaction, the neuro-hormonal control of appetite and the hypertrophy/atrophy pathways that govern muscle-wasting) has provided a new raft of biomarkers and therapeutic targets. Key defining features of cachexia in humans (weight loss, reduced food intake and systemic inflammation) now provide not only a framework for classification but also a rationale for targets for therapeutic intervention. The role of age and immobility in muscle-wasting also provides a rationale for the nature of nutritional support in cachexia. There is now a substantive evidence that multimodal approaches that address these key issues can stabilise and even improve the nutritional status, function and quality of life of at least a proportion of advanced cancer patients. Novel biomarkers for patient stratification and more specific techniques for the estimation of muscle mass and physical activity level herald a new era in trial design. The current evidence-base justifies new enthusiasm for the design of complex intervention studies in the management of cancer cachexia.

1. Introduction

Progress in the treatment of cancer cachexia has been slow. Contributory factors include the lack of a clear definition for cachexia, the multi-factorial nature of the condition, the lack of validated biomarkers, primitive clinical trial design and a paucity of interest by pharmaceutical/government sponsors of research. At present, the oncology community is divided between the majority who believe that weight loss is an inevitable consequence of progressive tumour growth versus a small minority who think that there is potential to significantly influence the patients' nutritional status (and thereby improve the quality and the quantity of life) independent of tumour status. The former look to better ways of controlling tumour growth whilst the latter await well-conducted randomised trials on which to find an evidence-base to enact the change in clinical practice. The aim of this article is to determine whether there are grounds for optimism.

2. Classification of cachexia

It would be surprising to find that progress had been made in the treatment of a condition for which there was no clear definition. Sadly, there is no agreed classification of cancer cachexia. What can be said is that cachexia is a multidimensional syndrome that affects every compartment of the body and is most easily recognised in its advanced form by the severe loss of subcutaneous fat and skeletal muscle. Attempts by clinical trialists to define cachexia have focused

* Tel.: +44 (0) 131 242 3615; fax: +44 (0) 131 242 3617.
E-mail address: k.fearon@ed.ac.uk
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generally at an earlier phase of cachexia and defined the condition using a certain percentage of weight loss or a particular level of body mass index. Unfortunately, these definitions have been somewhat arbitrary/non-specific and have not been adopted uniformly as trial entry criteria. Thus many intervention trials are not comparable, making meta-analysis or systematic analysis impossible. Equally, due to the lack of an evidence-base, it has not been possible to develop a classification system for the day-to-day management of cachexia. There is an urgent need to develop a classification system that will resolve this vicious circle.

In the search for a clinically meaningful classification system, it is important to recognise that cachexia represents a genuine spectrum (Fig. 1). Patients may first notice simple weight loss and then progress through degrees of severity to the point where they are depleted of energy reserves (fat), have gross muscle-wasting, are immunocompromised and will die primarily as a result of these issues. When trying to define cachexia and its impact, the initial phase (pre-cachexia) may have little clinical impact whereas the advanced phase (cachexia syndrome) will impact on both the quality and quantity of life.

In a recent study of patients with advanced pancreatic cancer,[1] we sought to define the features of cachexia that impact on patients' function and survival. Three key features were identified: weight loss (>10%), systemic inflammation (C-reactive protein >10 mg/l) and reduced food intake (<1500 kcal/d). When patients were grouped according to weight loss alone, nearly 80% fell into this category, yet this did not define patients with altered body composition or reduced subjective function or health status. In contrast, when grouped according to the presence of all three factors, patients demonstrated a reduced lean body mass, the reduced objective and subjective indices of function and a reduced health status (Fig. 2). Importantly, the number of patients who fulfilled the three-factor profile was only about 20% of the total population. Thus, although the prevalence of cachexia may be less when considered in a more multidimensional form, its impact on the patient is more devastating.

