

Anorexia in Pancreatic Adenocarcinoma

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ABSTRACT

Cancer of the pancreas is the fourth leading cause of cancer mortality; only 4% of those diagnosed with pancreatic cancer survive 5 years. The ever-increasing incidence of pancreatic cancer has become a health concern. Metabolic alterations such as diabetes, anorexia and weight loss have been reported as the first symptoms of pancreatic cancer tumors. About 80% of all pancreatic adenocarcinoma patients suffer from a wasting syndrome referred to as the Cancer Anorexia-Cachexia Syndrome (**CACS**) characterized by abnormally low weight, weakness and loss of skeletal muscle mass with or without loss of body fat, which directly impacts overall survival, quality of life, and physical activity.

Although anorexia is a common symptom in cachexia, it should not be used as a synonym. Anorexia, the loss of appetite or desire to eat, is one of the most common symptoms in patients with pancreatic cancer. The pathogenesis of anorexia is most certainly multifactorial but not yet well understood. The causes of anorexia seem to depend on a variety of factors including cytokine release, intermediate metabolites like lactate, ketones and oligonucleotides. A number of specific or exogenics have been developed to treat anorexia in cancer patients. The two major options for pharmacological therapy of anorexia have been either progestational agents or corticosteroids. Treatments to improve anorexia and stabilize or increase weight do exist, but their overall benefits in improving global quality of life and survival remain an issue of controversy.

INTRODUCTION

Pancreatic adenocarcinoma is the eighth most frequent cause of cancer mortality world-wide and the fifth most frequent cause of cancer death in most countries. More than 90% of pancreatic cancers are ductal adenocarcinomas, which often present with perineural and retroperitoneal infiltration [1,2]. Unfortunately, neither the incidence nor the survival rate of pancreatic adenocarcinoma has changed significantly over the past 25 years, and 5-year survival remains poor at approximately 4%. Pancreatic cancer due to aggressive behavior of the tumor and relative frequency that appears to be increasing is a major health problem [3-5].

The clinical presentation of pancreatic cancer can widely vary, due to tumor location and disease stage. The symptoms of pancreatic cancer are not limited to those associated with the energy demands of the tumor mass or the local tissue damage and blockage caused by the growth of the tumor [4,5]. Metabolic and nutritional complications rather than wide-spread carcinomatosis are the direct cause of death in many of these patients. Severe, early weight loss, anorexia, cachexia and metabolic complications such as diabetes are important characteristics of pancreatic cancer [3,6].

The pancreas crucial role in digestion is illustrated by the fact that many of pancreatic cancer patients have experienced extreme weight loss, with cancer cachexia present in approximately 80% of patients. This significant unintentional weight loss is a hallmark of the disease and may be attributed to malabsorption due to pancreatic exocrine dysfunction combined with anorexia [5,7]. Anorexia, defined as the loss of appetite and early satiety, is present in up to one-half of newly diagnosed cancer patients. Although anorexia is commonly associated with cachexia, it is unlikely that the weight loss in cancer arises primarily from the reduction in food intake [8,9].

CANCER ANOREXIA-CACHEXIA SYNDROME

Anorexia represents the result of a failure of the usual appetite signals whereas cachexia is the debilitating state of involuntary weight loss. This syndrome, referred to as the Cancer Anorexia-Cachexia Syndrome (**CACS**), usually consists of a combination of anorexia, tissue wasting, malnutrition, weight loss and loss of compensatory increase in feeding. About 80% of all pancreatic ductal adenocarcinoma patients suffer from this syndrome [4,10].

Although anorexia is a common symptom in cachexia, it should not be used as a synonym. Anorexia, defined as decreased desire to eat, is the leading cause of decreased food assumption, while cachexia is characterized by profound loss (up to 80%) of both adipose tissue and skeletal muscle mass that eventually leads to hypoalbuminemia and asthenia, which, together with anemia, a frequent comorbidity in cancer patients, limit physical activity and consequently inhibit protein synthesis. Cachexia is associated with characteristic metabolic alterations that are not present in anorexia. While loss of appetite and resultant decrease in energy intake undoubtedly contribute to weight loss associated with cancer cachexia, whether anorexia occurs by an independent process or is a result of the inflammatory process of cachexia is not fully understood. The occurrence of anorexia in cancer patients can be identified by evaluating relevant symptoms, such as taste alterations, nausea and early satiety; this latter, in particular, has been associated with worse outcome [4,11].

