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Original article

Ten years of Croatian national guidelines for use of eicosapentaenoic acid and megestrol acetate in cancer cachexia syndrome – Evaluation of awareness and implementation among Croatian oncologists

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SUMMARY

Background & aims: Cancer cachexia (CC) syndrome and anorexia–cachexia syndrome are common terms used to describe changes in metabolism with increased inflammatory activity and can progressively develop through various stages such as pre-cachexia; cachexia; and refractory cachexia. Therefore in year 2007 Croatian guidelines for use of eicosapentaenoic acid and megestrol acetate in cancer cachexia syndrome were published. Aim of this study was to assess the awareness and implementation of Croatian guidelines for use of eicosapentaenoic acid (EPA) and megestrol acetate (MA) into clinical practice among Croatian oncologists approximately 10 years after the publication, but also to point out the importance of adequate recognition and treatment of CC.

Methods: Survey with questions was designed to assess the awareness and implementation of Croatian guidelines for use of EPA and MA into clinical practice and was distributed among all Croatian oncologists in secondary and tertiary hospital centers. Survey was conducted in January 2011 (40 months following release of the guidelines), February 2013 and June 2018, and were formed in a way of yes/no answers. Additional multiple choice questions that focus on the implementation of guidelines were added in June 2018.

Results: A total of 128 oncologists completed a questionnaire. There was no statistically significant difference in follow up period (2011–2018) of percentage of oncologists that are familiar with Croatian guidelines for use of EPA and MA in CC, percentage of oncologists in which Croatian national guidelines changed their approach in treating patients with CC syndrome and proportion of oncologists that are using MA, enteral nutrition formulas with EPA or their combination. Most of the oncologists 38% ($N = 44$) are using >2.2 g of EPA per day. Nutritional support is prescribed in 25–50% of patients by 42% ($N = 48$) of oncologists and most of the oncologists (35%, $N = 41$) start with nutritional support when a body mass loss is >5%. Oncologists mostly recommend patients to use nutritional support during 1 year or more (43%, $N = 49$) or two months to 1 year (42%, $N = 48$). Compliance of patients with malignant diseases for using nutritional support was mostly evaluated as medium (69%, $N = 60$).

Conclusions: Results have shown that majority of oncologists who filled the questionnaire believe that the Croatian national guidelines for use of EPA and MA in CC syndrome changed their approach in treating patients with CC, but also that there are several targeted issues that can be significantly improved. The awareness of and adherence to national guidelines was maintained at high level even 11 years after the guidelines were published.

Abbreviations: CC, cancer cachexia; EPA, eicosapentaenoic acid; MA, megestrol acetate.

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1. Introduction

Loss of body weight and progressive body cell mass reduction are important problems that appear in more than 50% of patients with malignant tumors [1,2]. Cancer cachexia (CC) syndrome and anorexia–cachexia syndrome are common terms used to describe changes in metabolism with increased inflammatory activity and can develop through various stages such as pre-cachexia; cachexia; and refractory cachexia [3,4]. Differentiation from other syndromes of weight loss such as syndrome of starvation, sarcopenia and dehydration is crucial to prompt recognition and effective management [4–8]. CC syndrome is caused by various factors whose pathophysiology is still not completely understood [8–11]. 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 cell mass reduction in CC syndrome [7,12,13].

CC syndrome is a term used to describe undernourishment or malnutrition, continuous body cell mass reduction, and poor prognosis in treatment of patients with a tumor [14–16].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 [4,9,17–19]. Most notable manifestation is the loss of lean body mass. Patients with all types of malignancies are at risk, but mostly patients with gastrointestinal, head and neck, liver and lung cancers are at highest risk for malnutrition [7,20,21]. Risk of malnutrition in patients with malignant disease is also increased because of the side effects of the treatment (chemotherapy and radiotherapy) such as: nausea, vomiting, change in taste and mucositis [22].

In October 2006, members of the Croatian Medical Association, Croatian Society of Clinical Nutrition, Croatian Society of Oncology, Croatian Society of Medical Oncology, and experts from leading Croatian hospitals started developing guidelines for nutritional support and treatment of oncological patients in Croatia. Discussion was raised on the possible use of eicosapentaenoic acid (EPA) and megestrol acetate (MA) in CC. In August 2007, the final version was agreed and the guidelines were first published in the Croatian medical journal Lijecnicki Vjesnik in Croatian [23]. One of the conclusions was that the simultaneous use of metabolic modulators, EPA (2.2 g/day) and MA (400 mg/day) for 8 weeks may help in improving nutritional status.

