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Review

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ABSTRACT

Cachexia is defined as an unintended loss of stable weight exceeding 10%. Patients with advanced cachexia express anorexia, early satiety, severe weight loss, weakness, anemia, and edema. 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) and 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. In advanced cachexia (mostly in metastatic cancer and terminally disease) any interventions with nutritional suplements are ineffective. Therefore, nutritional support in the reversion of tumor cachexia and in the importance of maintaining patient weight, muscle mass, quality of life, has the exceptional importance, becouse good nutritional status of patients leads to the possibility of more aggressive and longer treatment and thus to longer survival.

Key words: *cancer, cachexia, anorexia-cachexia syndrome, malnutrition, nutrition supplements*

Introduction

In the year 2011, an international consensus defined cancer cachexia as a multifactorial syndrome characterized by ongoing loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment[1]. An international panel of experts on cachexia recently developed a classification system, which recognises that cachexia occurs across a continuum, varying in severity and stage: pre-cachexia: early clinical or metabolic signs of cachexia, low-grade weight loss, which may progress to cachexia, cachexia: weight loss >5% in the last 6 months or a combination of >2% weight loss with low muscle or low BMI, and refractory cachexia: occurs close to death due to rapidly progressing disease, which is unresponsive to anticancer therapy[2–4]. Diagnostic criteria include weight loss greater than 5% over the past 6 months, weight loss greater than 2% in individuals with body mass index (BMI) less than 20 kg/m^2, or evidence of sarcopenia with any degree of weight loss greater than 2%. »Cancer anorexia-cachexia syndrome« (CACS) and usually consists of a combination of anorexia, tissue wasting, malnutrition, weight loss and loss of compensatory increase in feeding. CACS is a multifactorial syndrome characterized by progressive loss of skeletal muscle mass with or without loss of fat mass that cannot be reversed by conventional nutritional support. The highest prevalence is seen in patients suffering from gastrointestinal and pancreatic adenocarcinoma with 80–90% incidence followed by prostate and lung cancer[3]. Malnutrition is the most common secondary diagnosis in cancer patients[4]. It is present in 8–88 % of cancers, and up to 80% in the cancer of the upper gastrointestinal tract[5].

Mechanisms of Cancer Cachexia

Systemic inflammation

Even patients who are eating can become malnourished because of specific biochemical and metabolic changes associated with cancer. These metabolic changes impair nutritional status and contribute to cancer-related malnutrition, anorexia, and cachexia. Recent reviews indicate cachexia is even more widespread among patients with advanced cancer. Malnutrition places patients with cancer at greater risk for complications associated with surgery,

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chemotherapy, and radiation therapy. Mechanical digestive abnormalities can result in a lack of appetite and reduced food intake[5]. Patients with pancreatic cancer suffer from pain, fatigue, nausea, dysphagia, gastroparesis, duodenal stenosis, pancreatic insufficiency and malabsorption, and constipation. Cancer cachexia is a multifactorial syndrome characterized by uncompensated adipose tissue and skeletal muscle loss in the setting of anorexia that leads to progressive functional impairment[6]. There is evidence that anorexia and hypercatabolism are driven by cytokines (IL-6, TNF-alpha), circulating hormones, neuropeptides, neurotransmitters, and tumor-derived factors. Elevated C reactive protein (CRP > 10 mg/L levels), an indirect measure of systemic inflammation, has been associated with cachexia and poor prognosis in pancreatic cancer patients. Cytokines produced by tumor cells or released by the host as a response to the cancer affect various pathways (central pathways, which are hypothalamus-mediated, and peripheral pathways, which involve direct lipolysis and proteolysis)[6]. Increased cytokine expression prevents the hypothalamus from responding appropriately to peripheral signals by persistent stimulation of anorexigenic pathways and inhibition of orexigenic pathways. Recent studies have also discovered neural invasion and abnormalities in the muscle microenvironment in pancreatic cancer cachexia[7].

