BMS

Review

Pancreatic cancer and nutrition

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ABSTRACT

Although there was a progress in surgical and oncological treatment of pancreatic cancer in a recent decade, pancreatic cancer remains a disease with a dismal prognosis, with 5-year survival of only 5 percent. Operable pancreatic cancer patients have better prognosis (around 25 percent are still alive after 5 years), but most of the patients are inoperable at the time of diagnosis. Considering low operability and higher tendency for weight loss and tumor-induced systemic inflammation, pancreatic cancer patients have high incidence of cachexia. Cachexia in cancer patients is associated with lower quality of life, shorter survival and lower tolerance of anti-tumor therapy. All pancreatic cancer patients, both with operable, inoperable or disseminated disease, should be screened and treated for cachexia. Nowadays, treatment of cachexia should me multimodal and multidisciplinary.

KEYWORDS: cachexia; malignant neoplasms; enteral nutrition

INTRODUCTION

In Croatia, pancreatic cancer is the 4th leading cause of cancer death, despite being the 8th most incident cancer, with stabile incidence and mortality rates in the last five years. Most of the patients with newly diagnosed pancreatic cancer are between 65-79 years of age (1). The majority of pancreatic adenocarcinomas are located in the head of the pancreas, with pain, jaundice and weight loss being the most common presenting symptoms (2). Because of the late presentation of the disease, only 15-20 percent of patients with pancreatic cancer have operable disease at the time of diagnosis. For operable pancreatic cancers, pancreaticoduodenectomy is the most common operative treatment. Although the mortality rates after pancreaticoduodenectomy have dropped to 5 percent in high-volume centers (3-5), the morbidity remains high, 30-45 percent. Most of the postoperative complications are intraabdominal abscess, sepsis, pancreatic fistula and delayed gastric emptying (4, 6-8).

PANCREATIC CANCER AND NUTRITION

More than 80% of patients with pancreatic cancer suffer from significant weight loss at the time of diagnosis and over time develop severe cachexia (9). Cachexia is 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, or infective diseases like tuberculosis or HIV infection. Most frequently it occurs with malignancies (10). Pancreatic, gastric,

esophageal and lung cancer patients have the highest risk for malnutrition and development of cachexia-anorexia cancer syndrome (11). In cancer patients, the presence of cachexia is associated with poor prognosis, reduced treatment tolerance and a marked reduction in the quality of life (QoL) (10). According to the international consensus from 2011, cachexia is defined as unintended weight loss of more than 5% of body weight or weight loss of more than 2% in individuals with a BMI of less than 20 kg/m2 over 6 months. Sarcopenia (skeletal muscle depletion) with any degree of weight loss of more than 2% is classified as cachexia (12).

Skeletal muscle depletion can be measured with anthropometry of mid-upper-arm muscle area, appendicular skeletal muscle index, lumbar skeletal muscle index and whole-body fat-free mass index without bone, determined by bioelectrical impedance (13). Recent studies, based on CT scan based measurement of different body tissue masses and quantification of tissue loss in muscle, subcutaneous and visceral adipose tissue, have shown that loss of muscle tissue and the loss of VAT worsens prognosis in pancreatic cancer patients (14, 15). The presence of muscle wasting in obese patients with advanced pancreatic cancer is associated with shortened survival (16).

Weight lost in pancreatic cancer patients is a result of reduced food intake, abnormal metabolism or the most commonly, combination of the two. Reduced food intake can be related to anorexia, fatigue, abdominal pain, vomiting, nausea, diarrhea, steatorrhea, or postoperative complication (delayed gastric emptying) (Figure 1).

The mechanisms that lead to cachexia are still poorly understood, but it is probably a complex of multiple, interactive patient- and tumor- specific components, such as metabolic and humoral changes as well as physiological issues, like anorexia, fatigue and adverse effects of anticancer therapies. The liver has a central role in development and regulation of cachexia in pancreatic cancer patients. An initiating step is the production of pro-inflammatory cytokines by the tumor (10, 17, 18).