MECHANISMS OF CANCER-RELATED ANOREXIA

The pathogenesis of pancreatic cancer-related anorexia is complex and multifactorial, implying perturbations of the physiological regulation of eating behavior at the hypothalamic level. In healthy individuals peripheral signals are integrated by the hypothalamus to modulate energy intake. Humoral mediators able to inhibit or stimulate energy intake have been described. In cancer patients the increased cytokine expression in the brain leads to disruption of hypothalamic neurochemistry, interfering with the regulation of satiety, at least in part through enhanced serotonin synthesis and release. Tumor-induced changes in energy metabolism of hypothalamic neurons are probably also involved in the pathogenesis of cancer anorexia. In this regard, discrimination of anorexia associated with psychological distress and dysphagia from that secondary to altered brain neurochemistry could be clinically relevant, in order to develop more specific therapies [11-13].

Overall, the causes of anorexia seem to depend on a variety of factors including cytokine release (TNF- α , interleukin-1), intermediate metabolites like lactate, ketones and oligonucleotides as well as Islet Amyloid Polypeptide (**IAPP**). These factors can be conveniently categorized as being due to central or peripheral mechanisms. In each group, there are also a series of secondary causes due to chemotherapy [14,15].

Centrally-Mediated Pathways

Central causes of anorexia can be depression, pain, or a variety of alterations in central neurotransmitters. Cancer anorexia may be partially due to derangement of peripheral signaling transduction into neuronal responses by the hypothalamus. There are two pathways that control energy expenditure and food intake within the hypothalamus: Neuropeptide Y (**NPY**)/Agouti-Related Peptide (**AgRP**) neurons that stimulate energy intake and Pro-Opiomelanocortin (**POMC**)/Cocaine And Amphetamine-Regulated Transcript (**CART**) neurons that inhibit intake [14,16].

Neuropeptide Y stimulates appetite on its own or via release of other orexigenic proteins. Neurons which release α -Melanocyte-Stimulating Hormone (**α -MSH**) and signal via Melanocortin-3 and 4 Receptors (**MC3R, MC4R**) result in decrease in food-seeking behavior, increased basal metabolic rate and decreased lean body mass. These neurons are constitutively active as mutation in the MC4R results in childhood obesity. Agouti-Related Protein (**AgRP**) is produced by neurons (which also produce neuropeptide Y) and counteracts the action of MC4R-stimulating proteins promoting appetite. These appetite neurons also express receptors for circulating leptin and interleukin-1 β (IL-1 β), both of which down regulate appetite and receptors for ghrelin (the orexigenic protein, which increases AgRP) [8,17].

The neurotransmitter changes in depression that lead to anorexia appear to be alterations in serotonin and Corticotrophin Releasing Factor (**CRF**). When cancer patients are infused with interferon, there is an increased kynurenic acid, which is associated with depression and anorexia. This leads to alterations in tryptophan and serotonin levels. Serotonin may also play an important role in the development of cancer anorexia through the melanocortin system. Studies have established that IL-1 stimulates the release of hypothalamic serotonin. Elevated serotonin levels, in turn, contribute to the persistent activation of POMC/CART neurons, resulting in decreased appetite and anorexia [14,16].

Leptin is a protein involved in regulating energy intake and expenditure. Leptin reduces appetite and increases energy expenditure via the Central Nervous System (**CNS**). Through feedback signaling, leptin controls the production, and activation of hypothalamic neuropeptides that regulate food intake and energy expenditure, including NPY and Corticotropin-Releasing Factor (**CRF**). Since leptin is primarily released by adipose tissue, decreased body fat mass or starvation leads to a decrease in leptin levels. Low leptin levels allow for increased production, release, and action of NPY, a potent orexigenic peptide, which subsequently results in the activation of the NPY/AgRP pathway [14,16].

