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EDITORIAL

Anorexia-Cachexia Syndrome in Pancreatic Cancer: Recent Development in Research and Management

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Despite more than 30 years of clinical trials, the cure rate for pancreatic cancer remains less than 5% and the yearly incidence rate of this tumor virtually overlaps the mortality rate [1]. Only a small portion of patients presents potentially resectable disease but even for the patients undergoing a "curative" pancreaticoduodenectomy, the five-year survival rate remains very poor. Close to 100% of patients with pancreatic cancer develop metastases and die from the debilitating metabolic effects of their unrestrained growth; the actual median survival rate for patients with advanced disease is a dismal 3 to 6 months [2]. Compared to other tumors, pancreatic cancer has the highest incidence of cachexia reaching as much as 80% at the time of diagnosis [3, 4]; as a consequence, palliation of this occurrence remains one the most important therapeutic targets in clinical practice. Over the last few years, important new developments regarding the pathogenesis of pancreatic cancer cachexia have been achieved; unfortunately, these insights into the mechanisms of pancreatic cancer cachexia have led to only a small number of related clinical studies addressed to investigating new efficacious treatment modalities for these patients. This typifies the situation existing in modern research; all around the world, public and private institutions and pharmaceutical companies are clearly more oriented to investigating new chemotherapeutic agents potentially able to counteract tumor growth and prolong survival rather than sponsoring clinical studies aimed at ameliorating the quality of life of terminally ill patients.

Pathogenesis of Anorexia-Cachexia in Pancreatic Cancer

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) [5, 6], usually consists of a combination of anorexia, tissue wasting, malnutrition, weight loss and loss of compensatory increase in feeding. CACS represents the result of a complex interaction between cancer growth and host response, and is associated with a poor response to chemotherapy and with an increase in drug-related toxicity. The pathogenesis is multifactorial and incompletely understood (Figure 1). In synthesis, loss of appetite is a consequence of abdominal pain, restricted dietary intake due to pancreatic cancer-associated stenosis of the duodenum or maldigestion with exocrine pancreatic insufficiency. In addition, early satiety due to a lack of gastric accom-modation, gastroparesis or delayed antropyloric emptying is always present and it is accompanied by early postprandial bloating and severe nausea. Pancreatic cancer patients may frequently suffer from depression, constipation, debility or the side effects of treatment such as radiotherapy or

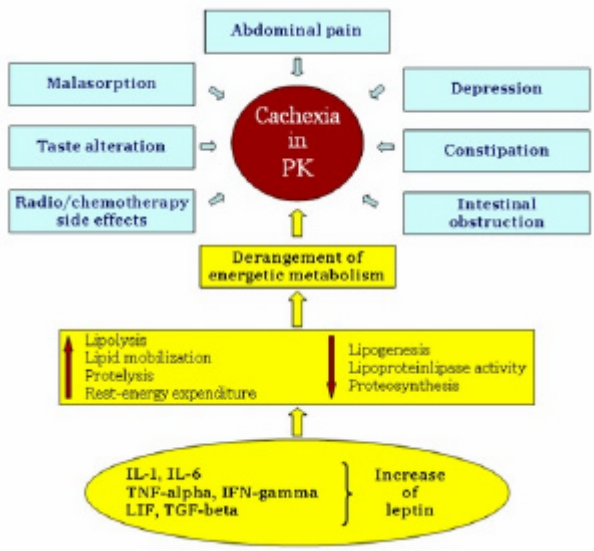


Figure 1. Pathogenesis of cachexia in pancreatic cancer. (PK: pancreatic cancer; IL-1: interleukin-1; IL-6: interleukin-6; TNF-alpha: tumor necrosis factor-alpha; IFN-gamma: interferon-gamma; LIF: leukemia inhibitor factor; TGF-beta: transforming growth factor-beta).

chemotherapy which may decrease food intake. It is also a common experience for physicians to observe deep changes in smell and taste in pancreatic cancer patients, with frequent aversion to specific foods capable of recalling unpleasant feelings, thus contributing to increasing anorexia. Another important pathogenetic factor is related to the occurrence of a complex catabolic state in pancreatic cancer patients, associated with specific disorders in host carbohydrate, protein, lipid and energy metabolism [6, 7, 8]. In other words, weight and muscle loss is not accounted for by the diminished nutritional intake alone but is also derived from some negative consequences of the host-tumor relationship and tumor-growth progression. The metabolic changes (Figure 1) seem to be mediated by a complex network of cytokines (proinflammatory, such as interleukins 1 and 6, tumor necrosis factor-alpha, interferon-gamma, leukemia inhibitor factor, transforming growth factor-beta), neuro-endocrine hormones and tumor-derived factors [9]. Chronic administration of the above-mentioned cytokines is able to reproduce the specific features of the CACS. These effects were obtained by means of long term inhibition of feeding by stimulating the expression and release of leptin. This hormone, secreted by adipose tissue, plays a crucial role in the homeostasis of body weight as its high levels in the brain decrease the activity of the hypothalamic orexigenic mediators (ghrelin, neuropeptide Y, agoutin, orexin, melanocortin-releasing hormone) and increase anorexigenic signals (cholecystok-inin, glucagon-like peptide, pro-opiomelan-ocortin, thyroid-releasing hormone, corticotrophin-releasing hormone, oxytocin). In addition, leptin levels regulate rest energy expenditure (high levels are capable of determining a considerable increase of energy expenditure). Thus, in pancreatic cancer, the equilibrium of body weight and energy regulation appears to be seriously compromised, through increased leptin levels, and oriented towards a continuous suppression of appetite and increase of energy expenditure [10].