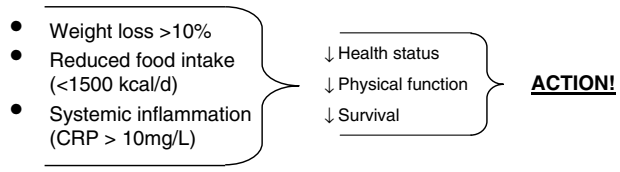

Fig. 2 – Definition of cachexia: patients with weight loss, reduced food intake and systemic inflammation require urgent treatment.

Equally, not all patients will progress down the full cachexia spectrum. Some may die of their primary disease before they develop advanced cachexia, whilst others may stabilise as a result of treatment of their primary disease or due to other clinical factors which preclude further progression. Such a heterogeneity makes it particularly difficult to trial or target prophylactic therapy successfully. Prophylaxis would be best initiated in the pre-cachexia phase, yet there are few robust biomarkers to guide such a strategy. The situation is made more complex when one considers that a substantial portion of the patients 'at risk' will be obese initially. Weight loss in obese patients may paradoxically improve the physical function or the quality of life – at least initially!

3. Prevalence and impact of cachexia

Approximately one-quarter of all deaths in Western Society are due to cancer. 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).[2,3] The incidence of weight loss upon diagnosis varies greatly according to the tumour site. The highest prevalence of weight loss is seen amongst patients with solid tumours, e.g. gastric, pancreatic, lung, colorectal and head and neck.[4] In patients with pancreatic cancer, 80% of patients have at least 10% weight loss at diagnosis and the cachexia syndrome is present in 20–25%.[1] The overall prevalence of weight loss in cancer patients may rise as high as 86% in the last 1–2 weeks of life.[5]

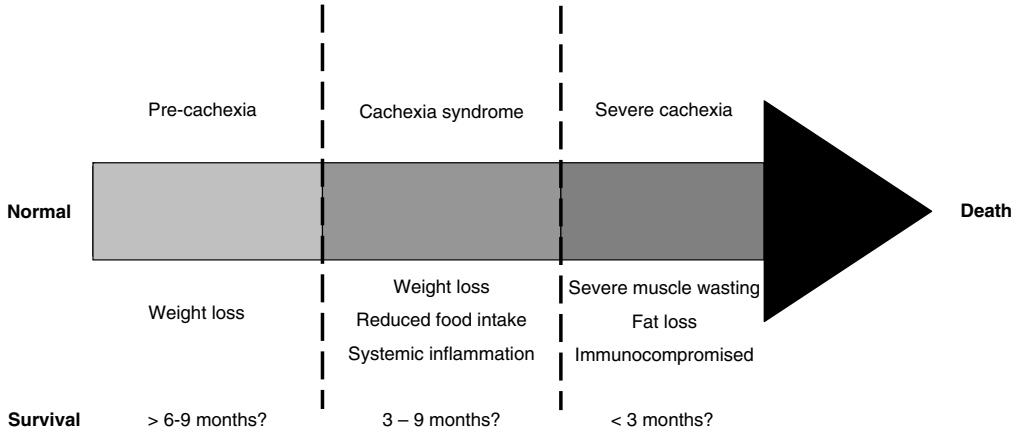

Fig. 1 – Classification of cachexia: cachexia represents a spectrum. Not all patients will progress down the spectrum. There are no robust biomarkers to identify those in the pre-cachectic phase who are likely to complete the journey or the rate at which they will do so.

3.1. *Impact on survival*

Based on the three-factor profile (weight loss, reduced food intake and systemic inflammation) of cancer cachexia syndrome, we have noted that pancreatic cancer patients who met at least two of the components had a significantly worse prognosis.[1] Alternatively, in a study of patients with oesophageal cancer, we have found that a weight loss of >2.75% per month is an independent prognostic indicator of decreased survival.[6] Paradoxically, high levels of absolute weight prior to diagnosis and substantial weight gain following diagnosis/treatment are associated with decreased survival in patients with breast cancer.[7] Thus, the impact of cachexia on cancer survival and the factors that contribute to such risk are probably tumour-type specific.