Peripheral Pathways

Cytokines not only corroborate and sustain the neurochemical changes responsible for anorexia; they have also been shown to induce lipolysis, muscle catabolism, and the hepatic Acute Phase Protein Response (**APPR**) through various pathways. Cytokines may inhibit the neuropeptide Y pathway or mimic negative feedback action of leptin on the hypothalamus, leading to anorexia. A number of proinflammatory cytokines such as Tumor Necrosis Factor- α (**TNF- α**) and Interleukin-1 (**IL-1**) act directly in the brain to produce anorexia. Receptors for TNF- α and IL-1 are detectable in the hypothalamic food-intake regulatory areas of the brain. IL-1 and the ventromedial hypothalamic serotonergic system appear to be closely linked because peripherally infused IL-1 increases brain tryptophan and serotonin concentrations. Anorexia induced by TNF- α also can be blocked by cyclooxygenase inhibitors. It is likely that the two cytokines act synergistically because TNF- α induces IL-1 secretion and both stimulate other cytokines such as IL-6 in a cascade manner [4,8,16].

It seems intermediary metabolites (e.g. lactate, ketones, oligonucleotides) that accumulate along an abnormal metabolic pathway, or other substances released by the tumor itself or by normal cells in response to the tumor have been involved in the development of anorexia. Malignant tumors often have an increase in glycolysis associated with an increase in Lactic Dehydrogenase Activity (**LDH**). Lactate levels increased contiguously with the onset of anorexia. Lactate infusion was associated with elevated levels of NPY in the ventromedial hypothalamus and dorsomedial hypothalamus, but there was no alteration in CRF. It would appear that lactate is a strong candidate for one of the reasons why cancer is associated with anorexia [14,18].

Furthermore, a number of gastrointestinal peptides such as amylin may have a role in causing anorexia. Islet Amyloid Polypeptide (**IAPP**) or amylin is one of the peptides that seems to be an important satiety factor regulating appetite and interfering with glucose metabolism and with the potential of causing reduction in food intake and thereby reduction in body weight. The pathways by which IAPP suppresses food intake are not well understood. Experimental evidence suggests that IAPP acts as an endocrine factor that is released from the pancreatic islets into the circulation after ingestion of nutrients. The brain is likely to be one of the target organs that mediate the satiating effects for IAPP. The effect of IAPP on food intake may also be mediated by inhibition of gastric emptying [3,15,19].

Zinc deficiency is well recognized to produce anorexia. In part, this is because low zinc levels result in hypogeusia. Zinc is a trace element needed in transcription, nutrition, gastrointestinal motility, digestion, oxidative processes, synaptic signalling, signal transduction, memory, ligand binding, apoptosis, and healing. Cancer disrupts zinc metabolism as a result of the acute phase response to inflammatory cytokine activity. There are several mechanisms of zinc deficiency in cancer patients: low albumin reducing zinc binding, anorexia contributing to low intake, ubiquitin-proteasome activation causing accumulation and wasting in muscle cells, gastrointestinal loss, diversion of zinc away from muscle production, and increased urinary excretion of zinc [14,20,21].

CLINICAL PRESENTATION AND DIAGNOSIS OF ANOREXIA

Cancer anorexia is a syndrome of loss of appetite, early satiety, bloating, taste and smell changes, and diurnal alterations in food intake. It can occur early in the disease process or later as the tumor grows and metastasizes [22,23]. Anorexia diagnosis is based on reduced appetite. However, the presence of anorexia could be characterized more effectively by identifying objective symptoms, including early satiety, taste alterations and nausea, and by assessing its severity. Consequently, a visual analog scale is often used, which is a useful tool in epidemiologic or prospective studies but may prove unreliable if small changes in appetite need to be detected [24,25].

Sometimes, the diagnosis of anorexia is based on the presence of reduced energy intake. Evaluation of food intake should be routinely performed. At the minimum, patients can be asked to estimate their overall food intake in relation to normal intake with dietary or recall records.

