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Cancer Cachexia

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Introduction

Cancer anorexia-cachexia (CACS) is defined 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]. Cancer cachexia occurs across a continuum, varying in severity and stage; according to new classification we have pre-cachexia (early clinical signs of cachexia, low-grade weight loss), which may progress to 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 due to rapidly progressing disease, and is unresponsive to anti-cancer therapy) [2-4]. CACS cannot be reversed by conventional nutritional support. The highest prevalence of this syndrom is seen in patients suffering from gastrointestinal and head and neck cancers (up to 90% of cases) [3-5].

Pathophysiology of Cancer Cachexia

Specific biochemical and metabolic changes are associated with cancer leading to impairment of nutritional status and contributing to cancer-related malnutrition, anorexia, and cachexia. Patients with cancer and CACS are at greater risk for complications associated with surgery, sistemic antitumor therapy and radiation therapy. Malnutrition can be also caused by mechanical digestive abnormalities and resulting in a lack of appetite and reduced food intake [5]. Cancer patients can express pain, nausea, dysphagia, they can develop duodenal stenosis, and peritoneal carcinomatosis which is also leading to malnutrition.

CACS is a multifactorial syndrome different of malnutrition and driven by complex pathophysiological pathways [6]. Anorexia and hypercatabolism are caused by cytokines (IL-6, TNF-alpha), hormones, neuropeptides, neurotransmitters, and tumor-derived factors. CACS is always connected to systemic inflammation (CRP >10 mg/L) [6,7].

Cancer affect central pathways which are hypothalamus-mediated, and peripheral pathways, which involve direct lipolysis and proteolysis, also cytokines production (by tumor cells or by the host) seems to be connected to that pathways [6]. Increased cytokine expression is precluding hypothalamus to responding appropriately to peripheral signals by persistent stimulation of anorexigenic pathways and inhibition of orexigenic pathways. Excess of cytokines in the serum due to cancer (eg, tumor necrosis factor alpha [TNFα], IL-6) and pro-catabolic factors (eg, zinc α_2-glycoprotein [ZAG]); and factors released by the host as a response (eg, interferon gamma [IFNγ] and ZAG), are responsible for promoting degradative pathways in skeletal muscle and adipose tissue [2,5]. Patients with pancreatic cancer and CACS have also abnormalities in the muscle microenvironment (neural invasion)[7]. In pancreatic cancer patients , zinc-α_2-glycoprotein (ZAG), apolipoproteins apo C-II and apo C-III and glucagon-like peptide-1 (GLP-1) were identified as markers for CACS. Function of lipids is crucial in malignant tissue due to providing the membrane constituents of proliferating cells and for energetic, biophysical, and signaling pathways that drive tumorigenesis (injection of lipid-mobilizing factor from cachectic cancer patients promotes whole body fatty acid oxidation in mice with non small cell lung cancer and cachexia) [2,5].

Muscle wasting in CACS is consequence of a disturbance of the tightly regulated balance of muscle protein breakdown and synthesis [5]. Proteolysis inducing factor (PIF) is inducing total protein degradation and myosin depletion while actin levels remain unchanged and is connected with the ubiquitin-proteasome proteolytic pathway. Protein degradation is mediated by the activation of $NF_{\kappa}B$ which is activated by PIF with till now, unclear mechanism. According to some studies, Lipid Mobilizing Factor (LMF) and ZAG are a possible markers for CACS. Through various pathways LMF/ZAG are increasing lipid mobilization and utilisation, and activates mitochondrial oxidative pathways in brown adipose tissue. Result is lipolysis, increased rest energy expenditure, and hypercatabolism. Furthermore, increased protein degradation of skeletal muscle can induce cachexia-associated insulin resistance [5,8].

Management of Cancer Cachexia

Clinical management of cachexia is currently limited and complex. Treatment strategies are based on antitumor therapy with control of the tumor, nutritional support and pharmacological treatment. Treatment must involve a multimodal approach. Appetite stimulation is mediated by interaction of endorphin receptors, synthesis of IL-1, and activation of cannabinoid receptors (which are involved in the neurochemical circuit of leptin), and prostaglandin synthesis inhibition [9-12] . Drugs acting in those areas are the most used as appetite stimulans.

