

Therapy Insight: cancer anorexia–cachexia syndrome—when all you can eat is yourself

Alessandro Laviano*, Michael M Meguid, Akio Inui, Maurizio Muscaritoli and Filippo Rossi-Fanelli

SUMMARY

Tumor growth is associated with profound metabolic and neurochemical alterations, which can lead to the onset of anorexia–cachexia syndrome. Anorexia is defined as the loss of the desire to eat, while cachexia results from progressive wasting of skeletal muscle mass—and to a lesser extent adipose tissue—occurring even before weight loss becomes apparent. Cancer anorexia–cachexia syndrome is highly prevalent among cancer patients, has a large impact on morbidity and mortality, and impinges on patient quality of life. However, its clinical relevance is frequently overlooked, and treatments are usually only attempted during advanced stages of the disease. The pathogenic mechanisms of cachexia and anorexia are multifactorial, but cytokines and tumor-derived factors have a significant role, thereby representing a suitable therapeutic target. Energy expenditure in anorexia is frequently increased while energy intake is decreased, which further exacerbates the progressive deterioration of nutritional status. The optimal therapeutic approach to anorectic–cachectic cancer patients should be based on both changes in dietary habits, achieved via nutritional counseling; and drug therapy, aimed at interfering with cytokine expression or activity. Our improved understanding of the influence a tumor has on the host's metabolism is advancing new therapeutic approaches, which are likely to result in better preservation of nutritional status if started concurrently with specific antineoplastic treatment.

KEYWORDS anorexia, cachexia, cancer, pathogenesis, therapy

REVIEW CRITERIA

Referenced papers were identified by searches of PubMed and MEDLINE using the search terms “cancer”, “anorexia”, “cachexia”, “pathogenesis” and “therapy”. Only papers published in English between 1 January 1980 and 31 August 2004 were included. Additional papers were identified from reference list of retrieved papers. Letters and reports from meetings were included only when they related directly to previously published work. Published abstracts were not considered.

A Laviano is Assistant Professor of Medicine, Department of Clinical Medicine, University La Sapienza, Rome, Italy. M M Meguid is Professor of Surgery, Department of Surgery, Neuroscience Program, University Hospital, SUNY Upstate Medical University, Syracuse, New York, USA. A Inui is Professor of Internal Medicine, Department of Behavioral Medicine, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan. M Muscaritoli is Associate Professor of Medicine, Department of Clinical Medicine, University La Sapienza, Rome, Italy. F Rossi-Fanelli is Professor of Medicine and Chairman, Department of Clinical Medicine, University La Sapienza, Rome, Italy.

Correspondence

*Department of Clinical Medicine, University La Sapienza, viale dell'Università 37, 00185 Rome, Italy
alessandro.laviano@uniroma1.it

Received 6 October 2004 Accepted 28 January 2005

www.nature.com/clinicalpractice
doi:10.1038/ncponc0112

INTRODUCTION

In recent years, our cumulative understanding of a number of scientific breakthroughs in the fields of tumor biology and genomics has translated into novel antineoplastic therapeutic approaches. Thus, the use of radiotherapy and chemotherapy is now complemented by gene-driven therapy that will yield improved response rates and prolonged survival, particularly in patients whose cancers are not susceptible to eradication.¹ Although many tumors can be treated, only a few patients with metastatic cancer are likely to be cured. Consequently, supportive care is a critical issue in the management of cancer patients, wherein oncologists positively influence not only survival, but quality of life and nutritional status.

The presence of a tumor can be clinically suspected when patients report anorexia accompanied by marked weight loss; both symptoms that frequently lead patients to seek medical advice. While anorexia is defined as the loss of the desire to eat, which frequently leads to reduced food intake, cachexia is characterized by profound loss (up to 80%) of both adipose tissue and skeletal muscle mass that eventually leads to hypoalbuminemia and asthenia, which, together with anemia, a frequent comorbidity in cancer patients, limit physical activity and consequently inhibit protein synthesis.² The weight loss caused by cancer differs from that observed during starvation, which is characterized by preservation of lean body mass. In contrast, both adipose tissue and, in particular, lean body mass are markedly depleted during cachexia.² Furthermore, in many cancer patients, particularly those with pancreatic or lung cancer, resting energy expenditure is not suppressed by progressive weight loss, but can even be increased, thus exacerbating the detrimental effects of wasting and reduced food intake on nutritional status.²

In cancer patients, anorexia and cachexia can co-exist, although the degree of weight loss cannot be ascribed completely to reduced food intake. Indeed, the muscle wasting observed in

cancer patients occurs even in the presence of a normal food intake, and increased muscle proteolysis is detectable even before weight loss occurs.³ Consequently, in cachectic cancer patients, the mere provision of nutrients via artificial nutrition is not effective in preventing muscle wasting or restoring lean body mass.⁴ Anorexia *per se* reduces food intake and promotes weight loss, but when it accompanies cachexia it acts synergistically to impact on patients' morbidity, mortality and quality of life. To paraphrase the clinical consequences of this deadly combination, all that anorectic-cachectic patients can eat is themselves.