Associated metabolic changes interest the main nutrients and are all oriented to a hypermetabolic status. Abnormalities in lipid metabolism include enhanced lipid mobilization (through the production of a specific lipid mobilizing factor by the tumor), decreased lipogenesis, and decreased activity of lipoprotein-lipase [11]. Protein metabolism is also affected by activation of proteolysis and inhibition of proteosynthesis; this results in a continuous loss of skeletal muscle mass and also appears to be related to the presence of a specific cancer proteolysis-inducing factor in the serum [12]. Cytokines and tumor products mediate wasting by suppressing gene products and the specific targets of these cachectic factors are presumed to be myofibrillar proteins. Experimental studies show that tumor necrosis factor-alpha and interferon-gamma strongly reduce myosin (heavy chain) expression through an RNA-dependent mechanism [13]. Protein degradation leads to the release of amino acids which are utilized in large amounts by the liver for gluconeogenesis. This extensive consumption of amino acids into the glucogenesis pathway causes wasting of lean body mass; in fact, glucose production for brain needs can not be replaced in pancreatic

cancer patients by the production of ketone bodies because of the severe depletion of body fat. The glucose catabolism by involving anaerobic metabolism more than oxidative metabolism may account for an additional daily energy loss [14].
Above all, complex metabolic and hormonal changes have recently been shown to be implicated in the CACS related to pancreatic cancer; many other mechanisms remain to be elucidated, including, for example, the role of the acute-phase protein-response produced by the host [8].

Attempts of Treatment

We all know that the best way to counteract CACS is to definitively cure the tumor responsible but, unfortunately, this represents a very infrequent event in pancreatic cancer. Despite trials of conventional and/or aggressive nutritional support using different feeding techniques, patients with CACS have failed to gain consistent significant benefits in terms of weight gain, quality of life or survival [15]. All the same, traditional approaches using enteral or parenteral nutrition in patients with pancreatic cancer undergoing pancreatic surgery have demonstrated no benefit either for symptom control or for survival [5, 7]. In addition, some experimental studies have suggested that intravenous and enteral nutrition may selectively stimulate tumor growth over host growth so that no positive effect can be gained [16]. For these reasons, quite recently, drugs capable of improving patient symptoms even without a significant improvement in their nutritional status have been investigated in CACS. In fact, the outcomes of drug studies on cachexia should realistically focus on the symptomatic and quality-of-life advantages rather than simply on nutritional end points, since the survival of CACS patients may be limited to weeks or months due to the incurable nature of the underlying malignancy.
The two major options for pharmacological therapy have been either progestational agents or corticosteroids. Progestogens, particularly megestrol acetate, are commonly used to treat CACS [l7]. 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. Recently, a meta-analysis (Cochrane Database Review [18]), involving 4,123 patients enrolled in randomized controlled trials, was carried out with the aim of investigating the efficacy of megestrol acetate as compared to a placebo or other drug treatments for anorexia-cachexia related to cancer, AIDS or other underlying pathologies. For all patient conditions, a meta-analysis showed the benefit of megestrol as compared to a placebo, particularly with regard to appetite improvement and weight gain in cancer patients. Unfortunately, there was insufficient information to define the optimal dose of megestrol in this setting. Because the bioavailability of megestrol acetate directly affects its efficacy and safety, the formulation was recently refined to enhance its pharmacokinetics. Such efforts yielded megestrol acetate in a tablet form, followed by a concentrated oral suspension form, and an oral suspension form developed using nanocrystal technology, designed specifically to optimize drug delivery and enhance the bioavailability of drugs which have poor solubility in water [19]. In clinical practice, megestrol (mean dosage of 320-480 mg/day) is often associated with corticosteroids (doses equivalent to about 40 mg daily of prednisone). 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 [2]. The effect 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. In long-term treatment, the negative effects of corticosteroids (dysmetabolism, osteoporosis, myopathy, increased risk of infections) could overwhelm potential advantages. Megestrol was also associated with ibuprofen, a cyclooxygenase inhibitor capable of inducing a decrease in resting energy expenditure in pancreatic cancer [20]. Two studies have been

published on this subject [21, 22] and the results seem to be encouraging.