Cytokines activate peripheral blood mononuclear cells as they pass through the tumor and induce a systemic inflammation through the hepatic acute-phase protein response (APPR) which increases the need for free amino acids. Skeletal muscle wasting is mostly caused by reduced protein synthesis which is actively inhibited by tumor derived or endogenous substances like proteolysis inducing factor, and increased muscle degradation caused by increased activity of proteolytic pathways (exact mechanism of
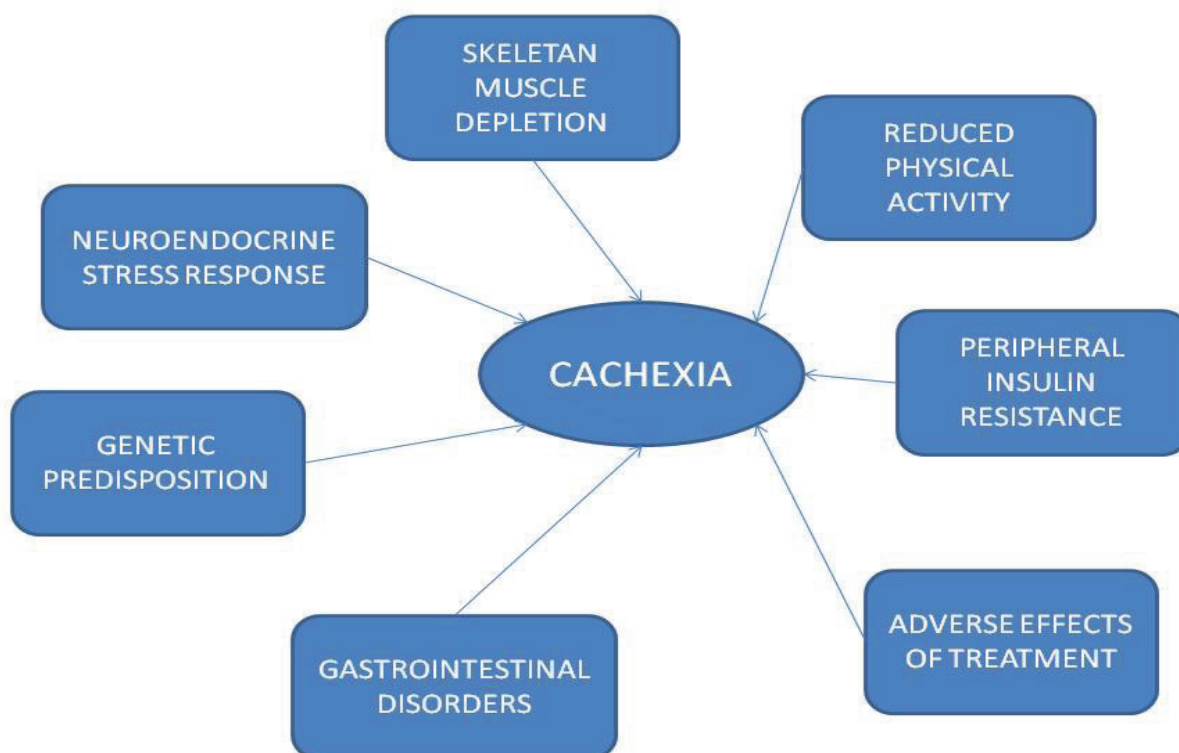
Figure 1. Development of cachexia.
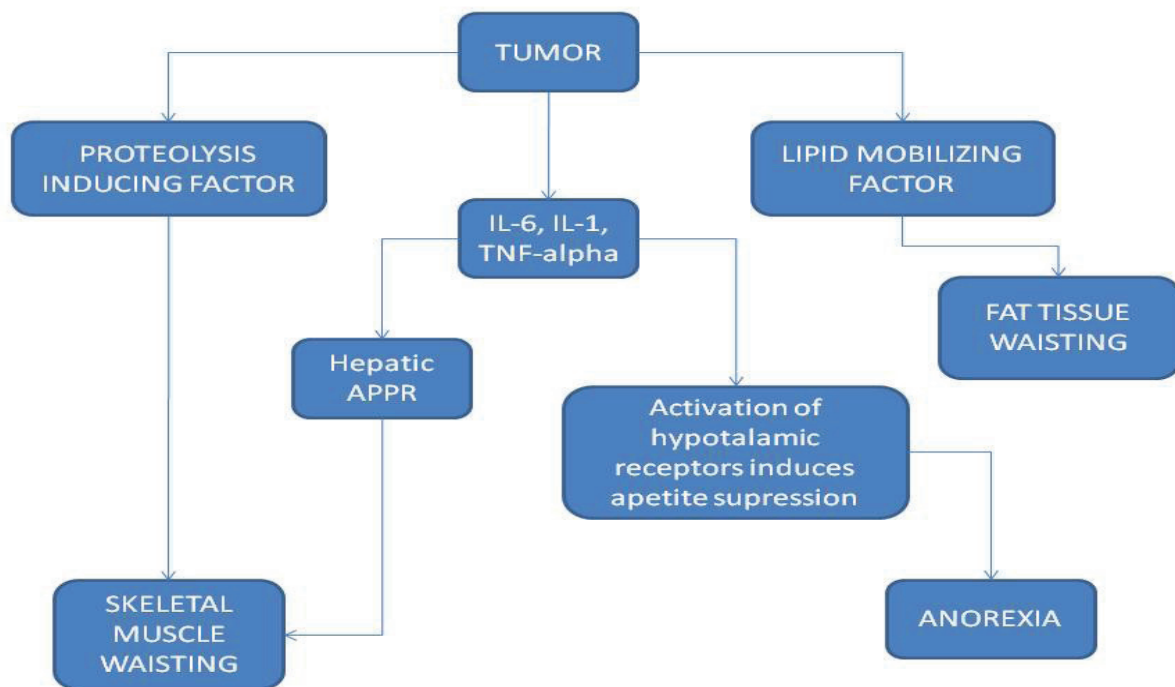
Figure 2 . Pro-inflammatory cytokines produced by the tumor.

