The Current Management of Cancer Cachexia

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Mechanisms of Cancer-Related Anorexia/Cachexia

The anorexia/cachexia syndrome is one of the most common causes of death among patients with cancer and is present in 80% at death [1]. The term 'cachexia' derives from the Greek *kakòs*, which means 'bad', and *hexis*, meaning 'condition'. The characteristic clinical picture of anorexia, tissue wasting, loss of body weight accompanied by a decrease in muscle mass and adipose tissue, and poor performance status that often precedes death has been named cancer-related anorexia/cachexia (CAC) [2–5]. Since the 1980s, the previous concepts explaining CAC were replaced by a more complex insight, which stresses the interaction between metabolically active molecules produced by the tumour itself and the host immune response. One of the main features of the cachectic syndrome is anorexia, which may be so significant that spontaneous nutrition is totally inhibited. The pathogenesis of anorexia is most certainly multifactorial but not yet well understood. It seems to be attributable, in part, to intermediary metabolites (e.g. lactate, ketones, oligonucleotides) that accumulate along an abnormal metabolic pathway, or other substances released by the tumour itself or by normal cells in response to the tumour [3]. However, anorexia cannot by itself account for the complex organic alterations seen in CAC. Indeed, nutritional supplementation alone cannot effectively reverse the process of cachexia. An increased resting energy expenditure may contribute to body weight loss in patients with cancer and may explain the increased oxidation of fat tissue. Futile energy-consuming cycles, such as the Cori cycle, may contribute to this increased energy demand. Unlike starvation, body weight loss in patients with cancer arises equally from loss of muscle and fat, characterised by increased catabolism of skeletal muscle and decreased protein synthesis [6]. Catabolic factors capable of direct breakdown of muscle and adipose tissue appear to be secreted by cachexia-inducing tumours and may play an active role in the process of tissue degeneration [6].

Metabolic Abnormalities

In addition to reduced food intake, important abnormalities in carbohydrate, protein and lipid biochemistry and metabolism and changes in energy metabolism have been observed, which may account for CAC.

The most important carbohydrate abnormalities are insulin resistance, increased glucose synthesis, gluconeogenesis and Cori cycle activity, and decreased glucose tolerance and turnover. The main pathological changes of protein metabolism include increased protein turnover, muscle catabolism, and liver and tumour protein synthesis, while muscle protein synthesis is decreased. The main abnormalities found in lipid metabolism are enhanced lipid mobilisation, decreased lipogenesis, decreased lipoprotein lipase activity, elevated triglycerides and decreased high-density lipoproteins, increased venous glycerol, and decreased glycerol clearance from the plasma [5, 7, 8].

Proinflammatory Cytokines

Cancer-related anorexia/cachexia may result from circulating factors produced by the tumour, or by the host immune system in response to the tumour, such as cytokines released by lymphocytes and/or monocyte/macrophages.

A number of proinflammatory cytokines, including interleukin (IL)-1, IL-6, tumour necrosis

factor-α (TNF-α), interferon (IFN)-α and IFNγ, have been implicated in the pathogenesis of cachexia associated with human cancer. TNF-α was first identified by Rouzer and Cerami [9] as a specific circulating mediator of the wasting resulting from a chronic experimental infectious disease and named cachectin, which was subsequently found to be identical to TNF-α. However, data from numerous clinical and laboratory studies suggest that the action of cytokines, although important, may not alone explain the complex mechanism of CAC [10–13].

IL-1 and TNF-α have been proposed as mediators of the host's response to inflammation [14]. Human IL-1 and TNF-α administered to healthy animals produced significant reduction in their food intake [15]. High serum levels of TNF-α, IL-2 and IFNγ have been found in patients or experimental animals with cancer [16], and although IL-6 levels appear to correlate with tumour progression in animal models [16], evidence has been provided to support a role for IL-6 as a cachectic factor in the development of cancer cachexia in an animal model system [17]. Chronically elevated levels of these factors, either alone or in combination, are capable of reproducing the different features of CAC [17–20].

More direct evidence of a cytokine involvement in CAC is provided by the observations that cachexia in experimental animal models [12, 21, 22] can be relieved by administration of specific cytokine antagonists. These studies revealed that cachexia can rarely be attributed to any one cytokine but rather is associated with a set of cytokines that work in concert. These cytokines seem to play central roles in both cachexia-related inflammation and the acute-phase response [23].

Additional factors and mechanisms thought to play a central role in CAC are the presence of a chronic systemic inflammatory state, circulating tumour-derived lipolytic and proteolytic factors, increased futile energy-consuming cycles, such as the Cori cycle, and a decreased food intake.

Circulating Tumour-Derived Catabolic Factors

In addition to chronic proinflammatory factors, circulating factors, such as lipid-mobilising factors (LMF), and proteolysis-inducing factor (PIF) may play a role in the development of CAC. These are tumour-derived catabolic factors acting directly on adipose tissue and skeletal muscle, without affecting food intake [24–28].

Systemic Inflammation

There is evidence that a chronic, low-grade, tumour-induced activation of the host immune system that shares numerous characteristics with the 'acute-phase response' found after major traumatic events and septic shock is involved in CAC. Septic shock is a situation characterised by an increased production of cytokines [29, 30], high levels of catecholamines, cortisol and glucagon [29, 31–33], increased peripheral amino acid mobilisation and hepatic amino acid uptake [29, 34], increased hepatic gluconeogenesis and acute-phase protein production [29, 35, 36], enhanced mobilisation of free fatty acids [37] and increased metabolism [38]. The acute-phase response is a systemic reaction to tissue injury, typically observed during inflammation, infection or trauma, characterised by the release of a series of hepatocyte-derived plasma proteins known as acute-phase reactants, including C-reactive protein, fibrinogen, complement factors B and C3, and by reduced synthesis of albumin and transferrin. An acute-phase response is observed in patients with cancer. In fact, the cytokines IL-1, IL-6 and TNF-α are regarded as the major mediators of acute-phase protein induction in the liver. Unfortunately, the role played by acute-phase proteins during cancer growth is still poorly understood.

Decreased Food Intake

Malnutrition may be considered one hallmark of cancer cachexia and it is associated with anorexia, that is, loss of appetite and/or decreased food intake. Appetite is a complex function resulting from the contribution of peripheral and central nervous afferents in the ventral hypothalamus. Stimulation of the medial hypothalamic nucleus inhibits feeding, while stimulation of the lateral nucleus promotes food intake. Among peripheral afferents, oral stimulation by pleasant tastes elicits

eating, whereas gastric distention inhibits it.

There is evidence that proinflammatory cytokines such as IL-1, IL-6 and TNF-α are involved in cancer-related anorexia and decreased food intake, but these cytokines do not seem to be the only mediators of CAC.

Since multiple factors are involved in the control of food intake, it is possible that there are also many factors contributing to the tumour-associated anorexia. Indeed, anorexigenic compounds are either released by the tumour into the circulation or the tumour itself may induce metabolic changes resulting in the release of such substances by host tissues. Changes in tryptophan levels in patients with cancer result in increased brain serotonin synthesis and, thus, serotonergic activity, which leads to reduced food intake. Other factors could be involved in promoting the inhibitory afferents to the hypothalamus by stimulating serotonergic and catecholaminergic fibres, such as increased lactate and fatty acid blood levels, both of which are associated with tumour burden. Few controlled clinical trials have investigated the incidence of cancer-related reduction of food intake: this fact may be because of the methodological difficulties associated with human diet analysis and the need for large patient and control groups.

Role of Leptin and Neuropeptides

Loss of body weight is a strong stimulus to food intake in humans. Therefore, the presence of CAC in patients with cancer suggests a failure of the adaptive feeding response. A large amount of evidence has been provided in the last few years on the regulation of feeding and body weight. Leptin, a recently found hormone produced by the adipocyte ob gene, has been shown to be an essential component of the homeostatic regulation of body weight. Leptin acts to control food intake and energy expenditure via a neuropeptidergic effect or molecules within the hypothalamus. Complex interactions take place among the nervous, endocrine and immune systems inducing behavioural and metabolic responses [38–44].

Proinflammatory cytokines, proposed as mediators of CAC, may have a central role in long-term inhibition of feeding by mimicking the hypothalamic effect of excessive negative feedback signalling from leptin. This could be via continuous stimulation of anorexigenic neuropeptides such as serotonin- and corticotropin-releasing factor, as well as by inhibition of the neuropeptide Y orexigenic network consisting of opioid peptides and galanin, and the recently identified melanin-concentrating hormone, orexin and agouti-related peptide. Such abnormalities in the hypothalamic neuropeptide loop in tumour-bearing animals lead to the development of CAC.

