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Impact of fish oil and melatonin on cachexia in patients with advanced gastrointestinal cancer: A randomized pilot study

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Abstract

Objective: The effect of fish oil (FO), melatonin (MLT), or their combination and dietary advice on cachexia and biochemistry variables reflecting cachexia were investigated in patients with advanced gastrointestinal cancer.

Methods: Twenty-four patients not amenable to standard anticancer treatment and with documented weight loss and/or decreased serum albumin were included. They were randomized to 30 mL/d of FO, which provided 4.9 g of eicosapentaenoic acid and 3.2 g of docosahexanoic acid, or 18 mg/d of MLT for 4 wk. During the next 4 wk, all patients had FO and MLT. Serum or plasma was analyzed for tumor necrosis factor-α, interleukin-1β, soluble interleukin-2 receptor, interleukin-6, and interleukin-8 and the fatty acids eicosapentaenoic acid, docosahexanoic acid, arachidonic acid, and linoleic acid.

Results: Serum levels of eicosapentaenoic acid and docosahexanoic acid increased as expected with FO. No major changes in biochemical variables and cytokines were observed with any intervention. In the FO group, 5 of 13 patients (38%) showed weight stabilization or gain compared with 3 of 11 patients (27%) in the MLT group. After combining interventions, approximately 63% of patients showed such responses.

Conclusions: FO, MLT, or their combination did not induce major biochemical changes indicative of a strong anticachectic effect. Nonetheless, the interventions used may have produced a weight-stabilizing effect. © 2005 Elsevier Inc. All rights reserved.

Keywords: Gastrointestinal cancer; Cachexia; Fish oil; Melatonin

Introduction

Cachexia is common in many tumor types in the advanced setting, especially so in, for example, cancers of the pancreas, lung, and colon, and is a major clinical problem with considerable effect on a patient's quality of life (QoL). Cancer cachexia is manifested as weight loss with depletion of skeletal muscle and adipose tissue, accelerated total protein turnover, and increased gluconeogenesis and resting energy expenditure [1]. The best way to reverse cancer cachexia is to provide efficient control of the cancer. However, in patients with advanced cancer, such therapy is frequently not available or provides only short-term beneficial effects. Nutritional support alone is not sufficient to counteract cachexia [1], indicating that specific mechanisms are responsible for the phenomenon.

Cancer cachexia is reminiscent of an inflammatory process, identified by an acute-phase protein response (APPR) with increased levels of C-reactive protein (CRP) and fibrinogen, which are poor prognostic factors in advanced cancer [2,3]. Knowledge of the pathophysiology behind cancer cachexia has expanded considerably during recent years. Thus, various cytokines produced by host immune cells in response to tumor seem to be causally related to the metabolic abnormalities [1,4].

Interleukin (IL) 1β is a potent anorexia-producing agent

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that causes increased resting energy expenditure, skeletal protein wasting, and leptin release [4]. IL-6 is associated with weight loss and increased hepatic protein synthesis and acts on the hypothalamus to impair eating activity [5]. Tumor necrosis factor-α (TNF-α) is also a potent anorexia-producing agent because it promotes skeletal protein wasting, inhibits lipoprotein lipase, and decreases synthesis of lipids [6]. High levels of TNF-α are seen in weight-losing patients with pancreatic cancer [5].

The effect of other cytokines is less well established in this context. However, IL-2, a key T-cell cytokine primarily produced by T cells of the T helper-1 type, interacts with a specific membrane IL-2 receptor, detectable in plasma as soluble IL-2 receptor (sIL-2R). Soluble IL-2R is high in cancer patients, is most pronounced in those with cachexia, and correlates with prealbumin, transferrin, and survival rate [7]. IL-8 is a proinflammatory cytokine that is involved in the regulation of satiety and modulates the APPR [8]. Peptides seemingly produced by tumors and that specifically induce proteolysis and lipolysis have been isolated recently [1,3].

Different pharmacologic agents have been used to manage cancer cachexia, and limited improvements in appetite and some weight gain have been observed [1]. However, the effects are modest, and to more substantially improve the management of cancer cachexia, approaches that exploit the pathophysiology of cachexia need to be considered. One mechanistically sound approach is the administration of ω-3 polyunsaturated fatty acids (ω-3 FAs), notably eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), which are plentiful in fish oil (FO). The ω-3 FAs are suggested to influence the development of cachexia by interfering with the catabolic processes that act on muscle and adipose tissue rather than as a nutritional supplement [9]. The ω-3 FAs might affect cytokine production and activity by interfering with the cyclo-oxygenase and lipoxygenase signaling pathways. Mostly studied in advanced pancreatic cancer, large doses of FO seem to partly counteract the cachectic process in this disease [10,11].

Another potentially interesting but less studied approach is the use of melatonin (MLT), a hormone produced by the pineal gland that participates in the regulation of biological rhythms and in the control of cell differentiation and proliferation [12]. MLT is suggested to inhibit tumor growth and stimulate host antitumor defense [13,14], decrease TNF-α, enhance survival, and increase the objective response rate when combined with chemotherapy [15].

The primary aim of the present study was to determine whether short-term intervention with large doses of FO and/or MLT combined with dietary advice in patients with advanced gastrointestinal cancer could influence a broad spectrum of variables presumed to reflect the development of cachexia, notably cytokines. Secondarily, we also studied clinical benefit as indicated by food intake, body weight, and QoL. FO and MLT have been studied in this setting, but data are limited and have not been studied in parallel or in combination.

Materials and methods

Trial outline

The study was a one-center, randomized, non–placebo-controlled, open study performed between January 1998 and May 2000. It was approved by the research ethics committee of the Faculty of Medicine, University of Uppsala (Uppsala, Sweden).

Patients who had advanced gastrointestinal cancer, visited the outpatient clinic, and fulfilled the inclusion criteria were asked to participate. Briefly, patients had to have metastatic or locally advanced gastrointestinal cancer not amenable to curative or standard palliative treatment, greater than 10% weight loss during the previous 6 mo, a serum albumin level no higher than 35 g/l, Karnofsky's performance status of at least 60, and, in the case of ongoing chemotherapy, at least two courses before beginning the study with therapy to continue. Concomitant medication with anticoagulative agents was not allowed; however, in the case of medication with non-steroidal anti-inflammatory drugs or corticosteroids, medication must have begun at least 2 wk before study inclusion. After baseline assessments, patients were given standard dietary advice and were randomized to a 4-wk intervention with FO or MLT followed by study assessments and a new 4-wk intervention period with FO and MLT and final assessments. Twenty-four patients were included and randomized. Key demographic data of patients at the start of intervention are presented in Table 1.

Assessments of biochemistry, performance status, QoL, and food intake

Blood samples for analyses of blood hemoglobin, serum albumin, serum lactate dehydrogenase, CRP, and plasma fibrinogen were obtained in the morning after overnight fasting at baseline and after each 4-wk intervention period. At the same time, serum was obtained and frozen at -70°C within 4 h of sampling for subsequent analyses of TNF-α, IL-1β, IL-6, IL-8, sIL-2R, EPA, DHA, linoleic acid, and arachidonic acid.

Performance status was measured with Karnofsky's performance status, and QoL was assessed by the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC-QLQ-C30) [16] at baseline and during the last weeks of the first and second intervention periods. The EORTC-QLQ-C30 is a 30-item cancer-specific questionnaire that consists of five functional scales (physical, emotional, cognitive, social, and role), three symptom scales (fatigue, pain, and nausea/vomiting), a global health or QoL scale, and six single items that assess symptoms and finan-

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