3.2. *Impact on the quality of life (QoL)*

Cachexia has a detrimental effect on patient QoL. Patients with cancer cachexia report an altered body image, which impacts their emotions, spirituality, relationships and social functioning. Lives are restricted and isolated, which is compounded by emotional distancing by carers and health care professionals.[8,9] These patients also experience anorexia and increased fatigue.[1,5,10] Overall, this results in decreased performance status and QoL indices.[11,12] It has been proposed that physical activity level may be a novel and robust outcome measure for intervention studies in cachexia.[13,14]

The devastating effect of cachexia is further characterised by considering the free-living physical activity of patients. We have recently characterised patients using an electrical activity monitor worn over a period of one week. Cachectic cancer patients demonstrate a level of physical activity that is reduced by approximately 40%.[15]

3.3. *Impact on treatment*

Cachexia has a significant impact on cancer treatment. Dewys and co-workers[4] defined weight loss >5% prior to the onset of chemotherapy as the defining point for the risk of poor response to therapy and shortened survival. A separate study in patients with lung cancer showed that patients with weight loss more frequently failed to complete at least three cycles of chemotherapy and had decreased survival duration.[16]

4. Pathophysiology of cachexia

Cancer patients lose weight as a result of reduced food intake (secondary to anorexia), abnormal metabolism or a combination of the two. For patients whose weight loss is predominantly due to anorexia, artificial nutritional support can be very successful. In this situation, the problem arises in balancing the use of invasive techniques against the preservation of the quality of life, in an individual whose lifespan is quite limited. However, this is not the situation in most cancer patients. The majority of weight-losing cancer patients probably have a mixture of anorexia and abnormal metabolism, and this situation is more challenging to treat. In these patients, it is clear that nutrition alone is not the answer. For reasons that are not completely understood, nutrition as a unimodal therapy is unable completely to reverse the wasting associated with cancer.[17] Suggested reasons include the promotional effect of nutrition on tumour growth and/or the tumour acting as a 'nitrogen trap' but the more likely explanation is the persistence of complex metabolic and catabolic processes involved in cancer cachexia. Needless to say, the most common reasons for oral (rather than enteral or intravenous) nutritional supplementation to fail in anorectic cancer patients are the persistence of the complex of primary and secondary factors leading to a limitation of food intake in the first place.[18]

Although the metabolic component of cancer cachexia remains largely unresolved, it has long been considered to be the result of a variety of interactions between the host and the tumour.[3] The presence of a tumour results in the initiation of a host inflammatory response probably mediated by tumour-derived pro-inflammatory cytokines.[19] Systemic inflammation then initiates a reprioritisation of protein metabolism with the induction of the acute phase response and the mobilisation of fat reserves. This together with pro-cachetic factors, secreted by the tumour, promotes protein and fat breakdown.[20,21] Other overlapping pathways such as upregulation of protein degradation pathways (e.g. the ubiquitin–proteasome system [UPS]) and dysregulation of the dystrophin glycoprotein complex (DGC) facilitate muscle catabolism.[22,23] Finally, the activation of neuroendocrine pathways may also contribute to hypermetabolism and increased catabolism.[24] Taken together these changes lead to enhanced substrate cycling (fat, carbohydrate and protein) which is associated with metabolic inefficiency, weight loss and a suboptimal response to nutritional support ('anabolic blockade').

In addition, however, patient factors including age and levels of physical activity and the specific mechanics of protein metabolism in cancer may also contribute to such an anabolic blockade.