PATHOGENESIS OF CACHEXIA AND ANOREXIA

Although cancer-associated anorexia and cachexia have been documented since the first tumor studies, it is only recently that advances in the field of molecular biology have shed light on their pathogenesis. Under physiologic conditions, the homeostasis of skeletal muscle mass is a dynamic process, in which a balance of protein degradation and protein synthesis is achieved. During cancer, progressive reduction of skeletal muscle mass occurs, although visceral protein reserves are preserved and the liver mass may actually increase.² Whole-body protein turnover is increased,⁵ due to an increase in muscle protein catabolism⁶ and an overall decrease in protein synthesis,⁷ despite the increase in hepatic acute-phase protein synthesis.⁸ There are three main proteolytic pathways responsible for protein catabolism in skeletal muscle. These are the lysosomal system, which is involved in proteolysis of extracellular proteins and cell-surface receptors;⁹ the cytosolic calcium-regulated calpains, which are involved in tissue injury, necrosis and autolysis;¹⁰ and the ATP ubiquitin-dependent proteolytic pathway.⁹ Of these, ubiquitin-dependent proteolysis is considered to be the most important for protein degradation in cancer cachexia.⁹

Cancer cachexia is also characterized by a marked reduction in adipose tissue, which is due to an increase in lipolysis rather than a decrease in lipogenesis.¹¹ In addition, energy metabolism is dysregulated during tumor growth, leading to continual increased energy expenditure, possibly via changes in the expression of genes encoding the uncoupling proteins.¹² These are a family of mitochondrial membrane proteins that mediate proton leakage and decrease the coupling of

respiration to ADP phosphorylation, resulting in the production of heat instead of ATP.

The dramatic metabolic changes that occur during tumor growth are triggered by a number of factors, including proteolysis-inducing factor, which induces protein degradation into amino acids in skeletal muscles,¹³ and lipid-mobilizing factor, which promotes breakdown of adipose tissue into free fatty acids.¹⁴ While proteolysis-inducing factor and lipid-mobilizing factor are produced by the tumor, other factors are released as a consequence of interactions between host cells and tumor cells, represented by a number of proinflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), and interleukin-6 (IL-6). Their role in cancer cachexia was first established in animal models, and supporting evidence in humans has been reported.¹⁵

The pathogenesis of anorexia is multifactorial and is related to disturbances of the central physiological mechanisms controlling food intake. Under normal conditions energy intake is controlled primarily in the hypothalamus by specific neuronal populations, which integrate peripheral blood-borne signals conveying information on energy and adiposity status.¹⁶ In particular, the arcuate nucleus of the hypothalamus transduces these inputs into neuronal responses, and, via second-order neuronal signaling pathways, into behavioural responses (Figure 1). Intuitively, anorexia might be considered secondary to defective signals arising from the periphery, perhaps due to an error in the transduction process or to a disturbance in the activity of the second-order neuronal signaling pathways. However, consistent data seem to suggest that cancer anorexia is mediated by the inability of the hypothalamus to respond appropriately to peripheral signals, indicating an energy deficit (Figure 2). Cytokines, including IL-1 and TNF- α , appear to mediate this 'hypothalamic resistance', by hyperactivating anorexigenic neurons and suppressing prophagic neurons.¹⁷ Cytokine-driven deregulation of the hypothalamic monoamine system contributes significantly to modulating these effects.¹⁷

DIAGNOSIS OF CACHEXIA AND ANOREXIA

Anorexia is defined as the loss of the desire to eat, and its diagnosis is based on reduced appetite. However, the presence of anorexia could be characterized more effectively by identifying objective symptoms, including early satiety, taste alterations and nausea, and by assessing its

