Chapter 8

Pancreatic Cancer Cachexia: Current Concepts and Clinical Management

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Additional information is available at the end of the chapter

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Abstract

There has been great progress over the last decade in understanding the pathophysiology of cachexia associated with pancreatic cancer. However, there is a large need to find better therapeutic options to successfully manage this complex and challenging condition. Patients with pancreatic cancer have some of the highest prevalence and often the most severe degrees of cachexia, which is described as a multifactorial metabolic syndrome that is associated with unintended weight loss of adipose tissue and skeletal muscle in the setting of anorexia. This chapter will review the current concepts surrounding pancreatic cancer cachexia, its clinical diagnosis, pathophysiology, and its known and proposed therapeutics. A multimodal approach utilizing nutritional support and pharmaceutical therapies is proposed to lead to the most successful management of pancreatic cancer cachexia.

Keywords: pancreatic cancer, cachexia, anorexia, metabolic syndrome, catabolism

1. Introduction

In western countries, pancreatic cancer represents the fourth leading cause of cancer-related death [1]. Among the many complications associated with this disease, cachexia marked by progressive weight loss represents one of the most distressing features related to pancreatic cancer. Cachexia is a multidimensional wasting syndrome that is characterized by unintended loss of both adipose tissue and lean body mass (LBM) that cannot be fully reversed through conventional nutritional support. It is a complex metabolic disorder frequently described in pancreatic cancer and represents a significant physical and psychological burden in approximately 80% of pancreatic cancer patients during the disease progression [2]. The complications

associated with cachexia, which include immobility, impaired immunity, and severe respiratory muscle impairment leading to cardiopulmonary failure, result in death in up to one-third of pancreatic cancer patients [3]. Cachectic patients are observed to have lower physical function, decreased tolerance to chemotherapy and radiation treatment, and generally worse prognosis than those with stable weight. Poorer outcomes after pancreaticoduodenectomy have also been observed in patients with preoperative signs of cachexia [4].

While research over the past decade has provided new insights regarding the pathogenesis of pancreatic cancer cachexia, the mechanistic pathology of this condition is still not entirely understood. In this chapter, we will provide a review of the current concepts, potential therapeutic targets, and management of this significant clinical condition.

2. Classification and progression of cancer cachexia

Cachexia has been established to be a common adverse effect of cancer. An international consensus in 2011 defined cachexia as a multifactorial condition recognized by ongoing skeletal muscle loss irreversible by standard nutritional support and eventual functional impairment [5]. The diagnostic criterion established for cancer cachexia is weight loss greater than 5% within 6 months or weight loss greater than 2% in patients already showing depletion (body mass index (BMI) < 20 kg/m^2) or evidence of sarcopenia determined by a dual energy X-ray absorptiometry (DEXA). A skeletal muscle index less than 7.26 kg/m^2 in males and 5.45 kg/m^2 in females is classified as cachexia and the majority of pancreatic cancer patients show signs of cachexia at the time of diagnosis [2].

Cachexia typically develops progressively through a continuum by way of three clinically relevant stages: precachexia, cachexia, and refractory cachexia [5]. A combination of degree of ongoing weight loss as well as depletion of energy stores and body protein mass (using BMI) can be used to classify the severity of the condition. At the precachexia stage, patients show metabolic signs such as anorexia and impaired glucose tolerance prior to significant unintended weight loss. Patients who continue to lose weight and meet the diagnostic criterion described above then transition to full-on cachexia. The cachexia is considered clinically refractory when the cancer is characterized as preterminal or when the individual becomes unresponsive to anticancer therapy. With the presence of uncontrollable catabolism and a life expectancy of less than 3 months, therapeutic interventions usually focus on palliating the symptoms and further preventing the complications of cachexia.

3. Assessment of cancer cachexia

A patient should be assessed for the following features to be characterized with cachexia: anorexia or reduced food intake, catabolic drivers, muscle mass and strength, and functional and psychosocial ability [5]. A recent study indicated that patients who exhibit these components have significantly worse prognosis. Weight loss (>10% weight loss), reduced food intake

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(<1500 kcal/day), and indication of systematic inflammation (C-reactive protein (CRP) > 10 mg/L) reduced subjective and objective functional ability in patients with at least two of these components [2].

Many underlying factors could contribute to anorexia or reduced food intake. Pancreatic cancer patients suffer from a reduced drive to eat, chemosensory disturbances (e.g., taste and smell), dysphagia, decreased gastrointestinal (GI) motility (e.g., early satiety and nausea), pain, and fatigue [5]. To detect the presence of these factors, food intake should be assessed routinely by the patient or a family member. At the minimum, the patient should estimate their overall food intake in comparison to their normal intake or have a family member perform a percentile calculation of food consumed during each meal [6]. The early detection of secondary causes of reduced food intake, such as stomatitis, constipation, dyspnoea, and poor dietary habits is important since some complications may be readily reversible [5].

A key component of pancreatic cancer cachexia is hypercatabolism due to tumor metabolism, systemic inflammation, or other tumor-mediated effects. Systemic inflammation is often indexed using serum C-reactive protein (CRP) levels [7]. Indirect indices such as responsiveness to chemotherapy and rate of disease progression should also be evaluated.

