

# Cancer Cachexia: It's Time for More Clinical Trials

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Cancer cachexia (CC) is a multifactorial paraneoplastic syndrome characterized by anorexia, body weight loss, loss of adipose tissue and skeletal muscle, accounting for at least 20% of deaths in neoplastic patients. CC significantly impairs quality of life and response to anti-neoplastic therapies, increasing morbidity and mortality of cancer patients. Muscle wasting is the most important phenotypic feature of CC and the principal cause of function impairment, fatigue and respiratory complications, mainly related to a hyperactivation of muscle proteolytic pathways. Most current therapeutic strategies to counteract CC have proven to be only partially effective. In the last decade, the correction of anorexia, the inhibition of catabolic processes and the stimulation of anabolic pathways in muscle have been attempted pharmacologically with encouraging results in animal models and through preliminary clinical trials. However, data in the clinical setting are still scanty and non definitive. It is time to start prospective, randomized, controlled trials to evaluate which drugs are effective in counteracting the loss of lean of muscle mass and in improving nutritional status and quality of life in patients affected by cancer-related cachexia.

**Key Words:** Cancer cachexia—Anorexia—Muscle wasting—Approved therapy—Candidate drugs.

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Cancer cachexia (CC) is a debilitating and life-threatening syndrome present in about 50% of the cancer patients. Its prevalence is higher in patients with tumours of the gastrointestinal tract and the lung, than in those with other solid neoplasms, such as breast and thyroid cancer, and haematological malignancies.<sup>1,2</sup>

The predominant feature of CC, the progressive loss of muscle mass and function, has been shown to be only minimally reversible with the currently available nutritional, metabolic or pharmacological tools.<sup>1,2</sup> Unfortunately, while many progresses have been made in the comprehension of the pathogenic mechanisms that lead to CC, the development of

early and effective interventions aimed at preventing and reversing the metabolic perturbations ultimately leading to muscle wasting marks time.<sup>1,2</sup>

A comprehensive literature review using PubMed and MEDLINE, all accessed from January 2001 to December 2005, shows that the words *cancer* and *cachexia* lead to 678 articles. Of these, 224 are review articles, 350 are experimental studies and 94 are human observational studies. Unfortunately, the human clinical interventional trials are very few, only ten (Fig. 1).

This article, after reviewing the clinical relevance, the pathogenic mechanisms and the current therapy of CC, will focus on nutritional and pharmacological approaches that need to be urgently validated through adequate clinical trials as effective treatments of CC.

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## CLINICAL RELEVANCE

CC is characterized by progressive weight loss, anorexia, metabolic alterations, asthenia, depletion of lipid stores and severe loss of skeletal muscle protein.

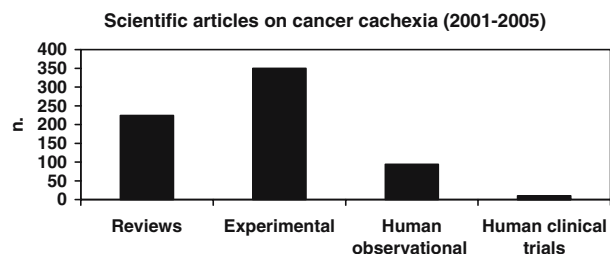


FIG. 1. Scientific articles on cancer cachexia published between January 2001 and January 2005.

Cachexia is present in most terminally ill cancer patients, but also in the earlier phases of cancer diseases. Indeed, 80% of the upper gastrointestinal tract and 60% of lung-cancer patients upon diagnosis have already experienced some degree of weight loss.<sup>1,2</sup> Moreover, most of the metabolic, biochemical and molecular alterations currently believed to be responsible for the phenotypic features of cachexia are already present upon first cancer diagnosis, even in the absence of significant body weight loss.<sup>1,2</sup> CC negatively affects patients' mortality, surgical risk, response to first- and second-line chemo-/radiotherapy and quality of life.<sup>1,2</sup>

## PATHOGENESIS

Reduced food intake, alterations in energy and substrate metabolism in the host and accelerated fat and muscle loss are the mechanisms that lead to CC.<sup>6</sup>

