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TOPIC HIGHLIGHT

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Cachexia and pancreatic cancer: Are there treatment options?

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Abstract

Cachexia is frequently described in patients with pancreatic ductal adenocarcinoma (PDAC) and is associated with reduced survival and quality of life. Unfortunately, the therapeutic options of this multi-factorial and complex syndrome are limited. This is due to the fact that, despite extensive preclinical and clinical research, the underlying pathological mechanisms leading to PDAC-associated cachexia are still not fully understood. Furthermore, there is still a lack of consensus on the definition of cachexia, which complicates the standardization of diagnosis and treatment as well as the analysis of the current literature. In order to provide an efficient therapy for cachexia, an early and reliable diagnosis and consistent monitoring is required, which can be challenging especially in obese patients. Although many substances have been tested in clinical and preclinical settings, so far none of them have been proven to have a long-term effect in ameliorating cancer-associated cachexia. However, recent studies have demonstrated that multidimensional therapeutic modalities are able to alleviate pancreatic cancer-associated cachexia and ultimately improve patients' outcome. In this current review, we propose a stepwise and pragmatic approach to facilitate and standardize the treatment of cachexia in pancreatic cancer patients. This strategy consists of nutritional, dietary, pharmacological, physical and psychological methods.

Key words: Cachexia; Pancreatic neoplasms; Nutritional support; Gastrointestinal neoplasms

Core tip: Cachexia in pancreatic cancer is frequently described and reduces survival and quality of life of the concerned patients. Despite intense pre-clinical and clinical research activities, there are still no pharmaceutical agents with proven effectiveness in the long term. Furthermore, it is evident that only multimodal concepts can improve patients' outcome. Therefore, the current pharmacological and nutritional therapy options are reviewed and a stepwise and pragmatic approach will be presented to facilitate and standardize the treatment of cachexia in pancreatic cancer patients. This strategy combines nutritional, dietary, pharmacological and as well physical and psychological methods.

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INTRODUCTION

Cachexia, definition and diagnostic criteria

Cachexia is a multi-factorial, systemic syndrome characterized by pathological weight loss due to excessive wasting of skeletal muscle and adipose tissue mass. It can occur in the course of chronic benign diseases like chronic heart failure or chronic obstructive pulmonary disease (COPD) as well as in the course of infectious diseases like tuberculosis or human immunodeficiency virus (H IV)-infection. However, it is most frequently observed concomitantly with malignancies, especially in pancreatic- and lung cancer. The mechanisms that lead to cachexia are still poorly understood, but consensus is that is has to be regarded as a complex of multiple, interactive patient- and tumor-specific components, such as metabolic and humoral changes as well as psychological issues, anorexia, fatigue and adverse effects of anticancer therapies (Figure 1).

In cancer patients, the presence of cachexia is associated with poor prognosis, reduced treatment tolerance and a marked reduction in quality of life (QoL)[1,2]. Therefore, the preservation of lean body mass (LBM) is critical for cancer patients, but despite all efforts an effective treatment for cachexia is still lacking.

The diagnostic criteria for cancer cachexia are still not very strictly defined. In addition, weight loss is multi-factorial and can be difficult to assess. In particular the loss of skeletal muscle tissue can be hard to quantify, especially in obese individuals. These problems combined with the use of different diagnostic criteria by different research groups in the past, has led to heterogeneity in clinical and experimental trials. Therefore, an international consensus regarding the definition of cachexia was made in 2011. According to this consensus, cachexia is defined by unintended weight loss of more than 5% of body weight or weight loss of more than 2% in individuals with a body mass index (BMI) of less than 20 kg/m^2, over 6 mo. Additionally, the presence of sarcopenia (skeletal muscle depletion) with any degree of weight loss of more than 2% should be classified as cachexia[3]. Sarcopenia can be detected by the following methods of assessment: anthropometry of mid-upper-arm muscle area (men < 32 cm^2, women < 18 cm^2), appendicular skeletal muscle index determined by dual-energy X-ray absorptiometry (men < 7.26 kg/m^2, women < 5.45 kg/m^2), lumbar skeletal-muscle index determined from oncology computed tomography (CT) imaging (men < 55 cm^2/m^2, women < 39 cm^2/m^2), and whole-body fat-free mass index without bone determined by bioelectrical impedance (men < 14.6 kg/m^2, women < 11.4 kg/m^2)[4].

Furthermore, reduced food intake, anorexia, markers of systemic inflammation like C-reactive protein (CRP), responsiveness to chemotherapy and disease progression should be assessed for the diagnosis of cancer cachexia[2,3]. However, studies published after 2011 still frequently use their own diagnostic criteria or cut off values for cachexia. New techniques, like measuring different body tissue masses based on a CT-scan may ultimately facilitate the standardization of diagnosis of cachexia in the future[5]. Furthermore, this method allows for the quantification of occult tissue loss in muscle, subcutaneous- and visceral adipose tissue (VAT), even in obese patients. It has been shown that not only the degree of weight loss impacts survival of pancreatic cancer patients, but also the proportion of muscle and fat loss in the different compartments[6,7]. To perform the assessment, cross-sectional areas of the left and right psoas muscles at the level of the fourth lumbar vertebra (L4) can be used. The surface is usually expressed in square millimeter[8]. Studies using these CT-image based techniques show that the loss of muscle tissue is particularly associated with a shorter survival in cancer patients[5]. Congruently, a recent study in which body tissue mass was measured by CT scans in pancreatic cancer patients, was able to show that sarcopenia in obese patients is an occult condition, associated with a shorter survival[7].

