Learning Objectives

- Know the relevant therapeutic problems in cancer cachexia;
- Know the pharmacological agents proposed to treat cancer cachexia;
- Know the evidence level of recommendations for anti-cachectic agents.

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Key Messages

• To improve appetite, psychological distress and chronic pain have to be treated;
• Pharmacological agents may help to relieve nausea and gastrointestinal dysfunction;
• Among appetite stimulating drugs, corticosteroids and progestins are best established; both have unwanted side-effects that need to be considered;
• Anti-inflammatory agents, like NSAIDs and N-3 fatty acids may be used to counteract chronic inflammatory states in cancer patients;
• Hunger-inducing peptides like ghrelin and MC4R antagonists, anabolic-androgenic agents and antibodies against myostatin and IL6 are being investigated as potential anticachectic agents;
• Anti-cachectic agents should always be accompanied by exercise training.
1. Introduction

Weight loss and loss of body cell mass are frequent and complex problems in cancer patients. The major factors leading to malnutrition and compromised prognosis are anorexia, gastrointestinal (GI) dysfunction, systemic inflammatory processes and a prevalence of catabolic signals (Table 1). These factors interact and may aggravate each other. Many different pharmacological approaches have been proposed to treat components of this cachexia network (Table 2). Several agents are used frequently in standard supportive and palliative care of cancer patients. However, of the numerous substances tested to correct or antagonize deranged metabolic pathways, only a few have so far been proven effective. Unfortunately, today there are still many more theoretical options than established treatments against cancer cachexia.

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BCAA: branched-chain amino acids
NSAID: non-steroidal anti-inflammatory drug
SARM: selective androgen receptor modulator
ATP: adenosine 5'-triphosphate

Anorexia is a hallmark sign of many cancers and may appear early and even before cancer is diagnosed. It is the result of complex neuro-hormonal interactions that lead to a declining or absent desire to eat (1). Chronic pain even at a low level may contribute to anorexia as may psychological and social stressors, which often are present during the course of a cancer disease and may peak during critical phases. Nausea and defects in smelling or tasting will similarly reduce or block any urge to eat.

Normal physiological function of the gastrointestinal tract is essential to the efficient intake, transport, breakdown and absorption of foods and nutrients. Dysfunction may occur at many different sites and be of diverse nature. To alleviate or correct disturbed GI functions targeted pharmacological treatments should be applied.
Systemic inflammation is present in many patients with advanced tumours. The associated immunological, endocrine, paracrine and metabolic changes will inhibit appetite and physical activity while increasing fatigue, lethargy and exhaustion. Resting energy expenditure is increased and inter-organ nutrient fluxes are redistributed. Anti-inflammatory agents may antagonize some of these effects.

Reduced energy intake and inflammation activate catabolic reactions leading to loss of protein and fat and of body cell mass. At the same time water is retained in the extracellular compartment resulting in subclinical and clinical oedema. Antagonizing catabolic pathways and activating anabolic processes may improve protein and performance status, vitality and quality of life.

When studying the effects of biologically active substances to treat anorexia or cachexia it is essential to understand that no agent will make muscles grow if they are not stimulated to work. Therefore, any pharmacological treatment in cancer patients should invariably be combined with exercise training.

2. Appetite Stimulants

Anorexia is a psychological burden for the patient and close relatives. Families may push patients to eat against their desire. Anorexia is a primary cause of reduced food intake and thus of weight loss. A number of agents has been proposed and studied to counteract anorexia and to increase appetite (Table 3).

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2.1 Corticosteroids

This group of drugs includes dexamethasone (DEX), prednisolone (PRED), methylprednisolone (MP) and hydrocortisone. These agents stimulate the appetite, they have an antiemetic activity and they are able to reduce asthenia. In addition they may increase general well-being. The mechanism of action upon appetite is not well understood but may involve suppression of production or release of prostaglandins and proinflammatory cytokines IL-1 and TNF-α. The effects upon appetite and well-being are usually temporary and limited to a few weeks.

Corticosteroids have been investigated in randomized controlled studies (RCT) since the 1970s. A systematic review (2) analyzed 6 studies involving a total of 647 patients. Intravenous or oral corticosteroids significantly improved appetite, pain, quality of life (QoL) scores, vomiting and well-being and performance status. Doses used were PRED 10 mg/d, MP 32-125 mg/d, DEX 3-8 mg. Improvements could be observed for several weeks; in one study, however, beneficial effects present after 2 weeks of treatment disappeared after 4 weeks.

Corticosteroids produce a number of unwanted effects if taken for prolonged periods, like myopathy, osteoporosis, immune suppression, susceptibility to infections, skin frailty,
accumulation of extracellular water, oedema, insulin resistance and increase of blood glucose, gastrointestinal ulcers and mood abnormalities.

Since beneficial effects usually are limited to a few weeks and prolonged treatment is associated with increasing side-effects, the use of corticosteroids should be restricted to patients with an expected survival of short duration.

### 2.2 Progestins

When progestins were used to treat hormone-responsive breast cancer, weight gain was observed as an unexpected side effect. Two synthetic progestins have been studied to increase appetite in cancer-associated anorexia: megestrol acetate (MA) and medroxyprogesterone acetate (MPA). Yavuszen reviewed 23 RCTs using MA at doses from 160 to 1600 mg/d and 6 RCTs using MPA at doses from 300 to 1200 mg/d (2) including a total of 4139 patients.