Adipose Tissue Depletion and Hypermetabolism

Zinc-α2-glycoprotein (ZAG), apolipoproteins apo C-II and apo C-III and glucagon-like peptide-1 (GLP-1) were identified as markers for pancreatic cancer-associated cachexia syndrome. GLP-1 secretion by ileal cells is dependent on the presence of nutrients in the lumen of the small intestine. It is a potent antihyperglycemic hormone, inducing glucose-dependent stimulation of insulin secretion while suppressing glucagon secretion.

Many tumors secrete pro-inflammatory factors tumor necrosis factor alpha (TNFα), interlekin (IL-) 6 and procatabolic factors ZAG. The factors released by the host as a antitumor immune response are interferon gamma (IFNγ). They are also responsible for promoting degradative pathways in skeletal muscle and adipose tissue[2,5]. Dysregulated lipid metabolism is a hallmark of cancer. Functions of lipids are critical in malignant tumors as they are necessary not only for providing the membrane constituents of proliferating cells but also for energetic, biophysical, and signaling pathways that drive tumorigenesis[2]. For example, injection of lipid-mobilizing factor from cachectic cancer patients promotes whole body fatty acid oxidation in mice and cachexia[5].

Protein degradation and Muscle Atrophy

Cachexia-related muscle wasting results from a disturbance of the tightly regulated balance of muscle protein breakdown and synthesis[5]. Some studies suggest that proteolysis inducinf factor (PIF) mediated protein degradation may involve the ubiquitin-proteasome proteolytic pathway. PIF has also been shown to induce total protein degradation and myosin depletion while actin levels remain unchanged. The mechanism for transcription factor NFκB activation by PIF is not fully understood. Protein degradation is thought to be mediated by the activation of NFκB. A recent study identifying serum proteins involved in pancreatic cancer cachexia identified ZAG as a possible marker. ZAG not only increases lipid mobilization through various pathways but it also increases substrate utilization and activates mitochondrial oxidative pathways in brown adipose tissue resulting in lipolysis, increased energy expenditure, and hypercatabolism. There also is evidence that cachexia-associated insulin resistance could result in increased protein degradation of skeletal muscle[8].

Management of Cancer Cachexia

Clinical management of cachexia is currently limited and complex. The current treatment strategies are based on the following factors: oncological therapy with optimal control of the tumor; nutritional support; and pharmacological treatment. Since cancer cachexia is a multifactorial syndrome, successful treatment will likely involve a multimodal approach.

Apetite stimulators

Megestrol acetate is a semi-synthetic progesterone currently used as an appetite stimulant[9]. When megestrol acetate was first introduced in the treatment of disseminated breast and endometrial cancer, patients developed weight gain and increased appetite as a side effect. The pharmacologic activity of megestrol acetate in appetite stimulation and weight gain may be related to decreased production and release of pro-inflammatory cytokines (IL-6, TNF-α) and stimulation of neuropeptides in the hypothalamus[10]. In 1993, the Food and Drug Administration (FDA) approved megestrol acetate for the treatment of cancer anorexia-cachexia syndrome. Corticosteroids are effective in ind. cing an increase in appetite, food intake, weight gain, and sense of well-being However, the effects are short lived (less than 4 weeks) and associated with long-term side effects, such as insulin resistance, fluid retention, steroid-induced myopathy, skin fragility, adrenal insufficiency, and sleep and cognitive disorders. Cannabinoids, dronabinol is effective in reducing nausea and increasing appetite with associated weight stabilization. A phase II trial showed that dronabinol reduced anorexia in 68% of patients, but 16% of patients had to suspend treatment due to toxicity[11]. Appetite stimulation appears to be mediated by interaction with endorphin receptors, interference with interlekin (IL-)1 synthesis, activation of cannabinoid receptors involved in the neurochemical circuit of leptin, and prostaglandin synthesis inhibition[12].