Although the present therapeutic use of neuropeptide agonists/antagonists is obesity treatment, this area could also be an effective target for the treatment of CAC, particularly in combination with other agents with different mechanisms of action [45, 46].

A study by our group [47] demonstrated very low leptin levels associated with high levels of inflammatory cytokines in patients with advanced-stage cancer, several of whom had a significant body weight loss.

Treatment of CAC

It is outside the scope of this chapter to review the current standard clinical management of patients with CAC. However, clinicians should consider the need to address the patient as a whole before planning a comprehensive treatment plan for CAC, including enteral and/or parenteral nutrition and pharmacological treatment, that is the use of orexigenic (appetite stimulants), anticatabolic (and anticytokine) and anabolic agents [48]. The management of CAC is challenging. This section examines therapies and drugs used in patients with CAC, distinguishing between those that are unproven, which are briefly mentioned, and those that have been proven to be effective or that are currently under investigation, which are discussed in greater detail.

Unproven or Ineffective Treatments

It was hoped that enteral or parenteral nutritional support would circumvent cancer anorexia cachexia and alleviate malnutrition. However, the

inability of hypercaloric feeding to increase lean mass, especially skeletal muscle mass, has been repeatedly demonstrated [49].

Dietary counselling, positioning of a fine-bore nasogastric tube and percutaneous gastrostomy (i.e. enteral nutrition), and total parenteral nutrition (TPN) are the possible options to counteract CAC by increasing food intake. However, none of these has proven to be effective.

Dietary counselling was reported to have no effect [6]. Nasogastric tube feeding showed a body weight increase in some studies [50] and a decrease in whole body protein breakdown in other studies [51]; however, the drawback to enteral tube feeding is the distress to the patients, especially in cases of long-term treatment [52].

Various systematic prospective studies that have evaluated the potential benefit of TPN have generally been disappointing [52–55]. Therefore, its use is not recommended in unselected patients, especially in view of the fact that TPN may itself have significant complications. However, it may be worthwhile further evaluating TPN in carefully defined settings, possibly in conjunction with other modalities such as synthetic progestagens or anabolic steroids [56]. Indeed, parenteral nutrition may facilitate administration of complete chemoradiation doses for oesophageal cancer [53] and may have beneficial effects in certain patients with decreased food intake because of mechanical obstruction of the gastrointestinal tract [57, 58]. Home parenteral nutrition can also be rewarding for such patients. Enteral nutrition has the advantages of maintaining the gut-mucosal barrier and immunological function, as well as having low adverse side-effects and low cost [57–59].

The effects of caloric intake on tumour development and growth are still being debated [60]. A clear benefit from nutritional support may thus be limited to a specific, small subset of patients with severe malnutrition who may require surgery or may have an obstructing, but potentially therapy-responsive tumour [1, 57, 61].

Cyproheptadine

Based on the evidence that CAC is associated with increased serotonergic activity in the brain [62], serotonergic blockade may be beneficial in reducing symptoms. One potentially interesting drug is cyproheptadine, a histamine antagonist with antiserotonergic properties and an appetite-stimulating effect. However, in a placebo-controlled clinical trial, cyproheptadine only induced a slight improvement of appetite without significant effect on body weight [63]. Its clinical use is not recommended, especially in view of its sedating effects. No other serotonin antagonists have been investigated in this patient population to date.

Hydrazine

Hydrazine inhibits hepatic gluconeogenesis in rats by inhibiting the enzyme phosphoenolpyruvate-carboxykinase [64]. However, three large, randomised, placebo-controlled trials have failed to observe any beneficial effect on appetite or body weight in patients with cancer [65–67].

Metoclopramide

Metoclopramide has been the most extensively used drug in patients with cancer for the prevention and treatment of chemotherapy-induced emesis and has yielded significant results [68]. As many patients with cancer have symptoms of delayed gastric emptying and gastroparesis that might increase the incidence of early satiety and negatively influence food intake [69–71], this prokinetic agent has been extensively studied in these patients. A recent randomised controlled trial reported that controlled-release metoclopramide every 12 hours was significantly more effective than immediate-release metoclopramide every 6 hours [72]. At present, the effectiveness of other prokinetic agents such as cisapride and domperidone needs to be demonstrated in randomised, controlled clinical trials.

Cannabinoids (Dronabinol)

The active ingredient of marihuana, dronabinol (Δ-9-tetrahydrocannabinol, THC) is known to have a positive effect on appetite, body weight and chemotherapy-induced nausea [73].

Dronabinol was first used as an antiemetic in patients with cancer; however, it was reported to have significant neurological and adverse effects including dizziness, euphoria and impairment of cognitive functions. Currently there is only one controlled trial comparing dronabinol vs megestrol acetate vs combination therapy in patients with CAC. This trial showed that oral megestrol acetate 800 mg/day provided superior anorexia palliation compared with oral dronabinol 2.5 mg twice daily, while combination therapy did not appear to confer additional benefit [74].

In the past, two open studies [75, 76] demonstrated some improvement in mood and appetite with no significant change in body weight. In the first study by Wadleigh et al. [75], with dronabinol in patients with advanced cancer, a subjective improvement in mood and appetite was observed at the higher dose studied, but all patients had a progressive body weight loss. In the second study, Nelson et al. [76] observed improved appetite and increased food intake using dronabinol 7.5 mg/day but the effect on body weight was not reported. A randomised controlled trial in patients with AIDS showed similar results [77]. Moreover, the significant adverse effects of this drug need to be taken into account. These include somnolence, mental confusion and cognitive status disturbances [77], which may worsen the mental status of patients with CAC, who are often receiving opioids and other psychoactive drugs.

Drugs Commonly Used

Progestagens

Progestagens were the first agents used and are the current first-line agents used in patients with CAC for which there is a track record of clinical research. An extensive amount of literature is available in patients with cancer, with the use of both megestrol and medroxyprogesterone.

Both drugs are synthetic progestagens that were first used to treat hormone-sensitive tumours [78, 79]. As a result of the observed body weight gain and appetite stimulation, independent of tumour response, in a number of patients receiving such therapy, several trials in the last two decades have addressed the use of progestagens for the management of CAC. The proposed mechanism of action of progestagens in CAC has not been completely elucidated. It may be related to glucocorticoid activity making these drugs similar to corticosteroids. Moreover, there is evidence that progestagens may stimulate appetite via neuropeptide Y in the central nervous system (ventromedial hypothalamus) [80]. Furthermore, they act, at least in part, by down-regulating the synthesis and release of proinflammatory cytokines, as shown by several experimental and clinical studies, including two of our studies [81, 82]. We have also previously published an overview of this topic [83].

In the first study [81], the effect of megestrol in patients with CAC was evaluated to determine its ability to increase appetite and body weight in patients with head and neck cancer with advanced-stage (III–IV) disease, treated with cisplatin-based neoadjuvant chemotherapy. Eleven male patients (mean age 57.8 years; range 43–69 years; Karnofsky performance status 90–100; body weight decrease > 10% of the ideal or customary body weight) were enrolled in the study. Ten patients were treated with megestrol during neoadjuvant chemotherapy and one was treated with megestrol during definitive locoregional radiation therapy administered at the end of primary chemotherapy. Clinical parameters evaluated before and after megestrol treatment included clinical response to chemotherapy after three cycles, body weight, appetite (using a visual analogue scale calibrated from 0 to 10), Karnofsky performance status, and quality of life (Spitzer's Quality-of-Life Index [QLI]). Serum levels as well as in vitro production of IL-1–α and β, IL-2, IL-6, TNF-α and sIL-2R were determined in patients before and after megestrol treatment and were compared with those of healthy individuals. Megestrol (160 mg tablets) was administered at a dosage of 320 mg/day during the interval between chemotherapy cycles, starting from the third day after the end of the cycle until the day before the next cycle (days 8–21) for a total of three consecutive cycles. During the cycles the dosage of megestrol ranged from 160 to 320 mg/day, based on clinical response. Of the 11 enrolled patients, nine (81.8%) were evaluable; two patients were not

evaluable because of major protocol violations (drug intake was < 90% of that scheduled). Except for performance status, all parameters showed an improvement following treatment with megestrol. In particular, increases were observed in average body weight (6.3 kg or 13.2%), appetite (by a score of 2.4 or 38.6%), and Spitzer's QLI (by a score of 2.4 or 36.2%). The serum levels of cytokines studied were significantly higher in patients before megestrol treatment than in healthy individuals. Serum levels of all cytokines, as well as IL-6 production in vitro, decreased in patients after megestrol treatment. Our results strongly supported the hypothesis that the beneficial therapeutic effects of megestrol in patients with CAC may be due in part to its ability to down-regulate the synthesis and release of key cytokines involved in CAC.