As cancer cachexia is characterized by ongoing muscle wasting, a routine assessment of muscle mass is performed with the various techniques currently available. The methods to measure muscle mass include cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI); appendicular skeletal muscle index obtained from DEXA, anthropometry (mid-upper muscle area); and bioimpedance analysis to obtain a whole body fat-free mass index [5, 8–10]. An imaging-based method is typically selected to quantify changes in body composition by factors such as skeletal muscle wasting, altered body fat distribution, and pathological accumulation of lipids in various tissues. An MRI provides a measurement of quadriceps muscle volume with a coefficient of variation <1% while diagnostic CT scans estimate the cross-sectional area of the abdominal muscle at the L3 area, which can be extrapolated to the lean body mass of the entire body. Muscle strength is typically assessed with an upper-limb hand-grip dynamometry [5].

Among pancreatic cancer patients, those who are overweight were found to be more likely to develop a condition termed as sarcopenic obesity or cachexia hidden in the context of obesity. Sarcopenic obesity is the substantial muscle loss and dysfunction associated with pathological accumulation of adipose tissue. While sarcopenia alone is not associated with decreased survival, being both overweight and sarcopenic does have a significant effect on mortality. With approximately 40% of obese pancreatic patients with detectable sarcopenic obesity, this condition needs to be recognized early on as it was also found to be an important prognostic factor for decreased survival [11]. A comprehensive approach including history, physical examination, and various imaging tests to properly identify this phenomenon can potentially increase the survival of pancreatic cancer patients.

Cancer cachexia contributes substantially to a decreased quality of life by adversely effecting physical and psychosocial functioning. As it is associated with symptoms such as fatigue, weakness, and poor physical performance, it leads to altered body images and can significantly impact

the patient's relationships and emotional well-being [12]. A recent study that used an advanced ambulatory pedometer technology found that physical activity was reduced by around 40% in cachectic cancer patients [13]. Since increased bed rest is known to reduce protein synthesis and contribute to the decrease in skeletal muscle mass in healthy patients, this decrease in physical function in cachectic patients adversely affects performance status, quality of social interactions, and ability to performance daily living tasks [14]. Currently, the most widely accepted method for assessing the effects of cancer cachexia is the routine use of patient-reported physical functioning, specifically using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 or the Eastern Cooperative Oncology Group (ECOG) questionnaire [15–17]. Physical functioning can also be assessed with physician-reported physical activity (the Karnofsky performance score) and objective methodologies including electric activity meters or checklists of specific activities [17].

4. Mechanisms of cancer cachexia

The pathophysiology of cancer cachexia is characterized by a negative protein and energy balance created by a combination of reduced food intake and abnormal metabolism that is mainly driven by a large increase in the rate of skeletal muscle proteolysis [5, 18, 19]. Anorexia and hypercatabolism have been found in cachectic patients to be driven by mechanical factors such as cytokines, circulating hormones, neuropeptides, neurotransmitters, and tumor-derived factors. Recent studies have also identified other processes that potentially contributed to the pathophysiology of pancreatic cancer cachexia, including neural invasion and abnormalities in muscle microenvironment [20–25]. The following section will review these currently proposed mechanisms that interact and contribute to the development of this disease.

4.1. Mechanical factors

Cancer-associated weight loss can be promoted and maintained by reduced food intake, which can be a result of loss of appetite driven by abnormal mechanical digestion [26]. Tumorigenesis is the main cause of these digestive abnormalities and frequently results in the obstruction of the pancreatic duct and/or GI tract, especially the second portion of the duodenum. This can directly lead to symptoms of pain, fatigue, nausea, dysphagia, gastroparesis, duodenal stenosis, pancreatic insufficiency and malabsorption, and constipation [27]. A pancreaticoduodenectomy to resect a pancreatic head mass is often performed following an obstruction and unfortunately can exacerbate pancreatic insufficiency and reduce oral intake [28, 29].

4.2. Cytokines and systemic inflammation

The hypercatabolic component of cachexia is largely caused by the systemic inflammation response, which in turn promotes fat and protein degradation. Serum C-reactive protein is utilized to indirectly index systemic inflammation, and elevated CRP levels (CRP > 10 mg/L) have been related to cachexia and poor performance in pancreatic cancer patients [2]. Elevated levels of the cytokines IL-6 and IL-10 have also been associated with weight loss, poor prognosis,

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and decreased survival in patients [7, 30]. The cytokines that are generated by tumor cells or released by the host in response to cancer have been found to contribute to pathways that result in anorexia and hypercatabolism. These pathways can be separated into the hypothalamus-mediated central pathways and the peripheral pathways, which control lipolysis and proteolysis.

