Nutritional support in multimodal therapy for cancer cachexia

Ingvar Bosaeus

Abstract

Introduction Malnutrition has since long been known to be associated with adverse outcomes in cancer patients. The wasting in cancer cachexia involves loss of muscle and fat and reflects a catabolic metabolism induced by an abnormal host response to tumour presence and/or tumour factors. Patients with cancer cachexia frequently develop a chronic negative energy and protein balance driven by a combination of reduced food intake and metabolic change. Thus, alterations in both energy intake and components of energy expenditure may contribute to progressive weight loss. Increased resting energy expenditure related to the systemic inflammatory response is common and a sustained hypermetabolism over a long period of disease progression can make a large contribution to negative energy balance and wasting if not compensated for by an increase in energy intake. Hypermetabolism and diminished energy intake due to anorexia may thus constitute a vicious circle in the development of cancer cachexia.

Discussion Though nutritional support alone can improve energy intake to a variable extent and for a variable period of time, it will not address the underlying catabolic metabolism and is thus likely to be of limited efficacy if attempts to attenuate the tumour-induced catabolic response are not carried out at the same time. Concomitant drug treatments for cancer cachexia may slow down the wasting process by reducing anorexia, attenuating the systemic inflammation, the skeletal muscle catabolism or stimulating the muscle protein anabolism.

Conclusion 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, strategies to counteract both hypermetabolism and reduced dietary intake have been demonstrated to be of importance for the survival, function and quality of life of cancer patients and should be further explored in interventional studies.

Keywords Nutritional support · Cachexia · Anorexia · Body composition · Energy balance

Introduction

In western countries, about half of cancer diagnoses end in cure, the other half in death. When the outcome is cure, nutritional problems are largely treatment-related and in most cases, improve during rehabilitation, whereas in incurable cancer, there is frequently a severe, progressive malnutrition and wasting [1]. The weight loss frequently seen in advanced cancer has long been recognised to be associated with a decreased survival [2]. The term cachexia refers to a
progressive weight loss with depletion of host reserves of skeletal muscle and adipose tissue. It also represents the complex and profound metabolic changes seen in advanced cancer, characterised by breakdown of skeletal muscle and abnormalities in fat and carbohydrate metabolism.

Cachexia is the most common paraneoplastic syndrome, often called the cancer anorexia–cachexia syndrome (CACS). Other important features of CACS are anorexia, early satiety, weakness and fatigue. The syndrome is, however, not well defined. The many aspects, “capture the context and convey a sense of the suffering” is not a strict definition [1]. 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 [3] and such patients should be evaluated for multimodal intervention as soon as identified.

The mechanisms of cancer cachexia have been extensively studied but not fully clarified. The development of cachexia reflects both a reduced food intake, where anorexia is a major factor is most cases, and a catabolic metabolism induced by an abnormal host response to tumour presence and/or tumour factors. From a nutritional point of view, this leads to a negative energy and protein balance, manifesting as weight loss as body stores are progressively depleted.

**Development of malnutrition in cancer**

Generally, when food intake is lower than requirements, body energy stores are mobilised to meet demands. Normally, there is a metabolic and behavioural adaptation, leading to decreased energy expenditure. Furthermore, body fat stores are preferentially used for fuel, with a relative sparing of the fat-free body mass. For instance, in cancer survivors free from cancer but with functional impairment after upper gastrointestinal cancer surgery, the composition of weight loss was approximately 90% fat and 10% fat-free tissue [4]. In cancer cachexia with systemic inflammation, there is an activation of protein breakdown in skeletal muscle and the amino acids thus generated are used to fuel hepatic protein and glucose synthesis (for a review, see [3]). Thus, there is a faster breakdown of skeletal muscle with a preservation of visceral organs. This is of particular importance for nutritional support in cancer where the provision of adequate amounts of energy and nutrients, e.g. by parenteral nutrition or tube feeding, is capable of restoring body fat, but muscle breakdown continues, driven by systemic inflammation [5, 6]. In addition, both starvation and systemic inflammation are associated with a relative increase in extracellular water. The active body cell mass (predominantly skeletal muscle tissue) and its associated intracellular water decreases, while the extracellular space is maintained or more slowly decreased, with or without clinical signs of oedema. Thus, body weight changes may, at least initially, not accurately reflect the amount of muscle and fat lost. To better characterise the depletion of cancer cachexia, the commonly used body mass index (BMI) should be expanded to reflect these body composition changes, for instance, using height-adjusted indices of fat-free mass (FFMI), fat mass (FFM) and skeletal muscle (SMI). However, these require defined reference values and standardised body composition measurements not readily available at present. In addition, body composition methods, when used to evaluate cancer patients, should take into account the possible effects of the altered water compartments mentioned above [7].