Cachexia in pancreatic cancer: incidence, impact on prognosis and outcome

In Western countries, pancreatic ductal adenocarcinoma (PDAC) is among the top five causes of cancer deaths[9]. Unfavorable prognosis of this cancer entity can be attributed to late diagnosis and aggressive tumor biology and affection other organ systems due to the function and anatomical location of the pancreas. Furthermore, among all malignancies patients with PDAC have the highest incidence of cancer cachexia and experience severe symptoms of this syndrome[6,10-13]. Cachexia has been shown to be present in up to 70%-80% of patients with PDAC and is associated with reduced survival, more progressive disease and higher rates of metastatic disease[12-15]. The presence of cachexia was shown to worsen the post-operative outcome of patients with pancreatic cancer[15,16]. However, currently the only hope for cure of pancreatic cancer is the complete surgical resection of the tumor, which is only possible in non-metastatic and locally restricted stages.

Especially the loss and the rate of loss of VAT tissue seems to be correlated with a worse prognosis in pancreatic cancer patients, possibly due to the metabolic activity of this tissue[17]. Moreover, an association of VAT-loss with the presence of diabetes and anemia was observed in these patients[6]. Alterations in metabolism and a systemic inflammatory reaction contribute largely to the wasting of muscle and adipose tissue in pancreatic cancer. A central role in the development and regulation of cachexia in pancreatic cancer is attributed to the inflammatory response in the liver[18]. The acute phase response in the liver is characterized by the production of inflammatory compounds like CRP as well as the *de novo* synthesis of pro-inflammatory cytokines like interleukin (IL)-6, IL-1β, IL-8 and tumor necrosis factor (TNF)-α. Additionally, high quantities of these cytokines are produced by peripheral mononuclear cells and pancreatic cancer cells[18,19]. These pro-inflammatory mediators not

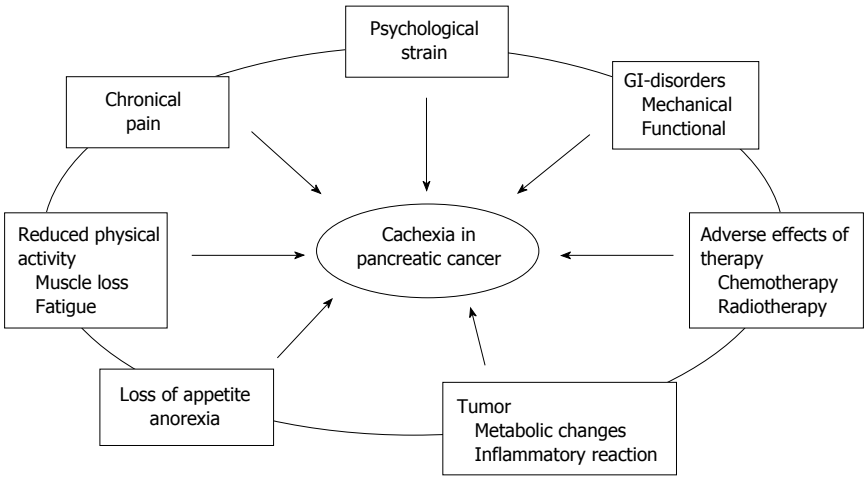

Figure 1 Multifactorial genesis of cachexia in pancreatic cancer. GI: Gastrointestinal.

only maintain the acute phase response in the liver, but also have effects on the central nervous system that lead to anorexia and fatigue. It was shown that patients with progressive weight loss exhibit increased levels of pro-inflammatory cytokines, which enhance lipid and protein catabolism whereas anabolic pathways [*e.g.*, IGF-1/Akt/mammalian target of rapamycin (mTOR)] seem to be inhibited[6,19-21]. In pancreatic cancer patients, elevated levels of these cytokines were associated with poor performance status and weight loss[22]. Accordingly, IL-1 and IL-6 gene polymorphisms have been shown to be associated with a higher incidence of cachexia and shortened survival in pancreatic cancer patients[23].

Moreover, neuro-endocrine hormones (*e.g.*, leptin, neuropeptide Y, corticotropin-releasing factor, melanocortin, neurotensin) and tumor-derived factors such as proteolysis-inducing factor or lipid mobilizing factor contribute to tissue catabolism and appetite regulation in a complex interaction which is not yet fully understood[12]. Finally, secondary symptoms of pancreatic cancer like chronic pain, nausea and pancreatic insufficiency additionally reduce appetite and food intake[24].

CURRENT TREATMENT OPTIONS OF CACHEXIA IN PANCREATIC CANCER PATIENTS

As mentioned above, the best way to treat pancreatic cancer patients is to surgically resect the tumor. However, less than 15% of patients are eligible for surgery at first presentation[25], and only approximately 70% of these tumors are fully resectable at the operation[14]. Palliative treatment of non-resectable pancreatic cancer consists of chemotherapy, radiotherapy (not routinely) and supportive care. An essential element of supportive care is the preservation of QoL. It was shown that cachexia substantially reduces QoL in pancreatic cancer patients. In addition, cachexia is exacerbated by systemic chemotherapy and decreases its tolerance[4,10]. Hence, treating cachexia and stabilizing weight can be crucial for patients with pancreatic cancer and may prolong their survival[23].