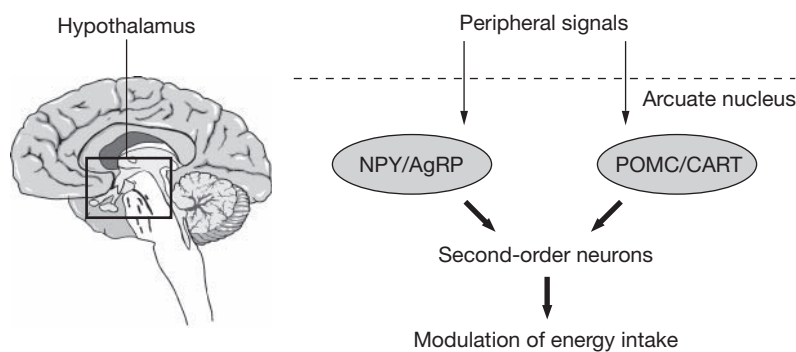


Figure 1 Diagram showing the modulation of food intake via the hypothalamus. In the hypothalamus, the arcuate nucleus receives information from the periphery and integrates these inputs to modulate food intake via second-order neurons. According to the information conveyed to the brain, peripheral signals may differentially activate/inhibit POMC/CART and NPY/AgRP neurons. When an energy deficit is signaled, anorexigenic POMC/CART neurons are inhibited and prophagic NPY/AgRP neurons are activated, resulting in increased energy intake. When an energy surplus is signaled, NPY/AgRP neurons are inhibited and POMC/CART neurons are activated.¹⁶ AgRP, agouti-related protein; CART, cocaine-amphetamine-regulated transcript; NPY, neuropeptide Y; POMC, pro-opiomelanocortin.

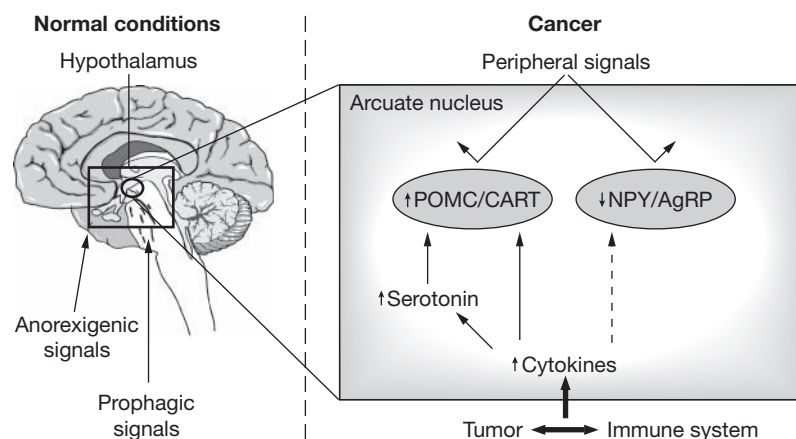


Figure 2 The balance between prophagic and anorexigenic signaling in the arcuate nucleus of the brain. Under normal conditions, energy intake is determined by the hypothalamic integration of peripheral signals conveying inputs on adiposity status, digestive processes, and metabolic profile. Some of these signals, including adipocyte-derived leptin, duodenum-derived cholecystokinin, and gut-derived peptide YY, inhibit energy intake. Other signals stimulate energy intake, including pancreas-derived insulin and stomach-derived ghrelin.¹⁶ During cancer, tumor-host immune interaction leads to neuroimmune activation. Increased brain cytokine expression disrupts hypothalamic neurochemistry, particularly in the arcuate nucleus, where cytokines activate POMC/CART neurons, which mediate satiety and reduced food intake. This effect is at least in part mediated via increased serotonin synthesis and release. In addition, cytokines probably inhibit NPY/AgRP neurons, which mediate appetite and energy intake. These changes in hypothalamic neurochemistry lead to 'resistance' to peripheral signals informing the brain of ongoing energy deficits in the periphery. Consistent evidence indicates that cytokines may have a pivotal role in the long-term inhibition of feeding by mimicking the hypothalamic effect of excessive negative feedback signaling.⁵⁸ Tumor-induced changes in energy metabolism of hypothalamic neurons are not presented in the figure, but they are probably involved in the pathogenesis of cancer anorexia.¹⁷ AgRP, agouti-related protein; CART, cocaine-amphetamine-regulated transcript; NPY, neuropeptide Y; POMC, pro-opiomelanocortin.

severity. Consequently, a visual analog scale is often used, which is a useful tool in epidemiologic or prospective studies but may prove unreliable if small changes in appetite need to be detected.¹⁸ Sometimes, the diagnosis of anorexia is based on the presence of reduced energy intake, but this could be misleading because the reduction of ingested calories might be the consequence of dysphagia or depression rather than because of anorexia. In addition, a number of symptoms interfering with food intake, which are likely to be linked to changes in the central nervous system energy intake control, have been identified (Box 1).¹⁹ The use of questionnaires to diagnose anorexia is increasing rapidly, thus highlighting their utility and reliability. However, considering that questionnaires provide only a qualitative assessment of the presence of anorexia, it is also advisable to quantify the degree of anorexia by using a visual analog scale.