Omega-3 polyunsaturated fatty acids have been shown to modulate levels of proinflammatory cytokines, hepatic acute-phase proteins, eicosanoids, and tumor-derived factors in animal models of cancer and may reverse some aspects of the process of cachexia [23]. 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 [24]. 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 [25]. In the study of Wingmore *et al*. [26], 18 patients with advanced pancreatic cancer received dietary oral supplementation with fish oil (12 g/day, with EPA 18% and DHA 12%). After a median 3-month supplement-ation, positive changes in weight together with a significant reduction of acute-phase protein production and the stabilization of resting energy expenditure were registered. Similar results were obtained in 20 patients receiving 2 g/day of EPA who showed a significant weight gain and improvement in performance status and appetite at 3 and 7 weeks of supplementation [27]. The same authors [28] observed a significant fall in the production of interleukin-6, a rise in serum insulin concentration, a fall in the cortisol-to-insulin ratio, and a fall in the proportion of patients excreting proteolysis-inducing factor in 20 weight-losing patients with pancreatic cancer assuming a nutritional supplement (600 kcal/day and 2 g/day of EPA for 3 weeks); all these changes occurred in association with significant weight gain. Recently, the results of a study aimed at comparing a protein and energy dense supplement enriched with n-3 fatty acids and antioxidants *versus* an isocaloric isonitrogenous control supplement in CACS patients with advanced pancreatic cancer were published [29]. A total of 200 patients were enrolled in a multicenter, randomized, double blind trial. Over the eight weeks of treatment, patients in both groups stopped losing weight and lean body mass to an equal degree. Comparisons based on the intention-to-treat approach indicated that, at the mean dose taken, enrichment with n-3 fatty acids did not provide a therapeutic advantage and that both supplements were equally effective in arresting weight loss. Post-hoc dose-response analysis suggests that, if taken in sufficient quantity, only the n-3 fatty acid enriched energy and protein dense supplement results in a net gain of weight, lean tissue, and improved quality of life.

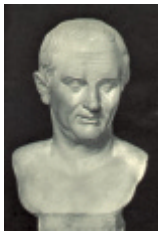
At the moment, considering the results of the above-mentioned clinical trials of n-3 polyunsaturated fatty acids, the conclusions should encourage further investigation into dietary fish oil supplementation for CACS, including the most effective route of administration and the proper dosage to promote optimal weight maintenance and to limit side effects [30].

Since proinflammatory cytokines, especially tumor necrosis factor-alpha, play a prominent role in the pathogenesis of CACS in pancreatic cancer, systemic inflammation remains an important area for novel therapeutic targets in combating this syndrome. Thalidomide, which is an inhibitor of tumor necrosis factor-alpha synthesis, may represent a rational therapeutic approach. In 2005, Gordon *et al*. published the results of an interesting study aimed at assessing the safety and efficacy of thalidomide in attenuating weight loss in patients with CACS secondary to advanced pancreatic cancer [31]. The study population consisted of 50 patients (who had lost at least 10% of their body weight) randomized to receive thalidomide 200 mg/day or a placebo for 24 weeks in a single centre, double blind, randomized controlled trial. The primary outcome of the study was a change in weight and nutritional status. Thirty-three patients (16 control, 17

thalidomide) were evaluated at 4 weeks, and 20 patients (8 control, 12 thalidomide) at 8 weeks. At 4 weeks, the patients who received thalidomide had gained, on average, 0.37 kg in weight and 1.0 cm^3 in arm muscle mass as compared to a loss of 2.21 kg (P=0.005) and 4.46 cm^3 (P=0.002) in the placebo group. At eight weeks, patients in the thalidomide group had lost 0.06 kg in weight and 0.5 cm^3 in arm muscle mass as compared to a loss of 3.62 kg (P=0.034) and 8.4 cm^3 (P=0.014) in the placebo group. The conclusions of the study strongly suggest that thalidomide was effective for attenuating loss of weight and lean body mass in patients with CACS due to advanced pancreatic cancer; furthermore, the drug was well-tolerated with additional advantages related to oral administration and to the low cost of the treatment.

Conclusions

In recent years, research has characterized CACS as a multidimensional complication of pancreatic cancer which results from a complex interaction of metabolic changes induced by the tumor directly or by the host-response, and from the presence of comorbidities. Now the time for the scientific community to step up the search for new therapeutic modalities and drugs capable of improving the quality of life in the final stages of pancreatic cancer. Psychological distress and psychiatric disorders frequently contribute to CACS; thus, the, contemporary use of psychological and behavioral interventions, such as relaxation, hypnosis or group-psychotherapy, should be investigated as they can potentially have a positive effect on the quality of life of these terminally-ill patients.



"… dolor …, ut eius magnitudinem celeritas, diuturnitatem allevatio consoletur. …"

"… promptness alleviates the intensity of pain and this relief is of some comfort over its long duration. …"

M. Tulli Ciceronis (106 B.C. - 43 B.C.) De Finibus Bonorum et Malorum Liber Primus.

Keywords Anorexia; Cachexia; Cytokines; Eicosapentaenoic Acid; Docosahexaenoic Acids; Pancreatic Neoplasms; Stress, Psychological; Thalidomide

Abbreviations CACS: cancer anorexia-cachexia syndrome; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid

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