In consistency with the multi-factorial pathogenesis of cachexia in pancreatic cancer, it is widely recognized that a multimodal treatment approach is necessary[1]. This includes nutritional support and exercise as measures to stabilize weight, as well as pharmacological treatment of inflammatory and metabolic changes, and the treatment of secondary symptoms that exacerbate cachexia such as loss of appetite, mechanical or functional impairment of the gastrointestinal tract, chronic pain, fatigue and depression[4].

However, there is currently no guideline on clinical management of cachexia in pancreatic cancer and - albeit extensive research - there is still no successful pharmacological treatment. In the following paragraphs, current treatment options will be discussed and a multimodal, stepwise approach will be presented (Figure 2).

Nutritional support for cachectic pancreatic cancer patients

Supportive nutrition and caloric supplementation are important components of supportive care for cachectic patients with pancreatic cancer[26]. Preferably nutrition should be delivered enteral to avoid the side effects of parenteral nutrition[27]. Cachectic patients should be supplemented with 1000-1500 calories per day (20-25 kcal/kg per day for bedridden and 25-30 kcal/kg per day for ambulatory patients) in form of a balanced essential amino-acid mixture, given between meals[27,28]. For an adequate enteral function, it is important that vitamin D and exocrine pancreatic insufficiency are treated by supplementation[26,28]. For a sufficient supplementation 2000 IE of pancreatic enzymes are needed per 1g of fat. Furthermore, other concomitant symptoms that affect appetite and food intake, like mechanical or functional gastrointestinal disorders as well as depression and fatigue need to be addressed.

Recent studies demonstrate a clear benefit of nutritional supplementation for patients with pancreatic can-

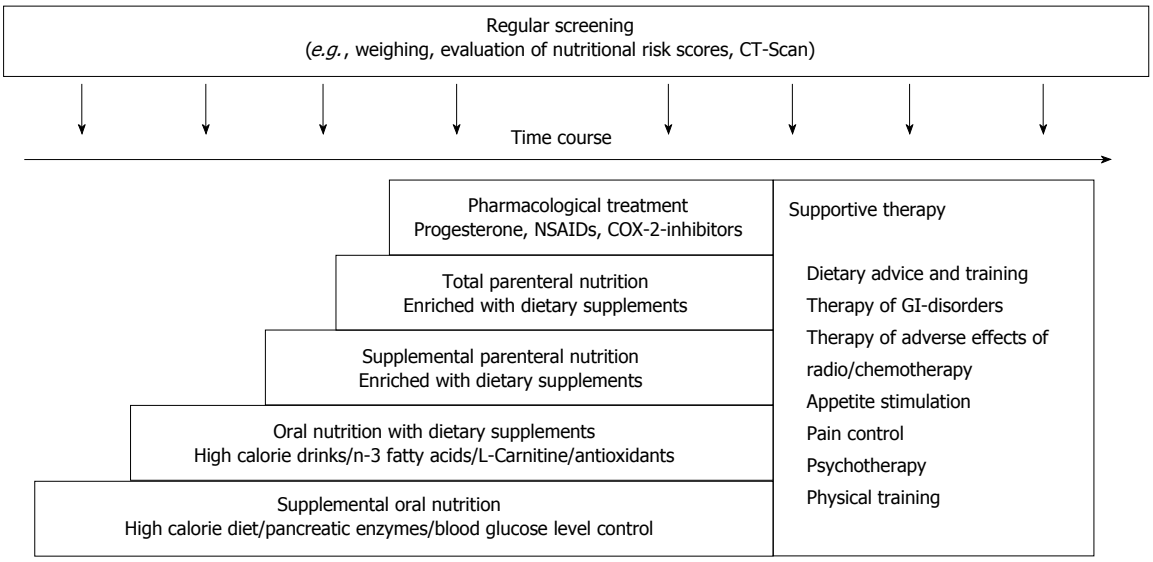

Figure 2 A stepwise, clinical approach for the treatment of cachexia in pancreatic cancer patients. GI: Gastrointestinal; NSAIDs: Non-steroidal anti-inflammatory drugs; COX-2: Cyclooxygenase-2; CT: Computed tomography.

cer. For example, a study using CT-imaging to monitor body tissue loss showed that independent of the disease stage, pancreatic cancer patients who received any type of nutritional supplementation lost less muscle tissue compared to those receiving no nutritional supplementation. Moreover, survival time was increased in patients which received nutritional supplementation[6]. However, the number of patients included in this study was low and a variety of different nutritional products were used. Another study of palliative pancreatic cancer patients demonstrated that compliance with oral nutrition prescription improved energy/protein intake and weight stabilization[29]. Furthermore, it was shown that nutrition intervention together with chemotherapy improved outcomes and QoL of patients with pancreatic or lung cancer, without inhibiting meal intake[30]. Additional parenteral nutrition for cachectic pancreatic cancer patients also showed improvements in BMI, phase angle and ratio of extracellular mass to body cell mass[31].

However, to which extend or in which combination oral or parenteral nutritional support should be provided is still under extensive discussion. According to the ESPEN-guidelines (European Society for Clinical Nutrition and Metabolism) parenteral nutritional support is indicated if inadequate food and enteral intake (< 60% of estimated energy expenditure) is anticipated for more than 10 d. Other indications are severe mucositis, radiation enteritis or intestinal failure and peri-operative support of cachectic patients. Parenteral nutrition should not be used and is probably harmful in well-nourished patients with adequate oral food intake[27].