Many preclinical and clinical studies have shown the efficiency of both (EPA) and (MA) as nutritional support separately, and a few studies have shown benefits of combined use of EPA and MA. Effects of using EPA and MA, or their combination, were compared in a study by Jatoi et al. [24]. The primary endpoint in this study was 10% increase in body weight from baseline, which we considered an inappropriate aim in a population of cancer patients. After recalculation of the results presented, authors 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 [25]. That is why 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 CC syndrome [26]. Another important thing we want to stress out, is 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 gastrointestinal symptoms connected to chemotherapy or radiotherapy [27,28]. This is followed by a oral nutrition supplements.

Aim of this study was to assess the awareness and implementation of Croatian guidelines for use of eicosapentaenoic acid (EPA) and megestrol acetate (MA) into clinical practice among Croatian oncologists 10 years after the publication, but also to point out the importance of adequate recognition and treatment of CC.

2. Materials and methods

An anonymous survey with questions designed to assess the awareness and implementation of Croatian guidelines for use of EPA and MA into clinical practice was distributed by post among all 152 Croatian oncologists in secondary and tertiary hospital centers who are also members of Croatian Society of Oncology and Croatian Society for Medical Oncology. First five questions that assess familiarity with guidelines, influence of guidelines on changing their approach and use of MA, EPA or their combination were distributed to Croatian oncologists in three time points. Survey was conducted in January 2011 (40 months following release of the guidelines), February 2013 and June 2018, and were formed in a way of yes/no answers. During the whole period of follow-up from the time of publishing guidelines constant promotional activities at Croatian congresses and meetings of Croatian Medical Societies were performed, and the full text of guidelines was distributed to all of the oncologists by post.

Questions with multiple choice answers numbered 6–10 that were added to the questionnaire in June 2018 focus on the implementation of guidelines; prescribed dosages of EPA, percentage of patients with malignant disease prescribing nutritional support, time of starting with nutritional support, recommendation of nutritional support duration and evaluation of patients compliance. The questionnaire is showed in Appendix.

Categorical variables are shown as percentages and the difference were tested using chi-squared test. A P value less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 23 (IBM Inc., USA).

3. Results

Questionnaire (showed in Appendix) was distributed to all 152 Croatian oncologists, and a total of 128 oncologists completed the questionnaire in year 2011, 110 in year 2013 and 115 in year 2018 with corresponding response rates of 84.2%, 72.3% and 75.6%, respectively (Table 1). The percentage of oncologists that are familiar with Croatian guidelines for use of EPA and MA in CC, proportion of oncologists in which Croatian national guidelines changed their approach in treating patients with CC syndrome and proportion of oncologists that are using MA, enteral nutrition formulas with EPA or their combination did not show statistically significant difference in the follow up period (2011–2018).

A total of 115 oncologists answered 5 additional questions in year 2018, with results showed as percentages (Table 2). Percentage of oncologists that use >2.2 g of EPA per day was 38% ($N = 44$). Nutritional support is prescribed in 25–50% of patients by 42% ($N = 48$) of oncologists. Of the oncologists, 35% ($N = 41$) start with nutritional support when a body mass loss is >5%. Oncologists mostly recommend patients to use nutritional support during 1 year or more (43%, $N = 49$) or two months to 1 year (42%, $N = 48$). Compliance of patients with malignant diseases for using nutritional support was mostly evaluated as medium (69%, $N = 60$).

4. Discussion

In everyday clinical practice it is important to recognize significant weight loss since it is present in 15–40% of cancer patients and indicates poor prognosis [29]. One of the most used screening tests is NRS-2002, which is recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) [30]. If the

Table 1
Data on yes/no answers on questions asked in years 2011, 2013 and 2018.

Question type	Answers						*P* value
	Year 2011 ($N = 128$)		Year 2013 ($N = 110$)		Year 2018 ($N = 115$)		
	Yes	No	Yes	No	Yes	No	
Familiar with guidelines	94	34	90	20	90	25	NS
	73.4%	26.6%	81.8%	18.2%	78.2%	21.8%	
Guidelines changed approach	110	18	92	18	91	24	NS
	85.9%	14.1%	83.6%	16.4%	79.1%	20.9%	
Use of MA	106	22	92	18	97	18	NS
	82.8%	17.2%	83.6%	16.4%	84.3%	25.7%	
Use of EPA	107	21	88	22	99	16	NS
	83.6%	16.4%	80.0%	20.0%	86.1%	13.9%	
Use of MA and EPA	91	37	75	35	89	26	NS
	71.1%	28.9%	68.2%	31.8%	77.4%	22.6%	

MA – megestrol acetate, EPA – eicosapentaenoic acid, NS – non-significant.