In contrast, the diagnosis of cachexia could be more difficult because it is latent, and its development often proceeds for a long time before its clinical manifestation.^{20,21} Cancer cachexia is biologically characterized by increased activity of intracellular proteolytic pathways, which is clinically manifest by loss of body weight, although the increased activity of the major muscular proteolytic system is observed even in the absence of any weight loss.³ Therefore, activation of the pathogenic mechanisms of cancer cachexia is an early phenomenon during tumor growth, and cachexia should be suspected even in the absence of weight loss, particularly in those patients whose tumors are known to negatively influence nutritional status (i.e. those of the pancreas, lung, esophagus, and stomach).²² Given these facts, cachexia should be treated in its preclinical stage, when the likelihood for effective prevention of muscle wasting is greater than during the advanced stages of the disease.

CLINICAL RELEVANCE

Owing to the difficulties in clearly defining and diagnosing cancer anorexia, its prevalence is yet to be precisely assessed. Based on different diagnostic tools, anorexia has been detected at the point of cancer diagnosis in 13–55% of patients.²³ Nevertheless, consistent evidence suggests that approximately 50% of cancer patients report abnormalities of eating behaviour at the time of first diagnosis,²⁴ and prevalence in terminally-ill cancer patients is even higher at approximately 65%.²⁵ The incidence

Box 1 Symptoms interfering with food intake and related to changes in the central nervous system regulation of energy intake. Patients reporting at least one of these symptoms are defined as anorectic.¹⁹

Symptoms

Early satiety
Taste alterations
Smell alterations
Meat aversion
Nausea/vomiting

of weight loss upon diagnosis varies greatly according to the tumor site (Table 1).^{22,26} In less aggressive forms of Hodgkin's lymphoma, acute nonlymphocytic leukemia, and in breast cancer, the frequency of weight loss is 30–40%. More aggressive forms of non-Hodgkin's lymphoma, colon cancer, and other cancers are associated with a frequency of weight loss between 50–60%.^{27–29} Patients with pancreatic or gastric cancer have the highest frequency of weight loss at over 80%.

The onset of anorexia–cachexia significantly influences the clinical course of the disease, and most antitumor therapies actually exacerbate anorexia and worsen body weight loss. As a consequence, the higher prevalence and greater severity of anorexia–cachexia syndrome in advanced cancer patients is mostly due to iatrogenic cause. The presence of early satiety at any stage of the disease can significantly increase the risk of death by 30%.³⁰ Similarly, the extent of body weight loss negatively influences survival not only *per se*, but also by delaying initiation and/or completion of aggressive antitumor therapy (Table 2).²⁶

An interesting aspect of the clinical impact of cancer anorexia–cachexia syndrome that has recently emerged is its influence on quality of life. Supporting this view, it was recently documented that quality-of-life function scores are largely determined by nutrient intake and weight loss, accounting for 20% and 30% of the total score, respectively.³¹ Despite the well-known and much-documented clinical impact of anorexia and cachexia on prognosis and quality of life, oncologists have suboptimal awareness of how to treat this syndrome. A recent survey showed that almost all of the responding oncologists agreed that all advanced cancer patients should receive concurrent

Table 1 Incidence of weight loss in cancers of different sites (adapted, with permission, from ref 22).

Tumor site	Incidence of weight loss (%)
Pancreas	83
Gastric	83
Esophagus	79
Head and neck	72
Colorectal	55–60
Lung	50–66
Prostate	56
Breast	10–35
General cancer population	63

Table 2 Effect of weight loss expressed as % of premorbid weight on median survival expressed in weeks (adapted, with permission, from ref 26).

Tumor	No WL	0–5% WL	5–10% WL	>10% WL	P value
NSCLC	20	17	13	11	<0.01
Prostate	46	30	18	9	<0.05
Colorectal	43	27	15	20	<0.01

Abbreviations: NSCLC, non-small-cell lung cancer; WL, weight loss.

supportive care, even if they are receiving anti-tumor therapy.³² Yet only a minority reported consulting frequently with a supportive care specialist, and almost half of respondents indicated that they were inadequately trained in this aspect of patient care. Surprisingly, an astonishing 30% did not disagree with the statement that “palliative care specialists steal patients who would otherwise benefit from medical oncology”. Therefore, it appears that most oncologists recognize the importance of supportive care for cancer patients. Despite this, many are inadequately trained, resulting in the delivery of suboptimal care.

During the past few years, the general awareness of the clinical relevance of anorexia–cachexia syndrome has increased, particularly because it is now clear that in cancer management it is important to add life to years and not just years to life. Therefore, it is expected that in the near future, cancer patients may start concurrent antitumor and anti-anorexia/cachexia therapies when a diagnosis is made. Such a combined therapy would have a synergistic effect on enhancing response rates and improving quality of life.

