
Review Article

Review of Croatian guidelines for use of eicosapentaenoic acid and megestrol acetate in cancer cachexia syndrome

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ABSTRACT: *In 2007, Croatian guidelines were developed for the use of eicosapentaenoic acid and megestrol acetate in cancer cachexia syndrome. These guidelines were first published in the Croatian medical journal Lijecnicki vjesnik (Krznnaric et al. Lijec Vjesn 2007; 129: 381-6) in Croatian. After numerous contacts and discussions with colleagues from the international medical community, we decided to present our guidelines in English for better exposure and to open our local guidelines for comment and even criticism. It is well known that many oncological patients show a substantial loss of body weight, fat, and proteins, with significant proinflammatory activity at the time of diagnosis. This wasting condition is known as cancer cachexia syndrome. Anorexia is an important part of this syndrome. Cancer cachexia sometimes reduces tumor response to treatment, and it is an indicator of poor prognosis. Because of this we need to start correcting these nutritional deficits immediately. In the presence of cancer cachexia it is extremely difficult to achieve protein anabolism and stop the body wasting, by standard nutritional formulas only. During the last few years, the use of eicosapentaenoic acid and megestrol acetate as anticachectic agents has been tested. These guidelines are intended to give evidence-based recommendations for the use of eicosapentaenoic acid and megestrol acetate in cancer cachexia syndrome. They have been developed by an interdisciplinary expert group of Croatian clinicians. Based on the relevant literature, we have concluded that the simultaneous use of metabolic modulators such as eicosapentaenoic acid and megestrol acetate for 8 weeks may help in improving the nutritional status of cachectic patients. A year after the presentation and implementation of these guidelines we can conclude that despite some shortcomings, they have improved our approach to treating cancer cachexia patients in Croatia. (Nutritional Therapy & Metabolism 2009; 27: 1-8)*

KEY WORDS: *Anorexia, Cancer cachexia, Eicosapentanoic acid, Guidelines, Megestrol acetate*

INTRODUCTION

Loss of body weight and progressive body composition deterioration are an important problem that appears in more than half of patients with malignant tumors (1, 2). *Cancer cachexia syndrome* and *anorexia-cachexia syndrome* are common terms used to describe changes in metabolism with augmented inflammatory activity. After a Cachexia consensus conference, December 13th and 14th, 2006, Washington, DC, United States, a definition of cachexia was agreed which still has not been tested in epidemiological or interventional studies. But this consensus operational definition provides an opportunity for further research (3).

Cancer cachexia syndrome is caused by various factors whose pathophysiology is still not completely clarified (3-5). From clinical practice we have become familiar with the adverse effects of anorexia and cachexia on treatment and prognosis of patients with malignant tumors. Unfortunately, it is known that standard nutritional support, even standard enteral and parenteral nutrition, cannot stop body composition deterioration in tumor cachexia syndrome (6, 7).

Aim of work

Nutrition support is a very important part of therapy for oncological patients and has a significant influence

on its progress and outcome (8, 9). In the last decade, the frequent use of drugs with pharmacological effects on processes of anorexia and cachexia was investigated in particular. Some of them significantly stimulate appetite, while others show remarkable effects on levels of cytokines and on decreasing production of proinflammatory cytokines and other mediators that stimulate catabolism (8, 9). In many studies, the role of megestrol acetate (MA) and eicosapentaenoic acid (EPA) in the treatment of oncological patients has been shown. Here we report the Croatian guidelines for use of EPA and MA in cancer cachexia syndrome.

METHODS

In October 2006, members of the Croatian Medical Association, Croatian Society of Enteral and Parenteral Nutrition, Croatian Society of Oncology, Croatian Society of Medical Oncology, and some experts from leading Croatian hospitals started with preparation of guidelines for nutritional support and treatment of oncological patients in Croatia. The possible use of EPA and MA in cancer cachexia was raised for discussion. Guidelines were made after a detailed study of Croatian medical practice, the available medical literature, and evidence-based medicine. In August 2007, the final version was agreed after intensive e-mail communications between the authors. The guidelines were first published in the Croatian medical journal *Lijecnicki Vjesnik* in Croatian (10).

Pathogenesis of cancer cachexia

Anorexia-cachexia syndrome is a term used to describe undernourishment or malnutrition, continuous body composition deterioration, and poor prognosis in treatment of patients with a tumor (5, 11). The syndrome develops because of decreased appetite and food intake (anorexia) and increased consumption of body reserves, especially proteins (cachexia), and it is present in a high percentage of patients with various malignant tumors (12, 13). Loss of body mass and of fat and skeletal musculature are the most notable clinical manifestations of anorexia-cachexia syndrome (14). Especially threatened groups of patients are those with malignancies of the gastrointestinal tract or lungs (15-17).