Nutrition supplemets

Nutritional support, addressing the specific needs of this patient group, is required to help improve prognosis, and reduce the consequences of cancer-associated nutritional

decline. Early intervention with nutritional supplementation has been shown to halt malnutrition, and may improve outcome in some patients. Nutritional counseling, supplemental feeding and pharmacological support do temporarily stop weight loss and improve appetite, social life and quality of life. The beneficial effect of eicosapentaenoic acid in cancer patients is widely described especially in relation to its role in tumour cachexia[13]. It is obtained in the human diet by eating oily fish or fish oil, e.g. cod liver, herring, mackerel, salmon, menhaden and sardine, and various types of edible seaweed. Benefits to patients included preservation of lean body mass, increased physical activity, improved appetite and weight gain[14–16]. Recent studies describing the cancer protective effect of the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have sparked a renewed interest in using these fatty acids for cancer prevention and treatment. EPA and DHA have been shown to have multiple anti-tumour actions that affect all of the original six essential alterations that dictate malignant growth. Furthermore, EPA and DHA, have immunomodulatory properties and have been shown to suppress production of pro-inflammatory cytokines, including IL-1, TNF-α, and IL-6 by periferal blood mononuclear cells. DHA is also known to modulate steroid receptors in human cancer cell lines[10]. EPA may also inhibit the downstream effects of Lipid mobilizing factor (LMF) and PIF. Supplementation based on an oral powder formula enriched with 1.5 g EPA during one month in cancer patients improved certain inflammatory parameters. Studies suggest that EPA, an omega-3 fatty acid, augments weight, appetite, and survival in cancer-associated wasting administered alone or with megestrol acetate[17]. Their anticancer actions is implicated in various stages of cancer development, including cell proliferation, cell survival, angiogenesis, inflammation, metastasis and epigenetic abnormalities that are crucial to the onset and progression of cancer[18]. DHA has also been shown to modulate heat shock proteins that act as »chaperones« in protein: protein interactions and in cell membrane transport[19]. EPA and DHA suppress nitrite oxide production in macrophage cell lines in a dose dependant fashion[20]. Total parenteral nutrition is a standard component of supportive treatment in oncology units for patients undergoing intensive therapy. Total parenteral nutrition (PN) has been shown to significantly affect postoperative outcomes in the severely malnourished patient group. It was shown that omega-3 fish oil fat emulsion-based parenteral nutrition alleviates the inflammatory reaction and reduces the rate of inflammatory complications[21]. In general cancer patient population, enteral formulations remain cheaper to administer than those given intravenously[22].

Future Directions

Immunotherapy

Tumor cells can manage to escape the anti-tumor immune responses. Revealing the underlying mechanisms for solid pediatric tumors could foster development of tumor-specific and immunologic anti-cancer therapies. Such immunological escape mechanisms could be treated pharmacologically. Immunotherapy with lenalidomide enhanced activation of natural killer cells and inhibited their suppression by NFκB induced IL-6 or transforming growth factor-β1 within the tumor environment[17]. Thalidomide is known to have anti-inflammatory and immunomodulatory properties[23]. It has been shown to downregulate the production of TNF-α and other cytokines, inhibit NFκB, downregulate cyclooksigenase (COX-)2, and inhibit angiogenesis. Multiple small studies have demonstrated the efficacy of thalidomide in improving appetite, weight gain, and sensation of well-being[24].

Zync

Altered Zn metabolism may contribute to systemic inflammation observed in cancer cachexia because Zn homeostasis is critical for efficient immune function. Zn dysregulation in the pathogenesis of pancreatic cancer and the use of Zn therapy and Zn transporters as potential therapeutic targets[25].

Ghrelin

Ghrelin, a 28-amino acid peptide, was isolated from the human and rat stomach and identified in 1999 as an endogenous ligand for the ghrelin receptor (GHS-R) type 1a. Ghrelin mediates its anorexigenic action via stimulation of neurons within the hypothalamus[26]. GHS-R is expressed in the vagus nerve. Brainstem and vagus nerve may contribute to the effects of ghrelin on food intake. Blockade of gastric vagal afferents in rats abolishes ghrelin-induced feeding. In neoplastic disorders, a proliferative effect of ghrelin has been documented as well[27].

