

Review Article

New strategies to overcome cancer cachexia: from molecular mechanisms to the 'Parallel Pathway'

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Cancer has always a negative impact on nutritional status, weight loss being a common feature in patients with neoplastic diseases. If left untreated, weight loss may evolve into cancer cachexia, a complex syndrome characterized by marked depletion of body weight, associated with profound alterations of both nutritional status and metabolic homeostasis. Progressive wasting of skeletal muscle mass and adipose tissue is a typical feature of cancer cachexia. Cachexia has a large impact on morbidity and mortality, and significantly affects patients' response and tolerance to treatments and quality of life. On this line, understanding the pathogenic mechanisms of cachexia is of crucial importance to define targeted therapeutic strategies. Well structured, systematic and timely appropriate nutritional intervention in cancer patients is of pivotal importance. Indeed, it has been shown that malnutrition in cancer patients can be delayed when nutritional supplementation is adopted early in the course of the disease. The preservation of a good nutritional status, in particular when it is achieved concurrently with specific antineoplastic treatments, will prevent or at least delay the onset of overt cachexia, allowing the use of more aggressive therapeutic regimens. The inclusion of specific, metabolically active nutritional substrates, such as branched chain amino acids or eicosapentaenoic acid may be helpful in interfering with the mechanisms responsible for the metabolic alterations and the perturbations of molecular pathways ultimately leading to the clinical picture of cancer cachexia.

Key Words: Cancer, malnutrition, cachexia, muscle wasting, nutrition, eicosapentaenoic acid (EPA)

INTRODUCTION

Cancer has always a negative impact on nutritional status, body weight loss (BWL) being highly prevalent in the general cancer population, irrespective of disease stage, occurring in 54 to 70% of cancer patients at diagnosis.^{1,2} Pretreatment weight loss in neoplastic patients often associates with poor tolerance to surgery, chemotherapy, or radiotherapy. By contrast, a good performance status positively correlates with tolerance to chemotherapy and radiotherapy, response rates to chemotherapy, and survival.² In advanced cancer, patients frequently develop a condition of general wasting known as cachexia, a multifactorial syndrome that complicates patients' management, increasing morbidity and mortality rates, reducing the tolerance to antineoplastic therapies, and severely impinging quality of life. Its prevalence is higher in patients with lung cancer or with tumors of the gastrointestinal tract than in those with other solid neoplasms, such as breast and thyroid cancer or hematologic malignancies¹. Approximately two million people die annually worldwide solely to the consequences of cancer-related cachexia.^{1,2} Besides BWL, the main features of cancer cachexia are the depletion of skeletal muscle and adipose tissue, asthenia, anorexia, and altered metabolic and hormonal homeostasis. Although the underlying mechanisms are yet not completely elucidated, the complex interplay between nutritional, endocrine, metabolic and immunological components is widely recognized as having a causative role. Although cancer cachexia is widely recognized as a major problem in clinical oncol

ogy,³ its treatment is generally included among terminal palliative cares, basically because of two reasons: i) cachexia is still considered a late event in the history of cancer patients and, ii) cachexia is substantially refractory to available treatments. By contrast, recent findings show that significant metabolic, biochemical and molecular changes that characterize cachexia already occur in patients before any evidence of body weight loss,^{4,5} consolidating the view cachexia should be regarded as an early phenomenon¹. This underscores the need of targeted therapeutic interventions which should be entertained well before the occurrence of full-blown body wasting.²

PATHOGENESIS OF CANCER-RELATED WEIGHT LOSS AND CACHEXIA

Cancer patients frequently experience a substantial reduction of food intake, that concurs to the loss of body weight. This may be due to several contributing factors such as obstruction of the gastrointestinal tract, malabsorption, vomiting, nausea, and pain, but a prominent role is played by *anorexia*. Anorexia is defined as the decreased desire to eat and is often one of the presenting symptoms of cancer.

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Its occurrence can be identified by evaluating relevant symptoms, such as early satiety, taste alterations and nausea, and its severity assessed accordingly. Sometimes, reduced energy intake is assumed as a measure of anorexia, however a note of caution should be introduced, since the reduction of ingested calories may result from dysphagia or depression rather than from anorexia. The diagnosis of anorexia by means of questionnaires is rapidly becoming a common practice, yet, considering that questionnaires only provide a qualitative assessment, it is advisable to gain a quantification of the degree of anorexia by using a visual analog scale.⁶

The pathogenesis of cancer-related anorexia is complex and multifactorial, implying a dysruption of the central and peripheral messages that physiologically regulate eating behaviour at the hypothalamic level.⁶ In the presence of cancer, the enhancement of cytokine expression in the brain leads to disruption of hypothalamic neurochemistry, interfering with the regulation of satiety, at least in part via increased serotonin synthesis and release, resulting in reduced food intake. Cytokines may contribute to the long-term inhibition of feeding by mimicking the hypothalamic effect of excessive negative feedback signaling,⁷ but tumor-induced changes in energy metabolism of hypothalamic neurons are also probably involved in the pathogenesis of cancer anorexia.⁶