The second study [82] addressed the question of whether the other synthetic progestagen more commonly used, medroxyprogesterone, at doses that are pharmacologically active in vitro (0.1, 0.2 and 0.4 mg/l), was able to influence the in vitro production and/or release of cytokines and serotonin (5-hydroxytryptamine) in patients with advanced-stage cancer. Ten patients with advanced-stage cancer at different sites were included in the study, which showed that the in vitro production of IL-1, IL-6, TNF-α and serotonin in these patients was significantly reduced in the presence of medroxyprogesterone. The concentration of medroxyprogesterone used in this study was within the range of plasma values seen in patients receiving oral medroxyprogesterone 1500/2000 mg/day. As shown in Table 1, megestrol has been the drug most widely studied for its effect on CAC, with eight randomised, double-blind, placebo-controlled trials [83–94], compared with medroxyprogesterone (two placebo-controlled studies) [95, 96].

Megestrol has shown a dose-related effect on appetite, body weight gain and subjective sensation of well-being with oral dosages ranging from 160 to 1,600 mg/day, with an optimal dosage of 480–800 mg/day. However, because a dosage of 160 mg/day has demonstrated a significant effect, the possible dose-related adverse effects of megestrol and the increased costs of higher dosages, we recommend, in agreement with Gagnon and Bruera [48] and on the basis of our experience, starting treatment at a low dosage (160 mg/day) and regulating the dose upwards according to clinical response.

Some patients may require up to 320 mg/day and a very few will respond only to 480 mg/day.

Medroxyprogesterone was used at dosages ranging from 300 mg/day to 4000 mg/day. The placebo-controlled study of Simons et al. [96] used oral medroxyprogesterone 1000 mg/day and reported a significant improvement of appetite and body weight. We currently recommend a medroxyprogesterone dosage of 1000 mg/day orally (equivalent to megestrol 160 mg/day). Most published studies using megestrol or medroxyprogesterone in patients with CAC have used tablets rather than the oral suspension formulation. However, oncologists are increasingly using megestrol or medroxyprogesterone oral suspensions in their patients with malignancies because of improved compliance and decreased cost [97].

Both megestrol and medroxyprogesterone may induce adverse effects. These are an increased risk of thromboembolic events, peripheral oedema, breakthrough bleeding, hyperglycaemia, hypertension and Cushing's syndrome [98–100]. However, it is very rare that patients taking megestrol or medroxyprogesterone have to stop the drug because of adverse effects [84, 85, 87, 101].

As the bioavailability of megestrol acetate directly affects its efficacy and safety, the formulation was refined to enhance its pharmacokinetics. Such efforts yielded megestrol acetate in a tablet form, followed by a concentrated oral suspension form, and, very recently, an oral suspension form developed using nanocrystal technology. Nanocrystal technology was designed specifically to optimise drug delivery and enhance the bioavailability of drugs with poor water solubility. Megestrol acetate nanocrystal oral suspension has been approved by the US FDA for the treatment of cachexia in patients with AIDS; clinical trials in patients with cancer cachexia will be carried out very soon. Preclinical pharmacokinetic data suggest that the new megestrol acetate formulation has the potential to shorten significantly the time to clinical response and thus may improve outcomes in patients with anorexia-cachexia [102].

Table 1. Summary of randomised, prospective, placebo-controlled trials of progestagens in patients with cancer-related anorexia/cachexia

Dosage	Duration of treatment	Study Design	No. of patients	Results	Adverse Effects	Reference Author
Megestrol						
480 mg/day	1 wk	pc, co	40	Improved appetite, caloric intake, energy level, bodyweight, tricep skinfold and calf circumference.	Mild oedema, nausea (similar to placebo)	Bruera E, et al. 1990
800 mg/day	1.6 mo	pc	133	Improved appetite, food intake, bodyweight; less nausea , less emesis compared with placebo	Oedema and thrombo-embolic events	Loprinzi CL, et al. 1990
1600 mg/day	1 mo	pc	89	Increased appetite, food intake, greater change in prealbumin; no change in athropometrics except bodyweight; nutrition impact symptoms improved *vs* no change or worsening in placebo; no differences in QoL, positive response with crossover design	Oedema, DVT	Tchekmedyian NS, et al. 1992
240 mg/dy	2 mo	pc	150	Bodyweight gain, increased appetite score, fewer patients with decreased performance status compared with lacebo	Oedema, DVT (no different from Placebo)	Feliu J, et al. 1992
160, 480 mg/day	12 wk	pc	240	Improved appetite, mood and overall QoL at both doses; possibly less nausea, emesis compared with placebo; sustained improved QoL; increase in prealbumin	None reported	Beller E, et al. 1997
480 mg/day	8 wk	pc	55	Sample too small for significant results	None reported	Schmoll E, et al. 1991
160 mg/day	6 wk	pc	64	Maintained bodyweight and nutritional parameters during chemo/radiotherapy compared with parameters deterioration in placebo; QoL maintained with megestrol	None reported	Fietkau R, et al. 1997
160, 480, 800, 1280 mg/day	66 days	rc	342	Improved appetite, food intake and bodyweight, decreased nausea	None reported	Loprinzi CL, et al. 1993
480 mg/day	10 days	pc, co	83	Improved activity, appetite and well-being. No increase of bodyweight	None reported	Bruera E, et al. 1996
480 mg/day	12 wk	pc	38	No Increase of bodyweight	None reported	McMillan DC, et al. 1994
160, 320 mg/day	1 mo	rc	122	Increased appetite	None reported	Gebbia V, et al. 1996
Medrossiprogesterone						
300 mg/day	6 wk	pc	60	Increased appetite, serum retinol binding protein and serum thyroid binding prealbumin	None reported	Downer S, et al. 1993
500 mg/day	12 wk	pc	206	Beneficial effect on appetite at 6 and 12 wk; bodyweight gain with medroxyprogesterone vs loss on placebo; no other measurable changes in QoL	None reported	Simons JPFHA, et al. 1996

co, crossover; *DVT*, deep vein thrombosis; *pc*, placebo-controlled; *QoL*, Quality of Life; *rc*, randomise, controlled (no placebo)

Corticosteroids

Although several randomised, placebo-controlled studies (shown in Table 2) demonstrated that corticosteroids, including dexamethasone, prednisolone and methylprednisolone, induce a usually temporary (limited to a few weeks) effect on symptoms such as appetite, food intake, sensation of well-being and performance status, none of these studies showed a beneficial effect on body weight. [103–107].

In addition, corticosteroids have an antiemetic activity [108] and are able to reduce asthenia [103] and to control pain [109]. Their mechanism of action in CAC is not well understood, although the inhibition of prostaglandin (PG) activity [110] and the suppression of IL-1 [111, 112] and TNF [113] production are the most well-recognised targets. In view of the wide range of well-known adverse effects and cautions to be advised with these agents, they should be used in patients in the end-stage phase of cancer with short expected survival, with the attempt to improve quality of life without affecting body weight.

The type, dosage and route of administration of corticosteroids are not established, although low dosages, less than 1 mg/kg of prednisone equivalent, are recommended in clinical practice.

Anticytokine Approaches to CAC Treatment

Proinflammatory cytokines such as IL-1, IL-6, and particularly, TNF-α have a prominent role in the pathogenesis of CAC. The specific neutralisation of these factors with antibodies in animal models of cachexia suggests that an anticytokine approach is worth pursuing, while taking into account that no single cytokine is responsible for all abnormalities found in CAC. However, in chronic human diseases such as cancer, the long-term administration of anticytokine antibodies could be of no practical use. Pentoxifylline and thalidomide are two agents with anticytokine activity currently being investigated as therapy for CAC.

Anti-IL-6 Monoclonal Antibody

Currently, although the therapeutic impact on CAC of anti-IL-6 monoclonal antibody (mAb) therapy could be of clinical benefit in cancer patients, no published clinical trial using this approach is yet available [114].

Anti-TNF-α mAb

On the basis of experimental data on the ability of anti-TNF-α mAb to neutralise the in vitro and in vivo biological effect on TNF-α [115] and animal studies carried out by Torelli et al. [116], a phase II multicentre, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of anti-TNF-α mAb to treat CAC in 90 patients with pancreatic cancer was carried out and completed in February 2006: the results are not yet known.

