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Review

Omega-3 supplements for patients in chemotherapy and/or radiotherapy: A systematic review

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SUMMARY

Background & aims: Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), *in vitro* and *in vivo*, used along with anticancer drugs, have improved cancer treatment outcome. Clinical studies have reported positive results with omega-3 supplements in oncologic patients. We summarized only randomized controlled clinical trials involving the administration of DHA and/or EPA during chemotherapy and/or radiotherapy to assess the effects on treatment outcomes.
Methods: We conducted a systematic literature search using specific terms. Of 157 publications, 10 were selected on the basis of their methodological quality, according to the Oxford Quality Scale and the Cochrane Concealment Assessment. Outcome included body weight and composition, peripheral neuropathy, immune, inflammatory and oxidative status, quality of life, and membrane omega-3 fatty acids incorporation.
Results: Treatment regimens included radiotherapy (1), chemotherapy (8), and chemoradiotherapy (1). The number of patients ranged from 11 to 92 and the daily dose of EPA and/or DHA from 600 mg to 3.6 g. For high quality methodology studies only, the combination of omega-3 fatty acids supplements with conventional chemotherapy was beneficial. None of the studies reported a worse outcome for the supplement patients.
Conclusions: There are beneficial effects of omega-3 fatty acids supplements in patients undergoing chemotherapy and/or radiotherapy on different outcomes, being the preservation of body composition the most evident. Some important outcome like decrease tumor size and prolonging patient survival, are not observed.

1. Introduction

The long chains polyunsaturated n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are naturally found in organisms of marine origin (e.g., fatty fish) and are present in oils extracted from these organisms (e.g. fish oils) [1]. DHA and EPA are incorporated as structural components into cell membrane phospholipids in the blood and tissues, and they mediate a number of biological effects [1]. They are involved in membrane organization, elasticity, ion permeability (including receptors, transporters, signaling proteins) and lipids mediators with less inflammatory and pro-resolving activity [2].

Cancer patients often suffer from metabolic alterations including inflammation; when associated with radiotherapy and chemotherapy there is more production of pro-inflammatory cytokines, prostaglandins and reactive oxygen/nitrogen species, inducing a cascade of events leading to a suppressed cellular immune function [3]. Omega-3 fatty acids have been considered potentially useful for adjuvant cancer therapy according to their properties on antitumor activity: anti-inflammatory, anti-proliferative, pro-apoptotic, anti-invasion, anti-metastatic and epigenetic regulation [4–6]. Accordingly, tumor cell response may be modified *via* multiple mechanisms [6,7].

The results of *in vitro* and *in vivo* studies have suggested that DHA and EPA favorably modulate anticancer treatment responses –

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promote cytotoxic effects and improvement of several anticancer drugs in different human cancer cells line (leukemia, colorectal [8–10], lung, breast [11–13], cervical, neuroblastoma, lymphoid, pancreatic, bladder, ovarian, glioblastoma) [6,7]. The results in humans seem to improve therapeutic outcome with fewer risks and side effects for patients [4,7,8]. Therefore, DHA and/or EPA can be administered in combination with chemotherapy or radiotherapy with a potential beneficial effect [14].

Based on the relevance of these results, clinical studies have been conducted to investigate whether supplementation of cancer therapy with omega-3 fatty acids improve chemotherapy and/or radiotherapy response. The aim of the present systematic review was to assess the effectiveness of EPA and/or DHA omega-3 fatty acid supplementation during chemotherapy and/or radiotherapy in outcome improvement. Better understanding the available results of EPA/DHA supplementation, in randomized controlled clinical studies, in terms of amount of dose, duration of supplementation and different outcomes could help to guide clinical practice.

2. Methodology

2.1. Literature search

A systematic literature search of the PubMed database, EMBASE database, and Portal Periodicos CAPES was conducted in May 2014 to identify studies published on omega-3 supplements and cancer therapy. Two independent reviewers process the search and selection. The following search terms were used for a search of titles and Abstracts: “radiotherapy” or “chemotherapy” or “chemoradiotherapy” or “antineoplastic therapy” and “cancer”; or “neoplasm” or “tumor” or “oncol” or “carcinoma” or “malignant” and “docosahexaenoic acid” or “eicosapentaenoic acid” or “fish oil” or “omega-3”. There was no language or time restriction for the searches performed. In PubMed database two filters were used: controlled clinical trial and humans.