4.1. *Age*

Generally speaking, most patients with cancer are aged over 70 years. From the age of 50 years onwards, ageing is associated with the degenerative loss of skeletal muscle, a condition known as sarcopaenia.[25] The mechanisms underlying this condition are various and include reductions in circulating levels of anabolic hormones, e.g. testosterone. Furthermore, sarcopaenia is exacerbated by chronic illness, inadequate diet and inactivity.[26] However, one of the predominant mechanisms appears to be the anabolic resistance of elderly muscles to post-prandial amino acid loading. Normally, in the physiological post-absorptive state there is a negative balance between whole-body protein synthesis and degradation. Any protein loss is immediately made up in the post-prandial state by protein gain stimulated by nutrient intake.[27] In human studies, the post-prandial increase in plasma amino acid concentration stimulates muscle and whole-body protein synthesis by 50% and 40%, respectively[28,29] and whole-body protein balance is reversed from negative to positive. Sarcopenia appears to be (at least partly) the result of deficits in intracellular anabolic signalling pathways normally involved in these processes.[26] Clearly, these phenomena may not only

be present in the skeletal muscle of elderly cancer patients but may also be exacerbated by the presence of ongoing systemic inflammation.

4.2. *Physical activity*

In a recent study of hypermetabolic, cachectic pancreatic cancer patients, it was shown that the measured mean physical activity level [ratio of total energy expenditure (TEE) to resting energy expenditure (REE)] was much lower (mean 1.24) than that recorded in healthy adults of similar age (mean 1.62).[30] This level of physical activity is comparable with that observed in spinal cord injury patients living at home.[31] It is also entirely plausible that the levels of activity as low as this may exacerbate muscle-wasting,[32] as it is well understood that, in any individual, a lack of physical activity will cause deconditioning and deterioration in skeletal muscle mass. The reduction in whole-body protein with physical inactivity is thought to be the result of the loss of the stimulatory effect of physical activity on amino acid-mediated promotion of muscle protein synthesis.[33] The ability of the combined insulin and glucose infusions to decrease whole-body proteolysis is unaffected by muscle inactivity,[32] and therefore this phenomenon appears specific to amino acid-induced anabolism. Furthermore, the loss of anabolic stimulation by physical activity only tends to affect bed-rested individuals during the fed state; protein balance is similar to that observed in healthy controls during the fasted state. When combined, these results suggest that a supra-normal protein intake is required to achieve the same post-prandial anabolic effect during muscle inactivity and cachexia. It also points to the importance of maintaining even modest levels of physical activity.

It is worth noting that in weight-losing pancreatic cancer patients who are not bed-ridden, it is possible to increase TEE and physical activity level with a specialised nutritional supplement containing eicosapentaenoic acid (EPA) (an *n*–3 fatty acid with anti-inflammatory properties) administered over an 8-week period, but not with an isocaloric, isonitrogenous control supplement.[30] As physical activity is also an important component of the physical and social domains of the quality of life (QoL), any restoration of physical activity level towards a normal level may translate into an improvement in QoL for cachectic patients.

4.3. *The kinetics of protein metabolism in cachectic patients*

To date, no clinically applied, nutritional regimen has been completely successful in reversing cancer-associated weight loss. This observation might be explained partly by the constant deleterious influence of the acute phase protein response (APPR). In weight-losing patients with pancreatic cancer, not only are the synthesis rates of hepatic export proteins (fibrinogen) elevated in the fasted state,[34] but also they rise even higher during enteral feeding.[35] Thus, feeding appears to accelerate one of the basic mechanisms that contribute to the loss of lean tissue and the deterioration of nitrogen economy.

It has been calculated that 2.6 g of muscle protein must be catabolised to produce 1 g of fibrinogen, emphasising both the significant mismatch between the essential amino acid composition of muscle and acute phase proteins[36] and the important role of the APPR as a driver of cachexia. This concept may help to explain the failure of simple nutritional programmes to reverse weight loss adequately in cancer patients;[17] without downregulation of the APPR, such a conservative approach is likely to fail. Anti-inflammatory nutraceuticals might be the key to combining high calorie/high protein nutrition with the modulation of hepatic export protein synthesis. Such a modulation has been demonstrated in cachectic pancreatic cancer patients receiving oral supplements enriched with EPA.[34]