Table 2. Placebo-controlled trials of corticosteroids in cancer-related anorexia/cachexia [38]

Drug	Dosage (mg)	Route	No. of patients	Significant symptoms outcomes	Effects on bodyweight	Reference
Dexamethasone	0.75 or 1.5 qid	PO	116	↑ Appetite	Ni	[95]
Prednisolone[a]	5 tid	PO	61	↑ Appetite	Ni	[96]
Methylprednisolone[a]	16 bid	PO	40	↑ Pain Control ↑ Appetite, food intake and performance status	Nil Not measured	[97]
Methylprednisolone	125 od	IV	403	↑ Quality of life	Ni	[98]
Methylprednisolone	125 od	IV	173	↑ Quality of life	Ni	[99]

[a] Crossover design
bid, twice daily; *IV*, intravenous; *od*, once daily; *PO*, oral; *qid*, 4 times daily; *tid*, 3 times daily; ↑, increase.

Pentoxifylline

Pentoxifylline is a methylxantine derivative approved for the treatment of intermittent claudication, which was subsequently found to have anti-inflammatory and immune-modulating effects mediated by the inhibition of phosphodiesterase. It has been shown to inhibit TNF-α production in humans in response to experimentally administered endotoxin [117]. Recent preliminary investigations in patients with cancer have suggested a potential role for pentoxifylline. Intravenous administration of pentoxifylline in 14 patients with cancer who had high serum TNF-α levels significantly reduced the serum levels of this cytokine [118]. However, a recent double-blind, placebo-controlled trial of pentoxifylline therapy in patients with CAC did not show a beneficial effect on appetite or body weight [119].

Thalidomide

Thalidomide was first clinically introduced as a sedative drug and in the 1960s it was withdrawn from use because of its established teratogenic effect. Thalidomide has complex immunomodulatory and anti-inflammatory properties. It has been shown to down-regulate the production of TNF-α and other proinflammatory cytokines, inhibit the transcription factor nuclear factor kB, down-regulate cyclo-oxygenase-2 and inhibit angiogenesis. In a recent randomised, placebo-controlled trial, thalidomide was found to be well tolerated and effective at attenuating loss of weight and lean body mass in 33 patients with cachexia due to advanced pancreatic cancer [120]. Randomised clinical trials with thalidomide in patients with CAC are awaited. That the mild sedative effect of thalidomide may make it difficult to mask the drug in placebo-controlled trials needs to be taken into account [48].

Emerging Drugs

Non-steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are very widely used in patients with cancer for the treatment of fever and pain. They act by inhibiting PG production by the rate-limiting enzymes known as cyclo-oxygenases (COX). Because traditional NSAIDs inhibit both COX-1 and COX-2, these drugs induce adverse effects such as gastrointestinal injury up to ulceration, reduced appetite and consequent reduced body weight: indeed, these drugs may be considered a potential cause of anorexia in patients with cancer.

On the other hand, ibuprofen, an inhibitor of the enzyme COX-1, was found to decrease C-reactive protein [121], produce body weight gain [122] and improve survival in patients with cancer [123].

The administration of indomethacin (50 mg twice daily) to a heterogeneous group of advanced cancer patients in a randomised controlled study has been shown to be associated with a long improvement in survival [123].

To date, no other studies on the beneficial effects of NSAIDs in human CAC are available, although placebo-controlled trials with these drugs may be justified.

COX-2 Selective Inhibitors (Celecoxib, Rofecoxib and Valdecoxib)

COX-2 is a bifunctional enzyme possessing both cyclo-oxygenase and peroxidase activities. Selective COX-2 inhibitors inhibit PG biosynthesis (anti-COX-2 activity) but do not, or only partially, affect the peroxidase activity of COX, which can generate proximate carcinogens. In experimental animals, selective inhibitors of COX-2 such as celecoxib reduce the formation of head and neck, colorectal, stomach, lung, breast and prostate tumours. In addition to preventing tumorigenesis, selective COX-2 inhibitors suppress the growth of established tumours. A selective COX-2 inhibitor was also observed to decrease the number and size of metastases. In most studies, selective COX-2 inhibitors decrease the rate of tumour growth rather than cause a reduction in tumour size [124–126]. Therefore, significant preclinical evidence strongly supports the potential role for these inhibitors for the treatment of cancer.

Currently, the COX-2 inhibitors are being studied in clinical trials to confirm their role in the prevention of cancer, particularly colon cancer [127], and in combination with chemotherapy and radia-

tion therapy to prove their effectiveness in cervical cancer, lung cancer and brain tumours [128].

Notwithstanding their potential interest also in the treatment of cancer cachexia, some questions have arisen on the clinical use of these agents because of their toxicity and particularly cardiovascular risks. For this reason, rofecoxib has been withdrawn by the manufacturer. Another drug in this class, valdecoxib, has shown an increased risk for cardiovascular events in patients after heart surgery. As regards celecoxib, in December 2004 the National Cancer Institute stopped celecoxib (Celebrex) administration in an ongoing clinical trial investigating a new use of the drug to prevent colon polyps because of an increased risk of cardiovascular events in patients taking Celebrex versus those taking a placebo. Patients in the clinical trial taking 400 mg of Celebrex twice daily had a 3.4 times greater risk of cardiovascular events compared to placebo. For patients in the trial taking 200 mg of Celebrex twice daily, the risk was 2.5 times greater. The average duration of treatment in the trial was 33 months. A similar ongoing study comparing Celebrex 400 mg once a day versus placebo, in patients followed for a similar period of time, has not shown increased risk. Based on the currently available data, the FDA has concluded in April 2005 that an increased risk of serious adverse cardiovascular events appears to be a class effect of non-steroidal anti-inflammatory drugs (NSAIDs; excluding aspirin). The FDA has requested that the package insert for all NSAIDs, including Celebrex, be revised to include a boxed warning to highlight the potential increased risk of cardiovascular events and the well-described risk of serious, and potentially life-threatening, gastrointestinal bleeding. The FDA has also requested that the package insert for all NSAIDs be revised to include a contraindication for use in patients immediately after coronary artery bypass (CABG) surgery. Consequently, the inclusion of celecoxib in clinical trials should be discouraged.

Melatonin

In a recent controlled trial in 100 patients with metastatic cancer, melatonin was shown to reduce significantly body weight loss [129]. Melatonin may act by decreasing circulating levels of TNF [130].

n-3 Fatty Acids

The supplementation of n-3 polyunsaturated fatty acids has been shown to inhibit IL-1 and TNF-α production through a blockade of the COX and lipo-oxygenase pathways.

Eicosapentaenoic acid (EPA) is the main component of this family and is found in large quantities in fish oil: at doses of 2–6 g daily it has been shown to lower the production of proinflammatory cytokines in healthy volunteers [131]. EPA is also able to down-regulate the acute-phase protein response [132, 133]. Its activity appears to be mediated by a blockade of the effects of proteolysis-inducing factor and lipid-mobilising factor [134]. In a study in patients with colorectal cancer, long-term treatment with EPA, docosahexaenoic acid (DHA) and α-linolenic acid induced a significant decrease in serum IL-1, IL-6, TNF-α and IFNα levels [135]. Two recent studies by Wigmore et al. [136, 137] reported the effects of n-3 fatty acid treatment in patients with pancreatic cancer who were losing weight. In the first study [136], oral supplementation with fish oil capsules (12 tablets per day, 18% EPA, 12% DHA) for 3 months led to a significant median body weight gain of 0.3 kg/month compared to a previous body weight loss of 2.9 kg/month. A significant reduction in acute-phase protein production was also observed. In the second study [137], 4 weeks of treatment with EPA reduced the C-reactive protein through the suppression of IL-6 production.

EPA has been shown to impair the growth of tumour cell lines in vitro and slow down the growth of experimental tumours in animal models [138, 139]. EPA has been found to stabilise weight in cachectic tumour-bearing mice independently of any anti-tumour effect [144]. In uncontrolled clinical trials with EPA or fish oil, a weight stabilisation was observed in weight-losing pancreatic cancer patients [136, 141].

Fearon et al. compared a protein- and energy-dense supplement enriched with n-3 fatty acids and antioxidants with an isocaloric isonitrogenous control supplement for their effects on weight, lean body mass (LBM), dietary intake, and quality of life in 200 cachectic patients with advanced pancreatic cancer. Intention-to-treat group comparisons indicated that, at the mean dose taken (1.4 cans/day),

enrichment with n-3 fatty acids did not provide a therapeutic advantage and that both supplements were equally effective in arresting weight loss. Post hoc dose-response analysis suggests that, if taken in sufficient quantity (> 1.5 cans/day), only the n-3 fatty acid-enriched energy- and protein-dense supplement results in net gain of weight, lean tissue, and improved quality of life [142].

