



Review article

Use and effects of oral nutritional supplements in patients with cancer

Marian A.E. de van der Schueren R.D., Ph.D. ^{a,b,*}^a HAN University of Applied Sciences, Dept. of Nutrition and Health, PO box 6960, 6503 GL Nijmegen, the Netherlands^b Amsterdam UMC, Vrije Universiteit, Dept. of Nutrition and Dietetics, PO box 7057, 1007 MB Amsterdam, the Netherlands

ARTICLE INFO

Article History:

Keywords:

Oral nutritional supplements
 Malnutrition
 Cancer
 Omega-3-fatty acids
 Nutritional counseling
 Immunomodulating nutrition

Introduction

Cancer and its treatment are often associated with disease and treatment-related side effects, leading to diminished nutritional intake and involuntary weight loss. Possible causes of weight loss and malnutrition in cancer include the following:

- Catabolic effects of the tumor/abnormal metabolism of nutrients;
- Inadequate intake due to tumor-induced anorexia;
- Reduced food intake secondary to treatment side effects such as nausea, vomiting, stomatitis, constipation, and malabsorption;
- Obstruction caused by the tumor or as a consequence of treatment; and
- Pain, anxiety, fatigue, or depression [1].

It has been reported that weight loss and malnutrition are associated with poorer treatment outcomes [2,3]. Even in the present era of obesity, involuntary weight loss is still highly prevalent in patients with cancer. A recent review depicts weight loss in large numbers of patients with cancer (from 10% of patients with prostate cancer, up to 70% of those with pancreatic cancer), especially those with cancers of the upper gastrointestinal (GI) tract [4].

It is now widely acknowledged that nutrition interventions in patients with cancer can improve nutritional intake, maintain or improve body weight, improve body composition, improve quality of life (QoL), reduce toxicity, and possibly prolong survival.

If patients are able to eat, it is important to first encourage a normal diet that is high in energy and protein, before starting supplements, to reach nutritional requirements. This includes choosing foods with a high(er) nutrient density, food fortification, or the use of extra snacks. The diet should be individually adapted to factors impeding nutritional intake, such as anorexia, nausea, taste and smell alterations, mucositis, constipation, dysphagia, chronic and abdominal pain, diarrhea, as well as aspects of GI function potentially responsible for these symptoms [5]. Oral nutritional supplements (ONS) should be considered when the intake remains insufficient, despite adaptations to the diet. Although there are no strict guidelines, ONS are usually prescribed if intake is (expected to be) <75% of requirements.

What are oral nutritional supplements?

ONS are commercially produced multi-nutrient liquid, semi-solid, or powder products that provide macro- and micronutrients with the aim of increasing oral nutritional intake. ONS are intended for the exclusive or partial feeding of patients whose nutritional requirements cannot be met by normal foods. ONS are different from supplements that provide vitamins, minerals, and trace elements in a pill format (also known as food supplements) and labeling and composition must comply with the Commission delegated Regulation (EU) 2016/128, effective from February 22, 2019 [6].

For a product to be considered nutritionally complete, it is mandatory that it has not only a balanced macronutrient composition but also sufficient micronutrients. The micronutrient content is defined in relation to energy provision, whereby 1500 kcal must contain 100% of the recommended daily allowance (RDA) for micronutrients. Standard (1 kcal/mL), high-energy (>1.2–2.4 kcal/

* Corresponding author: Tel.: +31-243531500
 E-mail address: marian.devanderschueren@han.nl

mL) or high-protein (>20% of energy derived from protein) products are most frequently prescribed. ONS may be milk- or soy-based or juice-based. ONS routinely contains fiber, but fiber-free products also are available. ONS are generally lactose free.

Occasionally, (partially) hydrolyzed ONS may be prescribed (also called [semi-]elemental), for example in patients with malabsorption. These products contain predigested macronutrients.

Disease-specific ONS have a macro- and micronutrient composition adapted to the predicted needs of a specific disease, digestive, or metabolic disorder [7]. Oncology feeds usually are energy and protein dense, containing ω -3 fatty acids in the form of eicosapentaenoic acid/docosahexaenoic acid, arginine, glutamine, nucleotides, or antioxidants. Their use are discussed later in this review.

How and when to use ONS

ONS should be recommended between or after meals and not before meals or as a meal replacement. This helps to maximize effectiveness and not affect appetite for usual meals. For ONS to be effective, at least two daily servings should be prescribed, for a period of ≥ 3 mo [8]. Patients prescribed ONS should be reviewed at regular intervals, to monitor adherence, to assess progress toward treatment goals, or to decide whether discontinuation is necessary in case of, for example, progressive disease or end of life, or in case of poor adherence.