activation is not yet known)(17) (Figure 2).

Hepatic acute-phase protein response is induced by pro-inflammatory cytokines: interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-alpha). Patients with APPR have significantly higher resting energy expenditure, an accelerated rate of weight loss and reduced survival. Systemic inflammatory response is represented by a serum C-reactive protein concentration of 10 mg/L and higher.

TNF-alpha, IL-1 and IL-6 are transported across the blood brain barrier and suppress appetite by acting on central receptors in the hypothalamus, causing dysfunction in hypothalamic processing of homeostatic feedback signals, causing anorexia and fatigue (17).

PREOPERATIVE EVALUATION

Because most of the patients with pancreatic cancer will develop cachexia during the course of the illness, all of the patients with pancreatic cancer should be evaluated for nutritional risk, using preoperative evaluation. Recent studies have demonstrated that multimodal therapeutic options can alleviate cachexia and improve patients' outcome (19).

Evaluation of the nutritional intake, weight loss in the last 6 months physical   performance, and measurement of body mass index (BMI) are necessary steps in preoperative evaluation and risk stratification. For risk stratification we can

use screening tools like SGA (subjective global assessment), MUST (malnutrition universal screening tool) and NRI (nutritional risk index). Also, CT scans are used for quantification of tissue loss in muscle, subcutaneous and visceral adipose tissue, which is especially important for obese patients because it can detect occult sarcopenia; and bioelectrical impedance analysis as a method for estimating body composition.

The aim is to detect nutritional dysfunction at early stage and to evaluate degree of systemic inflammation (low albumin levels, CRP higher than 10 mg/L), because early identification and intervention reduces morbidity, length of stay and admission cost in hospitalized patients (19).

PERIOPERATIVE AND POSTOPERATIVE NUTRITION

According to the ESPEN guidelines from 2016 in surgical cancer patients at moderate or severe nutritional risk preoperative nutritional support for 10-14 days is highly recommended, even if surgery needs to be delayed. Oral nutritional support is not indicated in well-nourished patients (20).