DIETARY SUPPLEMENTS AND CANCER CACHEXIA

In addition to the simple supplementation of calories, specific nutrients can be administered to fight cachexia in pancreatic cancer patients. The most frequently tested dietary supplements in the treatment of cancer cachexia are summarized in Table 1.

N3-fatty acids like eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), which are largely contained in fish oil, have been studied intensively as additional treatment for cancer cachexia[32-35]. N3- or omega-3 polyunsaturated fatty acids have been shown to modulate levels of pro-inflammatory cytokines, hepatic acute phase proteins, eicosanoids, and tumor-derived factors in animal models of cancer cachexia[12]. EPA and DHA are metabolized by cyclooxygenase (COX) and 5-lipoxygenase yielding in metabolites with less inflammatory and immunosuppressant potency than the substances derived from arachidonic acid[12]. Moreover, it was shown that EPA induced apoptosis in three different pancreatic cancer cell lines and inhibited cell growth in a dose-dependent manner[36]. N3-fatty acids are meanwhile ingredients of most enteral and in some parenteral supplements. However, in oral nutritional support the doses needed to achieve an effect are high and a large amount of product needs to be consumed, which can be problematic for cachectic patients.

Another dietary supplement that has been proposed for the treatment of cachexia treatment is L-Carnitine. L-Carnitine is required to transport long-chain fatty acids, as a major source of energy, into the mitochondrial matrix for β-oxidation. Highest levels of L-Carnitine are observed in skeletal and cardiac muscle. It has been suggested that a deficiency of L-Carnitine contributes to cachexia in cancer patients[37,38]. In animal models, supplementation of L-Carnitine resulted in a significant improvement of food intake, muscle weight and physical performance. On the molecular level L-Carnintine administration decreased proteasome activity and related gene-expression, as well as the expression of genes involved in apoptosis. In addition, it was shown that *in vitro*

Table 1 Dietary supplements in the treatment of cancer cachexia

Agent	Mechanism of action	Ref.
N3-fatty acids (EPA, DHA, fish oil)	Reduction of pro-inflammatory cytokines and acute-phase-response	[32-36]
L-Carnitine	Antioxidant, cofactor of mitochondrial production of Acetyl-coA (ß-oxidation, aminoacid metabolism)	[37-40]
Antioxidants (GSH, ALA, NAC, vitamins A/C/E)	Reduction of ROS-formation and oxidative stress	[42-45]
Branched-chain-amino acids	Anabolic effects, stimulation of appetite and food intake	[46-49]
Lactoferrin	Increase of hemoglobin in anemic patients, iron-metabolism, decrease of inflammatory response	[50]

EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; GSH: Glutathione; ALA: Alpha-lipoic acid; NAC: N-acetyl-cysteine.

application of L-Carnitine to muscle cells resulted in a direct decrease of the proteolytic rate[39]. Clinical trials have been reviewed by Silvério *et al*[38] in 2011. A recent randomized multicenter trial included 72 patients with pancreatic cancer and compared patients who received 4 g oral L-Carnitine for 12 wk to a placebo group. An increase in body weight, QoL and a trend towards increased overall survival was observed in the L-Carnitine-treated group[40].

Oxidative stress and the formation of reactive oxygen species (ROS) play an important role in the pathogenesis of cancer cachexia and represent another potential target for intervention. Mechanisms that lead to the accumulation of ROS are mainly the lack of natural antioxidants due to reduced food intake and the chronic inflammatory reaction. The formation of ROS is further exacerbated by the use of alkylating chemotherapeutic agents such as cisplatin[41,42]. Exogenous antioxidants are vitamins A, C, E and polyphenols. Endogenous antioxidants are a range of enzymes, especially glutathione peroxidase, as well as glutathione, alpha-lipoic acid (ALA), N-acetyl cysteine, reduced coenzyme Q10, melatonin, and plasma protein thiols[41,43]. A few clinical trials showed that antioxidants reduced levels of ROS and pro-inflammatory cytokines in advanced cancer patients[44]. However, in a recent study on melatonin as treatment for cancer cachexia it was shown that there was no improvement of weight, QoL or appetite in patients with advanced cancer[45].

Other dietary supplements in cachexia treatment include branched chain amino acids like valine, leucine and its metabolite β-hydroxy-β-methylbutyrate, which have anabolic effects on skeletal muscle mass. Experimental data suggests that they enhance protein anabolism and improve appetite and food intake in cancer cachexia[46,47]. However, results from clinical trials have been rather disappointing so far and have not yet led to a recommendation towards their use alone or in combination protocols[48,49].

Another nutritional supplement with potentially beneficial effects on cachexia is lactoferrin. In a recent clinical trial it was demonstrated that supplementation of lactoferrin was able to ameliorate cancer-associated anemia in patients with advanced stage (Ⅲ/Ⅳ) solid, malignant tumors (gynecological, colon, stomach, prostate, bladder, lung). Furthermore, there was a decrease of serum levels of inflammatory markers in the lactoferrin-treated arm[50].

Even though a large amount of clinical studies have investigated the effects of these dietary supplements in the treatment of cancer cachexia, many of which observed positive effects, the overall results remain inconclusive for a definite recommendation on their use in clinical practice. This is also due to the fact that design, products and used definitions of cachexia vary largely between the trials, a problem encountered generally in clinical trials of dietary supplements[51]. However, some of the trials specifically in patients with pancreatic cancer show promising results and should be verified in larger and standardized clinical trials.