A clinical trial using an EPA supplement vs megestrol acetate vs both in 421 patients with cancer-associated wasting was carried out by the North Central Cancer Treatment Group and the National Cancer Institute in Canada and failed to demonstrate an improvement of weight or appetite with EPA supplement [143].

Recently, a phase III, double-blind, randomised comparator study was carried out as a multicentre multinational study to assess the benefit of a protein- and energy-dense supplement enriched with n-3 fatty acids and antioxidants versus standard nutritional product in 240 patients with stage IV non-small-cell lung cancer. The primary end-point was preservation of LBM. The patient accrual ended at the beginning of 2005 and the results are not yet known.

Further trials are required to examine the potential role of n-3-enriched supplements in the treatment of CAC.

β2 Agonists

Clenbuterol is the most studied of the β2-adrenergic agonists. Treatment of tumour-bearing animals with salbutamol, salmeterol and clenbuterol had a positive effect on skeletal muscle mass, without influencing tumour growth or food intake [144].

One controlled trial reported that clenbuterol was able to improve muscle strength after orthopaedic surgery. These drugs, which are able to prevent or reverse muscle loss in sedentary people, such as patients with cancer, are potentially interesting and should be studied in clinical controlled trials. Clenbuterol could be used clinically in the treatment of patients with CAC.

In summary, the anabolic properties of β2-agonists are well established with the therapeutically relevant effects observed in animal models of cachexia. In addition, enhanced sensitivity to β2-agonists in cachectic subjects may suggest that β2-agonists can be of importance in the treatment of CAC.

Anabolic Agents

Anabolic agents have the potential to improve body composition by maintaining or improving lean body mass. These agents include growth hormone (GH), insulin-like growth factor (IGF)-1, testosterone, dihydrotestosterone and testosterone analogues.

Growth Hormone and Insulin-Like Growth Factor

Strong positive effects on nitrogen balance and protein mass have been demonstrated with GH in different clinical situations [145]. Most of its anabolic effects on protein synthesis are mediated by IGF-1, produced by the liver [146]. In a study in 10 patients with cancer, GH administered for 3 days increased plasma IGF-1 levels and decreased urinary nitrogen losses; however, an improvement of nitrogen balance was observed only in patients not overtly cachectic [147]. The effects of IGF-1 in patients with CAC have not been studied to date.

Anabolic Androgens

Anabolic androgens are synthetic derivatives of testosterone with more anabolic effect and less androgenic activity than testosterone itself. Although in other wasting diseases the anabolic steroids have shown a beneficial effect on body weight muscle mass and performance status, very few studies have been carried out to date in patients with cancer. In a randomised, prospective study in weight-losing patients with lung cancer, chemotherapy with or without nandrolone decanoate 200 mg weekly for 1 month was compared and no significant difference was observed in body weight loss between the study arms [148].

Branched-Chain Amino Acids

The anabolic properties of branched-chain amino acids (BCAAs), and in particular of leucine, have been known for many years, but only recently have their molecular mechanisms been elucidated.

Consistent experimental and clinical data indicate that BCAAs, and particularly leucine and its metabolite b-hydroxy-b-methylbutyrate, are highly effective in preventing CAC by enhancing protein metabolism and promoting appetite and food intake [149].

Specific Anticancer Treatments

Specific anticancer treatments may be employed in patients with advanced disease for palliation. Indeed, for instance, oral fluoropyrimidine tegafur/uracil prolonged survival and improved cancer cachexia in a colon-26-bearing murine cachexia model by decreasing the plasma levels of both IL-6 and tumour PGE2. These findings suggest that tegafur/uracil, at a low-toxic dose, could be useful in patients with CAC and poor performance status [150].

Assessment of the Quality of Life

It is important that all the interventions used in patients with CAC, i.e. nutritional, pharmacological, supportive care, are not evaluated merely in terms of objective medical (i.e. physical) parameters, such as body weight gain, increased food intake, etc., and that the assessment of any therapy also takes into account the self-assessed patient evaluation of treatment outcome, that is quality of life (QoL). There are no published QoL questionnaires devoted to evaluating specific symptoms present in patients with CAC. Different QoL questionnaires have been used in the different studies addressing this issue. Simons et al. [96] utilised the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC-QLQ-C30) [151], a widely used instrument developed for use in patients with cancer; Rowland et al. [152] used a patient-completed visual analogue QoL unit scale; Bruera et al. [153] used the Piper Fatigue Scale and the Functional Living Index-Cancer. Recently we have introduced the EQ-5D questionnaire in the QoL evaluation of cachectic patients. It is a standardised instrument applicable to a wide range of health conditions and treatments, which provides a simple descriptive profile and a single index value for health status. The EQ-5D self-report questionnaire essentially consists of two pages comprising the EQ-5D descriptive system and the EQ-5D VAS. The EQ-5D descriptive system assesses five dimensions of health: mobility, self-care, usual activities, pain/discomfort, anxiety/depression; each dimension comprises three levels (no problems, some/moderate problems, extreme problems) and a unique health state score is defined by combining the level from each dimension. EQ-5D VAS records the respondent's self-rated health status on a vertical graduated (0–100) visual analogue scale (http.www.euroqol.org/eq5d). It is hoped that QoL questionnaires that specifically address the most significant symptoms present in patients with CAC will be designed and validated.

Conclusions

Cancer-related anorexia/cachexia is a complex phenomenon, which involves a series of pathophysiological mechanisms such as major metabolic abnormalities, abnormal production and release of tumour byproducts and host cytokines, chronic activation and defective functioning of the host immune system, leading to a final outcome of 'cachexia'. Consequently, the management of CAC is a complex challenge, which may address the different causes underlying this clinical event, requiring clinicians to select for each individual patient the most appropriate treatment on the basis of known (e.g. serum cytokine level) or reasonably hypothesised causative factors. In this review, we have examined all the potential modalities of intervention from nutritional to pharmacological approaches, clearly distinguishing between unproven, investigational and well-established treatments. Among these latter there are progestagens, presently to be considered the most effective and well-tolerated drugs for CAC. Among the investigational agents, there are drugs such as anti-IL-6 mAb, anti-TNF-α mAb, thalidomide and formoterol, which acts on muscle mass and antagonises protein wasting. Finally, the aim of treatment in CAC should focus on symptomatic, subjective and QoL endpoints rather than just on objective (nutritional) ones, since patient survival is far beyond the scope of this treatment setting [48].

