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Managing Cancer-Related Anorexia/Cachexia

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Contents

Abstract

Cancer-related anorexia/cachexia (CAC) is a complex phenomenon in which metabolic abnormalities, proinflammatory cytokines produced by the host immune system, circulating tumour-derived catabolic factors, decreased food intake, and probably additional unknown factors, all play different roles.

This review examines the mechanisms of CAC and its management. All the potential modalities of intervention from nutritional to pharmacological approaches are included with a clear distinction between unproven, investigational

and well established treatments. Among the latter, the progestogens are currently considered the most effective and safest drugs for the management of CAC. Agents currently under investigation for CAC include thalidomide, pentoxifylline and melatonin, which most probably act on cytokine release, and clenbuterol, which acts on muscle mass and to antagonise protein wasting.

Our personal experience with the synthetic progestogens megestrol and medroxyprogesterone supports their use as first-line agents. In addition, our work on the potential role of antioxidant agents in counteracting the oxidative stress, which appears to be involved in CAC, shows them to be promising agents when used in combination chemotherapy regimens either alone or with other 'biologics'.

There is an ongoing need for quality of life questionnaires which specifically address the most significant symptoms present in patients with CAC.

1. Mechanisms of Cancer-Related Anorexia/Cachexia (CAC)

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 bodyweight 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has been named cancer-related anorexia/cachexia (CAC).[2-5] Since the 1980s, the previous concepts explaining CAC have been replaced by a more complex insight which stresses the interaction between metabolically active molecules produced by the tumour itself and the host immune response.

The onset of CAC has numerous negative consequences. It is the single most documented cause of death in cancer and the most significant independent negative predictor of treatment outcome,[6] and it has an important negative impact on quality of life.

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 is not able to effectively reverse the process of cachexia. An increased resting energy expenditure may contribute to bodyweight 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, bodyweight loss in patients with cancer arises equally from loss of muscle and fat, characterised by increased catabolism of skeletal muscle and decreased protein synthesis.[7] 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.[7]

1.1 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 in-

clude increased protein turnover, muscle catabolism, and liver and tumour protein synthesis, whereas 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.[5,8,9]

1.2 Proinflammatory Cytokines

CAC 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 (TNFα), interferon (IFN)-α and IFNγ, have been implicated in the pathogenesis of cachexia associated with human cancer. TNFα was first identified by Rouzer and Cerami[10] 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 TNFα. 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.[11-14]

IL-1 and TNFα have been proposed as mediators of the host's response to inflammation.[15] Human IL-1 and TNFα administered to healthy animals produced significant reduction in their food intake.[16] High serum levels of TNFα, IL-2 and IFNγ have been found in patients or experimental animals with cancer,[17] and although IL-6 levels appear to correlate with tumour progression in animal models,[17] 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.[18] Chronically elevated levels of these factors, either alone or in combination, are capable of reproducing the different features of CAC.[18-21]

More direct evidence of a cytokine involvement in CAC is provided by the observations that cachexia in experimental animal models[13,22,23] 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.[24]

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.

1.3 Circulating Tumour-Derived Catabolic Factors

In addition to chronic proinflammatory factors, circulating factors, such as lipid- and protein-mobilising factors (LMFs and PMFs), 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.[6,25-28]

1.4 Systemic Inflammation

There is evidence that a chronic, low-grade, tumour-induced activation of the host immune system, which 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 catecolamines, 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 TNFα 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.

1.5 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 TNFα are involved in cancer-related anorexia and decreased food intake (see section 1.2), 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 blood lactate and fatty acid 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.

1.6 Role of Leptin and Neuropeptides

Bodyweight loss 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 bodyweight. Leptin, a recently found hormone produced by the adipocyte *ob* gene, has been shown to be an essential component of the homeostatic regulation of bodyweight. Leptin acts to control food intake and energy expenditure via neuropeptidergic effector molecules within the hypothalamus. Complex interactions take place among the nervous, endocrine and immune systems inducing behavioural and metabolic responses.[39-44]

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 signaling 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 bodyweight loss.

2. Treatment of CAC

It is outside the scope of this paper to review the current standard clinical management of patients with CAC. However, clinicians need to 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), anti-catabolic (and anti-cytokine) 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.

2.1 Unproven or Ineffective Treatments

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.[7] Nasogastric tube feeding showed a bodyweight increase in some studies[49] and a decrease in whole body protein breakdown in other studies;[50] however, the drawback to enteral tube feeding is the distress to the patients, especially in long term treatment.[51]

Various systematic prospective studies that have evaluated the potential benefit of TPN have generally been disappointing.[51-54] 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 progestogens or anabolic steroids.[55]

2.1.1 Cyproheptadine

Based on the evidence that CAC is associated with increased serotonergic activity in the brain,[56] 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 bodyweight.[57] 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.