PHARMACOLOGICAL TREATMENT OF CACHEXIA IN PANCREATIC CANCER PATIENTS

Pharmacological treatment of cachexia includes drugs that improve appetite, the treatment of secondary symptoms that enhance cachexia, and newer drugs that specifically target the molecular mechanisms involved in the pathogenesis of cachexia[26,52]. The current pharmacological approaches are summarized in Table 2. Although more and more drug targets are proposed based on extensive research in animal models, so far very few pharmacological treatments have been translated into clinical practice and there is no single pharmacological treatment that successfully and consistently ameliorates cachexia in pancreatic cancer patients.

Appetite stimulation

Drugs that ameliorate appetite and food intake are an important component of cachexia therapy in cancer patients, since the majority of them suffer from anorexia. Drugs containing the active ingredient of cannabis (Tetrahydrocannabinol, THC) like dronabinol have been used to fight chemotherapy related nausea and anorexia in the past. The endocannabinoid system plays an important role in energy homeostasis. However, results of trials investigating the role of cannabis extracts in the treatment of cancer induced cachexia have been disappointing in terms of weight gain, although improvements in appetite and mood were observed in some studies[53]. Furthermore, there are significant side effects of this treatment, which is why it is currently not recommended in Europe. These include impairment of cognitive function, mental confusion and somnolence and may enhance depression and other psychiatric disorders[41].

Table 2 Pharmacological treatment approaches for cancer cachexia

	Agent	Mechanism of action	Ref.
Potentially effective therapies	Progesterone (MA, MPA)	Appetite stimulation through neuropeptide y down-regulation of pro-inflammatory cytokines	[59,61,90-92]
	Corticosteroids	Inhibition of prostaglandin activity, suppression of IL-1 and TNF-α	[62]
	Anabolic androgens	Muscle anabolism, up-regulation of protein synthesis, dose-dependent alterations of Akt-phosphorylation, GLUT-4 and ISR-expression	[64,65]
	SARMs	Selective modulation of androgen receptors in muscle tissue only	[67-69]
Experimental therapies	NSAIDs	Inhibition of COX-1 and -2 prostaglandin-synthesis, decrease of inflammatory reaction	[71,72]
	COX-2 selective inhibitors	Inhibition of prostaglandin-synthesis, decrease of inflammatory reaction, additional antineoplastic and anti-angiogenetic effects	[70,73,92]
	Thalidomide	Inhibition of TNF-α, and other pro-inflammatory cytokines, NF-κB, inhibition of COX-2	[74-76]
	Anti-TNF mAb	Inhibition of TNF-α	[78,79]
	Anti-IL-6 mAb	Inhibition of IL-6	[85]
	ACE-Inhibitors	Inhibition of angiotensin converting enzyme, role in cancer cachexia not yet fully understood	[88,89]
	Myostatin-inhibitors/ Act Ⅱ rb-antagonists	Inhibition of Act Ⅱ rb signaling, stimulation of muscle growth and regeneration	[4,66,86,87]
	Ghrelin/Ghrelin mimetics	Stimulation of GH-secretion, appetite stimulation though neuropeptide y, decrease of sympathetic nerve activity	[54-57]
	Mirtazepin, Olanzapine	Appetite stimulation through serotonergic blockade	[58,59]
Treatments without proven effectiveness	Pentoxifylline	Inhibition of TNF-α	[77]
	Insulin, IGF-1, GH	Regulation of body composition (fat, glucose and protein metabolism) *via* PI3K/Akt-, MAPK-pathways	[63,64,95]
	Cannaboids (dronabinol)	Appetite stimulation, energy hemostasis	[53]

MA: Megestrol acetate; MPA: Medroxyprogesterone acetate; COX-2: Cyclooxygenase-2; SARMs: Selective androgen receptor modulators; NSAIDs: Non-steroidal anti-inflammatory drugs; TNF: Tumor necrosis factor; IL: Interleukin; IGF: Insulin-like growth factor; GH: Growth hormone; GLUT-4: Glucose transporter-4; ISR: Induced systemic resistance; MAPK: Mitogen-activated protein kinase.

Another new approach to treat anorexia is to target the leptin/ghrelin/neuropeptide-γ axis. Ghrelin is a peptide hormone which is produced in the stomach and stimulates growth hormone (GH)-secretion and increases appetite through neuropeptide-γ system[52]. Ghrelin and the ghrelin receptor agonists (anamorelin and RC-1291) are currently in phase Ⅲ clinical trials and show promising preliminary results in increasing food intake and body weight in cancer patients, with minimal adverse effects[54-57]. In addition, these positive effects were shown to be potentiated by the traditional Japanese medicine Rikkunshito, which stimulates endogenous ghrelin production[55]. However, results from clinical trials are not univocal in terms of efficacy, dose prescription and more research is needed.

Neuroleptic drugs like mirtazapine and olanzapine are often used to treat chemotherapy-induced nausea through serotonic blockage. In addition, they increase appetite which is why they have been proposed as additional treatment of anorexia in cancer cachexia[58]. Furthermore, they might have positive effects on pro-inflammatory cytokine levels. However, the mechanisms of action are not fully understood and clinical trials are needed to evaluate their effect on cancer cachexia, specifically. A trial comparing treatment with the progesterone megestrol acetate (MA) in combination with olanzapine was more effective than MA alone in cachectic patients with advanced gastrointestinal or lung cancer (stage Ⅲ/Ⅳ)[59].