Table 2
Data on answers on multiple choice questions asked in year 2018.

Questions in year 2018 ($N = 115$)	%
If you are using eicosapentaenoic acid (EPA) enteral formulations, which daily doses of eicosapentaenoic acid are you using?	
<1.1 g/day	1%
<2.2 g/day	31%
>2.2 g/day	38%
Don't know	30%
What percentage of your patients with malignant disease do you prescribe nutritional support?	
0–25%	12%
25–50%	42%
50–75%	31%
75–100%	15%
When do you start with nutritional support?	
Immediately after diagnosis	14%
When a body mass loss is >5%	35%
When a body mass loss is >10%	33%
With advanced cachexia	9%
Prolonged therapy in remission phase if needed	9%
How long do you recommend your patients to use nutritional support?	
1–4 weeks	4%
4–8 weeks	11%
2 months to one year	42%
one year and more	43%
How do you evaluate compliance of patients with malignant disease for using nutritional support?	
High (2 packs per day as long as needed)	33%
Medium (1 pack per day 4–6 weeks or shorter)	60%
Low (occasionally during month to two)	5%
Bad (patients do not accept nutritional support)	2%

spontaneous weight loss in oncological patients in the previous 6 months is more than 5% of body mass, then CC should be suspected. Fearon et al. have recommended a simple model for easy evaluation of nutritional status of oncological patients [31]. If weight loss is more than 5% in the previous 3–6 months, food intake less than 1500 kcal per day, and C-reactive protein higher than 10 mg/L, then CC syndrome could be considered [32].

Cancer as a disease and malnutrition are closely linked and can rapidly develop into a vicious circle, in which disease causes decreased appetite or desire for eating, malabsorption and increased loss of nutrients, which in turn cause increased susceptibility to complications. Nutritional support depends on the stage of the disease. In the early stages dietetic counseling is always the best choice, which can in later stages be followed by oral nutritional supplements, enteral nutrition via tube and finally, parenteral nutrition whether used alone or in combination with enteral nutrition [8]. The pathophysiological and diagnostic complexity which can easily lead to overlooking of CC requires evaluation of awareness and implementation of national guidelines.

Results of this study show that the level of awareness of Croatian guidelines remains at high level over a follow-up period. Majority of oncologists, around 80% of responders, who filled the questionnaire believe that the Croatian national guidelines for use of EPA and MA in CC syndrome changed their approach in treating patients with CC. The majority of Croatian oncologists are familiar with national guidelines and the percentage remains at high level in the follow-up period, without significant decrease over follow-up period. This data are consistent with positive influence of guidelines over a significant period of time, partially due to constant promotional activities that are addressing the question of CC treatment among Croatian oncologists. Most of the oncologists that were familiar with Croatian guidelines use EPA, MA or their combination in cancer patient treatment in a high percentage, also without trend of significant decrease over time. Moreover, positive trends are observed in the use of EPA, MA or their combination. Educational activities encouraged oncologists to use nutritional support, especially combination of EPA and MA in therapy of CC, according to the recommendations.

In Croatian guidelines it is recommended that enteral nutrition (high-protein, high-energy, polymeric formula with increased intake of EPA, 2.2 g/day) should be the first choice in nutritional support with the majority of oncological patients (level of recommendation B/IIa). The results of our survey indicate that the use of enteral formulas enriched with EPA, n-3 polyunsaturated fatty acid (PUFA), that has a variety of biological activities including anti-inflammatory and anticancer effects, has been common among most of Croatian oncologists. There is no evidence that supplements enriched with EPA can improve symptoms associated with the cachexia syndrome if taken in insufficient quantity (less than 2.2 g per day) and in a period shorter than 8 weeks. According to the survey from year 2018, most oncologists in Croatia (38%) use EPA in sufficient quantity, but there is still large proportion of oncologists (31%) that prescribe EPA in insufficient quantity, and a large proportion of oncologists (30%) that don't know which doses they are using. Also, when prescribing nutritional support Croatian oncologists mostly recommend more than 8 weeks of using nutritional support which is according to recommendations. MA is efficient in treatment of patients with CC syndrome (400–800 mg daily) and is the first choice in pharmacotherapy of CC syndrome. The results showed that less oncologists prescribe MA, a synthetic derivative of progesterone, whose action is based on increase of appetite and augmentation of body mass, than EPA. Potential reason for that could be that incidence of adverse effects at the recommended doses of EPA is low. On the other hand, MA can have possible adverse effects that may appear during usage such as