Box 2 Currently available therapeutic strategies in cancer anorexia–cachexia.

Dietary counselling

Small but frequent meals
Energy-dense food
Limit fat intake
Avoid extremes in taste
Avoid extremes in smell
Pleasant environment
Presentation of food
Oral supplements

Drugs

Progestagens (MA, MPA)
Cannabinoids (dronabinol)^a
Corticosteroids (dexamethasone)^a

Abbreviations: MA, megestrol acetate; MPA, medroxyprogesterone acetate. ^aCannabinoids have not been shown to reverse weight loss in cancer patients. Similarly, long-term treatment with dexamethasone only increases the patient's sense of well-being.

THERAPY FOR ANORECTIC–CACHECTIC PATIENTS

The optimal therapy for anorexia and cachexia is curing the underlying cancer.²³ Unfortunately, this goal is often not attainable with currently available treatments. Thus, an integrated therapeutic approach should be devised to treat cancer anorexia and cachexia, and should include both nutritional counseling and pharmacologic approaches (Box 2).

Dietary habits

In anorectic–cachectic cancer patients, intensive individualized nutritional intervention based on nutrition counseling attenuates the deterioration of nutritional status, and accelerates recovery of global quality of life and physical function.³³ Food intake can be increased by providing frequent small meals that are energy-dense and easy to eat. Patients should be encouraged to eat in pleasant surroundings and attention should be given to the presentation of food. It is advisable to avoid high-fat food, because fat delays gastric emptying³⁴ and may exacerbate early satiety, a symptom of anorexia (see Box 1). Since changes in taste and smell occur in anorectic patients, extremes in food temperature and flavor should be avoided.²⁴

Drug therapy

Drug therapy should be directed at counteracting the etiologic mechanisms of anorexia and cachexia. Thus, targeting the synthesis

and/or activity of cytokines is a potentially effective approach, which is mainly represented in humans by progestagens but also cannabinoids and corticosteroids.³⁵

Progestagens (megestrol acetate and medroxyprogesterone acetate) are the first-line therapy for cancer anorexia and cachexia.³⁵ They are highly effective in relieving the symptoms of cancer anorexia. In a recent systematic review of randomized clinical trials, high-dose progestagens have been shown to improve food intake, and to a lesser extent body weight.³⁶ However, they should be used with caution in hormone-dependent tumors, and their use may lead to deep venous thrombosis, vaginal spotting and sexual dysfunction. Also, body weight gain induced by progestagens is mainly due to water retention, and no effect on skeletal muscle mass has been demonstrated.

THERAPY: WHAT'S NEXT?

Omega-3 fatty acids

The omega-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to suppress production of proinflammatory cytokines and arachidonic acid-derived mediators.³⁷ These *in vitro* effects have been exploited in the treatment of cancer patients, and it has been shown that adequate and prolonged EPA supplementation may lead to increased body weight and gain of lean body mass in cachectic cancer patients, probably due to suppression of either cytokine production or proinflammatory mediators, although this remains untested.³⁸ In addition, the use of an EPA-enriched, energy-dense oral supplement appears to increase physical activity, which may reflect improved quality of life.³⁹ Moreover, a comparison of the effects of megestrol acetate and of a caloric supplement enriched with EPA and DHA in anorectic cancer patients who had lost weight, showed that megestrol acetate and DHA/EPA supplementation are equally effective in improving appetite and body weight, although body composition was not assessed in this study.⁴⁰ A combination of both treatments did not increase response rate. The use of omega-3 fatty acids is limited by poor compliance to prolonged supplementation. Since not all cancer patients with cachexia benefit from omega-3 fatty acid supplementation,⁴¹ further studies are needed to define the clinical and genetic subset of cancer patients most likely to derive favorable effects.

Anticytokine agents

In animal models, anticytokine therapy is highly effective in counteracting cancer anorexia.⁴² In humans, a number of molecules exhibiting anticytokine activity have been tested. Anti-IL-6 monoclonal antibody therapy appears promising, but clinical data are still lacking.⁴³ The compounds pentoxifylline, thalidomide, and suramin have been demonstrated to significantly reduce cytokine release in humans.³⁵ Unfortunately, pentoxifylline failed to demonstrate any clinical benefit in cancer patients with anorexia–cachexia syndrome.³⁵ Thalidomide showed some promise in patients with multiple myeloma, but results were modest in solid tumors.⁴⁴ Also, the potential side effects of anticytokine therapy, including suramin-induced inhibition of chemotherapy-induced apoptosis,⁴⁵ suggest it should be used with caution.