ONS are more effective when prescribed and supervised by a dietitian. A recent pooled analysis in older adults (not patients with cancer) showed that dietary advice by a dietitian, including ONS when necessary, was more effective in achieving weight gain than the sole provision of ONS (this even had a negative effect on energy intake) [9]. These findings also were seen in a meta-analysis with patients with cancer, in which it was observed that nutritional counseling, with ONS when necessary, resulted in consistent improvements in different aspects of nutritional status [10], whereas ONS on its own resulted in only modest, non-significant effects.

Effectiveness of oral nutritional supplements

Several systematic reviews and meta-analyses have been published on the effects of ONS, alone, or as part of dietary counseling, on clinical outcomes. Of note, the studies included in these meta-analyses involved heterogeneous groups of patients: malnourished or not, different types of cancer, different cancer stages, and different types of treatment (chemotherapy, radiotherapy, surgery).

A systematic review by Baldwin et al. [11] showed that oral nutritional interventions are effective at increasing nutritional intake and improving some aspects of QoL in patients with cancer who are malnourished or are at nutritional risk, but do not appear to improve mortality. In this review, no subanalyses were performed for the different nutritional interventions (dietary counseling, ONS, or the combination of the two).

Lee et al. [10], in a systematic review, performed separate analyses for nutritional counseling without ONS (four studies), nutritional counseling plus ONS (five studies), and ONS without counseling (three studies). Results suggest that nutritional counseling, with or without ONS, was associated with better nutritional outcomes, but ONS without counseling was not. This review comprised different kinds and stages of cancer; differences in intervention duration; different comparisons in the control group; and treatment with radiotherapy, chemotherapy, or surgery. Heterogeneity was high, and therefore meta-analyses were not performed. Despite this heterogeneity, the fact that nutritional counseling, with or without ONS, showed positive outcomes on nutritional status, was consistent across all included studies.

Other reviews have focused on specific patient groups, or on specific types of treatment.

Two reviews in patients with head and neck cancer [12,13] treated with either radiotherapy or chemoradiotherapy confirm the positive effects of nutritional counseling on parameters of nutritional status and QoL, whereby the effects of ONS without dietary counseling were inconsistent.

A recent review on nutritional counseling with or without ONS, and ONS enriched with ω -3 fatty acids, in patients undergoing chemotherapy or chemoradiotherapy [14], showed beneficial effects of supplementation on body weight, but not on treatment toxicity or survival. Meta-analysis per subgroup showed no positive effects in the nutritional counseling (with or without ONS) subgroup. This review further explored whether the interventions were effective in reaching nutritional goals, and concluded that most included studies were ineffective in even getting their patients to reach nutritional requirements, which may explain why no positive effects were observed.

Of course, it would be useful to be able to demonstrate that dietary counseling and ONS are directly associated with favorable clinical outcomes such as improved overall or progression-free survival or better treatment tolerance. One has to realize, however, that nutritional intervention is only one covariate among many that may affect clinical outcomes and that malnutrition is invariably associated with disease, inflammation, altered body composition, and diminished biological function [15]. Thus, we have to wonder whether it is realistic to expect that ONS alone may improve long-term outcomes such as survival. A recent meta-analysis on multifaceted supportive care interventions shows that a combination of interventions (i.e., psychological support and symptom management) was effective in improving survival and QoL [16]. Although nutritional support was not explicitly mentioned in this review, it may well be that nutritional support, including ONS and treatment of nutrition impact symptoms, in combination with other care interventions, may be very effective in improving treatment outcomes. Large, multidisciplinary intervention studies to support this hypothesis should be carried out. Nutritional support thus should be considered an indispensable part of optimal supportive care and it is expected to yield best effects when combined with other supportive strategies such as pain control or psychological support.

Single studies are hampered by small sample sizes, selected patient populations, and in observational studies, possible selection bias, herewith lacking power to demonstrate positive results. Systematic reviews that included randomized controlled trials on patients with cancer, as previously described, show high clinical and statistical heterogeneity and meta-analyses are therefore hardly available. A recent, non-disease-specific meta-analysis on ONS including 1.2 million episodes of ONS use found that ONS was associated with decreased hospital length of stay, episode cost, and 30-d risk for readmission [17]. The reported cost-savings projections were impressive. A major strength of this retrospective study was its great power due to large sample size, a major limitation was that health and nutrition information were not available. Recent studies are encouraging.