2.1.2 Hydrazine

Hydrazine inhibits hepatic gluconeogenesis in rats by inhibiting the enzyme phosphoenolpiruvate-carboxykinase.[58] However, 3 large, randomised, placebo-controlled trials have failed to observe any beneficial effect on appetite or bodyweight in patients with cancer.[59-61]

2.1.3 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.[62] 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,[63-65] 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.[66] At present, the effectiveness of other prokinetic agents such as cisapride and domperidone needs to be demonstrated in randomised, controlled clinical trials.

2.1.4 Cannabinoids (Dronabinol)

The active ingredient of marijuana, dronabinol (Δ-9-tetrahydrocannabinol, THC) is known to have a positive effect on appetite, bodyweight and chemotherapy-induced nausea.[67]

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 are no published controlled trials with dronabinol in patients with CAC. Two open studies[68,69] demonstrated some improvement in mood and appetite with no significant change in bodyweight. In the first study by Wadleigh et al.[68] 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 bodyweight loss. In the second study, Nelson et al.[69] observed improved appetite and increased food intake using dronabinol 7.5 mg/day but the effect on bodyweight was not reported. A randomised controlled trial in patients with AIDS showed similar results.[70]

There is a need for controlled trials of this agent in patients with cancer. However, the significant adverse effects of this drug, such as somnolence, mental confusion and cognitive status disturbances,[70] which may worsen the mental status of patients with CAC who are often receiving opioids and other psychoactive drugs, need to be taken into account.

2.2 Drugs Commonly Used

2.2.1 Progestogens

Progestogens 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 progestogens which were first used to treat hormone-sensitive tumours.[71,72] As a result of the observed bodyweight gain and appetite stimulation, independent of tumour response, in a number of patients receiving such therapy, several trials in the last 2 decades have addressed the use of progestogens for the management of CAC.

The proposed mechanism of action of progestogens 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 progestogens may stimulate appetite via neuropeptide Y in the CNS (ventromedial hypothalamus).[73] Furthermore, they act, at least in part, by down-regulating the synthesis and release of proinflammatory cytokines (see section 1.2), as shown by several experimental and clinical studies, including two of our studies.[74,75] We have also previously published an overview of this topic.[76]

In the first study,[74] the effect of megestrol in patients with CAC was evaluated to determine its ability to increase appetite and bodyweight in patients with head and neck cancer with advanced stage (III to IV) disease, treated with cisplatin-based neoadjuvant chemotherapy. Eleven male patients (mean age of 57.8 years; range 43 to 69 years; Karnofsky performance status of 90 to 100; bodyweight decrease >10% of the ideal or customary bodyweight) 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 3 cycles, bodyweight, 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-1α and β, IL-2, IL-6, TNFα and sIL-2R were determined in patients before and after megestrol treatment and were compared with those of healthy individuals. Megestrol (160mg 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 cycle until the day before the next cycle (days 8 to 21) for a total of 3 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, 9 (81.8%) were evaluable; 2 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 fol-

lowing treatment with megestrol. In particular, increases were observed in average bodyweight (6.3kg 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 downregulate the synthesis and release of key cytokines involved in CAC.

The second study[75] addressed the question of whether the other synthetic progestogen 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; 5-HT) 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, TNFα 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 I, megestrol has been the drug most widely studied for its effect on CAC, with 8 randomised, double-blind, placebo-controlled trials,[77-87] compared with medroxyprogesterone (2 placebo-controlled studies).[88,89]

Megestrol has shown a dose-related effect on appetite, bodyweight gain and subjective sensation of well-being with oral dosages ranging from 160 to 1600 mg/day with an optimal dosage of 480 to 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.[89] used oral medroxyprogesterone 1000 mg/day and reported a significant improvement of appetite and bodyweight. 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.[90]

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.[91-93] However, it is very rare that patients taking megestrol or medroxyprogesterone have to stop the drug because of adverse effects.[77,78,80,94]

2.2.2 Corticosteroids

Although several randomised, placebo-controlled studies (shown in table II) 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 bodyweight.[95-99] In addition, corticosteroids have an antiemetic activity[100] and are able to reduce asthenia[95] and to control pain.[101] Their mechanism of action in CAC is not well understood, although the inhibition of prostaglandin (PG) activity[102] and the suppression of IL-1[103,104] and TNF[105] 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