Megestrol acetate is a semi-synthetic progesterone approved by Food and Drug Administration (FDA) as appetite stimulant in 1993 [9]. 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-1, IL-6, TNF-α) and stimulation of neuropeptides in the hypothalamus [10]. Corticosteroids are also increasing appetite, food intake, weight gain, and sense of well-being with the short lived effect (less than 4 weeks) but with long-term harmfull side effects, such as insulin resistance, fluid retention, steroid-induced myopathy, skin fragility, adrenal insufficiency, and sleep and cognitive disorders. Dronabinol (cannabinoid) is effective in reducing nausea and increasing appetite with associated weight stabilization, reducing anorexia in 68% of patients, but with toxicity in 16% of patients [11,12].

It is well known that "super nutrition" alone is not reversing CACS and is not preventing development of cachexia in cancer patients. Supplementing of eicosapentaenoic acid (EPA) and its beneficial effect (preservation of lean body mass, increased physical activity, improved appetite and weight gain) in cancer patients is widely described

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[13-16]. The omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have immunomodulatory properties and they are supressing production of pro-inflammatory cytokines [10]. EPA is also inhibiting the effects of LMF and PIF leading to increased weight, appetite, and survival in CACS administered alone or with megestrol acetate [17]. Moreover, EPA and DHA potentially have impact on cancer prevention and treatment. Omega-3 fatty acids are influencing multiple targets in cancer development pathways (cell proliferation and survival, angiogenesis, inflammation, metastasis and epigenetic abnormalities) [18]. DHA also modulate protein interactions in cell membrane transport and together with EPA suppress nitrite oxide production in macrophage cell lines in a dose dependant fashion [19,20]. Omega-3 fish oil fat in parenteral formulas alleviates the inflammatory reactions more intense than in enteral form, but for general cancer patient population, enteral formulations are cheaper way for administration [21,22].

Future Directions

Tumor cells can manage to escape the anti-tumor immune responses which could be treated pharmacologically. Immunotherapy with lenalidomide enhanced activation of natural killer cells and inhibited their suppression by NB induced IL-6 or transforming growth factor-$ß_1$ within the tumor environment [17]. Thalidomide with its anti-inflammatory and immunomodulatory properties downregulate the production of TNF-α and other cytokines, inhibit $NF_κB$, downregulate COX-2, and inhibit angiogenesis improving appetite, weight gain, and sensation of well-being [23,24]. Zync (Zn) dysregulation may contribute to systemic inflammation observed in cancer cachexia. The use of Zn therapy and Zn transporters as potential therapeutic targets [25]. Ghrelin, a 28-amino acid peptide is an endogenous ligand for the GHS-R type 1a with anorexigenic action via stimulation of neurons within the hypothalamus [26]. Brainstem and vagus nerve (GHS-R is expressed in the vagus nerve) may contribute to the effects of ghrelin on food intake. Proliferative effect of ghrelin has been documented in cancer patients [27]. Supplementation of L-Carnitine significantly improved the fatigue domain with clinical benefit in CACS pancreatic cancer patients with no drug related adverse effects [28]. In CACS muscle strength is very reduced, limiting the ability to perform daily activities and severely affecting the patient's quality of life. Beyond pharmacological strategies, there are evidences that chronic exercise can be a tool for alternative attenuation of cancer cachexia [29,30].

Conclusion

In conclusion we can say that nearly half of all cancer patients experience some degree of weight loss. The underlying mechanism of cancer cachexia is still not fully understood and there is no single therapy able to reverse CACS alone (which will include disruption of intermediary metabolism, endocrine dysfunction, compromised hypothalamic appetite control, and impaired immune function) , but proactive nutritional care can prevent or reduce the development of CACS. Nutritional support (nutritional counseling, supplemental feeding and pharmacological support) do temporarily stop weight loss and improve appetite, social life, quality of life and may improve outcome in some patients [31].

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