Progesterones, corticosteroids and anabolic hormones

Progesterones represent another pharmacological approach. The mechanism of progesterone action is to stimulate appetite through direct and indirect pathways in the central nervous system. In addition, it is suggested that they antagonize the catabolic effects and downregulate the production of pro-inflammatory cytokines[12]. Synthetic progesterones such as MA and medroxyprogesterone acetate (MPA) have been shown to significantly improve appetite and partially reverse fat loss in randomized controlled trials but failed to improve global QoL or survival in most cancer cachexia trials[41,60,61]. In a recent updated meta-analysis (35 trials, including almost 4000 patients) it has been shown that, compared to a placebo group, treatment with MA improved appetite, weight gain and QoL in patients suffering from cachexia due to cancer, HIV/AIDS or other pathologic conditions. However, significant side-effects were observed, in particular thromboembolic complications and edema[61]. Therefore, a careful and individual risk/benefit analysis should be performed before its application in cachectic patients with pancreatic cancer. Furthermore, the optimal dose for prescription of MA remains to be determined. In clinical practice, MA is often combined with corticosteroids and some older clinical trials also reported possible benefits of the combination of MA with ibuprofen in cancer patients[12].

Corticosteroids (*e.g.*, prednisolone, methylprednisolone) inhibit prostaglandin activity and suppress pro-inflammatory cytokines like IL-1 and TNF-α. Furthermore, there are central effects leading to improved appetite and euphoria. However, the effects generally don't last longer than 2-4 wk and long-term corticosteroid therapy is associated with substantial adverse effects like dysmetabolism, osteoporosis, myopathy and an increased risk of infec-

tions[12]. There are only a few, older trials that specifically evaluated corticosteroids in cancer cachexia. A recent randomized double blind study indicated that treatment with dexamethasone in patients with advanced cancer (all types of solid tumors) ameliorated fatigue and QoL[62].

It is widely recognized that during cachexia, signaling of insulin, insulin-like growth factor-1 (IGF-1) and GH is dysregulated. GH normally induces the production of IGF-1 in the liver and other tissues. IGF-1 stimulates protein synthesis, myoblast differentiation, and muscle growth, whereas it suppresses protein degradation. The dysregulation of this axis causes an anabolic/catabolic imbalance which leads to loss of LBM[63]. In cachetic patients low serum concentrations of IGF-1 have been observed, while there seems to be a peripheral GH and Insulin resistance, which leads to a negative protein balance, especially in skeletal muscle tissue. The United States Food and Drug Administration currently approved recombinant GH for treatment of muscle wasting in HIV/AIDS, parenteral nutrition-dependent short bowel syndrome, and pediatric chronic kidney disease[64]. However, the therapeutic application of Insulin, GH or IGF-1 for pancreatic cancer patients is currently not recommended due to adverse effects (paresthesia, arthralgia, sodium retention and peripheral edema) of the high doses that would be required due to the peripheral insulin and GH-resistance[63,64]. New experimental therapies try to target post-receptor pathways of IGF-1, GH and insulin, like the phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway. However, the oncogenic potential of cell growth promoting treatments has to be kept in mind, since alterations in the PI3K/Akt pathway are common in cancer[63].

Testosterone and its synthetic derivates (*e.g.*, nandrolone, oxandrolone) are anabolic steroid hormones. They increase muscle mass through upregulation of protein-synthesis. Furthermore, there is also interaction with the Insulin/IGF-1/GH system in terms of dose-dependent alterations of Akt-phosphorylation, glucose transporter-4 (GLUT-4) and insulin receptor-expression. Low doses of testosterone increase insulin sensitivity, while high doses increase insulin resistance[63]. In cachexia due to HIV/AIDS or COPD, treatment with testosterone has been shown to improve body weight and functional parameters, however there are only very few trials on its use in cancer cachexia[64,65]. Adverse effects reported are elevated transaminase levels, jaundice, virilization and decreased high density lipoprotein concentrations. Furthermore, there are many interactions with other medications, *e.g.*, oral anticoagulation. In addition, it has to be kept in mind that anabolic steroids potentially lead to fluid retention, which might cause false positive results in clinical trials on weight gain[64]. A more promising new approach is the treatment with SARMs. These molecules react with androgen-receptors in muscle tissue only, minimizing the systemic side effects of androgen therapy. Apparently, several pharmaceutical companies are currently testing these agents to fight sarcopenia due to aging and cancer cachexia[66]. For example, Ostarine has demonstrated promising results in Phase I and II clinical trials and may have the ability to perform as a potent anabolic agent with minimal side effects[67]. Similarly, Enobosarm is currently being tested in phase II clinical trials[68,69]. However, larger clinical trials are warranted to confirm these preliminary results.

Anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase-2 (COX-2)-inhibitors not only reduce the inflammatory response but also have a positive effect on resting energy expenditure (REE) and were shown to prolong survival in malnourished patients with advanced cancer (mostly gastrointestinal cancers)[70,71]. NSAIDs that have been evaluated in cancer cachectic patients are ibuprofen and indomethacin. A recent systematic review of 13 clinical trials found that all but two trials showed an improvement in body weight, physical performance and QoL, while side effects were extremely rare. However, the number of patients included in these trials is small and they used variable outcomes. Therefore, evidence is too frail to recommend the use of NSAIDs to treat cancer cachexia in clinical routine yet[72].