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

Dosage	Duration of treatment	Study design	No. of patients	Results	Adverse effects	Reference
Megestrol						
480 mg/day	1wk	pc, co	40	Improved appetite, caloric intake, energy level, bodyweight, tricep skinfold and calf circumference	Mild oedema, nausea (similar to placebo)	77
800 mg/day (tablets)	1.6mo	pc	133	Improved appetite, food intake, bodyweight; less nausea, less emesis compared with placebo	Oedema and thrombo-embolic events	78
1600 mg/day (tablets)	1mo	pc	89	Increased appetite, food intake, greater change in prealbumin; no change in anthropometrics except bodyweight; nutrition impact symptoms improved *vs* no change or worsening on placebo; no differences in QoL, positive response with crossover design	Oedema, DVT	79
240 mg/day (tablets)	2mo	pc	150	Bodyweight gain, increased appetite score, fewer patients with decreased performance status compared with placebo	Oedema, DVT (no different than placebo)	80
160, 480 mg/day (tablets)	12wk	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	81
480 mg/day	8wk	pc	55	Sample too small for significant results	None reported	82
160 mg/day (tablets)	6wk	pc	64	Maintained bodyweight and nutritional parameters during chemo/radiotherapy compared with parameters deterioration in placebo; QoL maintained with megestrol	None reported	83
160, 480, 800, 1280 mg/day	66 days	rc	342	Improved appetite, food intake and bodyweight, decreased nausea	None reported	84
480 mg/day	10 days	pc, co	83	Improved activity, appetite and well-being. No increase of bodyweight	None reported	85
480 mg/day	12wk	pc	38	No increase of bodyweight	None reported	86
160, 320 mg/day	1mo	rc	122	Increased appetite	None reported	87
Medroxyprogesterone						
300 mg/day	6wk	pc	60	Increased appetite, serum retinol binding protein and serum thyroid binding pre-albumin	None reported	88
500mg bid	12wk	pc	206	Beneficial effect on appetite at 6 and 12wk; bodyweight gain with medroxyprogesterone *vs* loss on placebo; no other measurable changes in QoL	None reported	89

co = crossover; **DVT** = deep vein thrombosis; **pc** = placebo-controlled; **QoL** = quality of life; **rc** = randomised, controlled (no placebo).

used in patients in the end-stage phase of cancer with short expected survival in an attempt to improve quality of life without affecting bodyweight.

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.

2.2.3 Anticytokine Approaches

As discussed in section 1.2, proinflammatory cytokines such as IL-1, IL-6, and particularly, TNFα 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 pursu-

ing, while taking into account that no single cytokine is responsible for all abnormalities found in CAC. However, in chronic human diseases such as cancer and AIDS, the long term administration of anticytokine antibodies is not a practical option. An ideal drug would be orally administered and well tolerated. Pentoxyfylline and thalidomide are 2 agents with anticytokine activity currently being investigated as therapy for CAC.

Pentoxifylline

Pentoxifylline (pentoxyfylline) is a methylxantine derivative approved for the treatment of intermittent claudication which was subsequently found to have anti-inflammatory and immunemodulating effects mediated by the inhibition of phosphodiesterase. It has been shown to inhibit TNFα production in humans in response to experimentally administered endotoxin.[106] 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 TNFα levels significantly reduced the serum levels of this cytokine.[107] However, a recent double-blind, placebo-controlled trial of pentoxifylline therapy in patients with CAC did not show a beneficial effect on appetite or bodyweight.[108]

Thalidomide

Thalidomide was first clinically introduced as a sedative drug and in 1960s it was withdrawn from use because of its established teratogenic effect. During the last 30 years, thalidomide has been found to have a significant anti-inflammatory activity in a range of disorders such as rheumatoid arthritis, cutaneous lupus erythematosus and chronic graft-versus-host disease.[109-111]

Thalidomide was recently shown to have an inhibitory effect on TNFα production when used as an experimental treatment for cachexia associated with AIDS and tuberculosis. These placebo-controlled clinical trials found that thalidomide, at dosages of 200 to 400 mg/day, resulted in significant bodyweight gain in patients with pulmonary tuberculosis who were either HIV-1 positive or HIV-1 negative: TNFα production was significantly reduced during thalidomide treatment.[112] In a pilot study in 39 patients with both HIV-1 and tuberculosis infections, thalidomide therapy was associated with a reduction in both plasma TNFα and HIV-1 levels. Patients receiving thalidomide treatment showed a significant bodyweight gain relative to placebo-treated patients. Patients with simultaneous HIV-1 and tuberculosis infection experienced a higher mean bodyweight gain during thalidomide treatment than the group of patients with HIV-1 infection only.[113] Moreover, a randomised, double-blind, placebo-controlled clinical trial in patients with HIV-associated wasting syndrome demonstrated significant bodyweight gain in patients receiving thalidomide.[114] Another study showed that thalidomide treatment induced bodyweight gain independently of an effect on appetite.[115] Plasma TNFα levels were not high at baseline and were not suppressed by thalidomide treatment. Instead, plasma levels of soluble IL-2 receptors increased