4.2.1. Centrally mediated pathways

The hypothalamus typically plays a role in energy intake by responding to peripheral signals regarding energy and adiposity status. A mechanical response is produced via these signaling pathways and abnormalities in these pathways can lead to anorexia. Current findings indicate that systemic inflammation plays a role in inducing cancer anorexia through the activation of a complex neurochemical cascade [24, 25, 31, 32]. Interference with the hypothalamus' normal response to peripheral signals is suggested to be a direct consequence of elevated tumor-mediated cytokine expression, which actively promotes anorexigenic pathways and inhibits orexigenic pathways [24, 25].

Derangements in the ability of the hypothalamus to transduce peripheral signals into neuronal responses may also be associated with cancer anorexia. There are two pathways that are responsible for energy expenditure and food intake within the hypothalamus: neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons that stimulate energy intake and proopiomelanocortin (POMC)/cocaine and amphetamine-regulated transcript (CART) neurons that inhibit intake. Research suggests that the hyperactivation of the POMC/CART pathways through the IL-1 and other pro-inflammatory cytokines could contribute to developing cancer cachexia [20–23].

Energy homeostasis is also regulated by a protein called leptin through feedback signaling via the central nervous system (CNS). By controlling the synthesis and activation of hypothalamic neuropeptides, such as NPY and corticotropin-releasing factor (CRF), leptin reduces appetite and increases energy expenditure. Since leptin is primarily released by adipose tissue, a lower body fat mass due to starvation leads to lower leptin levels, which allows for the production, release, and action of a potent orexigenic peptide called NPY. NPY then promotes the activation of the NPY/AgRP pathway that stimulates energy intake. Low levels of leptin also decrease the activity of anorexigenic neuropeptides that decrease appetite, which include CRF and melanocortin. Studies have found that cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin1 (IL-1), increase leptin mRNA expression in adipocytes and in plasma despite decreased adiposity [33–36]. Cancer anorexia might therefore be a consequence of increased leptin levels since compensatory mechanisms that typically occur with reduced food intake are inhibited. However, there is also evidence showing that cytokines can induce anorexia without leptin [37]. In some animal and clinical studies, leptin levels were found to not be elevated in tumor-bearing rats and patients with cancer cachexia [38–41]. Recent research demonstrated that in cancer cachexia, IL-1 and TNF-α mimic leptin signaling and result in the interference of the orexigenic pathway, which is normally a response to reduced leptin levels [24, 42]. This suggests that even during starvation, the inhibition of the orexigenic response and activation of the anorexigenic pathway can occur and lead to unopposed anorexia and elevated energy expenditure.

Serotonin may also contribute to the pathogenesis of cancer anorexia, specifically through the melanocortin system. Research has shown that IL-1 releases hypothalamic serotonin and indirectly alters food intake [43]. High levels of serotonin create a continuous activation of POMC/CART neurons, which causes decreased appetite and anorexia [44]. Additionally, higher levels of tryptophan, which is a precursor of serotonin, were also found in plasma and cerebrospinal fluids of cancer patients with cachexia compared to those without cachexia or healthy controls [45]. After tumor removal, tryptophan concentrations were normalized and subsequently improved appetite [46]. These facts concurrently suggest that serotonin plays a pivotal role in the development of cancer cachexia and is also a potential therapeutic target.

These hypothalamic pathways and neuropeptides were also found to have catabolic effects. The POMC/CART anorexigenic pathway activates the sympathetic nervous system and leads to the induction of mitochondrial uncoupling proteins, including UCP-1 and UCP-2 [47, 48]. By dissipating the proton gradient generated during respiration across the inner mitochondrial membrane and uncoupling respiration from ATP synthesis, UCP-1 and UCP-2 result in thermogenesis and energy expenditure in brown adipose tissue (BAT) [47, 48]. Increases in BAT thermogenesis have been associated with a cachectic state in both humans and experimental animals [49, 50].

4.2.2. Peripheral pathways

Not only have cytokines been proven to corroborate and sustain the neurochemical changes associated with cancer cachexia, but they have also been found to induce lipolysis, muscle catabolism, and the hepatic acute phase protein response (APPR) through multiple pathways [51–57]. The combined action of these cellular activities results in the development of progressive muscle and adipose tissue loss.

4.2.2.1. TNF-α

The cytokine TNF-α has been shown to result in profound metabolic changes, even when administered in low doses. Characterized as a potent anorexigenic agent, it promotes lipolysis, impairs lipogenesis, and increases mobilization of lean tissue reserves from skeletal muscle. TNF-α has been shown to induce lipolysis *in vitro* with increases in glycerol production in mouse and human adipocytes, likely through downregulation of perilipin [51]. Since perilipin typically coats intracellular lipid droplets, the decreased expression of perilipin thus enables the lipolysis regulator hormone-sensitive lipase (HSL) to access the surface of lipid droplets for breakdown [51, 52]. By acting as an inhibitory agent on adipocyte differentiation, TNF-α also results in impaired lipogenesis [53, 54].