Side effects of both MA and MPA were found to be acceptable. The optimal dose of MA was reported to be between 480 and 800 mg, while there are no data for an optimal MPA dose.

Compared to placebo both MA and MPA increased appetite and less reliably body weight, while there were only minimal effects on QoL. In increasing appetite, MA was similarly effective to corticosteroids, but MA was more effective than the cannabinoid dronabinol and the anabolic steroid fluoxymestrone.

A Cochrane meta-analysis of 31 RCTs and a total of 4123 patients showed a benefit of MA compared with placebo, particularly with regard to appetite improvement and weight gain in cancer patients, while again there was insufficient information to define the optimal dose of MA (3). A more recent meta-analysis (4) concluded that MA was able to reduce the symptoms of cancer cachexia with no effect on survival or quality of life.

The mechanism of action of progestins is still unclear. Progestins have been shown to reduce production of proinflammatory cytokines IL-1, IL-6 and TNF-α by peripheral blood mononuclear cells (5) and they may stimulate appetite via the neuropeptide Y orexigenic network in the ventromedial hypothalamus (6). Unfortunately, weight gain generally is not accompanied by an increase in lean body mass (7); thus weight gain is based on fat gain and accumulation of water. Under certain conditions progestins may even decrease muscle mass by reducing circulating androgen levels. On the other hand, very recent data in cachectic tumour-bearing rats reported an improvement in muscle mass after administration of MA.

Side effects of progestins include thromboembolism (reported in up to 5% of cases (8)), impotence in males and vaginal spotting or bleeding in females, hyperglycaemia, hypertension, peripheral oedema, alopecia, and adrenal insufficiency.

Progestins should not be offered to patients with a history or a high risk of thromboembolism. If side effects are acceptable, progestins may induce a long-term increase in appetite and weight. It has been suggested that the daily dosage should be started low and increased only if the expected effect on appetite does not occur after a trial period of two weeks.

### 2.3 Cannabinoids

Anecdotal reports and numerous small studies suggest that marijuana stimulates appetite (9). Cannabis extracts and the most active ingredient, tetrahydrocannabinol (THC), have been studied. The mechanism by which cannabinoids exert their effects has yet to be clarified. They bind to receptors of the endocannabinoid system in the central
nervous system; they might act by inhibiting prostaglandin synthesis or by inhibiting cytokine production and/or secretion.

An effect on appetite and mood is obtained by an administration of 5 mg/day, with about 2/3 of patients reporting that their appetites are stimulated. Neuropsychological effects are not uncommon, including nausea and slurred speech. Approximately 50% of patients tolerate 10 mg twice daily.

There are only a few valid studies reporting on cannabinoid effects on appetite. A RCT by Strasser et al. (10) did not show any benefit of oral administration of cannabis extract or THC (2.5 mg/d) on appetite or quality of life when compared with placebo. The dose used in the study, unfortunately, was fairly low. A 3-arm study compared THC (5 mg/d) with MA (800 mg/d) and a combination of both. MA improved appetite and QoL better than THC, but the combination of dronabinol with megestrol acetate did not offer any advantage over treatment with megestrol acetate alone (11).

Cannabinoids thus may be offered to individual patients if other orexigenics are unsuitable; the dose should be carefully increased to at least 5 mg, observing an effect on appetite as well as potential side effects.

2.4 Ghrelin and Analogues (Experimental Agents)

Ghrelin is a peptide hormone mainly produced in the stomach from a distinct group of endocrine cells located within the gastric oxyntic mucosa. Ghrelin stimulates food intake and adiposity. It stimulates growth hormone (GH) secretion via the GH secretagogue receptor, but it also promotes food intake via the orexigenic neuropeptide Y system and decreases sympathetic nerve activity. It also influences glucose and lipid metabolism (12).

In a small randomized, placebo-controlled, cross-over trial 7 anorectic cancer patients reported a marked increase in energy and food intake during a 3-hour ghrelin infusion compared with saline control, with all patients reporting a benefit (13). Strasser et al. (14) studied 21 adult patients in a randomized cross-over design to receive 60-minute ghrelin infusions or placebo. Nutritional intake and eating-related symptoms did not differ between ghrelin and placebo. In an RCT in 21 patients after total gastrectomy twice daily ghrelin infusions for 10 days induced higher appetite and food intake than placebo. Loss of body weight was smaller in the ghrelin group and lean body mass remained stable with ghrelin but decreased in the placebo group (15). In a randomized double-blind 8-week trial in 31 weight-losing cancer patients comparing two doses of daily subcutaneous ghrelin injections, high-dose ghrelin reduced the loss of body fat and showed a trend for improved energy balance; serum levels of tumour markers did not change and no adverse events were reported (16).

The orally active growth hormone secretagogue receptor agonist anamorelin (RC-1291) produces a dose-related increase in body weight in healthy volunteers (17). When administered in a randomized, placebo-controlled trial over 12 weeks to patients with a variety of cancers, RC-1291 produced an increase in body mass and grip strength and a trend towards increased lean mass but no benefit in quality of life (18).

In a multicentre, randomized, double-blind, crossover pilot study, anamorelin when given for 3 days resulted in significant increases of appetite and body weight; levels of GH, IGF-1 and IGF-binding protein increased in parallel (19).