The tendency towards loss of skeletal muscle mass (independent of the nutritional environment) may also be due to the direct activation of catabolic pathways within skeletal muscle by either cytokines or tumour-specific catabolic factors such as PIF. Of particular interest is the observation that the ubiquitin–proteasome pathway (UPP) is activated in patients with various forms of cancer,[37] even before they become cachectic. The UPP is a key regulator of many cellular functions and therefore complete inhibition would be harmful. At present, the drugs available to inhibit the UPP are relatively non-specific and have significant toxicity. Therefore, it is of little surprise that initial attempts to use drugs such as bortezomib (a known proteasome inhibitor) in human studies have not met with success.[38] Further elucidation of the specific components of the UPP involved in cancer cachexia and the development of more specific drugs to inhibit these components carry significant promise for the future.

4.4. *Implications for therapy*

Current understanding of the pathophysiology of anabolic blockade in cachexia has specific therapeutic implications (Fig. 3). The impaired anabolic response to nutrition during physical inactivity implies the need for a higher protein intake during inactive periods. Furthermore, acceleration of the reprioritisation of protein metabolism towards the liver in the fed state and during systemic inflammation demands the addition of an anti-inflammatory intervention. When devising a therapeutic programme for cancer cachexia, the emphasis should be placed on multimodal therapies that tackle all of these issues simultaneously. Such an intervention would, at least, combine the use of high protein nutrition, anti-inflammatory agents to downregulate the APPR and routine mobilisation programmes to prevent deconditioning and encourage physical activity-induced stimulation of post-prandial anabolism.

5. Biomarkers of cachexia

For the purposes of intervention trial design, there are a variety of novel biomarkers (Fig. 4) and end-points that should be considered. This area is developing rapidly and thus the following discussion is not exhaustive.

5.1. *Plasma biomarkers of cachexia*

Plasma is easily sampled and therefore an important compartment to study for potential biomarkers of cachexia. The

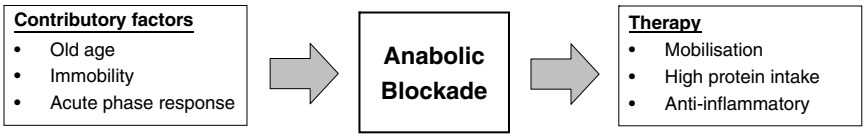

Fig. 3 – Cachectic cancer patients respond sub-optimally to nutritional support. Active mobilisation, high protein intake and administration of an anti-inflammatory can help overcome such anabolic blockade.

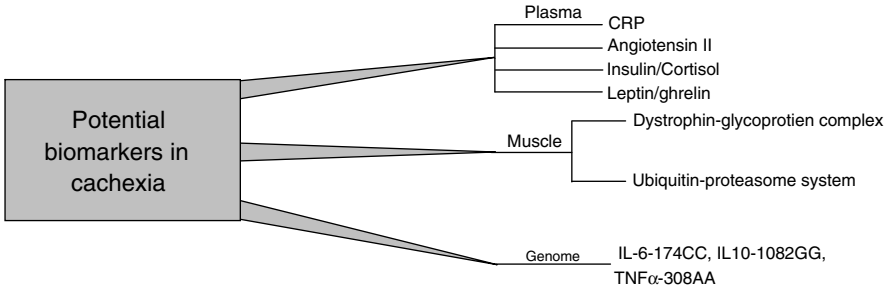

Fig. 4 – Potential biomarkers for patient stratification.

positive hepatic acute phase reactant, C-reactive protein (CRP), has been shown to be a robust marker of systemic inflammation in cancer patients and has been associated with the presence of anorexia, hypermetabolism, accelerated weight loss and shortened survival.[39–41] CRP has been studied in a wide variety of tumour types and has been incorporated into a three-factor mathematical definition of cachexia for patients with pancreatic cancer.[1] CRP is thought to be a key potential biomarker for cachexia.