Research has also indicated that TNF-α contributes to the muscle wasting that characterizes cancer cachexia. Mouse models demonstrated that TNF-α may promote muscle protein degradation by producing reactive oxygen species (ROS). Nuclear factor κB (NFκB) is activated as a result of this oxidative stress and then subsequently upregulates the ubiquitin-mediated proteasome pathway [55, 56]. Moreover, TNF-α has been shown to upregulate the expression of the 1/2- and 2.4-kb transcripts of ubiquitin and the ubiquitin ligase atrogin 1/MAFbx in

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skeletal muscle [55, 56]. *In vitro* experiments that involved NFκB-mediated downregulation of MyoD transcripts have also shown the ability of TNF-α to interfere with myogenesis [57].

While these studies indicate that TNF-α is involved in lipolysis and proteolysis, its relevance in cancer cachexia is still not well established. While some studies measuring TNF-α serum levels in pancreatic cancer patients with cachexia found the predicted inverse relationship between TNF-α levels and body weight as well as BMI; other studies involving advance-staged cancer patients demonstrate no such correlation between circulating TNF-α levels, weight loss, and anorexia. Because of the conflicted results produced from these studies, the significance of TNF-α in cancer cachexia still remains an active area of debate.

4.2.2.2. IL-6

Another important pro-inflammatory cytokine implicated in facilitating cachexia is IL-6, which has been associated with weight loss and reduced survival in pancreatic cancer patients [7, 30, 58]. The secretion of IL-6 is known to be induced by TNF-α and works synergistically with TNF-α in many of its cellular functions, including the triggering of other cytokines. Although the role of IL-6 in lipolysis is still unclear, a recent study using cachectic tumor-bearing mice demonstrated enhanced IL-6 signaling in brown adipose tissue, which suggests that IL-6 may be directly involved in activating thermogenesis [59]. More importantly, IL-6 is known to activate the hepatic APPR and stimulate tissue catabolism. The C-26 tumor-bearing mouse model of cancer cachexia established an IL-6 dependent loss of skeletal muscle during cancer cachexia and treatment with an IL-6 targeting antibody attenuated the development of weight loss [60]. Another study confirmed increased CRP levels and IL-6 production in pancreatic cancer patients with cachexia [7]. There is a strong correlation between heightened peripheral blood mononuclear cells (PBMCs) production of IL-6 and the presence of increased APPR [7, 58, 61]. The stimulation of APPR thus promotes the production of acute phase proteins like CRP and gives rise to hypercatabolism at the expense of skeletal muscle [62]. A twofold to threefold increase in fibrinogen production and elevated serum CRP is observed as a consequence of APPR activation [63]. The hepatic synthesis of acute phase proteins occurs due to the mobilization of peripheral amino acid reserves from lean muscle and contributes greatly to the observed weight loss. Both the overproduction of IL-6 and APPR thus have been shown to result in poor responses to chemotherapy in those surviving with pancreatic cancer cachexia [7].

4.3. Tumor-derived factors

In addition to cytokines and systemic inflammation, tumor-derived factors also contribute to the metabolic abnormalities leading to pancreatic cancer cachexia. Two of the most studied factors are lipid mobilizing factor (LMF) and proteolysis-inducing factor (PIF). Other factors that potentially lead to pancreatic cancer cachexia are still being established.

4.3.1. Lipid mobilizing factor

Another molecule associate with cancer is LMF, which was isolated from both a mouse model of cancer cachexia (MAC16 adenocarcinoma) and the urine of patients with unresectable pancreatic

cancer and weight loss [64]. Given that LMF was found only in pancreatic patients with weight loss and not in those without weight loss or even normal individuals, LMF/ZAG was identified as a serum protein that is a potential marker of pancreatic cancer cachexia [64, 65]. Additional immunohistochemical findings identified LMF/ZAG expression in pancreatic cancer cells and in the peritumoral stroma, with cachectic pancreatic cancer patients demonstrating stronger immunostaining results than those without cachexia or normal subjects [65].

LMF/ZAG has also been demonstrated through *in vivo* findings to cause selective reduction of carcass fat without altering levels of body water and nonfat mass [66]. This lipolysis is activated by the stimulation of adenylate cyclase in a GTP-dependent fashion and is proposed to be mediated by β3 adrenergic receptors [66–68]. When mice are treated with LMF/ZAG, elevated serum levels of glycerol and 3-hydroxybutyrate are observed as well as an increase of oxygen usage by BAT is observed, demonstrating the role of LMF/ZAG in stimulating lipid utilization [66]. This increase in lipid oxidation and utilization has been shown to be mediated by the $^{14}CO_2$ from [14C-carboxy]triolein and also potentially by β3 adrenergic receptors [69]. This function occurs with the increased expression of mitochondrial UCPs, particularly UCP-1, UCP-2, and UCP-3 in BAT, and UCP-2 in the skeletal muscle and liver [70]. LMF/ZAG also enhances the response of adipose tissues to the lipolytic effects of other stimuli such as catecholamines [66]. The plasma membranes of adipocytes contain Gs α-subunits (Gαs) that stimulate adenylate cyclase and Gi α-subunits (Gαi) that inhibit adenylate cyclase. LMF/ZAG favors mobilization of lipid stores from adipocytes and promotes hypercatabolism by increasing Gαs and decreasing Gαi expression [71]. By promoting both the lipid and substrate utilization as well as mitochondrial oxidative pathways in BAT, LMF/ZAG results in lipolysis, elevated energy expenditure, and a hypercatabolic state.