### Anorexia and Reduced Food Intake

A significant number of cancer-bearing patients experiences a substantial reduction in nutrient intake which certainly contributes to weight loss.<sup>4</sup> Insufficient energy and protein availability may well be the intuitive consequence of cancer and/or anti-neoplastic treatments and include mechanical obstruction in the gastrointestinal tract, mucositis, vomiting, malabsorption, pain and depression.<sup>4</sup> Besides these contributing factors, a prominent role is played by anorexia, that is the decreased desire to eat secondary to the presence of cancer that is often the presenting symptom and capable of initiating the development of weight loss. The pathogenesis of cancer-related anorexia is complex and multifactorial and implies a disruption of the central and peripheral messages physiologically regulating eating behaviour.<sup>4</sup> A comprehensive review of the pathophysiology and therapy of cancer anorexia has been recently published.<sup>3</sup>

### Altered Energy and Substrate Metabolism

The metabolic response to cancer in terms of resting energy expenditure (REE) is very heterogeneous, some patients showing hypermetabolism, others being frankly hypometabolic.<sup>5,6</sup> Indeed, in patients with overt cachexia and asthenia, total energy expenditure is reduced as a consequence of reduced physical activity.<sup>3</sup>

The energy substrate metabolism disturbance is characterized by glucose intolerance, insulin resistance, increased gluconeogenesis from amino acids and lactate, increased fat oxidation and reduced lipogenesis.<sup>1</sup> Protein metabolism is also affected, whole body protein turnover being increased in the majority of advanced cancer patients.<sup>7</sup>

Loss of fat mass is up to 85% when the total body weight loss reaches 30%<sup>8</sup> and is essentially secondary to enhanced lipid mobilization, decreased lipogenesis and decreased activity of lipoprotein lipase, the enzyme responsible for tryglicerides clearance from plasma.<sup>8</sup> Lipoprotein lipase inhibition, a consequence of the action of cytokines, would prevent adipocytes from extracting fatty acids from plasma proteins for storage. The lipid mobilization seems to be secondary to the action of a tumour catabolic factor named lipid mobilizing factor (LMF) which acts directly on adipose tissue with the release of free fatty acids (FFA) and glycerol through an elevation of the intracellular mediator cyclic AMP in a manner similar to that produced by the natural lypolytic hormones.<sup>9</sup> This factor was originally purified from a cachexia-inducing mouse colon adenocarcinoma, but it has also been found in the urine of cancer patients.<sup>10,11</sup> It has been shown that production of LMF by cachexia-inducing tumours may account for the loss of body fat and the increase in energy expenditure.<sup>12</sup>

Numerous experimental studies have demonstrated that several cytokines [tumour necrosis factor (TNF)- $\alpha$ , interleukins 6 and 1], mimic many of the metabolic abnormalities found in CC, such as changes in lipid and skeletal muscle protein metabolism, acute-phase protein synthesis.<sup>1,2</sup>

### Muscle Wasting

The loss of muscle mass, the most prominent phenotypic feature of CC, is the result of increased protein degradation, reduced protein synthesis, or both.<sup>13</sup> Muscle hypercatabolism depends on the activation of calcium-dependent proteases (calpains), essential for the initial degradation of myofibrillar proteins to release actin and myosin, and on the hy-

peractivation of the ATP-ubiquitin-dependent proteolytic pathways.<sup>13,14</sup> The ATP-ubiquitin-dependent protein degradation is made up of two main steps: first, through an enzymatic cascade (ubiquitin-activating, ubiquitin-conjugating and ubiquitin-ligating enzymes), multiple ubiquitin molecules are covalently attached to the protein substrate; then the polyubiquitinated protein is degraded by the 26S proteasome complex, whose catalytic core, the 20S proteasome, is characterized by five peptidase activities, namely the trypsin-like (TL), chymotrypsin-like (CTL), peptidyl-glutamyl peptidase (PGP), branched chain amino acid-preferring and small neutral amino acid-preferring activities.<sup>13</sup> Upregulation of components of the ATP-ubiquitin-dependent pathway has been reported in experimental models of wasting conditions such as sepsis, trauma, burns, renal failure, acidosis and cancer.<sup>13</sup> Recent studies have shown that in muscle biopsies obtained preoperatively in 20 patients undergoing surgery for gastric cancer ubiquitin mRNA expression was markedly and significantly increased<sup>16</sup> as well as proteasome activity.<sup>17</sup> Three intracytoplasmic ubiquitin-ligating enzymes, namely E3 $\alpha$  and ligases encoded by the genes *MURF-1* (muscle ring finger protein 1) and *MAFbx* (muscle atrophy F-box protein, also called Atrogin-1), play a key role in the onset of muscle atrophy.<sup>18,19</sup>