The plasma concentration of a variety of pro-inflammatory cytokines has been evaluated in numerous studies in human subjects in relation to the development of cancer cachexia, including TNF-α, IL-1, IL-6 and IFN-γ.[24,42–44] These studies, unfortunately, have not given a clear, reproducible pattern whereby the plasma concentration of any individual cytokine can be related to the development of cachexia. Controversy has surrounded the use of different cytokine assays, their variable sensitivity, the short half-life of cytokines and the presence of natural cytokine inhibitors.

In terms of the neuroendocrine axis, insulin resistance and hypercortisolaemia have been documented in the cachectic cancer patient;[45,46] however, these have not been studied in detail in terms of the early cachectic process. Hypogonadism in males is associated with sarcopaenia and has been shown to be highly prevalent in male patients with advanced cancer.[47] However, it is not clear just how independent of systemic inflammation the development and effects of hypogonadism in advanced cancer might be. Moreover, it is not clear how sex hormone levels influence muscle mass maintenance in female patients with cachexia. Angiotensin II has been shown to produce muscle catabolism and weight loss in murine models, and these effects are attenuated by angiotensin converting enzyme (ACE) inhibitors.[48] Angiotensin II therefore may be an interesting marker for cachexia.

Finally, other potentially useful plasma markers include peptides which are involved in the control of food intake such as leptin and ghrelin.[49,50] Whilst both factors have been implicated in the anorexia component of the cachexia syndrome, the complexity of their interaction with other factors (e.g. end-organ sensitivity) that control appetite makes them unlikely as robust biomarkers that can be used in isolation.

5.2. *Muscle biomarkers of cachexia*

Various aspects of the molecular mechanisms of muscle atrophy or hypertrophy have now been described in detail.[51] It would appear that in cancer cachexia, there is suppression of the hypertrophy pathways and upregulation of the atrophy pathways.[52] The hypertrophy pathways seem to predominate and in particular activation of the ubiquitin–proteasome pathway (UPP) which is the major catabolic pathway in cancer cachexia.[53] Overactivation of UPP has been documented in rodent models of cancer-associated muscle-wasting.[54] Research on human subjects with cancer has also demonstrated UPP overactivation.[55] Activation of the UPP has been ascribed in part to the presence of systemic inflammation.[56] Recent data have suggested that systemic inflammation may act in part through dysregulation of the dystrophin glycoprotein complex (DGC).[22] The DGC is a muscle-specific protein manifold that anchors muscle fibre membranes in place and prevents them from being torn by shear forces produced during muscle contraction. The dysregulation of DGC has been shown to correlate positively with weight loss in patients with gastro-oesophageal adenocarcinoma.[22] It remains, however, difficult to use skeletal muscle as an early biomarker as, at present, this would require percutaneous or open biopsy.

5.3. *Genetic biomarkers of cachexia*

Based on the current knowledge of demographic and clinical factors, it is not possible to predict, for any given cohort of patients, who will develop cancer cachexia and who will not. Moreover, even with the potential biomarkers described above, it is not possible to predict accurately who will develop cachexia quickly versus those who may develop the

syndrome at a slower pace. Such a variation may, in part, be due to the patient's genotype rather than the tumour phenotype. The case to support a genetic predisposition to cachexia is strengthened from the known genetic contribution to the activity of a variety of key mechanisms that underlie the cachexia syndrome (e.g. systemic inflammation). However, it must be said that, unlike other common diseases where twin studies have suggested a clear heritable component to the disease (e.g. Crohn's disease), no such studies support a heritable component to cachexia. Single nucleotide polymorphisms in candidate genes that have been linked to cancer cachexia mainly include the pro-inflammatory cytokines,[57–60] but genes linked to muscle atrophy ('atrogenes')[61] or the control of appetite may well be involved.

6. Novel end-points in cachexia intervention studies

Regulatory authorities are interested generally in a drug or treatment influencing favourably both body composition and physical function prior to licensing it for the treatment of cachexia. Until recently, it has been difficult for clinical investigators to provide accurate information on both domains. However, recent progress has opened new avenues.