ω -3 fatty acids

There has been much debate on the beneficial and possible adverse effects of ONS enriched with ω -3 fatty acids. Cancer-specific ONS enriched with ω -3 fatty acids have been developed with the idea of diminishing the cancer-associated inflammatory response. The safety of these products has been discussed as an interaction was observed between high fish-oil consumption and chemotherapy effectiveness in preclinical studies [18,19]. To date,

clinical data are not supporting the attenuation of chemotherapy efficacy by supplementation with ω -3 fatty acids.

Several systematic reviews have addressed the effects of ONS enriched with ω -3 fatty acids. Although three systematic reviews failed to find positive effects [20–22], four reviews pointed toward positive effects on body weight, appetite, body composition, and QoL [14,23–25]. Carefully weighting both the positive and the negative sounds surrounding these supplements, recent guidelines from the European Society for Clinical Nutrition and Metabolism suggest using supplementation with long-chain ω -3 fatty acids or fish oil to stabilize or improve appetite, food intake, lean body mass, and body weight [26].

Immunomodulating nutrition

Immunomodulating nutrition refers to ONS enriched with immunomodulating nutrients, such as arginine, glutamine, nucleotides, and/or ω -3 fatty acids. Often, these nutrients are provided in one product, so effects of the single nutrients cannot be distinguished. In patients undergoing surgery for upper GI cancers, positive effects of these immunomodulating nutrients have been described. A systematic review by Kim et al., included 28 studies with ONS (12 studies) or tube feeding (14 studies) or both (2 studies) in malnourished patients with cancer, whereby most studies applied immunomodulating products [27]. The comparisons were isocaloric control products, standard products, or a standard diet. The main outcome parameters were indices of nutrition status, immune function, and QoL. Among the studies measuring body weight, nearly 30% found improvements. One or more markers of immune function and inflammatory responses were improved by ONS in 65% of selected studies. Most of the studies did not find significant differences in the concentrations of serum inflammatory markers, possibly due to wide concentration variations. T-cell subset populations and events reflecting infections and complications responded relatively well to nutritional interventions. Eight studies reported on QoL, and in 75% there was a positive response to the nutritional intervention.

Use of ONS in palliative care

Use of ONS in palliative care should be assessed on an individual basis. As long as patients are treated (palliative treatment may last months to years), ONS are recommended to patients with a deficient nutrient intake to improve treatment outcomes. When a patient's condition is deteriorating, the disadvantages of ONS may outweigh the advantages, and ONS should be carefully (re)considered. Emphasis always should be on the enjoyment of food and drinks and maximizing QoL.

Summary

ONS play an important role in helping patients reach their recommended nutritional goals during cancer treatment. Consistent positive effects have been shown for increased nutritional intake and increased body weight. Positive effects on clinical outcomes are less well demonstrated, but larger, non-cancer-specific reviews showed positive effects. To be effective, ONS should be adapted to fit into the diet under supervision of a dietitian, as part as nutritional counseling, also taking into account symptoms affecting nutritional intake such as pain, nausea, vomiting, and constipation. There are careful indications that ONS enriched with ω -3 fatty acids or other immunomodulating agents may be beneficial for subgroups of patients with cancer.