Impaired anabolic response, consequence of a cancer-dependent reduced expression of positive regulators (i.e. MyoD) or an overexpression of negative regulators (i.e. myostatin) of skeletal muscle growth, play also a significant role in the onset of muscle loss in CC.

MyoD is a member of a skeletal muscle-specific family of transcription factors also known as myogenic regulatory factors that play a determinant role in myogenesis in cooperation with other transcriptional modulators of the MEF2 family.<sup>20</sup> MyoD induction is crucial for the muscle regenerative programme activated after injury which is based on satellite cells. Inflammatory cytokines such as TNF- $\alpha$  and interferon- $\gamma$  may impair the ability to activate this programme. Recently, MyoD protein downregulation has been documented in a experimental model of CC supporting the hypothesis that MyoD is implicated in the development of cancer-related muscle wasting.<sup>21</sup>

Myostatin, also known as GDF-8, belongs to the transforming growth factor- $\beta$  superfamily that controls the growth and differentiation of tissues throughout the body. The myostatin gene is expressed predominantly in the skeletal muscle, though it has also been detected in the heart, in the adipose

tissue and in the mammary gland.<sup>22</sup> Myostatin has been proposed to act as a negative regulator of skeletal muscle mass. Indeed, loss of function mutations of its gene have been detected in Belgian Blue and Piedmontese breeds of cattle, characterized by the so-called 'double-muscle' phenotype.<sup>23,24</sup> Consistently, adult mice in which the myostatin gene has been disrupted show a marked enlargement of the skeletal muscle mass.<sup>25</sup> This phenotype seems to depend on increased fibre number and diameter.<sup>25</sup> Conversely, systemic overexpression of the myostatin gene leads to a wasting syndrome characterized by extensive muscle loss (Zimmers Science) and male mice engineered to overexpress myostatin show a marked reduction of skeletal muscle mass.<sup>26</sup> Very recently, a case of a child, extraordinarily muscular, with protruding muscle in his thighs and upper arms with a loss-of-function mutation in the myostatin gene has been reported.<sup>27</sup>

Myostatin negatively regulates muscle growth by suppressing myoblast proliferation through the inhibition of cell cycle progression. Moreover, myostatin negatively regulates satellite cell activity and myoblast differentiation to myotubes through the decreased expression of MyoD.<sup>28,29</sup>

Myostatin expression in the skeletal muscle is enhanced during ageing, in denervation-induced muscle atrophy and after mechanical overloading.<sup>22</sup> In addition, increased myostatin gene expression has been associated with weight loss in men with AIDS-related cachexia, in young men after bed rest and in older men and women with muscle wasting.<sup>22</sup>

## APPROVED THERAPIES FOR CANCER CACHEXIA

Very few therapies are "approved" for the prevention and treatment of anorexia and cachexia of neoplastic patients (Table 1).