Selective inhibitors of COX-2 (*e.g.*, celecoxib) also received a lot of attention in the search for cachexia treatments. They reduce the systemic inflammatory reaction and there is evidence of anti-neoplastic properties in animal models[41]. Phase II clinical trials in cachectic cancer patients with solid tumors at different sites have shown an increase in LBM and QoL[73]. However, more clinical trials are needed to confirm these results.

Anti-cytokine strategies

Since pro-inflammatory cytokines, such as TNF-α and IL-6, play a prominent role in the pathogenesis of cachexia in pancreatic cancer, systemic inflammation remains an important area for novel therapeutic targets[74]. Results from animal models regarding anti-cytokine strategies provide evidence that targeting cytokine signaling can ameliorate cachexia, even though it has been widely accepted that this complex syndrome is not caused by only one single, specific cytokine[41].

However, most clinical trials of inhibitors of synthesis or activity of TNF-α have so far not proven to be effective in preserving lean body mass in cancer patients[60,74]. The drug thalidomide, which downregulates the production of TNF-α and other pro-inflammatory cytokines and inhibits NF-κB, COX-2 and angiogenesis, was shown to be effective in the treatment of cancer cachexia in patients with gastro-intestinal and pancreatic cancer[4,75]. However, thalidomide has strong adverse effects, which warrant a careful risk-benefit analysis. A recent meta-analysis concluded that evidence is not sufficient to recommend its routine use to treat cancer cachexia[76].

Pentoxifyllin, which is another inhibitor of TNF-α, failed to improve weight loss in cachectic cancer patients with different types of solid tumors[74,77]. Anti-TNF-α an-

tibodies such as infliximab and etanercept did not show any significant improvements in cachectic patients and were not well tolerated, either[78,79]. Finally, results from preclinical studies suggested a potential new treatment for cachexia by inhibiting TNF-α converting enzyme. However, some of these substances were patented but never achieved to pass phase Ⅱ clinical trials. Penna *et al*[74] have reviewed other patented substances that inhibit cytokines directly or *via* receptor modulation or inhibition of NF-κB in detail recently. Notably, none of these substances has been evaluated for their efficiency in ameliorating cachexia in pancreatic cancer in larger clinical trials so far.

Elevated IL-6 levels were quite consistently associated with weight loss and a reduced the rate of survival in cancer patients[18,22,80-82]. Iwase *et al*[83] even showed that IL-6 was elevated in cachectic patients, whereas TNF-α was not. Several studies showed that IL-6 was significantly over-expressed in pancreatic tissue, and serum levels were significantly elevated in cachectic compared to non-cachectic patients with pancreatic cancer[18,22,84]. Preclinical and clinical (phase I and Ⅱ) studies performed on the IL-6 antibody ALD518 in patients with non-small cell lung cancer (NSCLC) demonstrated that this treatment has the potential to improve anemia, reduce cancer-related cachexia and ameliorate fatigue, while having minimal adverse effects[41,85]. However, further research is clearly needed in this regard, since despite some promising results of small clinical trials, there is currently no approved anti-cytokine treatment for cancer cachexia[74].

Emerging pharmacological therapies

Recently, the myostatin/ActRⅡb pathway is receiving more and more attention in cachexia research. Animal models have shown that targeting this pathway can lead to dramatic increases in muscle mass[86,87]. ActRⅡb-receptor and myostatin inhibitors are currently being evaluated in clinical trials of muscle wasting and degenerative disorders. Among the first agents developed for clinical settings are the monoclonal anti-myostatin antibodies LY2495655 and BYM338, which are currently undergoing phase Ⅱ trials in patients with NSCLC and PDAC[4]. Apparently, several pharmaceutical companies have currently explored this pathway as therapeutic target in aging and sarcopenia, but their results have not yet been published[66].

Another interesting recent finding was that in patients with cachexia related to congestive heart failure, treatment with angiotensin-converting enzyme (ACE) inhibitors caused an increase in both subcutaneous fat and muscle mass[88]. There is also some preliminary evidence that ACE inhibitors have the potential to ameliorate cancer cachexia, at least in NSCLC patients[89]. However, the exact role of angiotensin Ⅱ in human cancer cachexia remains to be determined.

Searching the clinical trials databases of the NIH in the US (clinicaltrials.gov) or the EMA in Europe (clinicaltrialsregister.eu) for cachexia in pancreatic cancer, revealed only a very limited number of current trials. Only two ongoing trials are testing new pharmaceutical agents at the moment. One of these is a phase Ⅱ trial in advanced or metastatic pancreatic cancer. The other trial is a randomized, double-blind, placebo-controlled multicenter study for treatment of cachexia in patients with stage Ⅳ NSCLC or stage Ⅲ/Ⅳ pancreatic cancer. Beside these two industry-sponsored trials there is one more ongoing trial sponsored by the Greater Glasgow Health Board. This pre-MENAC study investigates the feasibility of a multimodal exercise/nutrition/anti-inflammatory treatment for cachexia in non-operable stage Ⅲ/Ⅳ NSCLC and pancreatic cancer.

COMBINATION PROTOCOLS

In regard to the multi-factorial pathogenesis of cachexia in pancreatic cancer, more and more clinical trials are testing combination protocols of the above-mentioned dietary supplements and pharmaceutical interventions.