thromboembolic incidents, peripheral oedema, hyperglycemia, hypertension, uterine bleeding and adrenal suppression.

According to the survey 54% of oncologists prescribe nutritional support to 50% or less of their patients, which means that the nutritional support is most likely prescribed to the majority that need it, but there is still a large proportion of oncologists who could be encouraged to more frequent prescription of nutritional support. Although the majority of oncologists start with nutritional therapy when a body mass loss is more than 5% or immediately after diagnosis, 42% of oncologists start nutritional therapy in advanced cachexia or when body mass loss is more than 10%. Therefore, we should encourage regular nutritional screening and earlier initiation of nutritional support.

Overall compliance of patients with malignant disease was mostly medium (69%) to high (33%) which means that the education of patients on beneficial effects of nutritional therapy in order to increase compliance should also be encouraged.

We find that the use of EPA and MA and their combination, with emphasis on the proper dosage should be further and more intensively promoted through educational programs due to the results that almost third of oncologists prescribe EPA in insufficient quantity, but also due to high percentage of late introduction of nutritional therapy. It is also important to stress out the importance of educating patients on beneficial effects of nutritional therapy in order to improve their compliance. Our survey has few limitations. It has to be evaluated in which indications oncologists are using EPA and MA, and special situations when they are using separately EPA and MA, or combination of EPA and MA. Moreover, questions regarding dietetic consultation and food fortification were not in the questionnaire.

5. Conclusion

Results have shown that majority of oncologists who filled the questionnaire believe that the Croatian national guidelines for use of EPA and MA in CC syndrome changed their approach in treating patients with CC, but also that there are several targeted issues that can be significantly improved. The awareness of and adherence to national guidelines was maintained at high level even 11 years after the guidelines were published.

Statement of authorship

Zeljko Krznaric (conception and design of study, critical review), Antonio Juretic (conception and design of study, critical review), Viktor Domislovic (practical performance, data analysis, manuscript preparation, critical review), Ana Barisic (practical performance, preparation manuscript), Domina Kekez (practical performance, preparation manuscript), Darija Vranesic Bender (design of study, preparation manuscript, critical review).

Conflict of interest statement

Authors have no conflict of interest.

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Appendix

Questions number 1 to 5 asked in years 2011, 2013 and 2018:

1. Are you familiar with Croatian national guidelines for the use EPA and MA in cancer cachexia syndrome?
2. Did the Croatian national guidelines for the use of EPA and MA change your approach in treating patients with cancer cachexia syndrome?
3. Do you use MA in treating patients with cancer cachexia syndrome?
4. Do you use enteral nutrition formulas enriched with EPA?
5. Do you use enteral nutrition enriched with EPA in combination with MA in the therapy of patients with cancer cachexia syndrome?

Questions number 6 to 10 added in year 2018:

6. If you are using eicosapentaenoic acid (EPA) enteral formulations, which daily doses of eicosapentaenoic acid are you using?
   a) <1.1 g/day
   b) <2.2 g/day
   c) >2.2 g/day
   d) Don't know
7. To what percentage of your patients with malignant disease do you prescribe nutritional support?
   a) 0–25%
   b) 25–50%
   c) 50–75%
   d) 75–100%
8. When do you start with nutritional support?
   a) immediately after diagnosis
   b) when a body mass loss is >5%
   c) when a body mass loss is >10%
   d) with advanced cachexia
   e) prolonged therapy in remission phase if needed
9. How long do you recommend your patients to use nutritional support?
   a) 1–4 weeks
   b) 4–8 weeks
   c) 2 months to one year
   d) one year and more
10. How do you evaluate compliance of patients with malignant disease for using nutritional support?
    a) High (2 packs per day as long as needed)
    b) Medium (1 pack per day 4–6 weeks or shorter)
    c) Low (occasionally during month to two)
    d) Bad (patients do not accept nutritional support)

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