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CLINICAL NUTRITION AND COLORECTAL CANCER

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Summary

Cachexia-anorexia syndrome, characterized by anorexia and loss of adipose tissue and skeletal muscle mass, is common feature in majority of patients with cancer, especially in cancer localized in gastrointestinal tract. Malnutrition is recognized as a negative prognostic factor in patients with colorectal cancer. Malnutrition in cancer patients reduces response to specific oncological therapy, slows down recovery after surgical treatment, leads to impairement of quality of life and decreases survival. It is considered that developement of cancer cachexia is a multifactorial process, however inflammation plays a major role. Therefore, targeting inflammation may represent an effective strategy to prevent/treat cachexia. Treatment should be patient-tailored and based on a multimodal approach.

Keywords: colorectal cancer; cancer anorexia-cachexia syndrome; nutritional support; eisosapentanoeic acid; megestrol – acetate.

INTRODUCTION

Colorectal cancer is the third most common cancer, with 1.4 million new cases diagnosed in 2012 [1]. Among patients with colorectal cancer, cancer anorexia-cachexia syndrome has a high prevalence and large impact on morbidity and mortality, as well as on patients quality of life [2]. In addition, it has been showed that undernutrition in patients with colorectal cancer represents economic burden to health care system, with average cost per patient about 1050 EUR [3].

According to recent definition, cachexia is defined as a multifactorial syndrome characterized by severe body weight, muscle and in lesser extent fat loss and increased protein catabolism, due to underlying disease[s]. Recent findings have revealed that biochemical, metabolic and molecular disturbances that lead to cachexia, are present even without significant body weight loss [4,5]. Goals of nutritional inter-

ventions are reduction of the prevalence and severity of cancer cahexia which would allow initiation and completion of active anticancer therapies (chemotherapy and or radiotherapy); and to improve quality of life [6,7].

PATHOGENESIS OF CANCER CACHEXIA IN COLORECTAL CANCER

There are several factors in patients with colorectal cancer that can lead to cancer anorexia-cachexia syndrome. Cancer growth and dissemination, as well as cancer treatments (surgery, chemotherapy, and radiation therapy), interfere with taste, ingestion, swallowing and digestion of food; which may predispose patients to malnutrition. Except reduced food intake, abnormal metabolism is an important factor in the pathophysiology of cancer-cachexia, characterised by a negative protein and energy balance.

It is considered that metabolic changes in cancer cachexia are mediated with proinflammatory cytokines [8,9]. Immune and tumor cells produce cytokines, which support the cancer growth and lead to psychobehavioural symptoms (fatigue, depression, cognitive changes), drug resistance and toxicity, pain, anorexia and cachexia, cancer recurrence and progression [10]. Mediators connected with development of cachexia are interleukin-1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor-TNF-α, and interferon-g (IFN-g); which are secreted from patients' mononuclear cells. Tumor cells also produce important factors: lipid mobilizing factor (LMF), that has an important role in stimulation of triglyceride hydrolysis in fat tissue; and proteolysis inducing factor (PIF) that activates NFkB and STAT3 which stimulate synthesis of IL-6 and IL-8, and promote the ATP-ubiquitin proteolytic pathway. This represents the most important factor in muscle mass degradation; it stimulates synthesis of acute phase proteins (especially C-reactive protein) and reduces synthesis of other proteins in liver. As previously mentioned, metabolic disturbances in cachexia cause loss of up to 80% of total body storage of fat tissue and especially muscle tissue.

In cancer cachexia syndrome gluconeogenesis from amino acids, lactate and glycerol, is frequently increased. Cory's cycle is activated, production and recycling of glucose is increased, and impaired glucose tolerance and insulin resistance are present [11,12,13].

There are also some important abnormalities in lipid metabolism. Lipoprotein lipase activity is reduced, lipogenesis decreased; while lipolysis, glycerol and fatty acids turnover, as well as lipid oxidation are increased [14,15].

Protein metabolism alterations in cancer cachexia syndrome are also frequently present and include previously mentioned synthesis of acute phase proteins and muscle wasting [2]. Except ATP-ubiquitin dependent pathway, three proteolytic sy-

stems have been described: the caspases, the lysosome, the Ca2+-dependent pathway. It is considered that all this systems have an important role in muscle depletion [16].

Imbalance between anti-inflammatory cytokines and pro-infalmmatory cytokines leads to increased resting energy expenditure, important factor in cancer cachexia pathogenesis [17].