At this time, ghrelin and anamorelin are still experimental agents and are only being used in clinical trials.
2.5 Melanocortin 4 Receptor (MC4R) Antagonists (Experimental Agents)

Systemic cytokines lead to the stimulation of the central melanocortin system in the hypothalamus and result in anorexia, increased energy expenditure and loss of lean body mass. Signalling involves the MC4 receptor. Antagonists for the melanocortin type 4 receptor are being developed and tested to inhibit inflammation-associated anorexia (20). Preclinical data obtained with the MC4R antagonist BL-6020/979 show positive effects on food intake, body weight, energy expenditure, body composition and fatigue (21). At this time (2014) no clinical trials using these substances have been reported.

2.6 Cyproheptadine

Cyproheptadine is a serotonin antagonist acting as a 5-HT2 receptor antagonist.

Cyproheptadine improved diarrhoea and promoted weight gain in patients with carcinoid tumours (22). An early study in anorexic adults yielded a significant improvement in appetite and body weight with cyproheptadine (23). In a randomized double-blind trial in cancer patients with anorexia or cachexia, however, it failed to prevent weight loss compared with the placebo group, while patients receiving cyproheptadine (24 mg/d) had less nausea but also less energy and more sedation and dizziness (24). A recent study demonstrated that cyproheptadine was able to enhance body weight in children with cancer-associated cachexia; the most prominent side effect was drowsiness (25).

Thus, cyproheptadine is not recommended in adult patients with cancer cachexia except in patients with carcinoid tumours.

2.7 Branched-chain Amino Acids (BCAA)

It has been proposed that increased ventromedial hypothalamic serotonin levels might play a role in the development of anorexia. Since BCAA compete with tryptophan for the same transport system across the blood-brain barrier, it has been suggested that BCAA might slow down the entry of this serotonin precursor into the brain, lead to decreased brain tryptophan concentration and reduced serotoninergic activity and finally decreased anorexia. In a randomized controlled study in 28 cancer patients BCAA (15 g/d) consumed for 7 days prior to planned surgery resulted in reduction of anorexia in the BCAA group which was not seen in the controls (26).
In a randomized study in 84 patients undergoing chemoembolisation for hepatocellular carcinoma 41 patients received BCAA (11 g/d) for 1 year. These patients had lower rates of ascites and oedema, higher serum albumin levels and better quality of life than the control group (27).

These data are not sufficient to recommend BCAA as appetite stimulants.

2.8 Herbal Medicines, Bitters

Herbal bitters and other herbal remedies have been used in many countries to increase or stabilize appetite (28). Clinical evidence to support the use of herbal medicine is very sparse. Data from preclinical studies suggest a stimulatory effect of the herbal medicine rikkunshito on ghrelin signaling (29); this might contribute to a postulated orexigenic effect. A recent systematic review reported on 2 small randomized studies using rikkunshito in combination with anticancer chemotherapy drugs; these studies reported significant beneficial effects of rikkunshito on nausea, anorexia and food intake (30).
3. Gastrointestinal Modulators and Other Supportive Agents

Antiemetics, psychotropic drugs and analgesics may diminish the burden of nausea and emesis, anxiety, restlessness and depression, or chronic pain in cancer patients. Since these symptoms invariably will diminish or abolish appetite and food intake, it is of considerable importance for the nutritionist to be aware of their presence. Any instance of nausea, psychological distress or chronic pain should be recognized and every effort should be undertaken to relieve these barriers to a normal appetite and adequate food intake (Table 4). These agents, however, will not be discussed here in detail.

Gastrointestinal (GI) functions are of prime importance for food intake, propulsion, digestion and absorption. Dysfunction or defects may prevent an adequate uptake of energy and nutrients. Modulators of GI function may thus help to antagonize weight loss in cancer patients (Table 4).

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3.1 Prokinetic Agents

Metoclopramide (80 mg/d) has been investigated in 2 studies with a total of 55 patients (2). Both studies found an improvement in nausea but no increase in caloric intake or appetite. Erythromycin improves delayed gastric emptying by binding to motilin receptors and inducing activity of the interdigestive migratory motor complex (31). Both metoclopramide and erythromycin are frequently used as prokinetics to improve the success of enteral feeding in critically ill patients (32).

3.2 Inhibitors of Gastrointestinal Motility

Diarrhoea induced by chemotherapy agents will lead to weight loss and exsikkosis. Inhibition of intestinal transit time may diminish diarrhoea by increasing the time for reabsorption of secreted intestinal fluids. Typical agents used are opioids, calcium channel blockers, and clonidine. Topical steroids like budesonide may antagonize diarrhoea induced by toxic effects on the small intestinal mucosa as for example from the active irinotecan metabolite SN-38.

3.3 Proton Pump Inhibitors

Drugs frequently used in cancer patients, e.g. corticosteroids, NSAIDs, chemotherapy treatments and other stressors, increase the occurrence of GI ulceration, which may lead to abdominal pain, nausea, vomiting, anorexia and weight loss. Inhibition of gastric acid secretion is an effective way to allow healing of ulcerations. Proton pump inhibitors are the most powerful drugs available to achieve this end.

3.4 Parasympathomimetics

Many drugs as well as radiotherapy to the head and neck region may cause dry mouth (xerostomia). Pilocarpine is a parasympathomimetic plant alkaloid; it is a non-selective muscarinic receptor agonist and stimulates the secretion of large amounts of saliva and...
sweat. This may help to increase appetite and achieve improved conditions for chewing and swallowing.