Postoperatively early initiation of oral liquids with simultaneous enteral nutrition supplied beyond anastomoses is recommended in patients that cannot achieve >60% of their nutritional needs within 10 days or with obvious undernutrition at the time of surgery. Later in the postoperative course, oral feeding is the preferred modality following

pancreatic surgery. If oral feeding is not possible, then enteral nutrition should be implemented via tube passed through the nose or abdominal wall. Compared to parenteral nutrition, enteral nutrition showed reduced infections rates, decreased mortality, shorter length of stay, and is more cost effective. Parenteral nutrition is indicated in malnourished patients in whom enteral nutrition is not tolerated within 7-10 days of their procedure (20, 21).

For malnourished cancer patients protein intake should be up to 1.5 g/kg/day and fat intake 35-50% of total energy requirements. Patient should consume high-protein oral or enteral nutritional supplements, 1000-1500 calories per day in the form of balanced essential amino-acid mixtures, given between meals. For patients with vitamin D and exocrine pancreatic insufficiency adequate supplementation should be given (20).

Some dietary supplements have beneficial impact on the reduction or reversion of weight loss, like omega fatty acids (EPA and DHA), derived largely from fish oil (22, 23), that modulate levels of pro-inflammatory cytokines, and L-carnitine who is required to transport fatty acids into the mitochondrial matrix (24).

TREATMENT OF CACHEXIA

Most cancer patients have a combination of reduced food intake caused by anorexia and metabolic changes. Although reduced food intake can be treated with additional nutritional support, the combination is more difficult to treat. Because of the high prevalence of malnourishment and rapid development of the anorexia-cachexia syndrome early nutritional intervention is crucial.

Considering the treatment of cachexia, clearly the best treatment is to remove the tumor. In addition to successful surgical procedure, or if removal of the tumor is not possible, additional measures include increased nutritional intake (small, frequent, high-calorie meals with high-protein nutritional supplements +/- dietary supplements are recommended)(20), the treatment of symptoms like chronic pain, depression, fatigue, nausea, vomitus, steatorrhea, GI obstruction, constipation and maintenance of adequate level of physical activity which support muscle mass and physical function (25).

For appetite stimulation, corticosteroids, progesterone analogs, cannabinoids and serotonin antagonists have been well evaluated. Corticosteroids and progesterone analogs have shown some benefit for appetite stimulation in cancer patients with cachexia. Corticosteroids, which inhibit activity of prostaglandin and suppress central effects of IL-1 and TNF alpha, were first–line therapy for appetite stimulation. Patients treated with corticosteroids have increase in appetite but do not gain weight. Corticosteroids can be administered only for short term use, up to 2 weeks, because of serious side effects (26-28). Other drug that can be used as appetite stimuli are progesterone analogs (megasterol acetate and medroxyprogesterone acetate) which act through neuropeptide Y. A Cochrane review from 2013 compared megestrol with placebo and concluded that megestrol improved appetite and weight in patients with anorexia-cachexia syndrome (29). In patients with advanced cancer synthetic cannabinoids did not show activity against anorexia and they are not recommended in Europe (30). Considering anti-inflammatory drugs, like non-steroid anti-inflammatory drugs (NSAIDs) (ibuprofen and indomethacin) and selective cyclooxigenase-2 inhibitors, a recent review showed an improvement in body weight and quality of life in cachectic patients, but because of a small number of patients involved, there are still no recommendations for use (31, 32). Anti-cytokine drugs like TNF-alpha inhibitors (thalidomide, pentoxifylline) or IL-6 antibodies failed to improve weight loss in cachectic cancer patients (33-35).

KEY POINTS

At the time of the diagnosis, we have to ask two questions: what is the nutritional status of the patient and must we provide perioperative nutritional support?

Prevention of cachexia is much more effective then treatment of cachexia, so all cancer patients should be screened for cachexia, first at the time of diagnosis and then later in the course of the disease. It is important to remember that early stages can easily be missed, especially in obese patients. Removal of the tumor is the best treatment, but if that is not possible, or in case or recurrent or disseminated disease, multimodal therapy should be offered to the patient, including nutritional support, exercise, appetite stimulation and treatment of secondary symptoms (pain, diarrhea, stomatitis, anemia, fatigue, depression, immunosuppression). Combination protocols, which will include oral nutritional supplementation with n-3 fatty acids and antioxidants in combination with anti-inflammatory drugs will be recommended in treatment of cachectic cancer patients.

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