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n-3 polyunsaturated fatty acid supplementation during cancer chemotherapy

Sarah Louise Morland, Karen J.B. Martins, Vera C. Mazurak*

Division of Human Nutrition, Department of Agricultural, Food and Nutritional Sciences, University of Alberta, 4-002C Li Ka Shing Centre for Health Research Innovation, Edmonton, AB, T6G 2E1, Canada

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ABSTRACT

Evidence from several clinical trials suggests that n-3 polyunsaturated fatty acid (n-3 PUFA) supplementation during cancer chemotherapy improves patient outcomes related to chemotherapy tolerability, regardless of the type of chemotherapy used. While the effects of n-3 PUFA supplementation during chemotherapy have been the subject of several reviews, the mechanisms by which n-3 PUFA improve patient responses through improved chemotherapy tolerability are unclear. There are several barriers currently hindering interpretation and comparison of studies, including small sample sizes, poor patient compliance, and variation in supplementation format and dose. Expansion of standard-of-care for specific patient populations to include n-3 PUFA supplementation concurrent with chemotherapy may reduce costs associated with delayed treatment, toxicities and unplanned hospitalization during cancer chemotherapy. The purpose of this review is to identify barriers to understanding mechanisms of host protection, highlight considerations for future clinical trials, as well as to propose potential mechanisms by which n-3 PUFA supplementation improves chemotherapy tolerability and ultimately patient outcomes.

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Contents

Abbreviations: DHA, docosohexaenoic acid; EPA, eicosapentaenoic acid; NSCLC, non-small cell lung cancer; ONS, oral nutritional supplement; PUFA, polyunsaturated fatty acid; CRP, C-reactive protein; PPAR-γ, peroxisome proliferator agonist receptor-gamma.

* Corresponding author.
E-mail addresses: morland@ualberta.ca (S.L. Morland), karen.martins@ualberta.ca (K.J.B. Martins), vera.mazurak@ualberta.ca (V.C. Mazurak).

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1. Introduction

1.1. n-3 polyunsaturated fatty acids and human health

The n-3 polyunsaturated fatty acids (n-3 PUFA) eicosapentaenoic acid (EPA; 20:5n-3) and docosohexaenoic acid (DHA; 22:6n-3) have been the focus of several clinical trials in a variety of healthy and disease populations due to their numerous benefits to human health (reviewed by Ref. [1]). Plant n-3 PUFA, alpha-linolenic acid (18:3n-3) is a dietary essential fatty acid that provides the substrate for enzymatic conversion to EPA and DHA in humans. However, conversion from alpha-linolenic acid may not provide adequate levels of EPA and DHA in humans with disease [2]. The occasional consumption of dietary sources of EPA and DHA, such as cold water fatty fish, may not provide adequate amounts of these fatty acids. Direct provision of EPA and DHA through supplementation may therefore benefit human health [3].

PUFA are a component of every cell membrane in the body; dietary n-3 PUFA are incorporated into cell membrane phospholipids in a dose-dependent manner, and modify host fatty acid profiles by decreasing the proportion of n-6 PUFA such as arachidonic acid [3]. Alteration of membrane composition influences membrane fluidity, receptor activity, signalling molecule production and lipid mediator production (reviewed by Ref. [3]) to evoke alterations in metabolism at the cellular and tissue levels.

1.2. Side effects of chemotherapy

There are several different effective modalities used to treat neoplasms, including surgery, radiation therapy and chemotherapy. While a positive relationship has been shown to exist between the total platinum dose delivered in adjuvant chemotherapy and overall survival [4], severe toxic side effects can lead to poorer chemotherapy outcomes such as fewer courses of chemotherapy delivered, dose reductions, treatment delays and decreases in overall treatment time, thereby interrupting the most beneficial course of treatment [4–6]. Unfortunately, there are a number of side effects related to chemotherapy. Apart from graded toxicities included in the National Cancer Institute Common Toxicity Criteria [7], additional side effects include decreased quality of life [8,9], changes in immune and inflammatory markers [10,11], higher nutritional impact symptoms and decline of nutritional status [9]. Collectively, it appears that improving chemotherapy tolerability could lead to maintenance of the most effective levels of dosing, increase adherence to chemotherapy schedules and improve the therapeutic index of treatments, ultimately improving patient outcomes.

The n-3 PUFA, EPA and DHA have been applied as an adjunct to chemotherapy in cancer patients and have been shown to improve the response of the tumor to drug treatment in a variety of settings while protecting the host from toxicities associated with the drug (recent reviews [12–23]). The collective evidence in humans suggests n-3 PUFA supplementation enhances drug efficacy to the tumors as well as improving other important clinical outcomes such as maintenance of muscle and quality of life. While these reviews make different conclusions regarding how patient outcomes were improved, almost all have highlighted the need for further clinical trials to optimize supplement dosage and determine mechanisms of action [13–22]. The purpose of this review is to identify potential targets influenced by n-3 PUFA supplementation during chemotherapy, with a focus on human evidence reporting a reduction in side effects. We identify barriers to conducting clinical trials, and highlight considerations for future trials that are required to define optimal timing, dose and format of n-3 PUFA supplementation during oncological treatment. As the focus of the current review is on clinical studies, we have not included data on preclinical models; we direct readers interested in this topic to reviews on the experimental literature [24–27].

2. Current evidence supporting n-3 PUFA supplementation during chemotherapy

2.1. Clinical trials

Several recent clinical trials have shown improved chemotherapy tolerability and patient outcomes associated with adjuvant n-3 PUFA supplementation. Although these trials were performed in different cancer populations using a variety of chemotherapy regimens, improvements were observed in all interventions [28–41] (Table 1). Highlights of these improvements are briefly discussed below.

2.1.1. Clinical outcomes

Cancer is an important health issue that influences quality of life and survival. Strikingly, breast cancer patients with high incorporation of supplemented DHA (i.e. extent of DHA increase above the median of 2.5% of total fatty acids) experienced longer time to disease progression (8.7 months *vs* 3.5 months) and significantly longer survival (34 months *vs* 18 months) compared to patients with lower incorporation of supplemented DHA [31]. Additionally,

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