4. Anti-inflammatory Agents

Systemic inflammation is a frequent and prognostically relevant phenomenon in patients with advanced cancer (33). An array of anti-inflammatory agents has been studied (Table 5).

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4.1 Steroids (Corticosteroids and Progestins) and Cannabinoids

See 26.4.2.1 through to 26.4.2.3

4.2 Non-Steroidal Anti-inflammatory Drugs (NSAID)

NSAIDs like indomethacin, ibuprofen and celecoxib inhibit prostaglandin production via the rate-limiting enzymes cyclo-oxygenases-1 and -2 (COX-1 and COX-2). While COX-1 is expressed constitutively in most tissues and appears to be responsible for the regulation of physiological functions, COX-2 is induced by cytokines, growth factors, and oncogenes, and it contributes to the synthesis of prostaglandins in inflamed and neoplastic tissues.

In 135 cancer patients with weight loss, indomethacin (100 mg/d) compared to prednisolone (20 mg) or placebo had no effect on body weight loss but prolonged the mean survival time considerably (34). In a single arm study ibuprofen (1200 mg/d) reduced elevated resting energy expenditure and C-reactive protein levels in 16 weight-losing pancreatic cancer patients (35). A randomized study in patients with gastrointestinal cancer and weight loss showed that ibuprofen combined with megestrol acetate (MA) increased quality of life (QoL) and body weight after 12 weeks, while patients treated with MA alone lost body weight and had no improvement in QoL (36).

Mantovani et al. studied the efficacy and safety of celecoxib (300 mg/d) for 4 months in 24 patients with cancer cachexia (37). There was no grade 3-4 toxicity and all patients could maintain the NSAID dose. There were significant improvements in lean body mass, grip strength, quality of life and performance status; TNF-α levels decreased significantly. In a small placebo-controlled study celecoxib (400 mg/d) given for 3 weeks to 11 cachectic patients with head and neck or gastrointestinal cancer significantly increased body weight and quality of life compared with placebo (38).

In a systematic review Solheim evaluated 13 clinical studies using NSAID to treat cancer cachexia (39). 7 of the 13 studies were one-arm studies without a comparator and most studies had serious limitations to study quality; however, 11 of the 13 studies reported beneficial effects on weight or lean body mass and only negligible side effects. Solheim et al. concluded that NSAID may improve weight in cancer patients with cachexia but that the evidence is too frail to recommend these drugs for the treatment of cachexia outside clinical trials.

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4.3 n-3 Fatty Acids (EPA, DHA)

Fish oil is particularly rich in long-chain n-3 polyunsaturated fatty acids including eicosapentaenoic (EPA; C20:5; n-3) and docosahexaenoic (DHA; C22:6; n-3) acids. These undergo biological transformation by cyclooxygenases (COX) to produce eicosanoids, which alter the production of inflammatory mediators including cytokines. EPA is a competitive antagonist of arachidonic acid and is transformed to less pro-inflammatory eicosanoids. Thus EPA may decrease inflammatory status.

Several RCT have studied the effects of n-3 fatty acids on cancer cachexia. In 2007 2 systematic reviews were published on 5 RCT (40) and on 17 clinical trials and prospective studies (41). The Cochrane Review concluded that there were insufficient data to conclude that oral EPA was better than placebo. The analyzed RCT, however, were hampered by poor patient compliance and short trial durations. The other review concluded, that oral n-3 fatty acids at a dose above 1.5 g/d increase body weight and appetite, improve QoL and reduce post-surgical morbidity. The levels of evidence for these conclusions, however, were grade B and C.

More recently, results from three further prospective trials have been reported. Van der Meij et al. in a randomized double-blind 4 week study compared two oral nutritional supplements with or without n-3 fatty acids (2 g/d of EPA plus 0.9 g/d DHA) in 40 patients with stage III non-small cell lung cancer undergoing multimodal cancer therapy (42). Patients receiving n-3 fatty acids lost significantly less weight and lean body mass; had lower resting energy expenditure and a higher energy and protein intake.

Murphy et al. used a non-randomized design and offered fish oil supplements (2.2 g/d EPA) to 40 patients with advanced non-small cell lung cancer undergoing first-line chemotherapy. 16 patients who accepted the offer to take fish oil maintained weight and muscle mass, while 24 patients who declined the offer lost weight (43). In a second study, of 46 patients with advanced non-small cell lung cancer undergoing chemotherapy 15 patients accepted the offer to consume fish oil (2.5 g/d of EPA+DHA); these patients had significantly better response rates to chemotherapy when compared to patients who chose not to take fish oil (44).

While well designed clinical trials reporting on effects of n-3 fatty acids on clinical outcome in cachectic cancer patients are lacking, the results of these recent trials are promising, and side effects of fish oil and n-3 fatty acids are minor. Thus, the decision to recommend supplements of n-3 fatty acids needs to be made on an individual basis.

4.4 Anti-interleukin 6 Antibodies (Experimental Agents)

Interleukin 6 (IL-6) is a major mediator of the acute phase response. IL-6 is associated with poor prognosis in patients with lung cancer and correlates with symptoms such as fatigue and cachexia (45).

The monoclonal antibody ALD518 targets IL-6 and is undergoing clinical testing in phase I and II trials with a focus on non-small cell lung cancer (NSCLC). It appears well tolerated and ameliorates NSCLC-related anaemia and cachexia (45).