Decreased food intake in cancer cachexia develops due to reduced appetite and sensation of early satiety, direct or indirect influence of proinflammatory cytokines on hypothalamus, nausea (due to changes in organism caused by the tumor per se or antitumor therapy), and/or mechanical obstruction or impairment of

the gastrointestinal tract. Pain often has a strong influence in reduction of food intake (18). Aside from disorders of food intake, disorders of food absorption are common. It is very important to distinguish simple starvation cachexia from what is a proinflammatory state (4, 19, 20).

Many metabolic changes mediated by proinflammatory cytokines cause cachexia (21, 22). Mediators connected with development of cachexia are tumor-necrosis factor- α (TNF- α), interleukin-1 (IL-1), interleukin 6 (IL-6), and interferon- γ (IFN- γ). These are all secreted from patients' mononuclear cells. An important role also belongs to molecules from cancer cells, such as lipid mobilizing factor (LMF) and proteolysis-inducing factor (PIF). LMF stimulates triglyceride hydrolysis in fat tissue. PIF activates NF κ B and STAT3 which stimulate synthesis of IL-6 and IL-8, and promote the ATP-ubiquitin proteolytic pathway. This is the most important factor in degradation of muscle mass; it stimulates synthesis of acute phase proteins (especially C-reactive protein) and reduces synthesis of other proteins in liver. Cytokine activity in many ways changes metabolic paths of carbohydrates, fat, and proteins. Metabolic disturbances in cachexia cause large loss of fat tissue and especially muscle tissue (even 80% of total body storage). Gluconeogenesis from amino acids, such as lactate and glycerol, is increased in tumor cachexia syndrome. Cory's cycle is activated, production and recycling of glucose is increased, and insulin resistance is a huge problem. Lipid metabolism is also changed. Lipolysis, glycerol turnover, turnover of fatty acids, and lipid oxidation are increased, and lipogenesis, as well as lipoprotein lipase activity, is decreased. Increases of plasmatic levels of nonessential fatty acids, as well as increase of plasmatic lipid levels, are inconsistent. Protein metabolism changes are crucial in tumor cachexia syndrome.

In one cohort of patients, the increase of basal metabolism was determined to be Dempsey et al, presented the increase of basal metabolism in gastrointestinal cancer patient for about 100 to 300 kcal daily, depending on type of tumor, which could result in a loss of up to 1 kg of body weight monthly (23). Changes of basal metabolism are not uniform, and we can testify to states in which basal metabolism is normal or decreased, but with no significant effect on stopping body composition deterioration.

Assessment of malnutrition

About 30% of all hospitalized patients are undernourished, but even more cancer patients are (24). There

are simple or extensive methods for assessment of metabolic risk (25). An example of a simple or quick screening method is NRS-2002, recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) (26). This method is a useful tool for assessment of patients during hospitalization, deterioration of nutritional status, and for reevaluation of hospitalized patients (27).

If the spontaneous weight loss in oncological patients in the previous 6 months is more than 5% of body mass, then malignant cachexia should be suspected. Fearon et al have recommended a simple model for easy evaluation of nutritional status of oncological patients (28). If weight loss is more than 5% in the previous 3-6 months, food intake less than 1,500 Kcal per day, and C-reactive protein higher than 10 mg/L, tumor cachexia syndrome could be considered.

Tumor cachexia syndrome and quality of life

Malignancy has a great influence on body functions and activity of the oncological patient; it affects mental status and social life. More and more effective oncological therapy has prolonged the life of oncological patients, and it has become necessary to keep their quality of life in mind (29-31). The maintenance of body integrity, beginning with body weight, has a considerable role in the management of the basic tumor process. On the other hand, weight loss and other nutritional problems decrease quality of life profoundly (32). Ravasco et al have published data in which it is shown that food intake affects quality of life significantly (33). Properly conducted nutritional support significantly influences patients' belief in a better outcome of treatment, and additionally improves their quality of life (34-36).

Therapy

Significant loss of body weight affects treatment outcome in oncological patients. Malnutrition in cancer cachexia reduces response to basic oncological therapy, slows down recovery after surgical treatment, and decreases survival compared with that of patients with the same diagnosis, but who are well nourished (37). Several forms of nutritional treatment are considered to slow or stop weight loss (38).

The current approach depends on the stage of cachexia. Dietetic counseling is always 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. In most patients, sip feeding is applicable. Parenteral nutrition is an optional therapeutic possibility whether used

alone or in combination with enteral nutrition.

A lot of studies have shown potential in controlling production of proinflammatory cytokines, which are molecular mediators of anorexia and cachexia (39-45). Nowadays in tumor anorexia and cachexia syndrome, the drugs most often used in treatment are corticosteroids, EPA and MA.