4.4. Proteolysis-inducing factor

In 1996, PIF was isolated from a murine tumor (MAC16) originating in an adenocarcinoma murine model of cachexia and was discovered to induce skeletal muscle catabolism in MAC16 [72]. In humans, PIF was also discovered in cachectic cancer patients, but not from patients with weight loss due to trauma, cancer patients with little or no weight loss or normal individuals [73]. Moreover, this compound was detected in the urine of 80% of pancreatic cancer patients with significantly higher total weight loss and rate of weight loss than those whose urine did not contain PIF [74]. Immunochemistry analysis also revealed the presence of PIF in the cytoplasm of GI tumors such as pancreatic adenocarcinoma [75].

PIF has been found to induce cachectic symptoms when injected intravenously in normal mice; body composition analysis revealed that PIF extracted from the urine of cachectic cancer patients induced reductions in lean body mass without reduction in food and water intake in murine models [76]. This decrease in muscle mass involved two components: an increase in protein degradation by 50% and a reduction in protein synthesis by 50% observed in gastrocnemius muscle [77]. Additional studies regarding the PIF-mediated reduction in protein mass implicate the ubiquitin-proteasome proteolytic pathway. Upon the administration of PIF in normal mice, mRNA levels for ubiquitin, $E2_{14k}$, and the C9 proteasome subunit are increased. An increase in the expression of the ubiquitin-proteasome pathway in skeletal muscle may

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contribute to this protein degradation; some studies suggest that this process is found to be mediated by the activation of NFκB [78–80]. While a reduction in protein mass as well as the depletion of myosin is observed, actin levels continue to remain unchanged with the administration of PIF [80].

The role of NFκB in protein degradation following administration of PIF is still not entirely elucidated. However, it is known that arachidonic acid originating from membrane phospholipids is released and then rapidly metabolizes into eicosanoids such as hydroxyeicosatetraenoic acid (15 -HETE) with phospholipase A_2 (PLA_2), which has also been shown to increase in the presence of PIF [81]. 15-HETE was also shown to cause the nuclear accumulation of NFκB and thus protein degradation [82]. The muscle degradation due to the PIF-induced expression of the ubiquitin-proteasome pathway is also largely reliant on NADPH oxidase and production of ROS [81, 83]. Protein kinase C (PKC) is necessary for the activation of NADPH oxidase and may also be dependent on 15-HETE. The generation of ROS stimulates IκB kinase (IKK) and phosphorylates and degrades IκB; this process then releases NFκB from its inactive cytosolic complex [84].

PIF results in the reduction of protein mass not only by causing degradation, but also by inhibiting protein synthesis. PIF activates double-stranded RNA-dependent protein kinase (PKR) through phosphorylation, which leads to the phosphorylation of eIF2; this in turn inhibits translation and subsequently protein synthesis [85]. PKR is also able to elevate the expression and activity of the ubiquitin-proteasome pathway by activating IKK, which then generates excessive NFκB [86].

APPR that is associated with cachectic pancreatic cancer patients may also be driven by PIF, which was found to play a role in excessively generating hepatic cytokines. Human hepatocyte cultures that were treated with PIF had increased NFκB, signal transducers, and activators of transcription (STAT3), which resulted in an increased production of IL-6, IL-8, and CRP, as well as decreased production of transferrin [87]. The same treatment given to human Kupffer cells and monocytes similarly resulted in an increased production of TNF-α, IL-6, and IL-8 [88].

4.5. Other proposed mechanisms

4.5.1. Pax7 dysregulation

Other contributory factors to muscle loss within a cachectic setting have also been investigated in recent studies and further characterize the muscle microenvironment. In pancreatic cancer patients with cachexia, activation of NFκB in satellite muscle progenitor cells resulted in muscle wasting caused by the dysregulation of the self-renewing transcription factor Pax7, which suppressed expression of MyoD and myogenin [89, 90]. These processes subsequently prevented the muscle progenitor cells that typically commit to a myogenic program from completing differentiation and inhibited myoblast fusion, which ultimately impaired muscle regeneration [90]. Furthermore, Pax7 was shown to be induced by serum factors from both cachectic mice and patients in an NFκB-dependent manner [90]. However, the exact circulating factors contributing to NFκB activation and Pax7 dysregulation still require further research.

4.5.2. Neural invasion

Pancreatic cancer patients often develop signs of neural invasion that can result in nerve damage from intraneural tumors of pancreatic cancer. Recent studies suggest that this process involving nerve damage is associated with cachexia as well as astrocyte activation and microglia stimulation in the spinal cord. These activated astrocytes may then stimulate the sympathetic nervous system, which has previously been shown to induce lipolysis and muscle atrophy [47, 91]. However, the mechanisms that potentially lead to cachexia still require further investigation.

4.6. Management of cancer cachexia

Since cachexia is a multifactorial condition, treatments involving combinations of therapies are more likely to be successful. Current therapeutic strategies involve an integrated and multimodal approach including oncological therapy for control of the tumor, nutritional support, and pharmacological treatment. The best supportive care practices also involve the management of the secondary causes of anorexia, such as pain, nausea, pancreatic insufficiency, and constipation.