Ando described a patient suffering from large-cell lung cancer, severe weight loss and an exaggerated inflammatory response, including elevated levels of IL-6 (46). After initiating treatment with tocilizumab anti-IL-6 receptor antibody, CRP levels normalized and appetite improved rapidly; during the following weeks albumin and body weight improved considerably and the overall condition could be stabilized for 9 months until the tumour progressed. Hirata et al. reported on 2 further patients with cancer-related cachexia who responded favourably to tocilizumab (47).
4.5 Anti-cytokine Agents

Pro-inflammatory cytokines mediate many of the metabolic derangements observed in cancer cachexia (48)(49)(50). Different strategies to suppress or block cytokines have been followed.

4.5.1 TNF-binding Agents

Tumour necrosis factor alpha (TNF-α) is a prominent pro-inflammatory cytokine involved both in survival and inducing cachexia (51)(52). In a randomized controlled study 89 patients with pancreatic cancer cachexia were treated for 8 weeks in addition to gemcitabine with 2 different doses of the anti-TNF-α monoclonal antibody (infliximab) or with placebo (53). At 8 weeks no significant differences were observed for changes in lean body mass or any of the secondary endpoints of overall or progression-free survival, performance status and quality of life.

The dimeric fusion protein etanercept binds to and neutralizes TNF-α. In a randomized controlled study 63 anorectic or weight-losing cancer patients were treated with etanercept or placebo for up to 3 months. Medication was injected twice weekly. Treatment with etanercept was associated with higher rates of neurotoxicity but lower rates of neutropenia or thrombocytopenia. Weight gain and changes in appetite were minimal and similar in both groups; median survival did not differ between groups (54).

Thus, use of TNF-binding agents currently cannot be recommended.

4.5.2 Pentoxifylline

The methylxanthine derivative pentoxifylline is a competitive non-selective phosphodiesterase inhibitor that suppresses TNF synthesis by decreasing gene transcription. In a double-blind placebo-controlled randomized study pentoxifylline (1200 mg/d) was compared to placebo in 70 anorectic or weight-losing cancer patients (55). Pentoxifylline failed to improve appetite, weight or subjective perception of benefit.

4.5.3 Thalidomide

Thalidomide is an anti-TNF agent. It inhibits the production of TNF-α by human macrophages by accelerating the degradation of TNF messenger RNA transcripts. In randomized studies thalidomide was shown to halt and reverse weight loss in AIDS associated cachexia (56).

Bruera et al. treated 72 anorectic or weight losing patients with advanced cancer with thalidomide (100 mg/d given at night) for 10 days. In 37 evaluable patients there was an improvement of anorexia, nausea, insomnia and well-being (56).

In an open-label study (57) 10 patients with inoperable oesophageal cancer were observed during 2 weeks of isocaloric diet and received additional treatment with thalidomide (200 mg/d) during the 2 subsequent weeks. Nine of the 10 patients lost weight during the first 2 weeks, while 8 of the patients gained weight during the second 2 weeks. A similar trend was recorded for lean body mass.

In a placebo-controlled trial 50 patients with advanced pancreatic cancer who had lost ≥10% of their body weight were randomized to receive thalidomide (200 g/d) or placebo for 24 weeks. 33 patients were evaluable at 4 weeks. Patients who received thalidomide had gained weight and arm muscle mass, while controls had lost both weight and arm muscle mass. The difference between groups increased at 8 weeks (58).

However, in 2012 a Cochrane review concluded that there is insufficient evidence to make an informed decision about thalidomide for the management of cancer cachexia.
(59). Thalidomide is teratogenic and in clinical use is associated with frequent and potentially severe side-effects, like peripheral neuropathy, fatigue and constipation, thromboembolism, pulmonary oedema, atelectasis, aspiration pneumonia, hypotension and renal insufficiency. Thus, despite the promising results on weight and muscle mass thalidomide treatment is not currently considered to be a standard of care.

4.6 Antibiotics: Clarithromycin

A single centre has reported on beneficial effects of the macrolide antibiotic clarithromycin in patients with advanced non-small cell lung cancer. Increased median survival was observed in patients treated with clarithromycin, and a cohort study was subsequently conducted. 33 patients with unresectable non-small cell lung cancer receiving clarithromycin for 3 months were compared with matched controls not receiving the macrolide. After 3 months the patients receiving clarithromycin had a significant decrease in interleukin 6 levels and an increase in body weight. Change in body weight correlated inversely with the change in interleukin 6. These parameters did not change in the control group (60).

This study supports the concept of antagonizing inflammation in advanced cancer; however, these data are not sufficient to recommend the routine use of clarithromycin.

4.7 Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a naturally occurring compound found in animals, plants and microbes. In mammals melatonin is secreted into the blood by the pineal gland in a diurnal rhythm. It has effects on the circadian rhythm and both natural and adaptive immune functions. Many biological effects are produced through activation of melatonin receptors, while others are due to its role as a powerful antioxidant (61).

Melatonin has been implicated in cancer prevention and in reducing the risk of death in cancer patients (62). In a randomized study in 100 patients with advanced cancer supportive care was compared to supportive care plus melatonin (20 mg/d at night) for 3 months (63). In 86 evaluable patients weight loss ≥10% occurred less often with melatonin treatment, while there was no difference in food intake. In the melatonin group TNF-α levels decreased significantly during the study period.