References

- [1] Henry L. Effect of malnutrition on cancer patients. In: Shaw C, editor. Nutrition and cancer, Chichester, UK: Wiley-Blackwell; 2011. p. 45–82.
- [2] Andreyev HJ, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer* 1998;34:503–9.
- [3] Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med* 1980;69:491–7.
- [4] Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. *Nat Rev Dis Primers* 2018;4:17105.
- [5] Omlin A, Blum D, Wierecky J, Haile SR, Ottery FD, Strasser F. Nutrition impact symptoms in advanced cancer patients: frequency and specific interventions, a case-control study. *J Cachexia Sarcopenia Muscle* 2013;4:55–61.
- [6] Food for Special Medical Purposes. Available at: https://ec.europa.eu/food/safety/labelling_nutrition/special_groups_food/medical_en. Accessed August 14, 2019.
- [7] Lochs H, Allison SP, Meier R, Pirlich M, Kondrup J, Schneider S, et al. Introductory to the ESPEN guidelines on enteral nutrition: terminology, definitions and general topics. *Clin Nutr* 2006;25:180–6.
- [8] Milne AC, Avenell A, Potter J. Meta-analysis: protein and energy supplementation in older people. *Ann Intern Med* 2006;144:37–48.
- [9] Reinders I, Volkert D, de Groot L, Beck AM, Feldblum I, Jobse I, et al. Effectiveness of nutritional interventions in older adults at risk of malnutrition across different health care settings: pooled analyses of individual participant data from nine randomized controlled trials. *Clin Nutr* 2019;38:1797–806.
- [10] Lee JL, Leong LP, Lim SL. Nutrition intervention approaches to reduce malnutrition in oncology patients: a systematic review. *Support Care Cancer* 2016;24:469–80.
- [11] Baldwin C, Spiro A, Ahern R, Emery PW. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* 2012;104:371–85.
- [12] Langius JA, Zandbergen MC, Eerenstein SE, van Tulder MW, Leemans CR, Kramer MH, et al. Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo)radiotherapy: a systematic review. *Clin Nutr* 2013;32:671–8.
- [13] Garg S, Yoo J, Winquist E. Nutritional support for head and neck cancer patients receiving radiotherapy: a systematic review. *Supportive Care Cancer* 2010;18:667–77.
- [14] de van der Schueren MAE, Laviano A, Blanchard H, Jourdan M, Arends J, Baracos VE. Systematic review and meta-analysis of the evidence for oral nutritional intervention on nutritional and clinical outcomes during chemo(radio)therapy: current evidence and guidance for design of future trials. *Ann Oncol* 2018;29:1141–53.
- [15] Jensen GL. Oral nutritional supplementation. *Am J Manag Care* 2013;19:119–20.
- [16] Hoerger M, Wayser GR, Schwing G, Suzuki A, Perry LM. Impact of interdisciplinary outpatient specialty palliative care on survival and quality of life in adults with advanced cancer: a meta-analysis of randomized controlled trials. *Ann Behav Med* 2019;53:674–85.
- [17] Philipson TJ, Snider JT, Lakdawalla DN, Stryckman B, Goldman DP. Impact of oral nutritional supplementation on hospital outcomes. *Am J Manag Care* 2013;19:121–8.
- [18] Daenen LG, Cirkel GA, Houthuijzen JM, Gerrits J, Oosterom I, Roodhart JM, et al. Increased plasma levels of chemoresistance-inducing fatty acid 16:4(n-3) after consumption of fish and fish oil. *JAMA Oncol* 2015;1:350–8.
- [19] Roodhart JM, Daenen LG, Stigter EC, Prins HJ, Gerrits J, Houthuijzen JM, et al. Mesenchymal stem cells induce resistance to chemotherapy through the release of platinum-induced fatty acids. *Cancer Cell* 2011;20:370–83.
- [20] Dewey A, Baughan C, Dean T, Higgins B, Johnson I. Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. *Cochrane Database Syst Rev* 2007;CD004597.
- [21] Mazzotta P, Jeney CM. Anorexia-cachexia syndrome: a systematic review of the role of dietary polyunsaturated fatty acids in the management of symptoms, survival, and quality of life. *J Pain Symptom Manage* 2009;37:1069–77.
- [22] Ries A, Trottenberg P, Elsner F, Stiel S, Haugen D, Kaasa S, et al. A systematic review on the role of fish oil for the treatment of cachexia in advanced cancer: an EPCRC cachexia guidelines project. *Palliat Med* 2012;26:294–304.
- [23] Colomer R, Moreno-Nogueira JM, Garcia-Luna PP, Garcia-Peris P, Garcia-Lorenzo A, Zarazaga A, et al. n-3 Fatty acids, cancer and cachexia: a systematic review of the literature. *Br J Nutr* 2007;97:823–31.
- [24] de Aguiar Pastore Silva J, Emilia de Souza Fabre M, Waitzberg DL. Omega-3 supplements for patients in chemotherapy and/or radiotherapy: a systematic review. *Clin Nutr* 2015;34:359–66.
- [25] van der Meij BS, van Bokhorst-de van der Schueren MA, Langius JA, Brouwer IA, van Leeuwen PA. n-3 PUFAs in cancer, surgery, and critical care: a systematic review on clinical effects, incorporation, and washout of oral or enteral compared with parenteral supplementation. *Am J Clin Nutr* 2011;94:1248–65.
- [26] Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* 2017;36:11–48.
- [27] Kim JM, Sung MK. The efficacy of oral nutritional intervention in malnourished cancer patients: a systemic review. *Clin Nutr Res* 2016;5:219–36.