Metabolic abnormalities significantly contribute to cancer-related wasting and involve carbohydrate, lipid and protein metabolism. Malignant tumors obtain as much as 50% of their energy from glycolysis.⁸ Glycolysis, however, is not an efficient way to produce energy, since glucose consumption is associated with the concomitant release of substantial amounts of lactate, in turn reconverted into glucose by the liver through the Cori cycle. This 'energy-wasting cycle' is increased up to 50% in activity in cancer patients, accounting for 60% of lactate production and for most of energy depletion.^{9,10} Impaired glucose tolerance is also observed in cancer patients. This may result from increased insulin resistance, likely mediated by cytokines such as TNF α ,^{9,11} via reduced phosphorylation of both the insulin receptor and the insulin receptor substrates (IRS-1 and IRS-2) and down-regulated expression of the glucose transporter GLUT-4.¹² Insulin-like growth Factors (IGF) signalling is also altered with similar mechanisms, since TNF α has been shown to prevent the increase in muscle protein synthesis induced by IGF-1.¹³

Alterations of lipid metabolism and reduced fat mass are commonly observed in cancer cachexia, fat depletion being associated with hyperlipidemia, reduced circulating levels of high density lipoprotein (HDL)-cholesterol, enhanced lipolytic rates, decreased lipogenesis¹⁴ and reduced activity of lipoprotein lipase (LPL).¹⁵ Fatty acids can be a preferred energy source even in the presence of hyperglycemia, and recent data show that the lipid oxidation rate is enhanced in weight-losing more than in weight-stable subjects.¹⁶ Lipid metabolism derangements frequently precede the onset of body weight loss and anorexia. Among the mediators possibly involved in such metabolic derangements, insulin is a good candidate,¹⁵

while the involvement of leptin in lipid depletion in cachexia is unlikely, as suggested by the observation that both its circulating levels and its expression in the adipose tissue decrease in tumor-bearing animals and in gastric cancer patients, even in the absence of fat wasting and anorexia.¹⁷ Cytokines also play a role: TNF α , IL-6, LIF and γ -IFN decrease LPL activity. TNF α also enhances both lipogenesis and VLDL production in the liver, contributing to the hyperlipidemia.³ The tumor-derived mediator named Lipid-Mobilizing Factor (LMF), isolated from the MAC16 tumor as well as from the urine of cachectic cancer patients¹⁸ also contributes to fat depletion, stimulating the release of free fatty acids and glycerol from adipose tissue¹⁸ through GTP-dependent activation of adenylate cyclase.¹⁹ LMF can also up-regulate uncoupling protein (UCP) 2 in both skeletal muscle and liver.²⁰ A role for UCP up-regulation in cancer cachexia has been proposed.

Depletion of skeletal muscle mass is the most important alteration of protein metabolism, and by far the most clinically relevant feature of cancer cachexia. Enhanced protein breakdown is the primary cause of this severely debilitating condition, although the mechanisms underlying accelerated muscle protein degradation in cancer still remain elusive.²¹ Similarly, the relative contribution of the different intracellular proteolytic pathways to muscle wasting, as well as the mechanisms responsible for their activation, are far from being fully elucidated. Of the four main proteolytic systems which have been characterized in the skeletal muscle, the lysosomes, the caspases, the Ca²⁺-dependent and the ATP-ubiquitin-dependent pathways, the latter is believed to play a prominent role in cancer-related muscle wasting.²² Caspases, a family of cysteine proteases mostly known for their role in the execution of the apoptotic process, have been involved in muscle atrophy, although their role in cancer cachexia is still a matter of debate.²³

Cytokines such as TNF α , IL-6, or γ -IFN have been proposed as mediators of muscle protein loss in different experimental models,²¹ but mediators different from classical cytokines such as PIF (Proteolysis Inducing Factor) are likely involved as well. Indeed, circulating PIF in experimental animals results in loss of body and muscle weight, and in enhanced muscle protein degradation rates.³ Several reports have suggested that hypoanabolism might be also involved in muscle wasting of cancer. Indeed, reduced MyoD levels have been shown in the gastrocnemius of tumor-bearing rats.²⁴ Myostatin negatively regulates skeletal muscle mass. Loss of function mutations of myostatin have been detected in breeds of cattle characterized by the so-called 'double-muscle' phenotype, and adult mice in which the myostatin gene has been disrupted show a marked muscle hypertrophy.²⁵ In muscles, myostatin expression is enhanced in ageing, denervation-induced atrophy or mechanical unloading,²⁶ and increased myostatin gene expression and circulating levels have been associated with weight loss in patients with AIDS-related cachexia.²⁷ The role of myostatin in cancer cachexia is currently under investigation in our laboratories.