4.6.1. Nutritional support

Nutritional deficit is one of the highest concerns among pancreatic cancer patients [92]. Involving dieticians and nutrition assessment programs early on in the disease progression is essential for the successful management of pancreatic cancer cachexia. These programs can provide essential dietary suggestions as well as recommendations for oral nutritional supplementation, enteral nutrition, and parenteral nutrition [93–96].

When concerned with appetite and weight management, professional dietary guidance can significantly increase oral caloric and protein intake [97]. Pancreatic cancer patients who were enrolled in studies requiring them to take oral nutritional supplementation found improvements in weight and appetite [98, 99]. Specifically, including L-Carnitine and omega-3 fatty acids as an addition to patients' diets may provide benefits [100, 101]. In a multicenter, randomized, double-blind trial that enrolled patients with advanced pancreatic cancer, L-Carnitine supplementation was found to significantly improve weight and body mass composition, which ultimately resulted in an increased global quality of life [101].

For patients with swallowing difficulties or severe dysphagia, a nasogastric tube or gastrostomy tube can be utilized to administer nutritional support. However, enteral feeding can be linked to morbidity resulting from aspiration, pneumonia, and diarrhea. For patients with bowel dysfunction and progressive weight loss despite enteral support, parenteral nutrition may be used to limit nutritional deterioration and provide temporary benefits [102].

While nutritional interventions can provide temporary stabilization in nutritional status and certain metabolic indices for cachectic cancer patients, response is often limited in these patients and is frequently lower than responses observed in noncancer patients receiving equivalent nutritional support [103]. A unimodal approach is still not sufficient and patients with pancreatic

cancer cachexia will therefore require a combination of therapies to successfully manage the cachexia.

4.6.2. Pharmacological approach

Since nutritional interventions produce only limited responses, many studies attempted to manipulate the process of cachexia using a variety of pharmacological agents. The mechanisms of these drugs are all based on modulation of cytokines, hormones, or other pathways involved in the pathophysiology of cancer cachexia.

4.6.2.1. Progestogens

Megestrol acetate (MEGACE) is a synthetic and orally active derivative of the naturally occurring hormone progesterone. It was first developed for the treatment of breast cancer and later for endometrial cancer, MEGACE is now used to stimulate appetite and increase weight in cancer-associated anorexia, as well as for other chronic conditions such as the human acquired immunodeficiency syndrome (AIDS) after being approved by the Food and Drug Administration (FDA) in 1993. Multiple trials have demonstrated that MEGACE (480–800 mg/day) resulted in significant improvements in appetite, food intake, nausea, and weight gain among pancreatic patients with cancer cachexia [27, 104–107]. This efficacy of MEGACE appears to be dose-dependent [106]. MEGACE is generally well-tolerated with low incidence of side effects, including rash, adrenal insufficiency, hyperglycemia, and thromboembolic events, which only have an incidence of less than 5% [105]. Since its approval, many studies have confirmed the effectiveness of MEGACE at increasing weight and thus quality of life when compared to other drugs potentially used for the management of cancer cachexia (cisapride, dronabinol, corticosteroids, and nandrolone) [108, 109]. Body composition analysis has also confirmed that the weight gain observed following MEGACE intake is predominately due to increases in adipose tissue and less from increases in body fluid [110]. However, there were no improvements in survival found in those who were treated with MEGACE [107, 109].

Some studies suggest that the mechanisms by which MEGACE stimulates appetite and weight gain is related to decreased production and release of pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) as well as the stimulation of NPY in the hypothalamus [111–113]. Another progestogen, medroxyprogesterone acetate, was demonstrated through *in vitro* experiments to decrease the production of cytokines and serotonin by PBMC of cancer patients [112, 113].

4.6.2.2. Corticosteroids

Corticosteroids are one of the most widely used appetite stimulants and are effective in inducing food intake and weight gain [114–116]. However, these do not result in lasting changes (less than 4 weeks) and may cause long-term side effects, such as insulin resistance, fluid retention, steroid-induced myopathy, skin fragility, adrenal insufficiency, and sleep and cognitive disorder [116]. The exact mechanisms of action of corticosteroids in a cancer cachexia context still remains unclear, but is likely to be related to the inhibition of IL-1, TNF-α, and

leptin as well as the stimulation of NPY [117]. Because of their short duration of effectiveness, corticosteroids may be useful for patient with short expected survival.

4.6.2.3. Cannabinoids

Cannabinoids, which are also called dronabinols, are a class of diverse chemical compounds that have a known effect on reducing nausea as well as weight gain and stabilization. A phase II trial found that dronabinol improved anorexia in 68% of patients, but also resulted in dangerous toxicity levels in 16% of patients who eventually suspended treatment [118]. In addition, dronabinol is associated with many adverse side effects, including euphoria, hallucination, psychosis, vertigo, and cardiovascular disorders. The mechanism of action appears to be mediated by interaction with endorphin receptors, interference with IL-1 production, activation of cannabinoid receptors associated with the neurochemical circuit of leptin, and inhibition of prostaglandin synthesis.