Among orexigenic agents, *megestrol acetate* is by far the most widely prescribed.<sup>30</sup> At least 15 randomized controlled studies have demonstrated that this drug, at doses ranging from 160 to 1600 mg/day, significantly improves appetite, with respect to placebo. It should be underlined, however, that although the increase in appetite represents an extremely positive perception for the patients and their relatives, in most of these trials no definite improvement in global quality of life was observed.<sup>30</sup> Possible explanations to these results might be related to: (a) the occurrence of undesired side-effects (thromboembolism, hyperglycemia, hypertension, peripheral edema, alopecia,

**TABLE 1.** *Approved therapies for cancer cachexia: results of clinical trials*

Author (year)	No. of patients	DIAGNOSIS	Type of intervention	Duration	Effect
Lopez et al. (2004) <sup>30*</sup>	3887	Cancer	Megestrol acetate	Various	Improvement in appetite and weight gain
Jatoi et al. (2002) <sup>33</sup>	469	Cancer	Dronabinol	~10 weeks	Dronabinol less effective than megestrol in treatment of anorexia
Wigmore et al. (2000) <sup>47</sup>	26	Pancreatic cancer	Eicosapentaenoic acid-enriched oral supplements	12 weeks	Prevention of weight loss
Fearon et al. (2003) <sup>48</sup>	200	Pancreatic cancer	Eicosapentaenoic acid enriched oral supplements	8 weeks	No nutritional advantage with respect to oral supplement alone
Moses et al. (2004) <sup>49</sup>	24	Pancreatic cancer	Eicosapentaenoic acid-enriched oral supplements	8 weeks	Increase in physical activity
Jatoi et al. (2004) <sup>50</sup>	400	Lung and gastrointestinal cancer	Eicosapentaenoic acid-enriched oral supplements	4 weeks	Less effective than megestrol acetate in weight gain

\* Systematic review.

adrenal insufficiency); and (b) the lack of a net improvement in lean body mass, in spite of significant weight gain, with no measurable effects on functional status. *Cannabinoids* are used for their ability to stimulate appetite; they are marijuana derivatives and act either through an interaction with cytokines network<sup>31–33</sup> or through an interaction with endocannabinoid receptors situated in the brain limbic system and in the hypothalamus or in peripheral organ systems like the intestine and the adipose tissue.<sup>32,33</sup> Dronabinol at 2.5 mg twice a day is the cannabinoid that has shown major prophagic effects. The patient-reported toxicities are: drowsiness, muddled thinking, loss of coordination, fluid retention, vomiting and impotence among the male population.<sup>32,33</sup>

### Artificial Nutrition

Oral nutritional supplements have been shown to provide a demonstrable benefit in patients who are malnourished, especially those with a body mass index of less than 20 kg/m<sup>2</sup>.<sup>34–36</sup> A recent Cochrane review have shown that these supplements produce a small but consistent weight gain, improvement in mortality and shorter hospital stays.<sup>35</sup>

Whether the use of enteral or parenteral nutrition is indicated in patients with cancer is an argument of debate. Enteral nutrition has been associated with improvements in nitrogen balance and is sometimes associated with weight gain.<sup>37</sup> Parenteral nutrition has been associated with improvements in nitrogen balance and seems to cause weight gain more consistently than enteral nutrition.<sup>37</sup> However, this weight gain is mainly body fat and not the desired lean body mass. Neither enteral nor parenteral

nutrition in cancer patients has beneficial effects in terms of significant reduction of morbidity and mortality.<sup>37–42</sup> According to American Society of Parenteral and Enteral Nutrition and European Society of Parenteral and Enteral Nutrition guidelines, the routine use of parenteral nutrition is not indicated in patients undergoing chemotherapy or radiotherapy for cancer. Parenteral nutrition is appropriate only in malnourished patients who are expected to be unable to ingest or absorb adequate nutrients for a long period, defined as longer than 7–10 days<sup>40,41</sup> and should be avoided if the life expectancy of the patient is less than 40–60 days.<sup>40,41</sup> If intravenous intervention is desired in an individual with a life expectancy of less than 40 days, intravenous fluids only are recommended.<sup>40,41</sup>

Parenteral nutrition seems to prevent weight loss and shorten the hospital stay in patients receiving stem-cell transplantation for hematologic diseases.<sup>40,41</sup> However, Lundholm et al. recently reported a large study of over 300 patients with solid tumours who were randomized to a palliative nutritional intervention or no treatment. The nutritional treatment consisted initially of dietetic consultation and provision of oral supplements to achieve a target intake of 30 kcal/kg body weight per day. If voluntary intake fell below 70% of these targets, parenteral nutrition was instituted. Patients who received nutrition experienced prolonged survival, increased energy balance and body fat, and a greater maximum exercise capacity.<sup>43</sup> Enteral nutrition is indicated in any malnourished patient with a functional gastrointestinal tract who is unable to ingest sufficient nutrients orally for a long period of time. Common indications include dysphagia because of head and