Glucocorticoids

Glucocorticoids have been frequently used in oncological patients. Corticosteroids decrease synthesis and release of IL-1 and TNF- α , whose increased production causes anorexia (directly or through other mediators – e.g., leptin or serotonin), and they have positive effects on increase of appetite and food intake (46). However, there is no study that has shown a positive effect of corticosteroid intake on increase of body mass. Long-term use of these drugs has been associated with different adverse effects (weakness, osteoporosis, immunosuppression, etc.). Prednisolone in a dosage of 15 mg/day (divided into 3 doses of 5 mg) and dexamethasone in a dosage of 3-6 mg/day have positive effects on the appetites of oncological patients.

Eicosapentaenoic acid (EPA)

Immunonutrition is defined as modulation of immune system activity or modulation of consequences of immune system activation with nutrients or special ingredients in preparations which are given in amounts more than normally present in diet (47). Food rich in omega-3 fatty acids belongs to immunomodulating nutrition (48). Intake of monosaturated fatty acids or different kinds of polysaturated fatty acids through diet can change the composition of membrane phospholipids. Prostaglandins and leukotrienes are produced by phospholipases, which are activated as a response to trauma or infection. Because of this, metabolic and physiological changes appear. Fat rich in omega-3 fatty acids or monounsaturated fatty acids or fat poor in omega-6 fatty acids decrease production of pro-inflammatory cytokines and rate of inflammation (49). Fat rich in omega-6 fatty acids has an adverse effect.

Experiments in cachectic mice showed that EPA induces suppression of \uparrow regulation \downarrow of proteasome expression. It is connected with a greater expression of myosin, which helps to maintain the quantity of contractile proteins (50). In a study of pancreatic cancer, it was shown that adding food rich in EPA for 12 weeks stops a trend toward losing weight. The average weight loss before nutritional intervention was 2 kg monthly. After 12

weeks, patients in the EPA group shifted to an anabolic phase and gained 0.5 kg monthly on average (51). Another study showed a significant decrease in production of IL-6 (from 16.5 to 13.7 ng/L), an increase in insulin serum concentration (3.3 to 5 mU/L), and a decrease in number of patients in whom PIF was secreted (88% to 40%) after receiving a diet rich in EPA (45).

Dewey et al published a review of trials that found that in weight-losing patients with advanced pancreatic cancer, an EPA nutritional supplement was no better than a non-EPA nutritional supplement. However, there was insufficient evidence to draw conclusions about its use in patients who have cancer of other tumor types (52).

Megestrol acetate

Megestrol acetate (MA) is a synthetic derivative of progesterone. Many studies have shown its positive effect in treatment of cancer cachexia, which is based on an increase of appetite and augmentation of body mass, and is dose dependent. Use of MA varies from 160 to 1,600 mg daily (52, 53). An increase in body mass in patients who have been treated with MA is due to increase in quantity of fat tissue and not only fluid retention (54). An increase in body weight has been noticed in several studies in almost all patients receiving MA for periods longer than 6 weeks. It is not completely defined when treatment should start and how long should it last (55). Possible adverse effects that may appear during usage are thromboembolic incidents, peripheral edema, hyperglycemia, hypertension, uterine bleeding, and adrenal suppression. Because of the listed side effects, application of MA is not recommended for patients with serious heart diseases, coagulation disorders, or fluid retention.

Croatian guidelines

Loss of body mass, especially of skeletal musculature, as well as progressive body composition deterioration, are issues occurring in many patients with malignancies. Metabolic abnormalities with augmented inflammatory activity are present in anorexia-cachexia syndrome.

It is reasonable to say that an indication for nutritional support is present in almost every patient with malignancy. The primary therapeutic goal in tumor cachexia is stopping loss of body mass and muscle tissue (56), which is connected with life quality improvement. At the same time, this trend can allow usage of more aggressive oncological treatment, whether it is chemotherapy, radiotherapy, surgical

treatment, or their combination (57). Effects of using EPA and MA, or their combination, were compared in a study by Jatoi et al (58). The primary end point in this study was 10% increase in body weight from baseline, which we consider an inappropriate aim in a population of cancer patients. After recalculation of the results presented, we found an increase of body weight of 1% or more, in 37% patients on EPA only, in 39% on MA only, and in a significant 45% using both EPA and MA (58). In the original text, Jatoi et al did not comment on their results in this way.