Antiserotonergic agents

Cancer anorexia and cachexia can be therapeutically treated by interfering with the neurochemical events downstream of cytokine activation. Serotonergic hypothalamic neurotransmission may represent a suitable example. Synthesis of serotonin in the hypothalamus depends on the availability of its precursor, the amino acid tryptophan. Such availability is reduced by the oral administration of branched-chain amino acids (BCAA) because they compete with tryptophan for the same transport system located on the blood–brain barrier (Figure 3).⁴⁶ In a pilot study, oral supplementation with BCAA improved anorexia and energy intake in anorectic cancer patients.⁴⁷ Although not tested in larger clinical trials involving cancer patients, the prophagic effects of supplementation with BCAA have been confirmed in patients with uremia and liver cirrhosis.^{48,49}

Another mechanism of action of BCAA could be that they act centrally to influence appetite and energy intake, while simultaneously inhibiting peripheral muscle wasting. Serotonin has been shown to activate hypothalamic melanocortin receptors,⁵⁰ which have been linked to muscle wasting.⁵¹ It is postulated that melanocortin receptors are less activated as a result of reducing brain serotonergic activity via BCAA, leading to reduced peripheral muscle wasting. Furthermore, recent experimental data show that leucine, one of the three BCAA, has inhibitory effects on ATP-dependent ubiquitin activity.⁵²

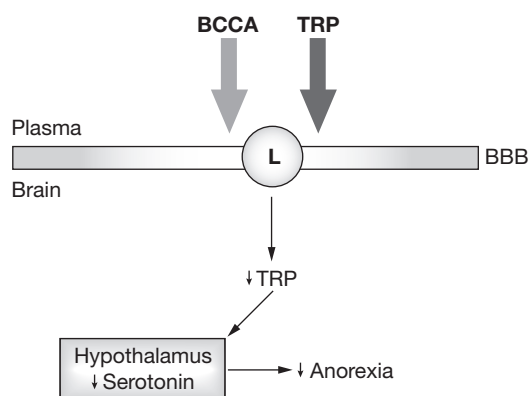


Figure 3 Anorexia improvements via oral supplements that compete with tryptophan to inhibit serotonergic signaling. Oral supplementation with branched-chain amino acids, by competing with tryptophan for the same carrier located on the blood brain barrier, the L-system, leads to reduced brain tryptophan entry, which in turn results in reduced hypothalamic serotonergic activity and improved anorexia. BBB, blood–brain barrier; BCAA, branched-chain amino acids; TRP, tryptophan.

Ghrelin

The role of ghrelin, an orexigenic peptide predominantly secreted from gastric cells,⁵³ is still controversial in cancer anorexia–cachexia syndrome. Although cachectic cancer patients appear resistant to the prophagic effects of ghrelin,⁵⁴ intravenous infusion of ghrelin to anorectic cancer patients has been shown to increase energy intake.⁵⁵ Ghrelin is a unique hormone that stimulates the release of growth hormone and increases appetite. In anorectic–cachectic cancer patients, it may simultaneously increase the intake of nutrients and favor their utilization, with the effect of preserving muscle mass. However, caution is advised with the use of ghrelin in cancer patients, because increased growth hormone production may stimulate tumor growth; although chronically administered ghrelin has not been tested in humans to ascertain whether the increased production of growth hormone is sustained.

Anti-inflammatory agents

The production of eicosanoids is involved in the pathogenesis of cancer anorexia and cachexia,^{2,17} and cyclooxygenase inhibitors have been shown to decrease tumor growth and improve anorexia in animal models.⁵⁶ In humans, it was recently demonstrated that an integrated nutritional and metabolic approach, consisting of systemic

anti-inflammatory treatment (indomethacin) combined with treatment to enhance erythropoietin levels, and individualized nutrition-focused patient care (oral nutritional support and/or home total parenteral nutrition), prolonged survival and increased maximum exercise capacity in cancer patients.⁵⁷

CONCLUSION

The incidence of anorexia–cachexia syndrome is high in cancer patients. This is clinically relevant because it significantly affects the course of the underlying disease. Unfortunately, awareness of its relevance is suboptimal among the health professionals involved in clinical management of cancer patients. As a consequence, severely compromised nutritional status and wasting are still common features of cancer patients. It is important to recognize and treat this syndrome as early as possible, even concurrently with anti-tumor therapy, in order to prolong survival and positively influence quality of life.