The study selection and construction of flow diagram was carried out using the guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [15]. A total of 157 records were identified. Nine of these in duplicated form and were removed. 149 records were screened and 76 full text articles were assessed eligibility criteria. Studies were included if: randomized controlled trials; subjects involved were adult; involving cancer treatment (chemotherapy and/or radiotherapy); intervention group received EPA and/or DHA. Were excluded studies in which omega-3 supplements was taken in combination with other immunonutrients such as amino acids and ribonucleic acids or with the conjugated drug, DHA-paclitaxel (Taxoprexin®).

2.2. Study quality

Data from each study were extracted and design quality was evaluated by two authors (first and second) afterward the data were compared and revised for a consensus. The methodological quality of the studies was evaluated using the Oxford Quality Scale, with a score of “1” indicating low quality, and a score of “5” indicating high quality [16]. The Cochrane Concealment Assessment was also applied: (A = adequate concealment, B = uncertain, C = clearly inadequate) [17]. A meta-analysis was not possible as a variety of outcome measures were used and study designs were not comparable.

3. Results

We summarize 10 studies that met the selection criteria and provided data from 383 patients (Fig. 1). The cancers associated with these ten studies included breast ($N = 1$), colorectal ($N = 3$), lung ($N = 4$), gastrointestinal ($N = 1$), and an indeterminate cancer ($N = 1$). The treatments associated with these studies included radiotherapy ($N = 1$), chemotherapy ($N = 8$), and chemoradiotherapy ($N = 1$). There were two papers [18,19] that were published on the same set of data, and they were evaluated as a single study. Omega-3 supplements was administered in the form of a soft gel capsule supplement ($N = 5$) or was ingested as part of a nutritional oral supplement ($N = 5$). The number of patients involved (Table 1) in each study ranged from 11 to 92, the dose of combination of EPA and DHA typically in the form of fish oil ranged from 600 mg to 3.6 g per day, with different ratios of EPA to DHA, and the time period for the duration of supplementation ranged from 1 to 12 weeks. In four studies [20–23] a fish oil group was compared to a group that did not receive nutritional intervention (and in one of these studies [21], fish oil was provided as part of an nutritional energy and protein oral complement), in two studies [24,25] fish oil was compared with other lipids, one study [26] was compared with an isocaloric diet and in three studies [18,19,27,28] fish oil was compared to nutritional supplements.

Study quality was measured and a few studies were classified as clearly inadequate (Table 1). Conversely, two studies [27,24] received the highest score according to the Oxford Scale, and no adequate concealment was observed according to the Cochrane criteria which would indicate bias. In the study by Faber et al., an energy dense supplement containing fish oil was compared with another supplement. However, it is not clear whether the two supplements were similar in appearance, and thus, whether the study was truly blinded. Similarly, Ghoreish et al. used sunflower oil for their control arm, and the capsules administered were from different companies. Therefore, it is possible that the capsules may not have matched, and it is known that taste usually differs between products. In addition, for both studies, the number and description of dropouts and an intention-to-treat analysis were not performed.

The outcomes investigated by the selected studies included: peripheral neuropathy ($N = 2$), body weight ($N = 9$), body composition ($N = 3$), immune and inflammatory status ($N = 7$), quality of life ($N = 4$), oxidative status ($N = 2$), and EPA and/or DHA incorporation ($N = 5$) (see Fig. 2). Studies by Ghoreishi et al. and Sánchez-Lara et al. assessed peripheral neuropathy, which has been reported to be a dose-limiting side effect of paclitaxel [13]. A lower incidence ($P < 0,05$) of peripheral neuropathy was observed for patients that consumed EPA and DHA omega-3 fatty acids [24,26].

3.1. Body weight

Body weight was assessed in 9 of the studies examined. In the Faber et al. (2013) study that was conducted with patients undergoing radiotherapy, body weight at day 7 increased in the fish oil group and decreased for the control group [27], albeit not significant [27]. In the van der Meij et al. (2010) study, the intervention group that received a nutritional supplement containing 2.0 g EPA and 0.9 g DHA exhibited better weight maintenance than the control group which received a standard nutritional supplement [18]. Moreover, both groups were undergoing chemoradiotherapy, and in the per protocol analysis, the effect on body weight after 1, 2, and 4 weeks was stronger (B = 2.2 kg, $P = 0.01$; B = 2.2 kg, $P = 0.01$; and B = 2.2 kg, $P = 0.04$, respectively) [18].

For the seven studies that were conducted during active chemotherapy treatment, three of these studies included daily administration of fish oil capsules containing 600–700 mg EPA + DHA. Moreover, these patients were compared with those that did not receive a nutritional supplement [20,22,23]. In the

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