Another simple method for prospective third-party assessment of food intake is the percentile calculation of food consumed at each meal by a family member. However evaluation of food intake can be misleading because the reduction of ingested calories might be the consequence of dysphagia or depression rather than because of anorexia. In addition, a number of symptoms interfering with food intake, which are likely to be linked to changes in the central nervous system energy intake control, have been identified [16,24].

Overall, the use of questionnaires to diagnose anorexia is increasing rapidly, thus highlighting their utility and reliability. However, considering that questionnaires provide only a qualitative assessment of the presence of anorexia, it is also advisable to quantify the degree of anorexia by using a visual analog scale [16,24].

TREATMENT OF ANOREXIA

Anorexia syndrome characterized by identifying specific symptoms including loss of appetite, early satiety, taste alterations and nausea, and by diurnal alterations in food intake. Therefore, it is unlikely that a single drug will be able to treat the anorexia syndrome. However, certain symptoms may be targeted by specific drugs. A variety of causes of anorexia exist, many which can be dealt with and managed as part of the palliation of pancreatic cancer patients. A number of specific or exigenics have been developed to treat anorexia in cancer patients. They have all been demonstrated to have some utility, but none of them are disease modifying [10,14,15].

Drug Therapy

The two major options for pharmacological therapy of anorexia have been either progestational agents or corticosteroids (Table 1). Progestogens, particularly megestrol acetate, are commonly used to treatment of anorexia. The mechanism of action of megestrol is believed to involve the stimulation of appetite by both direct and indirect pathways, and antagonism of the metabolic effects of the principal catabolic cytokines. The mechanism of action of corticosteroids seems to be related to the inhibition of tumor-induced and host induced substances and to a central euphoria. The effect of corticosteroids is generally believed to last between 2 and 4 weeks with a positive influence on asthenia as well as other symptoms such as nausea, appetite, and pain [10,26].

Table 1: Placebo-controlled trials of Progestogens and corticosteroids in patients with cancer-related anorexia/cachexia [18].

	Drug	Significant symptoms outcomes
Progestogens	Megestrol	Improved appetite, food intake, energy level, bodyweight, tricep skin fold and calf circumference; less nausea, less emesis compared with placebo
	Medroxyprogesterone	Increased appetite, serum retinol binding protein and serum thyroid binding pre-albumin
Corticosteroids	Dexamethasone	Increased Appetite
	Prednisolone	Increased Appetite
	Methylprednisolone	Increased Appetite, food intake and performance status

Progestogens

Progestogens were the first agents used and are the current first-line agents used in patients with CACS. An extensive amount of literature is available in patients with cancer, with the use of both megestrol and medroxyprogesterone. Both drugs are synthetic progestogens which were first used to treat hormone-sensitive tumors [18,27].

Megestrol was approved by the Food and Drug Administration in the USA to treat anorexia and weight loss in 1993. Megestrol acetate has been the standard treatment for increasing appetite and is a mixed drug having androgenic, corticosteroid, and progestogenic properties. Megestrol has been shown to increase NPY in a number of hypothalamic nuclei. When progesterone increases, NPY activity in the paraventricular nucleus also increases, coinciding with an increase in feeding activity. This suggests that the progestational action of megestrol is a major component in its ability to increase feeding. Corticosteroid Type II receptor stimulation has been also shown to increase NPY gene expression in the hypothalamus. Furthermore, there is also some evidence that megestrol may reduce serotonin [14,28].

Medroxyprogesterone Acetate (**MPA**) is a synthetic, orally active derivative of the natural steroid hormone, progesterone. The proposed mechanism of action of progestogen MPA has not been completely established. It may be attributed to glucocorticoid-like activity, making this drug similar to corticosteroids. Moreover, there is evidence that MPA may stimulate appetite via neuropeptide Y in the CNS (ventromedial hypothalamus). Furthermore, down regulating the synthesis and release of pro-inflammatory cytokines shown by experimental and clinical studies [18,29].

Corticosteroids

Studies have shown that corticosteroids, including dexamethasone, prednisolone and methylprednisolone, induce a usually temporary (limited to a few weeks) effect on symptoms such as appetite, food intake, sensation of well-being and performance status. In addition, corticosteroids have an antiemetic activity and are able to reduce asthenia and to control pain. Their mechanism of action is not well understood, although the inhibition of Prostaglandin (**PG**) activity and the suppression of IL-1 and TNF production are the most well recognized targets [18,30].