The same centre subsequently studied overall survival in patients with metastatic non-small cell lung cancer. 100 consecutive patients received in randomized order either chemotherapy or chemotherapy plus melatonin (20 mg/d at night). Chemotherapy response rates were improved and 5-year survival was significantly better with melatonin (6%) than without melatonin (0%) (64).

A systematic review and meta-analysis included 10 RCT (with a total of 643 patients) of melatonin in solid tumour cancer patients (62). All studies were performed in the same hospital network and all trials were unblinded. Melatonin significantly reduced the risk of death at 1 year by 34%. Effects were consistent across melatonin dose and tumour type. No severe adverse events were reported.

Unfortunately, all the trials in advanced cancer patients were from the same institution. Since confirmatory reports are still lacking, melatonin has not entered standard treatment protocols.

4.8 Antioxidants

Oxidative stress has been implicated in cancer initiation and progression (65). In addition, cancer-associated inflammation promotes production of reactive oxygen species. Thus, antioxidants have proposed to be beneficial in states of advanced cancer.
However, no reliable randomized studies have been published to judge the effect of antioxidants in cancer.

5. Anticatabolic and Anabolic Agents

A number of endogenous and exogenous agents are being used or investigated to inhibit proteolysis or to stimulate protein synthesis. The aim is to diminish loss and to initiate gain of muscle and lean body mass (Table 6).

<table>
<thead>
<tr>
<th>Anti-catabolic and anabolic agents</th>
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<tr>
<td>Insulin and insulin sensitivity modulators</td>
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<td>Growth hormone, GH secretagogues, IGF-1</td>
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<td>Anti-myostatin antibodies</td>
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5.1 Insulin and Insulin Sensitivity Modulators

Administration of insulin to cancer patients has resulted in a decreased whole body protein breakdown rate (67) and in an appropriate response of muscle protein synthesis (68), while there was resistance to the effect of insulin on glucose metabolism.

In a randomized study in 338 patients with cancer cachexia daily insulin treatment (0.11 IU/kg/d) in addition to basic supportive care increased whole body fat (but not lean body mass), improved metabolic efficiency during exercise (but not maximum exercise capacity or spontaneous physical activity) and improved overall survival (69).

Metformin activates AMP-activated protein kinase (AMPK) in the liver and in the muscle and thus increases insulin sensitivity (70). Metformin has been suggested as a novel anticancer agent (71). In patients with severe burn injury metformin has been shown to increase protein synthesis (72). Therefore, further study of this agent in cancer cachexia with associated systemic inflammation and insulin resistance is warranted.

5.2 Growth Hormone (GH), GH Secretagogues and IGF-1

Growth hormone (GH) is a polypeptide hormone, which stimulates growth, cell reproduction and regeneration in humans and other animals. In recent years, replacement therapies with GH have become popular in the battle against aging and in weight management. Reported effects on GH deficient patients (but not on healthy people) include decreased body fat, increased muscle mass, increased bone density, increased energy levels, improved skin tone and texture, increased sexual function and improved immune system function. As an anabolic agent, GH has been used by competitors in sports since the 1970s, and it has been banned by the IOC and NCAA.

There is concern regarding the use of growth hormones because of the possible stimulation of tumour growth. Preclinical data have not shown tumour progression (73); however valid clinical data are lacking.

A large randomized clinical trial including 552 critically ill adults demonstrated increased mortality for growth hormone treatment (0.1 mg/kg/d for 21 days) compared to placebo.
Since GH increases cytokine concentration in normal tissues it has been speculated that GH may complicate conditions in already compromised patients (75).

Ghrelin is a secretagogue, acting via the GH secretagogue receptor, a G protein-coupled receptor. For ghrelin see 26.4.2.4.

Insulin-like growth factor 1 (IGF-1) is an anabolic hormone similar in structure to insulin. IGF-1 is produced primarily by the liver as an endocrine hormone as well as in target tissues in a paracrine/autocrine fashion. Production is stimulated by GH. Recently, IGF-1 has been linked to tumour development and progression (76). Because of its anabolic effects, IGF-1 has been proposed for cachexia treatment (77), however, most current activities are aimed at introducing ghrelin and its oral analogues into cachexia treatment.

### 5.3 Anabolic-androgenic Steroids and SARMs (Selective Androgen Receptor Modulators)

Anabolic steroids or anabolic-androgenic steroids (AAS) are drugs which mimic the effects of the male sex hormones testosterone and dihydrotestosterone. They increase protein synthesis within cells, especially in muscle. Anabolic steroids also have androgenic and virilizing properties. In patients with advanced cancer decreased free testosterone levels are frequently observed.

In a randomized study 37 patients with advanced non-small cell lung cancer undergoing chemotherapy were treated with nandrolone decanoate (200 mg/week) or no additional steroid for 4 weeks. A trend for less weight loss was observed in the nandrolone group (78). Fluoxymesterone (20 m/d) was compared to megestrol acetate (800 mg/d) and dexamethasone (3 mg/d) in a RCT including 475 patients with cancer cachexia (8). The androgenic steroid resulted in less appetite stimulation than the other agents, while the rate of drug discontinuation because of toxicity was similar. Recently treatment with oxandrolone (20 mg/d) was compared to megestrol acetate (800 mg/d) in a randomized phase III study including 155 weight-losing patients with solid tumours receiving chemotherapy. Only 50% of patients remained in the study for the planned treatment period of 12 weeks. Patients treated with oxandrolone still lost weight but experienced an increase in lean body mass, a reduction in fat mass and reduced self-reported anorectic symptoms (7).