References

- Ayers M *et al.* (2004) Gene expression profiles predict complete pathologic response to neoadjuvant paclitaxel and fluorouracil, doxorubicin, and cyclophosphamide chemotherapy in breast cancer. *J Clin Oncol* **22**: 2284–2293
- Tisdale MJ (2002) Cachexia in cancer patients. *Nat Rev Cancer* **2**: 862–871
- Bossola M *et al.* (2001) Increased muscle ubiquitin mRNA levels in gastric cancer patients. *Am J Physiol Regul Integr Comp Physiol* **280**: R1518–R1523
- Bozzetti F *et al.* (1999) Artificial nutrition in cancer patients: which route, what composition? *World J Surg* **23**: 577–583
- Norton JA *et al.* (1981) Whole body protein synthesis and turnover in normal man and malnourished patients with and without known cancer. *Ann Surg* **194**: 123–128
- Lundholm K *et al.* (1982) Efflux of 3-methylhistidine from the leg in cancer patients who experience weight loss. *Cancer Res* **42**: 4802–4811
- Lundholm K *et al.* (1976) Skeletal muscle metabolism in patients with malignant tumour. *Eur J Cancer* **12**: 465–473
- Warren RS *et al.* (1985) Protein synthesis in the tumor-influenced hepatocyte. *Surgery* **98**: 275–282
- Lecker SH *et al.* (1999) Muscle protein breakdown and critical role of the ubiquitin-proteasome pathway in normal and disease states. *J Nutr* **129** (Suppl 1S): 227S–237S
- Goll DE *et al.* (1992) Role of the calpain system in muscle growth. *Biochimie* **74**: 225–237
- Drott C *et al.* (1989) Cardiovascular and metabolic response to adrenaline infusion in weight-losing patients with and without cancer. *Clin Physiol* **9**: 427–439
- Bing C *et al.* (2000) Increased gene expression of brown fat uncoupling protein (UCP)1 and skeletal muscle UCP2 and UCP3 in MAC16-induced cancer cachexia. *Cancer Res* **60**: 2405–2410
- Todorov P *et al.* (1996) Characterization of a cancer cachectic factor. *Nature* **379**: 739–742
- Russell ST *et al.* (2002) Role of β 3-adrenergic receptors in the action of a tumour lipid mobilizing factor. *Br J Cancer* **86**: 424–428
- Ramos EJ *et al.* (2004) Cancer anorexia–cachexia syndrome: cytokines and neuropeptides. *Curr Opin Clin Nutr Metab Care* **7**: 427–434
- Schwartz MW *et al.* (2000) Central nervous system control of food intake. *Nature* **404**: 661–671
- Laviano A *et al.* (2003) Cancer anorexia: clinical implications, pathogenesis, and therapeutic strategies. *Lancet Oncol* **4**: 686–694
- Stubbs RJ *et al.* (2000) The use of visual analogue scales to assess motivation to eat in human subjects: a review of their reliability and validity with an evaluation of new hand-held computerized systems for temporal tracking of appetite ratings. *Br J Nutr* **84**: 405–415
- Rossi Fanelli F *et al.* (1986) Plasma tryptophan and anorexia in human cancer. *Eur J Cancer Clin Oncol* **22**: 89–95
- Muscaritoli M *et al.* (2004) Therapy of muscle wasting: what is the future? *Curr Opin Clin Nutr Metab Care* **7**: 459–466
- Bruera E *et al.* (2003) Effect of fish oil on appetite and other symptoms in patients with advanced cancer and anorexia/cachexia: a double-blind, placebo-controlled study. *J Clin Oncol* **21**: 129–134
- Laviano A and Meguid MM (1996) Nutritional issues in cancer management. *Nutrition* **12**: 358–371
- Geels P *et al.* (2000) Palliative effect of chemotherapy: objective tumor response is associated with symptom improvement in patients with metastatic breast cancer. *J Clin Oncol* **18**: 2395–2405
- Sutton LM *et al.* (2003) Management of terminal cancer in elderly patients. *Lancet Oncol* **4**: 149–157
- Walsh D *et al.* (2000) The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. *Support Care Cancer* **8**: 175–179
- DeWys WD *et al.* (1980) Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med* **69**: 491–497
- Palesty JA and Dudrick SJ (2003) What we have learned about cachexia in gastrointestinal cancer. *Dig Dis* **21**: 198–213
- Ruiz-Arguelles GJ *et al.* (2004) Multiple myeloma in Mexico: a 20-year experience at a single institution. *Arch Med Res* **35**: 163–167
- Thammakumpee K (2004) Clinical manifestation and survival of patients with non-small cell lung cancer. *J Med Assoc Thai* **87**: 503–507
- Walsh D *et al.* (2002) Symptoms and prognosis in advanced cancer. *Support Care Cancer* **10**: 385–388
- Ravasco P *et al.* (2004) Cancer: disease and nutrition are key determinants of patients' quality of life. *Support Care Cancer* **12**: 246–252
- Cherny NI and Catane R (2003) Attitudes of medical oncologists toward palliative care for patients with advanced and incurable cancer: report on a survey by the European Society of Medical Oncology Taskforce on Palliative and Supportive Care. *Cancer* **98**: 2502–2510
- Isenring EA *et al.* (2004) Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer* **91**: 447–452
- Feinle C *et al.* (2003) Effects of fat digestion on appetite, APD motility, and gut hormones in response to duodenal fat infusion in humans. *Am J Physiol Gastrointest Liver Physiol* **284**: G798–G807
- Inui A (2002) Cancer anorexia–cachexia syndrome: current issues in research and management. *CA Cancer J Clin* **52**: 72–91