For example, a trial by Mantovani *et al*[90] compared 4 different treatments with a combination arm, recieving all 4 treatments (progesterones, EPA, L-Carnitine; thalidomide) over 4 mo in patients with advanced stage solid tumors at any site. The most effective treatment in terms of LBM gain, REE, fatigue, appetite, IL-6 levels and Eastern Cooperative Oncology Group performance status score was the combination regimen that included all agents. The same research group implicated a new combination protocol in a non-randomized trial. The 16-week treatment consisted of a diet with high polyphenol content, oral nutritional support enriched with n-3 fatty acids (EPA and DHA), MPA, antioxidant treatment with ALA and carbocysteine lysine salt, vitamins E, A and C, and celecoxib. This treatment resulted in a positive response with increase of LBM and QoL in patients with advanced stage solid tumors at any site. Furthermore, there was a decrease of ROS and pro-inflammatory cytokines. No adverse effects were observed[42].

Another phase Ⅲ randomized trial included 104 advanced-stage gynecological cancer patients and assigned them to receive either a combination of MA with L-Carnitine, celecoxib, and antioxidants or MA alone over 4 mo. It was demonstrated that the combination arm was more effective with respect to LBM, REE, appetite, fatigue and global QoL. The inflammation and oxidative stress parameters IL-6, TNF-α, CRP, and ROS decreased significantly in the combination arm, while no significant change was observed in the MA arm[91]. Similarly, another trial compared two combination treatment arms, with or without MA and found no superiority of additional MA administration[92].

MULTIMODAL THERAPY AND A STEPWISE APPROACH FOR CLINICAL PRACTICE

Considering the multidimensional background of cancer cachexia, it is more and more accepted that multimodal therapeutic approaches, including exercise, nutrient sup-

plementation, appetite stimulation and pharmacological intervention, have to be implemented and individually adjusted for patients at different stages of cachexia[4,93]. Successful surgical removal of the tumor and/or oncological treatments should be the starting point for rehabilitation of patients with cancer-associated muscle wasting[94].

Figure 2 shows a stepwise approach of multimodal therapy options. On the first level oral nutrition should be optimized by a high calorie diet, regulation of blood glucose levels and supplementation of pancreatic enzymes. Improving patients' metabolism by insulin or metformin treatment was shown to increase whole body fat (without counteracting muscle loss) and survival in initial study results[95]. If there is no response to these measures, oral nutrition should be supplemented with high calorie drinks, enriched with dietary supplements such as EPA, L-Carnitine and antioxidants. In case of insufficiency of food intake, supplemental parenteral nutrition should be considered. Only the next step would require total parenteral nutrition. A large-scale meta-analysis showed that nutritional interventions were successful in increasing energy intake, body weight and some aspects of QoL[96]. Since pharmacological treatments have so far not been consistently efficient in the long term, they represent the last step and should be applied in the setting of clinical trials.

Screening for cachexia should ideally be carried out at the time of diagnosis of pancreatic cancer since early stages (pre-cachexia) can easily be missed although they are probably the most susceptible to any treatment intervention. Optimal screening should be performed using CT-image based techniques, since they allow for the most accurate assessment of cachexia, especially in obese patients. Since these measurements are not a standard in all CT scans today, an individual agreement with the radiologist has to be defined. In addition, nutrition risk scores and performance indexes can be used to aid decisions about form and level of treatment necessary. Monitoring of course and progress of disease should be implemented in regular intervals and should be combined with dietary counseling.

Supportive multidimensional pharmacological therapy should aim at ameliorating anemia, immunosuppression, depression and fatigue[41]. Moreover, secondary symptoms like pain, diarrhea or stomatitis need to be managed correctly to evaluate the efficacy of new treatments of cancer cachexia[97]. The evidence for interventions with resistance exercise training is not as extensive yet, but first results are promising[4,98]. Finally, the contemporary use of psychological and behavioral interventions, such as relaxation, hypnosis or group-psychotherapy, as well as careful psychosocial counseling and access to self-help groups should be provided for these terminally ill patients[12,41].

CONCLUSION

Even though a substantial amount of experimental, preclinical and clinical research has been carried out in the past 10 years, there is still no effective treatment for cancer patients suffering from cachexia. In pancreatic cancer, cachexia is encountered in up to 80% of patients and significantly contributes to the related morbidity and mortality[12].

Since many factors lead to cachexia in these patients, a multimodal treatment approach is needed, including nutritional support and pharmacological intervention as well as the treatment of symptoms exacerbating weight loss such as chronic pain, gastrointestinal disorders, fatigue and depression. Furthermore, interventions should be implemented in a stepwise manner, starting with oral nutritional support and dietary counseling from the time of diagnosis. Screening and monitoring of cachexia should be performed regularly, ideally using CT-scan based techniques.

After reviewing the current nutritional and pharmacological approaches to treat cachexia, combination protocols using anti-inflammatory, anti-oxidative nutrients and drugs seem the most promising. Treatment with single agents such as progesterones or TNF-α inhibitors has not shown to be successful and unnecessarily expose these patients to the risk of substantial adverse side effects.

New targeted therapies derived from extensive research in animal models hold promise for the future. In particular drugs targeting IL-6 and its downstream targets as well as the myostatin/ActR Ⅱb pathway are up-and-coming. However, it is always challenging looking into the crystal ball and new therapeutic approaches will only be available outside of clinical trials when the marketing approval will be granted. This is at least valid for new chemical entities or new indications for already existing drugs. While waiting for the results of ongoing trials, we strongly encourage further research and clinical trials on new treatments for this devastating condition. Furthermore, diagnostic criteria and design of clinical trials should be standardized as far as possible to make analyses and comparisons of future intervention trials more meaningful.

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