**TABLE 2.** *Drug candidates for for the treatment of cancer cachexia*

Drug	Type of study	Mechanism of action	Effect
Ghrelin	Human clinical trial	Stimulation of appetite	Energy intake increase and improvement in the perceived pleasantness of meal
Antagonist melanocortin receptor	Experimental studies	Blockade of the melanocortin receptor	Increase in food intake, energy expenditure decrease, weight gain
Pentoxifylline	Human clinical trial	Downregulates the production of TNF- $\alpha$	No significant effects on nutritional status
Thalidomide	Human clinical trials	Downregulate the production of TNF- $\alpha$ and other proinflammatory cytokines	Improvement of subjective symptoms of cachexia, weight gain, reduction in loss of lean body mass
Anti-cytokine antibodies		Inhibit the action of inflammatory cytokines	
Angiotensin-converting enzyme inhibitors	Experimental study	Reduction of protein breakdown	Weight gain
Melatonin	Human clinical trials	Downregulates the release of cytokines	Weight stabilization or gain
Nandrolone decanoate/oxandrolone	Human clinical trials	Stimulation of protein anabolism in muscle	Weight gain and improvement of lean body mass
Anti-myostatin antibodies	Experimental studies	Inhibition of myostatin action	Improvement of muscle function and reduction of muscle degeneration

neck cancer, esophageal obstruction and gastric outlet obstruction.<sup>44,45</sup>

### Eicosapentaenoic Acid (EPA)

Eicosapentaenoic acid is the only known nutritional supplement capable of interfering with proteasome activity through different mechanisms, at least in experimental conditions.<sup>46</sup> Preliminary studies in humans showed that EPA supplementation at a dose of 2.2 g/day prevented weight loss in patients with pancreatic cancer.<sup>47</sup> However, the results obtained in pilot studies have not been completely confirmed in a subsequent, large multicentre study on 200 patients with cancer of the pancreas, probably because many patients in the experimental group did not assume the prescribed dose of EPA.<sup>48</sup> Interestingly enough, in a post-hoc analysis of this trial,<sup>49</sup> EPA supplementation was shown to increase total energy expenditure with a parallel improvement in the physical function. Another multi-institutional trial including more than 400 patients with cancer-associated wasting has demonstrated that EPA supplementation was less effective than megestrol acetate in causing a 10% weight gain, but that it was relatively comparable with megestrol acetate with respect to appetite stimulation, survival and quality of life.<sup>50</sup> It seems that further studies are needed to evaluate if this nutritional substrate, because of its largely

demonstrated anti-inflammatory properties, may become an 'indispensable ingredient' in nutritional formulations for cancer patients.

### DRUGS CANDIDATES FOR FUTURE CLINICAL TRIALS

In the last two decades, basic and preliminary clinical studies have shown that some drugs may be possibly effective for the treatment of CC (Table 2).

#### Antagonists of Melanocortin Receptor

The melanocortin system, one of the central feeding circuits, has been recognized as an important regulator of energy balance for several years.<sup>51</sup> Activation of hypothalamic MC4 receptor by the endogenous agonist  $\alpha$ -melanocyte-stimulating hormone decreases food intake and leads to an increase in energy expenditure, whereas blockade of the MC4 receptor by the endogenous MC4-R inverse agonist, the agouti-related protein, increases food intake, decreases energy expenditure and leads to weight gain. It has been demonstrated, in experimental studies, that MC4-R blockade through the central administration of AgRP or the MC3/4-R antagonist SHU-9119 protects animals against cancer-induced anorexia.<sup>52</sup> Moreover, Markison et al. have shown that a selec-



tive, low molecular weight, MC4-R antagonist, administered peripherally was able to reduce tumour-induced anorexia and increase lean body mass when compared with placebo.<sup>53</sup> Finally, Nicholson et al. have investigated the effect of chronic peripheral administration of a MC4-R ligand in a murine model of cachexia. Cumulative 13-day light-phase food intake was significantly increased by the MC4-R ligand in both sham and tumour-bearing mice whereas there was no effect on cumulative 13-day 24-h food intake either in the sham or the tumour-treated groups. However, in the tumour groups, the body weight of placebo-treated and MC4-R ligand-treated mice tended to decrease during the 21-day period. Interestingly, the tumour-vehicle mice lost lean body mass whereas the tumour-bearing mice receiving the MC4-R ligand were protected from this loss.<sup>54</sup>