- 36 Pascual Lopez A *et al.* (2004) Systematic review of megestrol acetate in the treatment of anorexia-cachexia syndrome. *J Pain Symptom Manage* **27**: 360–369
- 37 Jho DH *et al.* (2004) Role of omega-3 fatty acid supplementation in inflammation and malignancy. *Integr Cancer Ther* **3**: 98–111
- 38 Fearon KC *et al.* (2003) Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. *Gut* **52**: 1479–1486
- 39 Moses AW *et al.* (2004) Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. *Br J Cancer* **90**: 996–1002
- 40 Jatoi A *et al.* (2004) An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: a North Central Cancer Treatment Group and National Cancer Institute of Canada collaborative effort. *J Clin Oncol* **22**: 2469–2476
- 41 Burns CP *et al.* (2004) Phase II study of high-dose fish oil capsules for patients with cancer-related cachexia. *Cancer* **101**: 370–378
- 42 Torelli GF *et al.* (1999) Use of recombinant human soluble TNF receptor in anorectic tumor-bearing rats. *Am J Physiol* **277**: R850–R855
- 43 Trikha M *et al.* (2003) Targeted anti-interleukin-6 monoclonal antibody therapy for cancer: a review of the rationale and clinical evidence. *Clin Cancer Res* **9**: 4653–4665
- 44 Eleutherakis-Papaiakevou V *et al.* (2004). Thalidomide in cancer medicine. *Ann Oncol* **15**: 1151–1160
- 45 Eichhorst ST *et al.* (2004) Suramin inhibits death receptor-induced apoptosis *in vitro* and fulminant apoptotic liver damage in mice. *Nat Med* **10**: 602–609
- 46 Diksic M and Young SN (2001) Study of the brain serotonergic system with labelled α -methyl-L-tryptophan. *J Neurochem* **78**: 1185–1200
- 47 Cangiano C *et al.* (1996) Effects of administration of oral branched-chain amino acids on anorexia and caloric intake in cancer patients. *J Natl Cancer Inst* **88**: 550–552
- 48 Hiroshige K *et al.* (2001) Oral supplementation of branched-chain amino acid improves nutritional status in elderly patients on chronic haemodialysis. *Nephrol Dial Transplant* **16**: 1856–1862
- 49 Marchesini G *et al.* for the Italian BCAA Study Group. (2003) Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. *Gastroenterology* **124**: 1792–1801
- 50 Heisler LK *et al.* (2002) Activation of central melanocortin pathways by fenfluramine. *Science* **297**: 609–611
- 51 Marks DL *et al.* (2003) Differential role of melanocortin receptor subtypes in cachexia. *Endocrinology* **144**: 1513–1523
- 52 Smith HJ *et al.* (2004) Effect of eicosapentaenoic acid, protein and amino acids on protein synthesis and degradation in skeletal muscle of cachectic mice. *Br J Cancer* **91**: 408–412
- 53 Inui A *et al.* (2004) Ghrelin, appetite, and gastric motility: the emerging role of the stomach as an endocrine organ. *FASEB J* **18**: 439–456
- 54 Shimizu Y *et al.* (2003) Increased plasma ghrelin level in lung cancer cachexia. *Clin Cancer Res* **9**: 774–778
- 55 Neary NM *et al.* (2004) Ghrelin increases energy intake in cancer patients with impaired appetite: acute, randomized, placebo-controlled trial. *J Clin Endocrinol Metab* **89**: 2832–2836
- 56 Cahlin C *et al.* (2000) Effect of cyclooxygenase and nitric oxide synthase inhibitors on tumor growth in mouse tumor models with and without cachexia related to prostanoids. *Cancer Res* **60**: 1742–1749
- 57 Lundholm K *et al.* (2004) Palliative nutritional intervention in addition to cyclooxygenase and erythropoietin treatment for patients with malignant disease: effects on survival, metabolism, and function. *Cancer* **100**: 1967–1977
- 58 Inui A (1999) Cancer anorexia-cachexia syndrome: are neuropeptides the key? *Cancer Res* **59**: 4493–4501

Competing interests

F Rossi-Fanelli declared competing interests; go to the article online for details. The other authors declared they have no competing interests.