In a controlled clinical trial, dronabinol was compared to megestrol acetate in cachectic cancer patients [119]. A total of 469 patients were enrolled in the study and were instructed to take megestrol acetate 800 mg/day or dronabinol 2.5 mg/12 h or both. The findings indicate that megestrol is superior to dronabinol in terms of increasing appetite and weight: 75 vs. 49% ($P = 0.0001$) increase in appetite, respectively and 11 vs. 3% ($P = 0.02$) increase in weight gain of at least 10% from baseline, respectively [114]. There were no differences in appetite and weight between the combination treatment group compared to the megestrol acetate only group (66 vs. 75%, $P = 0.17$, for appetite and 8 vs. 11%, $P = 0.43$, for =10% weight gain, respectively). While megestrol acetate seems to be more effective than dronabinol, cannabinoid is still able to stimulate in appetite and reduce nausea. It is available as an alternative option as an appetite stimulant and antiemetic.

4.6.2.4. Anti-inflammatory agents

Systemic inflammation plays an important role in the pathophysiology of pancreatic cancer cachexia. Pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6, have been implicated in the progression of cancer cachexia in a potentially synergistic way. These findings have prompted the development of treatments to curtail the inflammatory response by inhibiting the synthesis or action of cytokines.

Research has indicated that nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors, indomethacin, and ibuprofen, have the ability to reduce acute phase proteins and cytokines [120–122]. The inhibition of prostaglandin synthesis has been shown *in vivo* to attenuate tumor progression and decrease incidence of cancer cachexia [123, 124]. NSAIDs inhibition of prostaglandin synthesis blocks downstream effects of systemic inflammation; thereby interfering with the cytokines that depend on signal transduction mediated by eicosanoids. In cachectic patients with metastatic solid tumors, indomethacin use may prolong survival and offer palliative support to those with advanced cancer, including pancreatic cancer patients [125]. Other controlled clinical trials have shown that ibuprofen can reduce CRP levels, increase body weight and muscle mass, and improve

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global quality of life, especially when combined with progestogens [122, 126, 127]. McMillan et al. conducted a multicenter, randomized, control trial that involved 73 cachectic patients with advanced GI cancers, predominately pancreatic cancer (67% of patients) [126]. This study reported that taking a combination of ibuprofen (1200 mg/day) and megestrol acetate (480 mg/day) resulted in more significant improvements in weight and increased quality of life compared to those only consuming megestrol acetate [128]. Similar side effects were present in both groups, including venous thrombosis, upper GI bleeding, and ascites. However, due to disease progression, there was a high attrition rate with 63% failing to complete the 12-week assessment. These provide promising results that would benefit greatly from larger studies that can better evaluate the clinical role of NSAIDs in the management of pancreatic cancer cachexia.

Research has also shown that thalidomide has anti-inflammatory and complex immunomodulatory properties. Thalidomide results in the downregulation of the production of TNF-α as well as other pro-inflammatory cytokines in monocytes, inhibits NFκB, downregulates cyclooxygenase 2, and inhibits angiogenesis [129]. Many controlled trials showed that thalidomide is well-tolerated and successful in improving appetite, weight gain, and sensation of well-being [130, 131]. One specific double-blind, placebo-controlled, randomized clinical trial of thalidomide recruited 50 pancreatic cancer patients with cachexia to take either 200 mg/day of thalidomide or a placebo [131]. The study found that after 4 weeks, patients in the thalidomide group had significant increases in weight compared to the placebo group (0.37 vs. −2.21 kg, $P = 0.005$) and significant improvements in lean body mass (1.0 cm^3 in arm muscle mass vs. −4.46 cm^3, $P = 0.002$) [131]. There were some adverse reactions to thalidomide, including peripheral neuropathy, dizziness, somnolence, constipation, rash, and possible increased risk of venous thromboembolism in the setting of malignancy. These preliminary results are encouraging, but merits further investigation to confirm the efficacy of thalidomide in treating pancreatic cancer cachexia.

Some therapeutic approaches also involve pharmaconutrients with anti-inflammatory activity, such as the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Both found abundantly in fish oil, EPA and DHA both have immunomodulatory properties that allow for the suppression of pro-inflammatory cytokines, including IL-1, TNF-α, and IL-6 by PBMC [132, 133]. Research on EPA has also suggested its ability to inhibit the downstream effects of LMF and PIF [134–136]. In past studies involving patients with unresectable pancreatic cancer, fish oil supplementation containing both EPA and DHA as well as high-purity EPA administration have both been associated with weight stabilization [137, 138]. A study conducted by Barber et al. further demonstrated the efficacy of EPA, which were taken through oral supplementation, at producing significant increases in weight, dietary intake, and performance status in cachectic patients with advanced pancreatic cancer [100]. However, recent data from a multicenter, double-blind, placebo-controlled, randomized clinical trial provided conflicting results suggested that single agent EPA administration is not effective in treating cancer cachexia [139]. Another multicenter clinical trial that compared EPA, megestrol acetate, and a combination treatment determined that megestrol acetate alone resulted in more weight gain than EPA administration or a combination therapy [140]. While the role of EPA in the management cancer cachexia still remains unclear, recent data

demonstrates EPA's lack of effectiveness as a single agent or even in combination regimens for the management of pancreatic cancer cachexia.