Selective androgen receptor modulators (SARM) have been developed for treatment of muscle wasting and osteoporosis. The oral SARM enobosarm (Ostarine) was tested in phase II clinical trials in elderly women and men and compared to placebo; it resulted in improved lean body mass and muscle function; the safety profile was favourable and no serious adverse events were reported (79).

Recently, Dobs et al. published a double-blind randomized study in 100 weight-losing cancer patients comparing two doses of enobosarm with placebo given for 113 days. Both enobosarm doses (1 and 3 mg/d) improved lean body mass, while placebo treatment did not; in addition, enobosarm improved muscle function as measured by stair-climbing power (80).

Two large randomized phase 3 trials have been designed to study the effects of enobosarm on muscle wasting in patients with non-small cell lung cancer undergoing combination chemotherapy treatment (GTx company). In 2014 preliminary data were presented (15th World Conference on Lung Cancer): enobosarm resulted in better maintenance/improvement of LBM and in better muscle function (measured as stair climb power) than placebo.

SARM are promising agents for future treatment of cancer cachexia; they might also be good candidates for combination with other anticachectic agents.
5.4 Amino Acids and Metabolites

In-vitro and in-vivo work has demonstrated anti-catabolic effects of leucine and its metabolite α-ketoisocaproate (81). Because of discrepancies between in-vitro and in-vivo studies, Abumrad and coworkers postulated that a further leucine metabolite, the ketone body β-hydroxy β-methylbutyrate (HMB), may be responsible for the leucine inhibitory effect on protein breakdown (70). HMB inhibits proteolysis in vitro possibly via the mTOR and proteasome pathways (82). In volunteers during resistance exercise training for 2-7 weeks, HMB supplementation (3 g/d) decreased exercise-induced muscle proteolysis and increased free mass (70).

To increase anabolic effects, HMB has been supplemented in combination with glutamine and arginine, and this nutrient mixture has been investigated in several randomized trials. In 43 patients with HIV-associated wasting 8 weeks of treatment with HMB (3 g/d) plus L-glutamine (14 g/d) plus L-arginine (14 g/d) resulted in more gain of weight and lean body mass than placebo (83). The same mixture, however, was no more effective than a mixture of 5 other amino acids in 40 patients with rheumatoid cachexia (84).

The same mixture and doses of HMB/glutamine/arginine were compared in a RCT to an isonitrogenous mixture of non-essential amino acids in 32 patients with cancer cachexia; after 4 and after 24 weeks HMB/glutamine/arginine improved lean body mass, while the control group lost lean body mass (85). A subsequent larger RCT including 472 patients with cancer cachexia, however, could not detect any positive effects on lean body mass when comparing the same combination of HMB/glutamine/arginine with an isonitrogenous control mixture (86), perhaps because compliance with the protocol was low, only 37% of the patients completing the planned 8-week course of treatment.

More recently, HMB has been studied in a small group (N=24) of healthy elderly subjects undergoing a 10 day period of bed rest. Using a randomized trial design, daily supplementation with 3 g/d HMB when compared to an inactive placebo powder prevented the decrease of lean body mass induced by bed rest (87).

Deutz et al. have investigated the effect of protein and leucine dose in a randomized clinical trial. In a small group (N=25) of cancer patients in an inflammatory state, consumption of a high-protein (40 g/d, including 4 g/d free leucine) oral nutritional supplement compared to a control supplement (24 g/d protein) resulted in increased plasma leucine levels and an increase in the fractional rate of muscle protein synthesis (88).

Thus, there is accumulating evidence that protein, and especially leucine and its metabolite HMB, may support muscle mass by increasing synthetic rate and/or decreasing protein breakdown. Even though these mechanisms appear plausible, more solid evidence from high-quality studies in cancer patients is required before the use of leucine and HMB can be generally recommended.

5.5 Experimental Agents

5.5.1 Anti-myostatin Antibodies

Myostatin is a member of the transforming growth factor-β superfamily and downregulates skeletal muscle mass by binding to the activin A receptor IIB (Act RIIB). Myostatin levels are increased in tumour-bearing rats and thus might be a therapeutic target in cancer cachexia (89). In a mouse model injection of the myostatin binding soluble Act RIIB after tumour cell implantation resulted in reversal of tumour-induced weight loss and improved survival.

At this time (2014), two myostatin antibodies are undergoing phase 2 multi-centre randomized double-blind clinical trials to assess anabolic effects in weight-losing cancer patients with cancer cachexia.
patients. BYM338 is being tested in patients with pancreatic or lung cancer (NCT01433263), and LY2495655 in patients with advanced pancreatic cancer receiving gemcitabine chemotherapy (NCT01505530).

5.5.2 Selumetinib

Induction of muscle anabolism by physical activity occurs by pathways involving RAF, MEK and MAPK/ERK kinases (90). The anti-cancer agent selumetinib is a MEK inhibitor, has tumour suppressive activity and has been shown to inhibit IL-6 production. In a phase II trial, retrospective analysis of skeletal muscle mass demonstrated that patients with cholangiocellular carcinoma were markedly catabolic and lost muscle mass when undergoing standard treatment, but gained muscle mass when treated with selumetinib (90). It is not known whether interaction with IL-6 synthesis or other processes are responsible for the anabolic effect. Further investigation of these beneficial effects is required.