### Subcutaneous Ghrelin

Ghrelin is the only circulating appetite-stimulating hormone identified to date. Ghrelin is expressed in the stomach and activates neurons of the arcuate nucleus of the hypothalamus. Endogenous ghrelin levels peak before each meal and fall within 1 h of eating.<sup>55</sup> Ghrelin infusion has been demonstrated to increase food intake in male and female healthy volunteers in a double-blind, randomized, controlled trial.<sup>55</sup> Also when administered subcutaneously, ghrelin stimulates energy intake in healthy lean human volunteers.<sup>56</sup> Neary et al. have investigated the effect of ghrelin infusion on energy intake and appreciation of food in cancer patients with appetite loss. Energy intake from the buffet lunch was increased by 31% during ghrelin infusion compared with the saline control. Moreover, every patient consumed more on his/her ghrelin administration day. No side effects were observed. In particular, there were no differences in pulse and blood pressure recording between ghrelin and saline infusion days. There was no evidence of compensatory decrease in food intake after ghrelin treatment as assessed by 24-h food diary. Analysis of the visual analogue score revealed a significant increase of 23% in the perceived pleasantness of the meal on the ghrelin administration day compared with the saline administration day.<sup>57</sup>

The effect of chronic ghrelin administration on body weight, nutritional parameters, quality of life, morbidity and mortality in patients with CC remains to be investigated. Similarly, it is mandatory to establish whether chronic ghrelin administration has any long-term adverse effects.

### Inhibitors of Cytokine Production and/or Release

The attenuation of muscle loss has long been attempted through an *upstream approach* that was mainly based on the knowledge that proinflammatory cytokines are amongst the most important humoral mediators of muscle catabolism in both experimental and human CC. Thus, drugs capable of inhibiting the synthesis and/or release of cytokines (pentoxifylline, thalidomide, melatonin, statins, ACE-inhibitors and anti-COX-2), drugs and other molecules interfering with cytokine actions [anti-cytokine antibodies, suramin (SUR)] and anti-inflammatory cytokines (IL-12, IL-15) have been extensively tested in experimental CC,<sup>58–65</sup> with substantially positive results. Clinical trials testing the efficacy of this approach in human beings are few but most have provided promising results.<sup>66–80</sup>

Based on the evidence that *pentoxifylline* inhibits TNF, Golderg et al. randomized 70 patients with an Eastern Cooperative Oncology Group performance status of 0–2 and with cancer anorexia and/or cachexia (defined by a weight loss of  $\geq 5$  lb in the preceding 2 months or a caloric intake  $< 20$  kcal/kg/day) to receive pentoxifylline (400 mg three times daily) or identical-appearing placebo tablets in a double-blind fashion.<sup>66</sup> Pentoxifylline failed to improve appetite or induce weight gain. However, it must be considered that the population entered was a heterogeneous group of patients with cancers arising in a variety of primary sites and in various stages of advanced disease. It is amenable that larger trials in the next future will test if this drug is really ineffective or has a role in the treatment of CC.