SCREENING AND ASSESSMENT OF MALNUTRITION

A simple and quick screening method for assessment of metabolic risk, recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN), is NRS-2002 and can be used in all oncological patients (18). In addition, Fearon et al. have recommended a model for evaluation of nutritional status of oncological patients. This group of authors proposed a definition of cachexia: cachexia is generally defined as being involuntary weight loss of >5 % from historical weight, a body mass index (BMI) <20 kg/m^2 with any degree of weight loss >2 % or a skeletal muscle index consistent with sarcopenia with any degree of weight loss >2 %. Furthermore, it was emphasized that cachexia represents a spectrum: patiens can progress from pre-cachectic phase to cachexia syndrome and finally to refractory cachexia, the point at which the disease is no longer responsive to treatment or when treatment benefits are outweighed by burden and risk [19]. Nutritional assessment should include clinical and nutritional history, stage of disease (predictor of risk of malnutrition), physical assessment, functional assessment (eg. hand-grip test, spirometry), anthropometric measurements (body weight, body mass index), laboratory tests (C-reactive protein, CBC, serum albumin, creatinine, electrolytes, etc.), body composition and energy expenditure [16].

TREATMENT OF CANCER CACHEXIA

Currently, international guidelines on nutrition support in patients with cancer have been established, such as the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines and the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines [20-22]. Croatian national guidelines for treatment of patients with cancer cachexia are available since 2007 [23]. Several years ago Muscaritoli and his collaborators have developed a new approach to cancer cachexia, called ''parallel pathway'' [16]. This pathway represents a multidisciplinary approach to cancer patients through a collaboration between physician, dietician, psychologist and nurse. The goal of ''parallel pathway'', showed in *figure 1*, is prevention and correction of malnutrition, and prevention or delay the onset of cancer

cachexia. The current approach in treatment of cancer cachexia depends on the stage of cachexia. Nutritional counseling is the first step. Enteral nutrition via tube can be applied in severe cachectic patients with a functional gastrointestinal tract, but who are not capable of oral food intake. However, in most patients, sip feeding is applicable. Parenteral nutrition is an optional therapeutic modality and can be used alone or in combination with enteral nutrition.

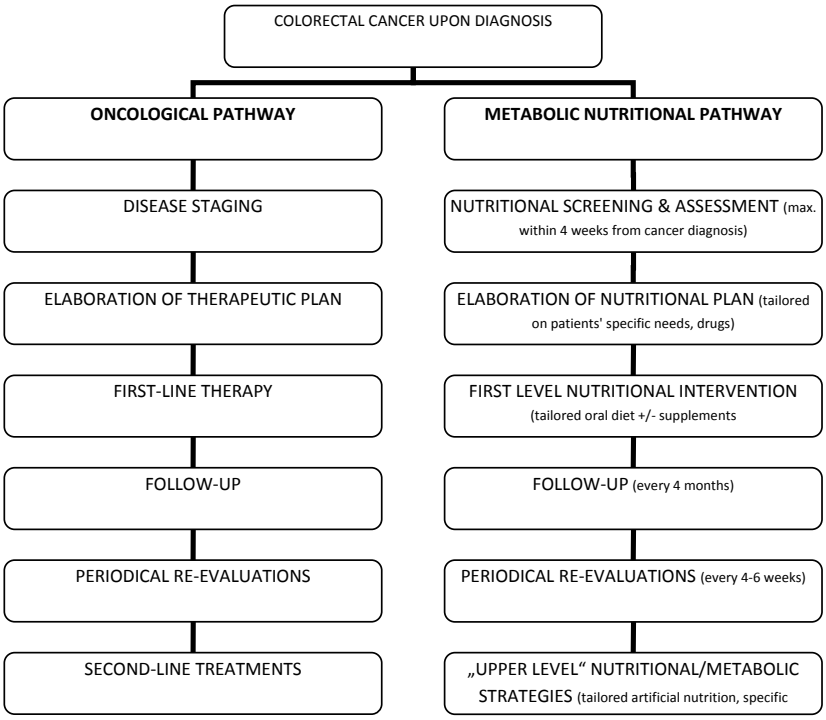

Figure 1. Adapted from *The ''parallel pathway'': a novel nutritional and metabolic approach to cancer patients by Maurizio Muscaritoli, et al.* **Left side:** The oncological pathway during cancer patient's diagnosis and treatment is displayed. **Right side:** The nutritional and metabolic intervention according to the relative oncological step

Nutritional counseling has an important role in cancer patients management. Results of Ravasco et al. prospective, randomized, controlled trial have shown that nutritional counseling in patients with colorectal cancer treated by radiotherapy is the most effective method to improve nutritional status, nutritional intake, and

quality of life in this clinical setting [24]. Recently published randomized controlled trial evaluated the effect of dietary advice dedicated to increase intake in older patients at risk for malnutrition during chemotherapy, versus usual care, on one-year mortality. Results have shown that early dietary counseling was efficient in increasing intake but had no beneficial effect on mortality or secondary outcomes. This lack of effect can be explained by cancer cachexia antianabolism [25]. Evaluation of effectiveness of nutritional support in patients with colorectal cancer recieving chemotherapy demonstrated that simultaneous individualized dietary counseling and nutritional support are effective in improving nutritional status thereby reducing chemotherapy-induced morbidity [26].