References

1. Nelson KA (2000) The cancer anorexia-cachexia syndrome. Semin Oncol 27:64–68
2. Heber D, Byerley LO, Chi J (1986) Pathophysiology of malnutrition in the adult cancer patient. Cancer Res 58:1867–1873
3. Bruera E (1992) Clinical management of anorexia and cachexia in patients with advanced cancer. Oncology 49(Suppl 2):35–42
4. Brennan MR (1997) Uncomplicated starvation vs cancer cachexia. Cancer Res 37:2359–2364
5. Nelson K,Walsh D (1991) Management of the anorexia/ cachexia syndrome. Cancer Bull 43:403–406
6. Tisdale MJ (1997) Cancer cachexia: metabolic alterations and clinical manifestations. Nutrition 13:1–7
7. Devereaux DF,Redgrave TG,Tilton M et al (1984) Intolerance to administered lipids in tumor bearing animals. Surgery 100:292–297
8. Vlassara H, Spiegel RJ,Daval DS et al (1986) Reduced plasma lipoprotein lipase activity in patients with malignancy-associated weight loss. Horm Metab Res 18:698–703
9. Rouzer CA, Cerami A (1980) Hypertriglyceridemia associated with Trypanosoma brucei brucei infection in rabbits: role of defective triglyceride removal.Mol Biochem Parasitol 2:31–38
10. McNamara MJ, Alexander HR, Norton JA (1992) Cytokines and their role in the pathophysiology of cancer cachexia. JPEN J Parenter Enteral Nutr 16(Suppl 6):50S–55S
11. Tisdale MJ (1997) Biology of cachexia. J Natl Cancer Inst 89:1763–1773
12. Noguchi Y,Yoshikawa T, Matsumoto A et al (1996) Are cytokines possible mediators of cancer cachexia? Surg Today 26:467–475
13. Espat NJ, Copeland EM, Moldawer LL (1994) Tumor necrosis factor and cachexia: a current perspective. Surg Oncol 3:255–262
14. Moldawer LL, Gelin J, Schersten T et al (1987) Circulating interleukin 1 and tumor necrosis factor during inflammation. Am J Physiol 253:R922–R928
15. Moldawer LL, Andersson C, Gelin J (1988) Regulation of food intake and hepatic protein synthesis by recombinant-derived cytokines. Am J Physiol 254:6450–6456
16. Moldawer LL, Rogy MA, Lowry SF (1992) The role of cytokines in cancer cachexia. JPEN J Parenter Enteral Nutr 16:43S–49S
17. Strassmann G, Fong M, Kenney JS et al (1992) Evidence for the involvement of interleukin-6 in experimental cancer cachexia. J Clin Invest 89:1681–1684
18. Busbridge J, Dascombe MJ, Hoopkins S (1989) Acute central effects of interleukin-6 on body temperature, thermogenesis and food intake in the rat. Proc Nutr Soc 38:48A
19. Gelin J, Moldawer LL, Lonnroth C (1991) Role of endogenous tumor necrosis factor alfa and interleukin 1 for experimental tumor growth and the development of cancer cachexia. Cancer Res 51:415–421
20. McLaughlin CL, Rogan GJ, Ton J (1992) Food intake and body temperature responses of rat to recombinant interleukin 1 beta and a tripeptide interleukin 1 beta antagonist. Physiol Behav 52:1155–1160
21. Sherry BA,Gelin J, Fong Y (1991) Anticachectin/tumor necrosis factor alpha antibodies attenuate development of cancer cachexia. Cancer Res 51:415-421
22. Matthys P, Billiau A (1997) Cytokines and cachexia. Nutr 13:763–770
23. Moldawer LL, Copeland EM (1997) Proinflammatory cytokines, nutritional support, and the cachexia syndrome: interactions and therapeutic options. Cancer 79:1828–1839
24. Simons JP (1997) Cancer cachexia. Simons JP, Maastricht
25. Beck SA, Mulligan HD, Tisdale MJ (1990) Lipolytic factors associated with murine and human cancer cachexia. J Natl Cancer Inst 82:1922–1926
26. Beck SA, Groundwater P, Barton C et al (1990) Alterations in serum lipolytic activity of cancer patients with response to therapy. Br J Cancer 62:822–825
27. Taylor DD, Gercel-Taylor C, Jenis LG et al (1992) Identification of a human tumor-derived lipolysis-promoting factor. Cancer Res 52:829–834
28. Todorov PT, Cariuk P,McDevitt TM et al (1996) Characterization of a cancer cachectic factor. Nature 379:739–742
29. Byerley LO, Alcock NW, Starnes HF (1992) Sepsis induced cascade of cytokine mRNA expression: correlation with metabolic changes. Am J Physiol 261:E728–E735
30. Waage A, Brandtzaeg P, Halstensen A et al (1989) The complex pattern of cytokines in serum from patients with meningococcal septic shock. J Exp Med 169:333–338
31. Wilmore DW, Long JM, Mason AD et al (1974) Catecholamines: mediator of the hypermetabolic response to thermal injury. Ann Surg 180:653–668
32. Stoner HB, Barton RN, Little RA et al (1977) Measuring the severity of injury. BMJ 2:1247–1249
33. Wilmore DW, Moylan JA, Pruitt Bam Lindsey CA et al (1974) Hyperglucagonaemia after burns. Lancet 1:73–75
34. Rosenblatt S, Jr Clowes GH,George BC et al (1983) Exchange of amino acids by muscle and liver in sepsis. Arch Surg 118:167–175
35. Long CL (1997) Energy balance and carbohydrate metabolism in infection and sepsis. Am J Clin Nutr 30:1301–1310
36. Baumann H, Gauldie J (1994) The acute phase response. Immunol Today 15:74–80

37. Nordenstrom J, Carpentier YA, Askanazi J et al (1983) Free fatty acid mobilization and oxidation during total parenteral nutrition in trauma and infection. Ann Surg 198:725–735
38. Oliff A, Defeo-Jones D, Boyer M et al (1987) Tumor secreting human TNF/cachectin induce cachexia in mice. Cell 50:555–563
39. Campfield LA, Smith FJ,Guisez Y et al (1995) Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. Science 269:546–549
40. Stephens TW, Basinski M, Bristow PK et al (1995) The role of neuropeptide Y in the antiobesity action of the obese gene product. Nature 377:530–532
41. Halaas JL, Gajiwala KS, Maffei M et al (1995) Weight reducing effects of the plasma protein encoded by the obese gene. Science 269:543–546
42. Schwartz MW, Baskin DG, Bukowski TR et al (1996) Specificity of leptin action on elevated blood glucose levels and hypothalamic neuropeptide Y gene expression in ob/ob mice. Diabetes 45:531–535
43. Billington CJ, Briggs JE, Grace M, Levine AS (1991) Effects of intracerebroventricular injection of neuropeptide Y on energy metabolism. Am J Physiol 260(2Pt 2):R321–R327
44. Dryden S, Frankish H, Wang Q, Williams G (1994) Neuropeptide Y and energy balance: one way ahead for the treatment of obesity? Eur J Clin Invest 24:293–308
45. Inui A (1999) Cancer anorexia-cachexia syndrome: are neuropeptides the key? Cancer Res 15:4493–4501
46. Inui A (1999) Neuropeptide Y: a key molecule in anorexia and cachexia in wasting disorders? Mol Med Today 5:79–85
47. Mantovani G, Macciò A, Mura L et al (2000) Serum levels of leptin and proinflammatory cytokines in patients with advanced-stage cancer at different sites. J Mol Med 78:554–556
48. Gagnon B, Bruera E (1998) A review of the drug treatment of cachexia associated with cancer. Drugs 55:675–688
49. Kotler DP (2000) Cachexia. Ann Intern Med 133:622–634
50. Bennegard K, Eden E, Ekman L et al (1983) Metabolic response of whole body and peripheral tissues to enteral nutrition in weight-losing cancer and non cancer patients. Gastroenterology 85:92–99
51. Dresler CM, Jeevanandam M, Brennan MF (1987) Metabolic efficacy of enteral feeding in malnourished cancer and non cancer patients. Metabolism 36:82–88
52. Laviano A, Meguid MM (1996) Nutritional issues in cancer management. Nutrition 12:358–371
53. Klein S, Kinney J, Jeejeebhoy K et al (1997) Nutrition support in clinical practice: review of published data and recommendations for future research directions. Clin Nutr 16:193–218
54. Sikora SS, Ribeiro U, Kane JM 3rd et al (1998) Role of nutrition support during induction chemoradiation therapy in esophageal cancer. JPEN J Parenter Enteral Nutr 22:18–21
55. Lipman TO (1991) Clinical trials of nutritional support in cancer: parenteral and enteral therapy. Hematol Oncol Clin North Am 5:91–102
56. Nelson KA,Walsh D, Sheehan FA (1994) The cancer anorexia-cachexia syndrome. J Clin Oncol 12:213–225
57. Body JJ (1999) Metabolic sequelae of cancers (excluding bone marrow transplantation). Curr Opin Clin Nutr Metab Care 2:339–344
58. Body JJ (1999) The syndrome of anorexia-cachexia. Curr Opin Oncol 11:255–260
59. Nelson KA,Walsh D, Sheehan FA (1994) The cancer anorexia-cachexia syndrome. J Clin Oncol 12:213–225
60. Miller M (1998) Can reducing caloric intake also help reduce cancer? J Natl Cancer Inst 90:1766–1767
61. Nitenberg G, Raynard B (2000) Nutritional support of the cancer patient: issues and dilemmas. Crit Rev Oncol Hematol 34:137–168
62. Laviano A, Meguid MM,Yang ZJ et al (1996) Cracking the riddle of cancer anorexia. Nutrition 12:706–710
63. Kardinal CG, Loprinzi CL, Schaid DJ et al (1990) A controlled trial of cyproheptadine in cancer patients with anorexia and/or cachexia. Cancer 65:2657–2662
64. Ray PD, Hanson RL, Lardy HA (1970) Inhibition by hydrazine of gluconeogenesis in the rat. J Biol Chem 245:690–696
65. Kosty MP, Fleishman SB, Herndon JE et al (1994) Cisplatin, vinblastine and hydrazine sulfate in advanced, non-small-cell lung cancer: a randomized placebo controlled, double-blind phase III study of the cancer and leukemia group B. J Clin Oncol 12:1113–1120
66. Loprinzi CL, Kuross AS, O'Fallon JR et al (1994) Randomized placebo-controlled evaluation of hydrazine sulfate in patients with advanced colorectal cancer. J Clin Oncol 12:1121–1125
67. Loprinzi CL, Goldberg RM, Su JQ et al (1994) Placebo controlled trial of hydrazine sulfate in patients with newly diagnosed non-small-cell lung cancer. J Clin Oncol 12:1126–1129
68. Gralla RJ, Itri LM, Prisko SE et al (1981) Antiemetic efficacy of high-dose metoclopramide: randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. N Engl J Med 305:905–909
69. Grosvenor M, Bulcavage L, Chlebowski RT (1989) Symptoms potentially influencing weight loss in a cancer population. Cancer 63:330–334
70. Shivshanker K, Bennett RW, Hayne TP (1983) Tumor associated gastroparesis: correction with metoclopramide. Am J Surg 145:221–225
71. Nelson KA, Walsh TD, Sheehan FG et al (1993) Assessment of upper gastrointestinal motility in the cancer associated dyspepsia syndrome. J Palliat Care 9:27–31
72. Bruera E, MacBachern T, Spachynski K et al (1994)