NUTRITIONAL SUPPORT

Consensus is consolidating that preserving or restoring an adequate nutritional status is critical in providing neoplastic patients with more opportunities to recover and to better tolerate aggressive therapeutic regimens. Weight loss is a reliable predictor for both treatment toxicity and short survival in cancer patients,²⁸ and it is apparent that both weight loss and decreased food intake are significant determinants of the patient's perception of his/her quality of life²⁹. Unfortunately, weight loss of cachexia cannot be reverted simply by nutrient provision, which in contrast is able to restore body weight and protein mass after simple starvation.³⁰ Early nutritional and metabolic intervention is therefore crucial to effectively manage both nutritional status and physical conditions in cancer patients. However, in order to adopt early interventions, the condition of 'latent' cachexia needs to be recognized as soon as possible. This implies that any single cancer patient should be regarded to as a potential candidate to develop the detrimental consequences of weight loss and cachexia, underscoring the need for routine screening and tailored intervention. This approach has been referred to by us as the 'parallel pathway',¹ which starts at the moment the diagnosis of cancer is made, and runs parallel to the pathway of cancer therapies. During this period the patient receives systematic nutritional and psychological advice, together with periodical screening and assessment administration as a single agent does not exert statistically significant benefit in the treatment of consolidated cancer cachexia of nutritional status, anorexia, performance status and muscle function, aimed at providing the best intervention according to disease type, site, stage and concomitant antineoplastic therapy. This may include nutritional counselling,³¹ administration of oral nutritional supplements, nutraceuticals and/or drugs to improve appetite or counteract the negative effects of inflammation on muscle, or artificial nutrition, in order to provide optimal and customized nutritional and metabolic support^{1,6,30,32} in any phase of the neoplastic disease.

THE ROLE OF NUTRACEUTICALS

Among the compounds that can be used to prevent nutritional deterioration in cancer patients, branched-chain amino acids (BCAA), namely leucine, isoleucine and valine, deserve particular attention. BCAA act as orexigenic agents in view of their capability to decrease brain tryptophan entry across the blood-brain barrier, thus decreasing hypothalamic serotonin synthesis. Beyond their prophagic effects, BCAA appear to exert anticatabolic effects by promoting protein synthesis and inhibiting intracellular proteolytic pathways. The anabolic properties of BCAA, and in particular of leucine, have been known since many years, but only recently their molecular mechanisms have been partially elucidated. Interestingly, it has been recently demonstrated that beta-hydroxy-beta-methylbutyrate (HMB), a leucine metabolite, is highly effective in inhibiting muscle protein degradation.³³ Based on the knowledge that systemic inflammation plays a crucial role in the pathogenesis of cancer-related weight loss and cachexia, it has been proposed that dietary supplements with anti-inflammatory properties may be

beneficial.³⁴ Omega-3 polyunsaturated fatty acids (PUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) suppress the production of proinflammatory cytokines, of molecules deriving from the arachidonic acid cascade, and of acute phase reactants such as C-reactive protein.^{1,32} EPA administration to animals bearing experimental tumors results in increased body weight and attenuates the effects of both LMF and PIF.^{1,32} In particular, EPA has been shown to inhibit the activity of the ubiquitin-proteasome-dependent proteolysis, reducing the wasting of skeletal muscle. Finally, experimental studies suggest that omega-3 PUFA may impair both tumour growth and metastatic spread, mainly by inducing apoptotic cell death, reducing pro-angiogenic factors and inhibiting oncogene expression.^{1,32} Clinical trials performed in malnourished patients have shown that EPA reduces PIF levels in the urine and promotes weight gain.³⁵ The anti-inflammatory properties of omega-3 PUFA have been proposed to account for the increased body weight and the gain of lean body mass that is observed in cancer patients after EPA supplementation.³² A large multicenter study performed on patients affected by advanced pancreatic cancer³⁶ has shown that an EPA-containing protein- and energy-rich oral nutritional supplement may maintain body weight and lean body mass, provided that it is taken in adequate amounts. A second study including more than 400 subjects has shown that while megestrol acetate is more effective than EPA in inducing weight gain (but not lean body mass), the two drugs are comparable in terms of appetite stimulation, quality of life and survival.³⁷ Quite recent data show that EPA.³⁸ In the clinical practice the exploitation of the potential benefits of omega-3 PUFA administration are still largely limited by the scarce knowledge of their mechanism(s) of action and since a poor compliance to prolonged supplementation has been reported.

Taken together, the available data on EPA supplementation in cancer suggest that future studies should concentrate on adequate timing of administration, concomitant provision of adequate amounts of protein and calories, and on the role of these metabolically active lipid substrates in preventing/delaying the onset of cachexia, rather than attempting to revert it, once the clinical picture of body wasting has consolidated.^{1,30}

In conclusion, available experimental and clinical evidence demonstrate that cancer cachexia results from profound metabolic alterations due to the combined action of factors released either by the tumor or by the host. The underlying metabolic disturbances can occur very early in the course of the disease, even before weight loss is apparent. On these bases, timely approaches aimed at interfering with the onset of tissue wasting are warranted, based on multimodal interventions, including nutrition, drugs and metabolically active nutritional substrates. The role of early nutritional metabolic/interventions aimed at preventing the decline of nutritional status is becoming increasingly clear. Once the strategies to prevent or reverse weight loss and cachexia will be consolidated, a more effective global management of cancer patients is to be expected.

AUTHOR DISCLOSURES

Maurizio Muscaritoli, Paola Costelli, Zaira Aversa, Andrea Bonetto, Francesco Maria Baccino and Filippo Rossi Fanelli, no conflicts of interest.

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