The routine use of parenteral nutrition for patients with colorectal cancer is not recommended. However, results from a prospective, randomized clinical trial have shown that early supplementation of parenteral nutrition is capable of improving quality of life, chemotherapy-related toxicity and body composition in patients with advanced colorectal carcinoma undergoing palliative treatment [27].

Patiens with colorectal cancer often undergo elective or urgent surgery. Traditionally, postoperative management of this patients involved avoidance of oral intake of fluids or nutrients. However, new studies indicate that early oral feeding after elective colorectal surgery is not only well tolerated by patients but also have positive effects on postoperative outcomes [28]. Furthermore, it has been shown that early enteral nutrition is associated with less anastomotic leakage in patients undergoing extensive rectal surgery [29].

Except nutritional counseling and nutritional support, physical activity plays an important role in management of patients with cancer cachexia. Proposed mechanisms which can lead to improvement are: increase in insulin sensitivity, protein synthesis rate and anti-oxidative enzyme activity; and a suppression of the inflammatory response and an enhancement of immune function [30,31].

AGENTS STUDIED IN CANCER CACHEXIA

There are several nutrients, such as eicosapentaenoic acid (EPA), an omega-3 polyunsaturated acid, and drugs such as appetite stimulans, antioxidans and antiinlammatories, that have been proposed as a potential treatment options for cancer cachexia sydrome. Bearing on mind complex nature of cancer cachexia in colorectal cancer, there is no one specific, globally effective or accepted treatment for this condition.

It has been shown that EPA inhibits cancer growth during tumorigenesis and early stages of development through a variety of mechanisms. Proposed mechanisms are apoptosis, cell signaling and gene expression. The anti-tumor properties of

EPA continue with disease progression, improving the efficacy of chemotherapy by protecting non-target tissues and improving its effect on tumor tissue. EPA supplementation may be responsible for stabilization in dose-limiting toxicity [32,33].

Another widely used agent, in treatment of cancer cachexia, is megestrol acetate (MA) that increases appetite and augmentation of body mass. However, during usage of MA, possible adverse effects, such as thromboembolic incidents, uterine bleeding hypertension, hyperglycemia, peripheral edema and adrenal suppression may occur. Progestational drugs, cannabinoids, and cyproheptadine are used in the clinic as appetite stimulans in the therapy of cancer-induced anorexia and cachexia syndrome. These drugs have been shown to be partially effective in reversing or maintaining the symptom of body weight loss in patients with chronic illness [34, 35]. There are several other agents evaluated in studies, such as thalidomide, branched chained amino acids, corticosteroids, anabolic steroids, hydralazine sulfate and ghrelin. Probably combination therapies that target multiple pathways, such as eicosapentaenoic acid administered in combination with exercise, appetite stimulants, antioxidants or anti-inflammatories, have potential in the treatment of this complex syndrome and require further development [35].

CURRENT CROATIAN NATIONAL GUIDELINES

In 2007, Croatian guidelines were developed for the use of eicosapentaenoic acid and megestrol acetate in cancer cachexia syndrome. Based on relevant literature, guidelines suggest simultaneous use of EPA at a standard dosage of 2.2 g/day and MA at a dosage of 400 mg/day for 8 weeks in menagemement of patiens with cancer cachexia.

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Sažetak

Klinička prehrana i kolorektalni karcinom

Kaheksija-anoreksija sindrom je karakteriziran anoreksijom i gubitkom masnog tkiva i skeletne mišićne mase. Sindrom je prisutan u većine onkoloških bolesnika, osobito u bolesnika s tumorima probavnog sustava. Odavno je prepoznato kako malnutricija predstavlja negativni prognostički faktor kod bolesnika s kolorektalnim karcinomom. Malnutricija u onkoloških bolesnika dovodi do slabijeg odgovora na specifičnu onkološku terapiju, sporijeg oporavka nakon kirurških zahvata, do smanjenja kvalitete života, ali i sveukupnog preživljenja. Istraživanja su pokazala kako je tumorska kaheksija multifaktorijalan proces. Međutim, smatra se kako glavnu ulogu u patogenezi tumorske kaheksije ima upala. Stoga je upravo djelovanje na upalni proces potencijalni terapijski cilj u liječenju, odnosno prevenciji kaheksije. Liječenje tumorske kaheksije trebalo bi biti individualizirano i temeljeno na multimodalnom pristupu.

***Ključne riječi*:** kolorektalni karcinom; sindrom tumorske kaheksije-anoreksije; nutritivna potpora; eikosapentanoična kiselina; megestrol-acetat.

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