5.5.3 Interleukin 15

The cytokine IL-15 shares biological activities with IL-2, but is not produced by activated T cells but by skeletal muscle, kidney, lung and heart. IL-15 favours muscle fibre hypertrophy and partly inhibits muscle wasting in tumour-bearing rats (91). Overexpression of IL-15 induces skeletal muscle hypertrophy accompanied by increased levels of sarcomeric myosin heavy chain and alpha-actin in the culture of differentiated myotubes. IL-15 stimulates protein synthesis as well as inhibiting protein degradation (92). No clinical trials using IL-15 have yet been reported.

5.6 Proteasome Inhibitors (Bortezomib)

Bortezomib is an inhibitor of NFkB and ubiquitin-proteasome. In mice with cancer cachexia pharmacological inhibition of NF-κB and MAPK, but not of the proteasome system, induced a substantial restoration of muscle mass and force (93).

Although potentially promising, preliminary results showed negligible effects from this compound on cancer-related weight loss in patients with metastatic pancreatic cancer. The authors concluded that further study of bortezomib in this setting and for this indication were not warranted (94).

5.7 ß-Adrenergic Receptor Modulators

ß-Adrenergic receptors are involved in anabolic signaling, with effects on skeletal muscle (95) which may increase body cell mass, and they affect resting energy expenditure which may promote weight loss.

Hyltander et al. (96) studied resting energy expenditure (REE) in 10 weight-losing cancer patients. Treatment with a selective ß1-antagonist (atenolol) as well as with a non-specific ß1,ß2-adrenoreceptor (propranolol) antagonist reduced REE; part of this reduction was explained by a decline in heart rate. Propranolol dosing to decrease the resting heart rate by 20% improved muscle protein balance in 25 children with acute and severe burns (97).

Administration of the ß2-agonist formoterol to both rats and mice bearing highly cachectic tumours resulted in a reversal of the muscle wasting process (98). Recently, in a small group of frail, comorbid patients with advanced cancer and involuntary weight loss, intake of formoterol in combination with the progestin megestrolacetate for 8 weeks resulted in an increase in quadriceps and hand grip strength (99). Further investigation of this concept appears warranted.
Because both β-receptor agonists and antagonists have been proposed possibly to improve weight and muscle mass, further studies are required to establish the balance of wanted and unwanted effects.

5.8 Hydrazine Sulfate

Hydrazine is a non-competitive inhibitor of phosphoenolpyruvate carboxykinase, one of the enzymes needed for gluconeogenesis. Gold proposed that inhibiting gluconeogenesis would stop host energy-loss and thus development of cachexia (100). In a randomized placebo-controlled study in 38 weight-losing cancer patients hydrazine sulfate (180 mg/d) for 30 days resulted in a decrease in glucose production and improved glucose tolerance (101).

Five randomized placebo-controlled studies were published from 1987 to 1994 reporting on the effects of hydrazine sulfate (180 mg/d) on appetite and body weight in advanced cancer patients. One 30-day study in 101 patients observed an improvement in appetite and body weight with hydrazine (102). Of the long-term studies, another trial by Chlebowski et al. in 65 patients reported higher caloric intake in the hydrazine group, but no other benefit (102), while none of the other trials found any benefit of hydrazine treatment on appetite or weight. In fact, 2 studies (a total of 370 patients) reported a trend for poorer survival in the hydrazine group (103)(104) and 1 study (266 patients) reported significantly poorer quality of life in the hydrazine group.

Hydrazine is toxic and carcinogenic; short-term effects are usually mild and include minor nausea, vomiting, dizziness, excitement, and polyneuritis; however, in rare cases fatal liver and kidney failure and severe neurotoxicity were reported.

Hydrazine is not recommended for treatment of anorexia or cachexia.

5.9 Adenosine 5’-triphosphate (ATP)

Adenosine 5’-triphosphate is a naturally occurring nucleoside triphosphate that plays a central role as an energy source in every cell of the human body. Extracellular ATP is involved in the regulation of a variety of biological processes. In non-randomized studies involving patients with different tumour types, ATP infusions appeared to inhibit loss of weight and deterioration of quality of life and performance status.

Agteresch et al. (105) randomly assigned 58 patients with non-small cell lung cancer to receive intravenous 30-hour infusions of ATP every 2 to 4 weeks or no ATP. After 28 weeks, patients who received ATP retained their original weight, while the control group lost 1 kg per month (105). In addition, muscle strength and quality of life scores were more favourable in the ATP-treated group. In weight-losing patients overall survival was significant longer in patients receiving ATP (102).

Beijer et al. randomly allocated 99 preterminal cancer patients to receive either intravenous ATP weekly for 8 weeks or no ATP. Triceps skinfold thickness and 8-week survival was significantly better in the ATP treated patients (106), while there was no improvement in quality of life, functional status or fatigue (107).

Side effects of ATP infusions are tolerable and include dyspnoea, chest discomfort and the urge to take a deep breath. All studies on ATP were performed by one study group. ATP is a promising agent but is not recommended outside clinical trials.

6. Short Summary of the Module
Anorexia, gastrointestinal dysfunction, systemic inflammatory processes and a prevalence of catabolic signals are prognostically relevant factors in advanced cancer. Of the factors studied so far the following agents have been shown to be effective in certain circumstances: corticosteroids, progesterins, insulin, NSAIDs and N-3 fatty acids. Other promising agents are under investigation.

7. References


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