Table II. 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	Nil	95
Prednisolone[a]	5 tid	PO	61	↑Appetite	Nil	96
Methylprednisolone[a]	16 bid	PO	40	↑Pain control	Nil	97
				↑Appetite, food intake and performance status	Not measured	
Methylprednisolone	125 od	IV	403	↑Quality of life	Nil	98
Methylprednisolone	125 od	IV	173	↑Quality of life	Nil	99

a Crossover design.

bid = twice daily; **IV** = intravenous; **od** = once daily; **PO** = oral; **qid** = 4 times daily; **tid** = 3 times daily; ↑ = increase.

significantly during treatment, suggesting a paradoxical drug-induced immune activation.

Published reports on the specific use of thalidomide as therapy for CAC are not available. However, the recent finding that thalidomide is able to inhibit tumour growth through an inhibition of neoangiogenesis[116] has led to investigational studies of this drug as an antineoplastic agent for different tumours.[117,118]

Randomised clinical trials with thalidomide in patients with CAC are justified, both as a single agent and in combination with an appetite stimulant such as an oral progestogen. 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]

2.3 Emerging Drugs

2.3.1. Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are very widely used in patients with cancer for the treatment of fever and pain. They act by inhibiting prostaglandin production by the rate-limiting enzymes known as cyclo-oxygenases. Because traditional NSAIDs inhibit both cyclo-oxygenase (COX)-1 and COX-2, these drugs induce adverse effects such as gastrointestinal injury up to ulceration, reduced appetite and consequently reduced bodyweight: 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,[119] produce bodyweight gain[120] and improve survival in patients with cancer.[121] 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.

The recent discovery and introduction into clinical practice of selective inhibitors of COX-2 enzyme, celecoxib and rofecoxib, which are almost completely devoid of gastrointestinal toxicity and maintain an high anti-inflammatory activity, suggest that these agents will meet the need for well tolerated and effective therapeutic alternatives to conventional NSAIDs.

Moreover, interestingly, evidence was provided that COX-2 and COX-2–derived prostaglandins may play a major role in development of cancer through several biochemical mechanisms, including stimulation of tumour cell growth and neoangiogenesis, and that celecoxib is able to block angiogenesis and suppress tumour growth.[122] The results of animal studies strongly suggest that celecoxib may potentially be an effective chemopreventive agent for the secondary prevention of colon cancer.[123]

2.3.2 Melatonin

In a recent controlled trial in 100 patients with metastatic cancer, melatonin was shown to significantly reduce bodyweight loss.[124] Melatonin may act by decreasing circulating levels of TNF.[125]

2.3.3 Omega-3 Fatty Acids

The supplementation of omega-3 polyunsaturated fatty acids has been shown to inhibit IL-1 and TNFα production through a blockade of the COX and lipo-oxygenase pathways. In a study in patients with colorectal cancer, long term treatment with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and γ-linolenic acid induced a significant decrease in serum IL-1, IL-6, TNFα and IFNγ levels.[126] Two recent studies by Wigmore et al.[127,128] reported the effects of omega-3 fatty acid treatment in patients losing weight with pancreatic cancer. In the first study,[127] oral supplementation with fish oil capsules (12 tablets per day, 18% EPA, 12% DHA) for 3 months led to a significant median bodyweight gain of 0.3 kg/month compared to a previous bodyweight loss of 2.9 kg/month. A significant reduction in acute-phase protein production was also observed. In the second study,[128] 4 weeks treatment with EPA reduced the C-reactive protein through the suppression of IL-6 production. Further randomised clinical trials are required to establish the effectiveness of omega-3 fatty acids in CAC.

2.3.4 β_2 Agonists

Clenbuterol is the most studied of the β_2-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.[129] 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.