**Energy balance in cancer**

Weight stability, or more precisely, stable body composition, indicates energy balance, i.e. energy intake equals total energy expenditure. Energy intake is usually characterised by the macronutrient composition, i.e. the proportions of protein, fat and carbohydrate (and alcohol). Energy expenditure is usually subdivided in the components resting energy expenditure (REE), thermic effect of food (TEF) representing the energy cost of postprandial metabolism of food and activity energy expenditure (AEE). Negative energy balance leading to progressive weight loss can be attributed to changes in energy intake, components of energy expenditure or both, mediated by metabolic alterations. Anorexia is very common in progressive cancer disease. Increased REE is frequently found and a large span in REE from hypo- to hypermetabolism has been reported in malnourished cancer patients. Sustained hypermetabolism over a long period of disease progression can make a large contribution to negative energy balance and wasting if not compensated for by an increase in energy intake. Hypermetabolism and diminished energy intake due to anorexia may thus constitute a vicious circle in the development of cancer cachexia [8]. In addition, a host of metabolic derangements may contribute to the progressive wasting of cancer. These metabolic changes differ from those induced by decreased energy intake or starvation alone. In simple starvation, muscle mass tends to be preserved at the expense of body fat depots, which are preferentially used to provide energy. In contrast, relatively more muscle tissue is lost in the development of cancer cachexia and these changes in body composition are not reversed if adequate energy and other nutrients are provided, as may occur in starvation states. Several aspects of the energy balance equation and body composition changes in advanced cancer are not well known.
Energy intake

Several factors may contribute to a decreased intake of food in cancer patients. Anorexia, due to the disease itself or its treatment, is a commonly recognised problem. Cancer patients may also frequently suffer from symptoms from the gastrointestinal tract due to, for instance, physical obstruction, constipation or malabsorption. Effects of treatment such as opiates, radiotherapy or chemotherapy may all decrease food intake.

Diminished food intake is a prominent feature in weight-losing cancer patients, with most [9–12], but not all studies [13, 14] reporting a low intake. In one of our studies [15], we found a low intake in 297 patients with advanced cancer, mainly gastrointestinal tumours. Mean dietary intake was below maintenance requirements, 26 kcal/kg/d. Weight loss of more than 10% was present in 43% of the patients and elevated REE (>110% of predicted) in 48%. Dietary intake did not differ between normo- and hypermetabolic patients. Weight loss could not be accounted for by diminished dietary intake, since energy intake in absolute amounts was not different and intake per kg of body weight was higher in weight-losing patients compared to weight-stable patients. Thus, a reduced dietary intake has been repeatedly, but not consistently, shown in weight-losing cancer patients, though long-term dietary intake may be difficult to assess precisely. Low intake is a predictor of decreased survival [3]. We also found an association between low energy intake and decreased survival. Further, patients who managed to increase energy intake during 4 months follow-up had an increase in survival (mean survival with increased intake 480 days, with decreased intake 331 days) [16]. The relation of reduced intake to weight loss is, however, not clear and diminished food intake cannot alone explain the weight loss in advanced cancer, as found in our study mentioned above [15]. Thus, other components of the energy balance equation must be also taken into account.

Energy expenditure

Increased resting energy expenditure in cancer is a frequent, but not universal finding, in cancer patients with progressive weight loss [17–19]. Also, in studies of malnourished cancer patients, a large span from hypo- to hypermetabolism has been reported [20, 21]. It would thus seem that cancer patients have a very variable response to underfeeding, some being able, at least for a period of time, to adapt with reduced resting energy expenditure, while others show a hypermetabolic response, which would further aggravate a negative energy balance. This is in contrast to uncomplicated starvation, where adaptation generally occurs more effectively to reduce energy expenditure.

Patients with cancer in some particular sites, such as the lung and pancreas, may be more prone to develop hypermetabolism [22, 23]. Animal studies of cancer cachexia have suggested that there is change in metabolic pattern over time, with an initial hypermetabolic phase followed by a decrease to a preterminal hypometabolic phase [24]. Little is known about longitudinal changes in REE in cancer patients [22]. Jatoi et al. [25], studying a small group of lung cancer patients, found a decreased disease-free survival in eight hypometabolic compared to nine hypermetabolic patients.

In the study of Bosaeus et al. [15], about half of the patients had an elevated REE, defined as 110% or more of predicted REE. This increase in energy expenditure was not associated with a different dietary intake compared with patients with normal REE and an increase in REE thus directly contributed to a negative energy balance.