As the mechanisms involved in the development and progression of cancer cachexia continues to be elucidated, the management of this multifactorial syndrome has made improvements towards developing a multimodal approach. Recent data from a large multicenter trial suggests that a combination therapy with megestrol acetate (320 mg/day), EPA supplementation, L-carnitine (4 g/day), and thalidomide (200 mg/day) provides more effective results in improving lean body mass and appetite than single agents [141]. Future progress in the field of cancer cachexia will be realized through the development of combined pharmacological therapies given along with nutritional supplementation in the context of supportive care.

5. Future directions

Despite a significant increase in research on cancer cachexia, there are currently no therapies available for pancreatic cancer cachexia that results in lasting effects on weight management and improvements in prognosis. Developing an effective and powerful treatment for this disease still remains an ongoing challenge.

Recent studies have focused on targeted therapies with anti-inflammatory activity. IL-6 has been identified as a promising target, but most of the studies investigating IL-6 antibodies have involved nonsmall cell lung cancer (NSCLC) patients with cachexia [142–145]. In a phase II randomized, double-blind, placebo-controlled trial with NSCLC patients, the humanized monoclonal IL-6 antibody called ALD518 (also known as BMS-945429) was evaluated for its safety and efficacy in treating cancer cachexia. This safe and well-tolerated antibody effectively increased hemoglobin levels and prevented loss of lean body mass [142, 143]. Rigas et al. also reported statistically significant improvements in fatigue score in the ALD518 group vs. placebo group that persisted over a 12-week period [142].

Another agent that was found to have anti-inflammatory properties is OHR/AVR118, which is an immune modulator that targets both TNF-α and IL-6. In a phase II study by Chasen et al. administering OHR/AVR118 in cachectic patients with advanced cancer resulted in improvements in anorexia, dyspepsia, strength, and depression [146]. A current phase IIb study is advancing the understanding of the role and efficacy of OHR/AVR118 in enhancing appetite as well as improving weight, lean body mass, strength, and quality of life [147]. Additional research is still needed to evaluate the safety and efficacy of these agents in pancreatic cancer patients with cachexia.

Studies have discovered the therapeutic potential of inhibiting myostatin and activin type IIB (ActRIIB) in treating cancer cachexia. ActRIIB is a high affinity activin receptor that mediates signaling through a subset of TGF-β ligands including myostatin and activin and both play a critical role in regulating muscle mass [148]. These ligands inhibit myogenesis and the Akt/mTOR pathway involved in muscle protein synthesis and upregulate the expression of ubiquitin ligases that degrade muscle. In several models of cancer cachexia, Zhou et al. reported the

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prevention of muscle wasting as well as prolonged survival through the pharmacological inhibition of the ActRIIB pathway [148]. One myostatin inhibitor BYM338 has been developed by Novartis (Hanover, NJ, USA) and is currently being investigated for the efficacy of myostatin inhibitors in attenuating loss of body mass. This compound is currently being evaluated in a multicenter, randomized, double-blind, placebo-controlled phase II trial that involves cachectic patients with either stage IV NSCLC or stage III/IV pancreatic cancer [149]. LY2495655 is another humanized antimyostatin antibody currently investigated in a multicenter, randomized, double-blind, placebo-controlled phase II trial that recruited patients with locally advanced or metastatic pancreatic cancer. Patients were administered with one of two different doses of LY2495655 in combination with gemcitabine to evaluate potential dose-dependent effects on survival, lean body mass, and physical performance [150].

6. Conclusion

Cancer cachexia is still regarded as noncurable and is diagnosed in approximately 80% of pancreatic cancer patients. Among these patients, 30% eventually die from cachexia-related complications [2, 151]. As a multifactorial condition, pancreatic cancer cachexia is complex disease that is associated with anorexia and excessive catabolism mediated by mechanical factors, pro-inflammatory cytokines, neuropeptides, hormones, and tumor-derived factors. The pathophysiology of cachexia in pancreatic cancer is characterized by compromised energy homeostasis driven by decreased food intake and abnormal metabolism. This negative protein and energy balance leads to unintentional skeletal muscle and adipose tissue mass, which greatly decreases the overall prognosis of pancreatic cancer patients.

While the management of cancer cachexia has improved dramatically in the past decade, more research is still needed to further understand the complex mechanisms involved in the pathogenesis and maintenance of pancreatic cancer cachexia. Current research identifies targeted immunotherapy as a promising treatment option for cachexia and successful intervention of this condition will most likely involve a multimodal approach to aid in developing potential therapeutics. Future progress in the management of cancer cachexia will likely be realized through a combined approach that includes nutritional support, multiple agents, and targeted therapies to improve the quality of life and general outlook of patients with pancreatic cancer.

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