2.3.5 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 1

Strong positive effects on nitrogen balance and protein mass has been demonstrated with GH in different clinical situations.[130] Most of its anabolic effects on protein synthesis are mediated by IGF-1, produced by the liver.[131] 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.[132] 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 bodyweight, 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 bodyweight loss between the study arms.[133]

2.4 Antioxidant Agents

An imbalance between oxidants and antioxidants in favour of the oxidants can potentially lead to cell damage and is termed 'oxidative stress'. These oxidants, also termed reactive oxygen species (ROS), are present as a normal product of aerobic metabolism but can be produced at elevated rates under pathophysiological conditions. They are superoxide radicals, hydroxyl radicals, hypochlorous acid, peroxyl radicals and singlet oxygen, and can cause cell damage by oxidising nucleic acid, proteins and membrane lipids.[134] ROS may act at different stages in the establishment and progression of cancer. It has recently been well documented that ROS are also involved in tissue wasting and CAC. Moreover, some cytokines involved in CAC, especially TNFα, are inducers of ROS, which seem to be part of the final common pathway through which cell damage takes place. Thus, oxidative stress, which is one of the causes of and in turn may be worsened by CAC, is promoted by an excess of ROS and some proinflammatory cytokines, such as IL-1, IL-6 and TNFα.[76]

α-Lipoic acid (ALA) is present in human cells in a bound lipoillysine form in mitochondrial proteins that play a central role in oxidative metabolism and it has recently gained considerable attention as an antioxidant.[135] It has been reported to have beneficial effects in disorders associated with oxidative stress, inducing a substantial increase in cellular reduced glutathione (GSH) and restoring severely GSH deficient cells.[136] N-Acetyl cysteine (NAC) is another known precursor for GSH synthesis that has been shown to act on redox balance and to be capable of significantly improving the antioxidant potential by elevating reduced GSH levels.[137]

In an *in vitro* study, we showed a favourable effect of antioxidant agents ALA and NAC on several important T cell functions in patients with advanced stage cancer.[138] We use ALA and NAC as

antioxidant agents in patients with cancer by including these drugs in combination chemo-hormone-immunotherapy regimens not only in patients with CAC but with the aim of preventing it. The dosages we use are ALA 400 mg/day (4 × 100mg capsules) and NAC 1800 mg/day (3 × 600mg tablets) for at least 6 months. The results of our clinical phase II study of weekly combination chemotherapy plus medroxyprogesterone, recombinant IL-2, ALA and NAC in patients with stage IIIB-IV non-small-cell lung cancer are not yet published. In patients with cancer having obtained an objective clinical response or stable disease after chemotherapy and no longer eligible for chemotherapy regimens, we used ALA and NAC at the above dosages in association with medroxyprogesterone: the treatment is continued indefinitely. We observed an optimal patient compliance and no treatment-related adverse effects were recorded.

Among the antioxidants, one of the most interesting is amifostine, a phosphorylated aminothiol prodrug that is dephosphorylated at the tissue site by membrane-bound alkaline phosphatase to its active metabolite, the free thiol, WR-1065.[139,140] In clinical use, the reduced incidence and severity of neurotoxicity, nephrotoxicity and haemotological toxicity achieved with the addition of amifostine to chemotherapeutic regimens is well established.[139]

2.5 Specific Anticancer Treatments

Specific anticancer treatments may be employed in patients with advanced disease for palliation. Indeed, for instance, the oral fluoropyrimidine tegafur/uracil (UFT) 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 PGE_2. These findings suggest that tegafur/uracil, at a low-toxic dose, could be useful in patients with CAC and poor performance status.[141]

3. Assessment of the Quality of Life

It is important that all the interventions used in patients with CAC, i.e. nutritional, pharmacological and supportive care, are not evaluated merely in terms of objective medical (i.e. physical) parameters, such as bodyweight 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 evaluate specific symptoms present in patients with CAC. Different QoL questionnaires have been used in the different studies addressing this issue. Simons et al.[89] utilised the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC-QLQ-C30),[142] a widely used instrument developed for use in patients with cancer; Rowland et al.[143] used a patient-completed visual analogue QoL unit scale;[144] Bruera et al.[145] used the Piper Fatigue Scale and the Functional Living Index-Cancer. It is hoped that QoL questionnaires which specifically address the most significant symptoms present in patients with CAC will be designed and validated.

4. Conclusions

CAC is a complex phenomenon which involves a series of pathophysiological mechanisms such as major metabolic abnormalities, abnormal production and release of tumour by-products 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 individaul 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 progestogens, presently to be considered the most effective and well tolerated drugs for CAC. Among

the investigational agents, there are drugs such as thalidomide, pentoxifylline and melatonin, which most probably act on cytokine release, and clenbuterol, which acts on muscle mass and antagonises protein wasting.

Finally, the aim of treatment in CAC should focus on symptomatic, subjective and QoL end-points rather than just on objective (nutritional) ones, since patient survival is far beyond the scope of this treatment setting.[48]

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