*Thalidomide* has complex immunomodulatory and anti-inflammatory properties. It has been shown to downregulate the production of TNF- $\alpha$  and other proinflammatory cytokines, inhibit the transcription factor nuclear factor-kB, downregulate cyclooxygenase 2 (COX-2) and inhibit angiogenesis.<sup>67–69</sup> In the study of Bruera et al. who treated 37 patients with metastatic cancer and weight loss of more than 5% of their usual adult weight with thalidomide (100 mg) for a period of 10 days, thalidomide appeared to be capable of improving the subjective symptoms of cachexia. In fact, improvement in symptom intensity was observed for difficulty in falling asleep in 49% of the patients, for restedness in the morning (64%), insomnia (69%), nausea (44%), appetite (63%), and well-being (53%).<sup>67</sup> In the study of Khan et al.,<sup>68</sup> ten patients with non-obstructing and inoperable oesophageal cancer were established on an isocaloric diet for 2 weeks, followed by 2 weeks on thalidomide,

200 mg daily. Nine of ten patients lost weight on diet alone while the mean weight gain during thalidomide treatment was 1.29 kg. A similar trend was shown in lean body mass, with a reduction during the diet alone and a 1.75 kg gain in the following 2 weeks. The Karnofsky index, used to measure the quality of life, improved in eight patients whilst on thalidomide treatment, in 4 by a score of 10 and in 4 by a score of 20. Gordon et al.<sup>69</sup> randomized 50 patients with pancreatic cancer who had lost at least 10% of their body weight to receive thalidomide 200 mg daily or placebo for 24 weeks. Thirty-three patients were evaluated at 4 weeks and 20 at 8 weeks. Overall, thalidomide appeared to be well tolerated. At 4 weeks, patients who received thalidomide had gained an average of 0.37 kg in weight and 1.0 cm<sup>3</sup> in arm muscle mass compared with a loss of 2.21 kg and 4.46 cm<sup>3</sup> in the placebo group. At 8 weeks, patients in the thalidomide group had lost .06 kg in weight and 0.5 cm<sup>3</sup> in arm muscle mass compared with a loss of 3.62 kg and 8.4 cm<sup>3</sup> in the placebo group. There was no significant difference in global health score or physical functioning between the two groups from the baseline in either group. The results of this study suggest that thalidomide attenuate weight loss and that this is associated with a reduction in loss of lean body mass. This is a clinically important finding as it is well known that patients with unresectable pancreatic cancer show inexorable weight and muscle loss.

*Melatonin* is a hormone produced by the pineal gland that participates in the regulation of biological rhythms and in the control of cell differentiation and proliferation.<sup>70–73</sup> In the study of Lissoni et al.,<sup>71</sup> 100 untreatable metastatic solid tumour patients were randomized to receive either supportive care alone, or supportive care plus melatonin (20 mg/daily orally in the evening). Among the 86 evaluable patients, the frequency of weight loss (> 10%) was higher in patients treated by supportive care alone than in those concomitantly treated by melatonin. Person et al.<sup>72</sup> randomized 24 cancer patients not amenable to standard anticancer treatment and with documented weight loss and/or decreased serum albumin to 30 mL/day of fish oil or melatonin (18 mg/day) for 4 weeks. During the next four weeks all patients received both fish oil and melatonin. No major changes in biochemical variable and cytokines were observed with any intervention. Weight stabilization or gain was observed in 38% of the patients of the fish oil group and in 27% of those who received melatonin. After combining interventions, 63% of patients showed such responses.

Based on the hypotheses that downregulating the acute phase response and stimulating the appetite might be effective in reversing or halting weight loss, Mc Millan et al.<sup>73</sup> administered a combination of megestrol acetate (480 mg/day) and *ibuprofen* (1200 mg/day) or megestrol acetate alone to 73 patients with locally advanced or metastatic gastrointestinal cancer with more than 5% of weight loss. Only 37% of the patients completed the final 12-week assessment. Among these, there was a decrease in weight (median 2.8 kg) in the megestrol acetate group compared with an increase (median 2.3 kg) in the megestrol acetate/*ibuprofen* group, the difference being statistically significant. This weight gain was associated with an improvement in the quality of life.