Comparison of the efficacy, safety and pharmacokinetics of controlled release and immediate release metoclopramide for the management of chronic nausea in patients with advanced cancer. Cancer 74:3204–3211
73. Foltin RW, Fishman MW, Byrne MF (1988) Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. Appetite 11:1–14
74. Jatoi A, Windschitl HE, Loprinzi CL, et al (2002) Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. Support Care Cancer 10:71–75
75. Wadleigh R, Spaulding M, Lembersky B et al (1990) Dronabinol enhancement of appetite and cancer patients. Proc Am Soc Clin Oncol 9:331 (abs)
76. Nelson K, Walsh D, Deeter P et al (1994) A phase II study of deltanine-tetrahydrocannabinol for appetite stimulation in cancer-associated anorexia. J Palliat Care 10:14–18
77. Beal JE, Olson R, Laubenstein L et al (1995) Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage 10:89–97
78. Cavalli G, Goldhirsch A, Jungi F et al (1984) Randomized trial of low-versus-high-dose medroxyprogesterone acetate in the treatment of postmenopausal patients with advanced breast cancer. In: Pellegrini A, Robustelli Della Cuna G (eds) Role of medroxyprogesterone in endocrine-related tumors, vol 3. Raven Press, New York, pp 79–89
79. Tchekmedyian NS, Tait N, Moody M et al (1987) Highdose megestrol acetate: a possible treatment for cachexia. JAMA 257:1195–1198
80. McCarthy HD, Crowder RE, Dryden S et al (1994) Megestrol acetate stimulates food and water intake in the rat: effects on regional hypothalamic neuropeptide Y concentrations. Eur J Pharmacol 265:99–102
81. Mantovani G, Macciò A, Bianchi A et al (1995) Megestrol acetate in neoplastic anorexia/cachexia: clinical evaluation and comparison with cytokine levels in patients with head and neck carcinoma treated with neoadjuvant chemotherapy. Int J Clin Lab Res 25:135–141
82. Mantovani G, Macciò A, Esu S et al (1997) Medroxyprogesterone acetate reduces the in vitro production of cytokines and serotonin involved in anorexia/cachexia and emesis by peripheral blood mononuclear cells of cancer patients. Eur J Cancer 33:602–607
83. Mantovani G,Macciò A,Lai P et al (1988) Cytokine activity in cancer-related anorexia/cachexia: role of megestrol acetate and medroxyprogesterone acetate. Semin Oncol 25(2 Suppl 6):45–52
84. Bruera E,MacMillan K, Hanson J et al (1990) A controlled trial of megestrol acetate on appetite, caloric intake, nutritional status and other symptoms in patients with advanced cancer. Cancer 66:1279–1282
85. Loprinzi CL, Ellison NM, Shaid DJ et al (1990) Controlled trial of megestrol acetate for the treatment of cancer, anorexia and cachexia. J Natl Cancer Inst 82:1127–1132
86. Tchekmedyian NS, Hakman M, Siau J et al (1992) Megestrol acetate in cancer anorexia and weight loss. Cancer 69:1268–1274
87. Feliu J, Gonzalez-Baron M, Berrocal A (1992) Usefulness of megestrol acetate in cancer cachexia and anorexia. Am J Clin Oncol 15:436–460
88. Beller E, Tattersall M, Kumley T et al (1997) Improved quality of life with megestrol acetate in patients with endocrine-insensitive advanced cancer: a randomised placebo-controlled trial. Ann Oncol 8:277–283
89. Schmoll E, Wilke H, Thole R (1991) Megestrol acetate in cancer cachexia. Semin Oncol 1(Suppl 2):32–34
90. Fietkau R, Riepi M, Kettner H (1997) Supportive use of megestrol acetate in patients with head and neck cancer during radio(chemo)therapy. Eur J Cancer 33:75–79
91. Loprinzi CL, Michalak JC, Shaid DJ (1993) Phase three evaluation of four doses of megestrol acetate as therapy for patients with cancer anorexia and/or cachexia. J Clin Oncol 11:762–767
92. Bruera E, Ernst S, Hagen N et al (1996) Symptomatic effects of megestrol acetate (MA): a double-blind, crossover study. Proc Am Soc Clin Oncol 15:531 (abs)
93. McMillan DC, Simpson JM, Preston T et al (1994) Effect of megestrol acetate on weight loss, body composition and blood screen of gastrointestinal cancer patients. Clin Nutr 85–89
94. Gebbia V, Testa A, Gebbia N (1996) Prospective randomised trial of two levels of megestrol acetate in the management of anorexia-cachexia syndrome in patients with metastatic cancer. Br J Cancer 73:1576–1580
95. Downer S, Joel S, Allbright A et al (1993) A double blind placebo controlled trial of medroxyprogesterone acetate (MPA) in cancer cachexia.Br J Cancer 67:1102–1105
96. Simons JP, Aaronson NK,Vansteenkiste JF et al (1996) Effect of medroxyprogesterone acetate on appetite, weight, and quality of life in advanced-stage non-hormone-sensitive cancer: a placebo-controlled multicenter study. J Clin Oncol 14:1077–1084
97. Ottery FD, Walsh D, Strawford A (1998) Pharmacologic management of anorexia/cachexia. Semin Oncol 25(Suppl 6):35–44
98. De Vita Jr VT, Hellman S, Rosenberg SA (1997) Cancer principles and practice of oncology.Vol 1, 5th ed. Lippincott-Raven, Philadelphia
99. Bruera E, Fainsinger RL (1993) Clinical management of cachexia and anorexia. In: Doyle D, Hanks G, MacDonald N (eds) Oxford textbook of palliative medicine. Oxford Medical Publications, London, pp 330–337