6.1. Cross-sectional imaging

Both MR and CT cross-sectional imaging can be used to provide accurate and precise estimates of body composition. Both techniques are particularly useful in the assessment of skeletal muscle mass. For example, MR can measure the volume of the quadriceps muscle in the leg with a coefficient of variation <1%. Modern imaging analysis packages can use diagnostic CT scans to estimate abdominal muscle cross-sectional area at the L3 level and this can be extrapolated to whole body lean body mass.[62] Such techniques offer much more robust 'field' methods with which to estimate the efficacy of interventions designed to reverse muscle-wasting than those hitherto available (e.g. bioelectrical impedance analysis).

6.2. Physical activity monitoring

Cancer clinicians are used to assessing patients' performance status (e.g. WHO or ECOG scores) but these are blunt tools that lack objectivity. Recently, it has become possible to assess a patient's ambulatory function under free-living conditions using either stable isotope methodology or small electrical activity monitors.[15] The latter have been shown to be reliable for use in cachexic cancer patients, but await extensive testing in the context of randomised trials.

7. Treatment options

Clearly, the best way to cure cachexia is to cure the cancer and a clear focus on optimal oncological management is important. It is also vital to recognise that comprehensive general medical management of the patient is essential to assess and treat secondary factors that might contribute to anorexia or metabolic decline. Thus, the pancreatic cancer patient with ongoing cholangitis, steatorrhoea or unrecognised diabetes is not going to respond to anti-cachexia therapy until he receives antibiotics, pancreatic enzyme supplements and insulin therapy. The question of best supportive care for trials of anti-cachexia therapy remains unresolved. Most trials to date have failed to define the best supportive care. The outcomes of such studies should be considered against this background.

7.1. Unimodal adjuncts

A large variety of single agents have been tested mostly in relation to cancer anorexia. However, as pointed out previously, improving food intake is only part of the problem and therefore these interventions have only met with limited success. The interventions used in the clinic at present include

(A) *Progestational agents:* the commonest drug tested in this category is megestrol acetate. A recent Cochrane review concluded that megestrol acetate improved appetite and weight gain.[63] However, fat mass rather than lean body mass improves and there is no benefit in the quality of life.
(B) *Steroids:* prednisolone or dexamethsone have been tested in randomised trials. Appetite and well-being are increased to a greater extent than with placebo.[64] However, weight is not improved and muscle-wasting is a recognised side-effect.
(C) *Anabolic androgenic steroids:* these agents are well used by body builders and sports enthusiasts and stimulate muscle protein synthesis, resulting in net gain in muscle mass. Testosterone, nandrolone decanoate and oxandrolone have all tested positive in a number of catabolic states but their potential in cancer cachexia is largely unknown.
(D) *Oral nutritional supplements:* the average calorie deficit in weight-losing patients is approximately 250–400 kcal/d. One calorie per ml sip feeds have been shown not to improve the nutritional status of patients undergoing palliative chemotherapy.[65] However, recent studies using more calorie dense (1.5 kcal/ml), high protein feeds have suggested that at least weight stabilisation can be achieved.[66]

7.2. Multimodal adjuncts

For the majority of cancer patients, weight-loss is due to a combination of reduced food intake and metabolic change. Thus, it would seem logical to test combination regimens that address these issues simultaneously. Studies, which have evaluated such regimes, are relatively infrequent but some examples are given below.

(A) *Megestrol acetate/ibuprofen:* megestrol was given to stimulate appetite and ibuprofen to reduce systemic inflammation and thereby attenuate the metabolic abnormalities underlying cachexia.[67] In gastrointestinal cancer patients, the combination was shown to be associated with significant weight gain when compared with megestrol alone. Confirmatory studies are awaited.
(B) *Oral nutritional supplements/eicosapentaenoic acid(EPA):* high protein, energy-dense, oral nutritional supple-