Our guidelines specify that the first step in the nutritional therapy of oncological patients is dietetic advice regarding types of acceptable food, which can diminish the stage of anorexia or other dyspeptic problems (59, 60). The second step is implementation of peroral nutritional supplements, where enteral nutrition with increased intake of EPA has an important role. Enteral nutrition via tube or by stoma is the mode of nutritional support for severe cachectic patients with a functional gastrointestinal tract but without the possibility of sufficient oral intake (9). Partial or total parenteral nutrition is applied to patients who do not tolerate peroral intake or enteral nutrition given through a tube, because of impairment of their gastrointestinal tract (61).

Enteral nutrition (high-protein, high-energy, polymeric formula with increased intake of EPA, 2.2 g/day) is the first choice in nutritional support with the majority of oncological patients (62). MA is efficient in treatment of patients with anorexia-cachexia syndrome (400-800 mg daily) and is the first choice in pharmacotherapy of tumor anorexia-cachexia syndrome. The combination of EPA (2.2 mg/day) and MA (400 mg/day) for a minimum duration of 8 weeks is a desirable therapeutic approach in patients with different stages of cancer anorexia and cachexia syndrome.

The guidelines have been presented with levels of recommendations for each of the statements given (Tabs. I and II).

We are aware that there are different opinions regarding the use of the combination of EPA and MA. Dewey et al concluded that EPA combined with a protein energy supplement versus a protein energy supplement (without EPA) in the presence of an appetite stimulant (MA) provided no evidence that EPA improves symptoms associated with the cachexia syndrome often seen in patients with advanced cancer (52). We agree with this statement, but we would like to stress here the importance of early use of enteral nutrition enriched with EPA in combination with MA. It is not possible to stop or even reverse cachexia in patients with advanced cancer.

CONCLUSION

Cancer cachexia and consequential body composition deterioration is an unpleasant and frustrating condition for patients and their families, as well as for their doctors. Unfortunately, at the present time, there is no widely agreed usable definition of cachexia.

The goal of the interdisciplinary expert group that formulated the Croatian guidelines for use of EPA and MA in patients with cancer cachexia syndrome was to standardize therapeutic procedures for nutritional support of this devastating condition.

EPA and MA achieve positive effects by interactions

on cellular and molecular structures, and not just by the classical increase of nutrients and energy (64). Many preclinical and clinical studies have shown the efficiency of both preparations, separately. A few studies have shown benefits of combined use of EPA and MA.

We concluded with the recommendation in our guidelines of 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.

A year after the presentation and implementation of the guidelines, we can conclude that despite some shortcomings this has improved our approach to cancer cachexia patient treatment in Croatia.

TABLE I - CROATIAN GUIDELINES FOR USE OF EICOSAPENTAENOIC ACID (EPA) AND MEGESTROL ACETATE (MA) IN CANCER CACHEXIA SYNDROME

Guideline	Grade of recommendation*
1. Malnutrition as a part of cancer anorexia and cachexia syndrome is a common problem in the treatment of oncological patients.	C
2. Diagnosing malnutrition is done with simple clinical indices and basic anthropometric parameters.	C
3. Clinical nutrition is an important component of supportive treatment of oncological patients in various stages of disease. Cancer cachexia syndrome can appear in the earliest stages of disease.	B
4. Depending on the stage of cancer cachexia, the nutritional approach is as follows:	
a) first step: nutritional counseling or dietetic advice regarding type of acceptable food;	B/III
b) second step: oral nutritional supplements, where enteral nutritional formulas with increased administration of EPA have an important role;	B/IIb
c) enteral nutrition given by tube or stoma to severe cachectic patients with functional gastrointestinal tract but without sufficient oral intake;	C
d) partial or total parenteral nutrition is applied to patients who can not tolerate peroral intake or enteral nutrition given by tube, because of impairment of gastrointestinal tract.	B/III
5. Enteral nutrition per os as an nutritional supplement (high-protein, high-energy, polymeric formula with increased intake of EPA, 2.2 g/day) is first choice in use of nutritional support.	B/IIa
6. Megestrol acetate is effective in treatment of patients with anorexia-cachexia syndrome (400-800 mg/day) and is a first choice in pharmacotherapy.	A/Ia
7. Combination of megestrol acetate and enteral nutrition with increased intake of EPA for a minimum of 8 weeks is a desirable therapeutic approach.	B/III

*For explanations of grades of recommendations, see Table II.

TABLE II - GRADES OF RECOMMENDATIONS AND LEVEL OF EVIDENCE (63)

Grade of recommendation	Level of evidence	Requirement
A	Ia	Meta-analysis of randomized controlled trials.
	Ib	At least 1 randomized controlled trial.
B	IIa	At least 1 well-designed controlled trial without randomization.
	IIb	At least 1 other type of well-designed, quasi-experimental study.
	III	Well-designed nonexperimental descriptive studies such as comparative studies, correlation studies, case-control studies.
C	IV	Expert opinions and/or clinical experience of respected authorities.

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