Other drug

Cannabis has long been recognized to improve appetite, decrease nausea, and enhance food taste. It is now known that endogenous cannabinoids (anandamide) acting through the four-protein Coupled-Cannabinoid receptors (**CB1**) increase appetite. Cannabinoids increase NPY in the hypothalamus. Activation of the CB1 receptor results in stimulation of AMP-activated protein kinase. Another mechanism by which cannabinoids may regulate feeding is directly at the intestinal level where release of anandamide acts as a hunger signal while another fatty acid

ethanolamide, oleoylethanolamide, is increased during feeding and acts as a satiation signal. It appears that these signals are transmitted to the brain through ascending fibres of the vagus nerve. There is some evidence that anandamide may be negatively linked to PYY, which peripherally causes weight loss. When smoked medicinal cannabis was used in HIV-infected adult men, PYY was decreased, and ghrelin levels increased [14,18].

Ghrelin is a 28-amino-acid peptide secreted from the fundus of the stomach. It increases food intake through a nitric oxide-dependent mechanism. It also improves memory and results in growth hormone release from the pituitary. The ghrelin analogue's effects were coupled with a significant increase in hypothalamic NPY and AGRP [14,18].

Anticytokine Agents

Since pro-inflammatory cytokines, especially TNF- α , play a prominent role in the pathogenesis of anorexia in pancreatic cancer, systemic inflammation remains an important area for novel therapeutic targets in combating this syndrome. Anticytokine therapy is highly effective in counteracting cancer anorexia. Anti-IL-6 monoclonal antibody therapy appears promising, but clinical data are still lacking. The compounds pentoxifylline, thalidomide, and suramin have been demonstrated to significantly reduce cytokine release in humans. Thalidomide, which is an inhibitor of TNF- α synthesis, may represent a rational therapeutic approach. However, the potential side effects of anticytokine therapy, including suramin-induced inhibition of chemotherapy induced apoptosis, suggest it should be used with caution [10,24].

Omega-3 polyunsaturated fatty acids have been shown to modulate levels of pro-inflammatory cytokines, hepatic acute phase proteins, eicosanoids, and tumor derived factors and may reverse some aspects of the process of cachexia. These effects are related to the uptake of Eicosapentaenoic Acid (**EPA**) and Docosahexaenoic Acid (**DHA**) into the cellular substrate pool and their competitive metabolism with arachidonic acid at the cyclooxygenase and 5-lipoxygenase levels. The metabolites of EPA and DHA have less inflammatory and immunosuppressant potency than the substances derived from arachidonic acid. In addition, it has been demonstrated that, in patients with pancreatic cancer, an n-3 fatty-acid-enriched nutritional supplement determines a decrease in the acute-phase protein response together with an increase of albumin and fibrinogen in the liver [10,31].

Anti-inflammatory Agents

The production of eicosanoids is involved in the pathogenesis of cancer anorexia, and cyclooxygenase inhibitors have been shown to decrease tumor growth and improve anorexia. In humans, it was recently demonstrated that an integrated nutritional and metabolic approach, consisting of systemic anti-inflammatory treatment (indomethacin) combined with treatment to enhance erythropoietin levels, and individualized nutrition focused patient care (oral nutritional support and/or home total parenteral nutrition), prolonged survival and increased maximum exercise capacity in cancer patients [24,32].

CONCLUSION

Pancreatic cancer due to aggressive behavior of the tumor and relative frequency that appears to be increasing is a major health problem. About 80% of all pancreatic adenocarcinoma patients suffer from the cancer anorexia-cachexia syndrome. Although anorexia might be present, it is a phenomenon distinct from the loss of body tissue in cachexia. The pathogenesis of anorexia is most certainly multifactorial but the primary cause is often an increase in pro-inflammatory cytokines. Treatments to improve anorexia and stabilize or increase weight do exist, but their overall benefits in improving global quality of life and survival remain an issue of controversy.

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