100. Steer KA, Kurtz AB, Honour JW (1995) Megestrol-induced Cushing's syndrome. Clin Endocrinol 42:91–93
101. Heckmayr M, Gatzeneier U (1992) Treatment of cancer weight loss in patients with advanced lung cancer. Oncology 49(Suppl 2):32–34
102. Femia RA, Goyette RE (2005) The science of megestrol acetate delivery: potential to improve outcomes in cachexia. Bio Drugs 19:179–87
103. Moertel CG, Schutt AJ, Reitemeier RJ, Hahn RG (1974) Corticosteroid therapy of preterminal gastrointestinal cancer. Cancer 33:1607–1609
104. Willox JC, Corr J, Shaw J et al (1984) Prednisolone as an appetite stimulant in patients with cancer. Br Med J (Clin Res Ed) 288:27
105. Bruera E, Roca E, Cedaro L et al (1985) Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. Cancer Treat Rep 69:751–754
106. Della Cuna GR, Pellegrini A, Piazzi M (1989) Effect of methylprednisolone sodium succinate on quality of life in preterminal cancer patients: a placebo-controlled, multicenter study. The Methylprednisolone Preterminal Cancer Study Group. Eur J Cancer Clin Oncol 25:1817–1821
107. Popiela T, Lucchi R, Giongo F (1989) Methylprednisolone as palliative therapy for female terminal cancer patients. The Methylprednisolone Female Preterminal Cancer Study Group. Eur J Cancer Clin Oncol 25:1823–1829
108. Bruera ED, Roca E, Cedaro L et al (1983) Improved control of chemotherapy-induced emesis by the addition of dexamethasone to metoclopramide in patients resistant to metoclopramide. Cancer Treat Rep 67:381–383
109. Watanabe S, Bruera E (1994) Corticosteroids as adjuvant analgesics. J Pain Symptom Manage 9:442–445
110. Fuinsinger R (1996) Pharmacological approach to cancer cachexia and cachexia. In: Bruera E, Higginson I (eds) Cachexia-anorexia in cancer patients. Oxford University Press,Oxford, pp 128–140
111. Plata-Salaman CR (1991) Dexamethasone inhibits food intake suppression induced by low doses of interleukin-1 beta administered intracerebroventricularly. Brain Res Bull 27:737–738
112. Uehara A, Sekiya C, Takasugi Y et al (1989) Anorexia induced by interleukin 1: involvement of corticotropinreleasing factor. Am J Physiol 257(3 Pt 2):R613–R617
113. Han J, Thompson P, Beutler B (1990) Dexamethasone and pentoxifylline inhibit endotoxin-induced cachectin/tumor necrosis factor synthesis at separate points in the signaling pathway. J Exp Med 172:391–394
114. Trikha M, Corringham R, Klein B, Rossi JF. (2003) Targeted anti-interleukin-6 monoclonal antibody therapy for cancer: a review of the rationale and clinical evidence. Clin Cancer Res 9:4653–4665
115. Siegel SA, Shealy DJ, Nakada MT et al (1995) The mouse/human chimeric monoclonal antibody cA2 neutralizes TNF in vitro and protects transgenic mice from cachexia and TNF lethality in vivo. Cytokine 7:15–25
116. Torelli GF, Meguid MM, Moldawer LL et al (1999) Use of recombinant human soluble TNF receptor in anorectic tumor-bearing rats. Am J Physiol 277:R850–R855
117. Zabel P, Wolter DT, Schonharting MM, Schade UF (1989) Oxpentifylline in endotoxaemia. Lancet 2:1474–1477
118. Lissoni P, Ardizzoia A, Perego MS et al (1993) Inhibition of tumor necrosis factor-alpha secretion by pentoxifylline in advanced cancer patients with abnormally high blood levels of tumor necrosis factor-alpha. J Biol Regul Homeost Agents 7:73–75
119. Goldberg RM, Loprinzi CL, Mailliard JA et al (1995) Pentoxifylline for treatment of cancer anorexia and cachexia? A randomized, double-blind, placebo-controlled trial. J Clin Oncol 13:2856–2859
120. Gordon JN, Trebble TM, Ellis RD et al (2005) Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. Gut 54:540–545
121. Wigmore SJ, Falconer JS, Plester CE et al (1995) Ibuprofen reduces energy expenditure and acute-phase protein production compared with placebo in pancreatic cancer patients. Br J Cancer 72:185–188
122. McMillan DC, O'Gorman P, Fearon KC, McArdle CS (1997) A pilot study of megestrol acetate and ibuprofen in the treatment of cachexia in gastrointestinal cancer patients. Br J Cancer 76:788–790
123. Lundholm K, Gelin J, Hyltander A et al (1994) Anti-inflammatory treatment may prolong survival in undernourished patients with metastatic solid tumors. Cancer Res 54:5602–5606
124. Masferrer JL, Leahy KM, Koki AT et al (2000) Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. Cancer Res 60:1306–1311
125. Moore RJ, Zweifel B, Heuvelman DM et al (2000) Enhanced antitumor activity by co-administration of celecoxib and chemotherapeutic agents cyclophosphamide and 5-FU. Proc Am Assoc Cancer Res 41:409
126. Kishi K, Petersen S, Petersen C et al (2000) Preferential enhancement of tumor radioresponse by a cyclooxygenase-2 inhibitor. Cancer Res 60:1326–1331
127. Reddy BS, Hirose Y, Lubet R et al (2000) Chemoprevention of colon cancer by specific cyclooxygenase-2 inhibitor, celecoxib,administered during different stages of carcinogenesis. Cancer Res 60:293–297
128. Dicker AP (2003) COX-2 inhibitors and cancer therapeutics: potential roles for inhibitors of COX-2 in combination with cytotoxic therapy: reports from a symposium held in conjunction with the Radiation Therapy Oncology Group, June 2001 Meeting. Am J

Clin Oncol 26:S46–S47
129. Lissoni P, Paolorossi F, Tancini G et al (1996) Is there a role for melatonin in the treatment of neoplastic cachexia? Eur J Cancer 32A:1340–1343
130. Lissoni P, Barni S, Tancini G et al (1994) Role of the pineal gland in the control of macrophage functions and its possible implication in cancer: a study of interactions between tumor necrosis factor-alpha and the pineal hormone melatonin. J Biol Regul Homeost Agents 8:126–129
131. Meydani SN, Lichtenstein AH, Cornwall S et al (1993) Immunologic effects of national cholesterol education panel step-2 diets with and without fish-derived N-3 fatty acid enrichment. J Clin Invest 92:105–113
132. Wigmore SJ, Fearon KC, Ross JA (1997) Modulation of human hepatocyte acute phase protein production in vitro by n-3 and n-6 polyunsaturated fatty acids. Ann Surg 225:103–111
133. Barber MD, Ross JA, Preston T et al (1999) Fish oil-enriched nutritional supplement attenuates progression of the acute-phase response in weight-losing patients with advanced pancreatic cancer. J Nutr 129:1120–1125
134. Tisdale MJ (1996) Inhibition of lipolysis and muscle protein degradation by EPA in cancer cachexia. Nutrition 12:S31–S33
135. Purasiri P, Murray A, Richardson S et al (1994) Modulation of cytokine production in vivo by dietary essential fatty acids in patients with colorectal cancer. Clin Sci (Lond) 87:711–717
136. Wigmore SJ, Ross JA, Falconer JS et al (1996) The effect of polyunsaturated fatty acids on the progress of cachexia in patients with pancreatic cancer. Nutrition 12:S27–S30
137. Wigmore SJ, Fearon KC, Maingay JP, Ross JA (1997) Down-regulation of the acute-phase response in patients with pancreatic cancer cachexia receiving oral eicosapentaenoic acid is mediated via suppression of interleukin-6. Clin Sci (Lond) 92:215–221
138. Falconer JS, Ross JA, Fearon KC et al (1994) Effect of eicosapentaenoic acid and other fatty acids on the growth in vitro of human pancreatic cancer cell lines. Br J Cancer 69:826–832
139. de Bravo MG, de Antueno RJ, Toledo J et al (1991) Effects of an eicosapentaenoic and docosahexaenoic acid concentrate on a human lung carcinoma grown in nude mice. Lipids 26:866–870
140. Beck SA, Smith KL, Tisdale MJ (1991) Anticachectic and antitumor effect of eicosapentaenoic acid and its effect on protein turnover. Cancer Res 51:6089–6093
141. Barber MD,Wigmore SJ, Ross JA et al (1997) Eicosapentaenoic acid attenuates cachexia associated with advanced pancreatic cancer. Prostaglandin Leukot Essent Fatty Acids 57:204
142. Fearon KC, Von Meyenfeldt MF, Moses AG 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
143. Jatoi A, Rowland K, Loprinzi CL et al; North Central Cancer Treatment Group (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
144. Carbo N, Lopez-Soriano J, Tarrago T et al (1997) Comparative effects of beta2-adrenergic agonists on muscle waste associated with tumor growth. Cancer Lett 115:113–118
145. Ziegler TR, Wilmore DW (1993) Anabolic effects of growth hormone administration in adults. In: Muller EE, Cocchi D, Locatelli V (eds) Growth hormone and somatomedins during lifespan. Springer Verlag, Berlin, pp 312–328
146. Froesch ER, Schmid C, Schwander J et al (1985) Actions of insulin-like growth factors. Ann Rev Physiol 47:443–467
147. Tayek JA, Brasel JA (1995) Failure of anabolism in malnourished cancer patients receiving growth hormone: a clinical research center study. J Clin Endocrinol Metab 80:2082–2087
148. Ottery FD (1996) Supportive nutritional management of the patient with pancreatic cancer. Oncology 10:26–32
149. Laviano A, Muscaritoli M, Cascino A et al (2005) Branched-chain amino acids: the best compromise to achieve anabolism? Curr Opin Clin Nutr Metab Care 8:408–414
150. Nukatsuka M, Fujioka A, Saito H et al (1996) Prolongation of survival period and improvement of cancer cachexia by long-term administration of UFT. Cancer Lett 104:197–203
151. Aaronson NK, Ahmedzai S, Bergman B et al (1993) The European Organization for Research and Treatment of Cancer QLQC30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365–376
152. Rowland Jr KM, Loprinzi CL, Shaw EG et al (1996) Randomized double-blind placebo-controlled trial of cisplatin and etoposide plus megestrol acetate/placebo in extensive-stage small cell lung cancer: a north central cancer treatment group study. J Clin Oncol 14:135–141
153. Bruera E, Ernst S, Hagen N et al (1998) Effectiveness of megestrol acetate in patients with advanced cancer: a randomized, double-blind, crossover study. Cancer Prev Control 2:74–78