L-carnitine

Patients with pancreatic cancer may have a clinically relevant benefit from the inexpensive oral supplementation of L-Carnitine. L-Carnitine significantly improved the fatigue domain. Carnitine was well tolerated, and no drug-related adverse effects were identified. Intravenous L-carnitine treatment increased plasma carnitine concentrations, improved patient-assessed fatigue[28].

Exercise

During cachexia muscle strength and endurance are dramatically reduced, limiting the ability to perform daily activities and severely affecting the patient's quality of life. Different studies have emphasized that a single therapy may not be completely successful in the treatment of cachexia. Beyond pharmacological strategies, growing evidence, nevertheless, shows that chronic exercise, employed as a tool to counteract systemic inflammation, may represent a low-cost, safe alternative for the prevention/attenuation of cancer cachexia. Despite the well-documented capacity of chronic exercise to counteract sus-

tained disease-related inflammation, few studies address the effect of exercise training in cancer cachexia[29]. When considering exercise in cancer, several factors have to be taken into consideration, in particular those alterations that could limit the capacity to perform exercise and consequently the resulting beneficial or detrimental effects. Actually, many cancer patients suffer from chronic fatigue, either from the disease itself or its treatment, the latter being a confounding factor that limits exercise practice.

Conclusion

Cachexia is a complex metabolic syndrome characterised by unintentional weight loss and depletion of skeletal muscle, with or without loss of adipose tissue. Cachexia is prevalent in chronic or end-stage cancers, and nearly half of all cancer patients experience some degree of weight loss. The original principles of nutrition care for people diagnosed with cancer were developed in 1979 and are still very relevant today. Proactive nutritional care can prevent or reduce the complications typically associated with the treatment of cancer. Two decades of exploratory investigation of the manifestations, meaning and management of cancer cachexia reveal emotional and social impacts for both patients and their carers. Although new insights to the pathogenesis of cancer cachexia have been gained over the past decade, the underlying mechanisms leading to this syndrome are not fully understood[30]. At the moment, there is no single therapy able to reverse cachexia many symptoms, which include disruption of intermediary metabolism, endocrine dysfunction, compromised hypothalamic appetite control, and impaired immune function, among other.

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NUTRITIVNA POTPORA KOD BOLESNIKA S KARCINOMOM

S A Ž E T A K

Kaheksiju definiramo kao nenamjerni gubitak stjelesne težine više od 10%. Bolesnici s uznapredovalom kaheksijom i izrazitom anoreksijom imaju jak gubitk tjelesne težine, slabost, anemiju i edeme. Anoreksija predstavlja nastanak gubitka apetita dok je kaheksia stanje stalno prisutnog mršavljenja. Ovaj sindrom, nazivaju »karcinom anoreksija – kaheksija sindrom« i obično se sastoji od kombinacije anoreksije, slabog apetita, opće slabosti, progresivnog gubitka težine te gubitka kompenzacijskog povećanja hranjenja. »Karcinom anoreksija – kaheksija sindrom« je rezultat složenog međudjelovanja između napredovanja karcinoma i odgovora domaćina te je povezana s lošim odgovor na kemoterapiju i povećanjem toksičnosti povezane s lijekom. U uznapredovaloj kaheksiji (uglavnom kod metastatskog karcinoma u terminalnoj fazi bolesti) bilo kakve intervencije dodavanja nutritivne potpore su ipak neuspješne. Dakle, nutritivna potporu potrebno je na vrijeme započeti stoga što uhranjenost tj. neuhranjenost bolesnika dovodi u pitanje primjenu agresivnije i dugotrajnije terapije i na taj način dulje preživljavanje onkološkog bolesnika.