Of the other components of the total energy expenditure (TEE), i.e. thermic effect of food (TEF) and activity energy expenditure (AEE), little is known in cancer cachexia. Physical activity assessed by questionnaire was found to predict chemotherapy toxicity in older lung cancer patients [26]. A study in eight patients with advanced lung cancer found that TEE was not increased despite an increase in REE, indicating a diminished activity [27]. A recent study made the same observation, assessing TEE by doubly labelled water in 24 patients with advanced pancreatic cancer. REE was increased but TEE indicated a low AEE [28]. During 8 weeks of treatment with a control nutritional supplement, TEE, REE and AEE was unchanged, but in patients receiving a supplement enriched with EPA, physical activity was increased [28]. Thus, low physical activity levels may be an important feature of the energy balance in cancer patients, which may affect functional performance and quality of life.

Treatment of cancer cachexia

The best way to treat cancer cachexia is obviously to cure the cancer, thus normalizing the metabolic abnormalities induced by the tumour and/or tumour/host interactions. When cure cannot be achieved, an obvious next option would be to increase nutritional intake by dietary counselling and oral nutritional supplements or by artificial nutrition. A number of studies have tried to achieve this. However, no benefits were found in terms of anthropometric measures, response rate to therapy, survival or quality of life.

Parenteral nutrition is difficult to supply 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, which showed no benefit but an increase of infectious complications. A
position paper of the American College of Physicians in 1989 stated that “parenteral nutritional support was associated with net harm, and no conditions could be defined in which such treatment appeared to be of benefit” [29]. Though many of the studies on which this statement was based appeared to have design flaws and used nutritional regimens which may be regarded as suboptimal by current standards, there is still no evidence that an increased nutritional intake alone is effective in the palliation of cancer cachexia.

The disappointing results of stand-alone conventional nutritional supplementation in cancer patients has led to a focus on the metabolic changes in cancer cachexia and attempts to manipulate the metabolic alterations with a variety of pharmacological agents. Thus, strategies to counteract the inflammatory response and its metabolic consequences would seem to be an option.

Steroids have been widely used and have been shown to improve appetite. However, steroids will not reverse ongoing weight loss and muscle wasting, symptomatic benefits are often short-lived and they are associated with a number of adverse effects. Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce acute phase proteins and REE and preserve body fat in patients with advanced cancer [30] and treatment with indomethacin has been shown to stabilise performance status and prolong survival [31]. NSAIDs therefore seem to have a role in the palliation of cancer cachexia, though the effect size is still not well known.

Anabolic androgenic steroids stimulate 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, but their therapeutic potential in cancer cachexia is largely unknown. Much interest has also focused on the importance of the growth hormone (GH)/insulin-like growth factor (IGF-1) axis on the anabolic regulation of skeletal muscle mass, but in cancer patients, there remains the ongoing worry that growth factors may stimulate tumour growth and these concerns have limited trials in this area.

We have recently shown that low-dose insulin treatment (0.11 ±0.05 units/kg/day) stimulated carbohydrate intake and metabolic efficiency during exercise and improved survival in cancer cachexia. However, fat-free mass, maximum exercise capacity and spontaneous physical activity were unaffected [32]. The role of treatments to reverse the underlying metabolic changes in cancer cachexia is still unclear.

We have studied the effect of nutritional support in combination with anti-inflammatory treatment (NSAID) and anemia prevention (erythropoietin) in 309 patients with progressive cachexia due to solid tumours (predominantly gastrointestinal tumours) [33]. As-treated analysis demonstrated that patients receiving nutritional support had a prolonged survival, accompanied by improved energy balance, body fat, and a greater maximum exercise performance. The results support that nutrition is a limiting factor influencing survival and that treatment targeted towards both diminished nutritional intake and metabolic alterations may be more effective. A recent study of patients on palliative chemo/radiotherapy given oral nutrition support plus parenteral nutrition (30% of requirements) also showed an improved 48-week survival, body composition and quality of life [34].

Conclusions

The metabolic alterations in advanced cancer have many parallels to a chronic systemic inflammatory response and differ considerably from the metabolic changes in starvation. Nutritional support alone does not appear to affect overall survival in advanced cancer, but in combination with treatment targeted against the inflammatory response and/or metabolic abnormalities, focussing also on energy expenditure, may be of greater value. Therapeutic strategies aimed at modulating the mediators of the catabolic response, such as cytokines and eicosanoids, or metabolic regulation, such as with anabolic and anti-catabolic agents, may thus offer more promise in the future. Also, early detection and intervention may be more effective. An optimal therapeutic approach to cancer cachexia is not yet available. Strategies to counteract both hypermetabolism and reduced dietary intake may be important for the survival, function and quality of life of cancer patients and should be further explored in interventional studies.

References