### Nandrolone Decanoate and Oxandrolone

Stimulation of protein anabolism in muscle may be attempted through anabolic androgenic steroids (AASs), a large family of testosterone-related hormones which vary in terms of chemical structure, mode of action, anabolic effects and risk of undesired side effects.<sup>74</sup> AAS administration induces increases in mRNA expression of skeletal muscle androgen receptor, increases the intracellular utilization of amino acids derived by protein degradation and stimulates net muscle protein synthesis.<sup>75</sup> Positive effects have been documented with nandrolone decanoate and oxandrolone in burned,<sup>76</sup> HIV-infected<sup>77</sup> and chronic obstructive pulmonary disease<sup>78</sup> patients. Data on cancer patients are limited but promising.<sup>79,80</sup> Chlebowski et al. evaluated in a randomized prospective trial the effect of short-term administration of nandrolone decanoate to combination chemotherapy in patients with unresectable non-small cell lung cancer. There was a trend for less severe weight loss on the nandrolone decanoate arm (200 mg intramuscularly weekly for 4 weeks) with half as many patients experiencing weight loss on nandrolone decanoate.<sup>79</sup> In an open-label, 4-month study, 131 patients with cancer received 20 mg of oxandrolone per day and were also educated about nutrition and exercise. Eighty per cent of patients maintained or gained weight, the average increase in lean tissue being 4 lbs. Moreover, the ECOG scores improved from an average of close to 2 (unable to perform work) to nearly 1 (able to perform light work).<sup>80</sup>

### Anti-myostatin Antibodies

Recently, two independent groups reported that inhibiting myostatin activity resulted in improved

muscle function and reduced muscle degeneration in dystrophic mice.<sup>81,82</sup> Indeed, in the study of Bogdanovich et al., blockade of endogenous myostatin by using intraperitoneal injections of blocking antibodies for 3 months resulted in an increase in body weight, muscle mass, muscle size and absolute muscle strength in mdx mouse muscle along with a significant decrease in muscle degeneration and concentrations of serum creatine kinase.<sup>81</sup>

### A PROPOSAL FOR ADDITIONAL STUDIES

Overall, it seems that many drugs might be evaluated in the very next future through adequate, prospective, controlled, randomized trials to define if they are able to prevent and/or reverse anorexia and/or cachexia in cancer patients and if this translates in an improvement of quality of life and better response to chemo- and radiotherapies.

Among these, primary candidates include thalidomide and melatonin that inhibit the production and release of inflammatory cytokines. The encouraging results obtained in preliminary studies authorize to design larger clinical trials.

Moreover, considering the mechanisms of action, drugs that inhibit the action of cytokines also might be proposed and tested as anti-cachectic strategies such as anti-cytokine antibodies (infliximab, etanercept). A pilot study on safety and pharmacokinetics of infliximab in non-small cell lung cancer patients has shown that this drug, in combination with docetaxel, a commonly used chemotherapy agent, was safe and well tolerated.<sup>83</sup> Similarly, combining etanercept with docetaxel in a small group of patient with advanced malignancies has been shown to be safe, to increase chemotherapy tolerability and improve fatigue.<sup>84</sup>

Further controlled clinical trials evaluating both the long-term efficacy as well as the risk of dangerous side effects are strongly warranted for nandrolone decanoate and oxandrolone.

It is amenable that in the next future the encouraging results obtained in experimental studies will prompt continuous clinical research aimed at clarifying the role of melanocortin receptor antagonist in cancer-related anorexia and cachexia.

The possibility to induce muscle hypertrophy through myostatin inhibition via specific blocking antibodies is extremely intriguing and is possible that the development of specific anti-myostatin antibodies will probably speed research into the therapeutic

targeting of myostatin in muscle-wasting disorders, such as sarcopenia and cancer-related cachexia.

### CONCLUSION

Cancer cachexia still represents a frustrating condition for both the patient and his physician. Very few therapies are "approved" for the prevention and treatment of anorexia and cachexia of neoplastic patients. In the last decade, various drugs have been tested in experimental animal models and in preliminary human trials, with promising results. Overall, it seems that it is time to start prospective, randomized, controlled trials to evaluate which of these drugs are effective in counteracting the loss of lean of muscle mass and in improving nutritional status and quality of life in patients affected by cancer-related cachexia. Fortunately, the development of early and effective interventions aimed at preventing and reversing the metabolic perturbations ultimately leading to muscle wasting and cachexia is now perceived as a mandatory need by the scientific community, and is fostering the continuous effort of basic and clinical research.

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