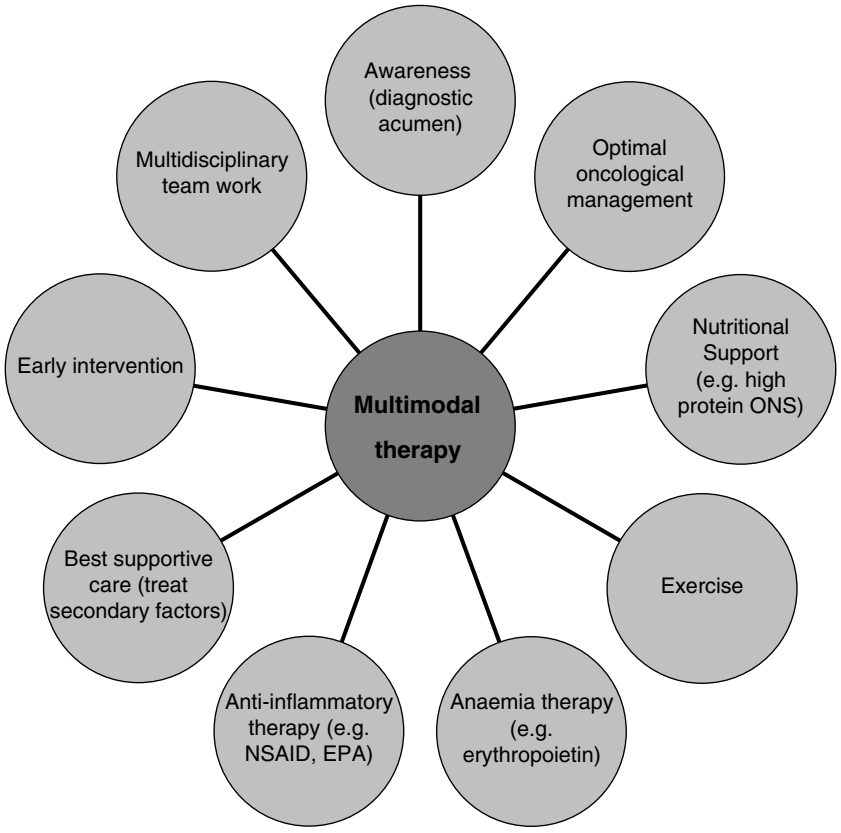

Fig. 5 – Multimodal rehabilitation for cancer cachexia. Stabilisation of weight and physical performance are reasonable goals which may be exceeded in some and unmet in others.

ments were given to improve food intake and EPA (derived from fish oil) to attenuate the metabolic abnormalities associated with cachexia. Randomised trials have shown an improved net food intake[66] and increased physical activity.[30] No benefit in terms of LBM or survival has been demonstrated. However, post hoc analysis demonstrated a linear relationship between plasma EPA level and increase in LBM.

(C) *Nutritional support/anti-inflammatory/anaemia therapy:* Nutritional support (oral nutritional supplements and/or home parenteral nutrition) was given to improve nutrient intake, indomethacin to reduce systemic inflammation and erythropoietin to improve anaemia (when present). Nutritional support improved metabolism, body composition and physical function when given together with anti-inflammatory and targeted anaemia therapy.[68] The Swedish group who have undertaken these studies have now treated several thousand patients using such principles and have some evidence of prolonged survival.[69] An emphasis on early intervention and a multi-disciplinary team approach is also important.[70]

8. Conclusions

There is an urgent need for further development of a formal definition of the cachexia spectrum and robust biomarkers of pre-cachexia and patient-oriented outcomes for cachexia randomised intervention trials. Recent advances in pathophysiology emphasise the need for improved food intake (especially protein), exercise and use of anti-inflammatory agents. Not all patients will respond equally. However, multimodal strategies to tackle both food intake and metabolic change have been demonstrated to improve function and the quality of life. There is now sufficient evidence to support the concept that multimodal management (Fig. 5) of cachexia can stabilise nutritional status independent of tumour progression. This justifies large-scale complex intervention trials.

Conflict of interest statement

None declared.

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