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Effects of Eicosapentaenoic and Docosahexaenoic n-3 Fatty Acids From Fish Oil and Preferential Cox-2 Inhibition on Systemic Syndromes in Patients With Advanced Lung Cancer

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Abstract: *Under the common denomination of Systemic Immune-Metabolic Syndrome (SIMS), we grouped many symptoms that share a similar pathophysiologic background. SIMS is the result of the dysfunctional interaction of tumor cells, stroma cells, and the immune system, leading to the release of cytokines and other systemic mediators such as eicosanoids. SIMS includes systemic syndromes such as paraneoplastic hemopathies, hypercalcemia, coagulopathies, fatigue, weakness, cachexia, chronic nausea, anorexia, and early satiety among others. Eicosapentaenoic and docosahexaenoic n-3 fatty acids from fish oil can help in the management of persistent chronic inflammatory states, but treatment's compliance is generally poor. Preferentially, Cox-2 inhibition can create a favorable pattern of cytokines by decreasing the production of certain eicosanoids, although their role in SIMS is unknown. The aim of this study was to test the hypothesis that by modulating systemic inflammation through an eicosanoid-targeted approach, some of the symptoms of the SIMS could be controlled. We exclusively evaluated 12 patients for compliance. Patients were assigned 1 of the 4 treatment groups (15-, 12-, 9-, or 6-g dose, fractionated every 8 h). For patients assigned to 15 and 12 doses, the overall compliance was very poor and unsatisfactory for patients receiving the 9-g dose. The maximum tolerable dose was calculated to be around 2 capsules tid (6 g of fish oil per day). A second cohort of 22 patients with advanced lung cancer and SIMS were randomly assigned to receive either fish oil, 2 g tid, plus placebo capsules bid ($n = 12$) or fish oil, 2 g tid, plus celecoxib 200 mg bid ($n = 10$). All patients in both groups received oral food supplementation. After 6 wk of treatment, patients receiving fish oil + placebo or fish oil + celecoxib showed significantly more appetite, less fatigue, and lower C-reactive protein (C-RP) values than their respective baselines values ($P < 0.02$ for all the comparisons). Additionally, patients in the fish oil + celecoxib group also improved their body weight and muscle strength compared to baseline values ($P < 0.02$ for all the comparisons). Comparing both groups, patients receiving fish oil + celecoxib showed significantly lower C-RP levels ($P = 0.005$, t-test), higher muscle strength ($P = 0.002$, t-test) and body weight ($P = 0.05$, t-test) than patients receiving fish oil + placebo. The addition of celecoxib improved the control of the acute phase protein response, total body weight, and muscle strength. Additionally, the consistent nutritional support used in our patients could have helped to maximize the pharmacological effects of fish oil and/or celecoxib. This study shows that by modulating the eicosanoid metabolism using a combination of n-3 fatty acids and cyclooxygenase-2 inhibitor, some of the signs and symptoms associated with a SIMS could be ameliorated.*

Introduction

Advanced cancer patients present with multiple concurrent symptoms, making it difficult to conduct interventional clinical trials in this category of patients. Moreover, many of the symptoms tend to be multidimensional, and patients cannot easily distinguish between some of them (e.g., fatigue and weakness). In recent years, as a way to overcome this limitation and facilitate the clinical management, several groups have been focusing on symptom clusters rather than individual symptoms (1–3). Symptoms clusters can be statistically identified by means of unsupervised hierarchical clustering. By using a different approach, we considered under the common denomination of Systemic Immune-Metabolic Syndrome (SIMS) (4) a group of symptoms that share a similar pathophysiologic background. SIMS include systemic syndromes (in contrast to local/regional and distant syndromes) such as paraneoplastic hemopathies, hypercalcemia, coagulopathies, fatigue, weakness, cachexia, chronic nausea, anorexia, and early satiety among others. SIMS is characterized by a dysregulation of the psycho-neuro-immune-endocrine homeostasis and, as other systemicsyndromes, can

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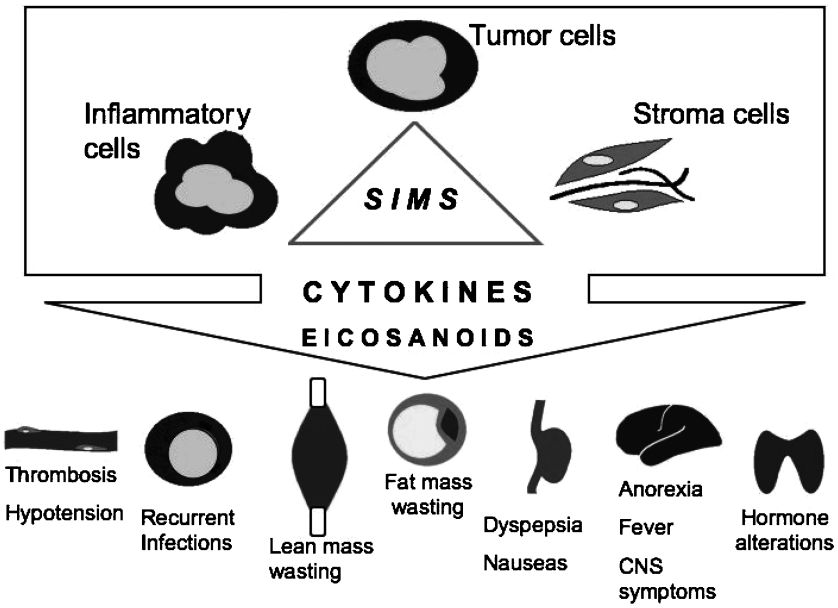

Figure 1. Cytokines and eicosanoids derived from the interaction of tumor, stroma, and inflammatory cells can play a role in generating a systemic response (with proinflammatory and antiinflammatory components) that may directly or indirectly (through other mediators such as hormones, neuropeptides, lytic factors, etc.) target the general metabolism and specific organs evidencing as a variety of signs and symptoms. SIMS, Systemic Immune-Metabolic Syndrome; CNS, central nervous system.

lead to a poor performance status affecting the quality of life (5) and the survival of cancer patients. Our hypothesis, exemplified in Fig. 1, is that SIMS is the result of the dysfunctional interaction of tumor cells, stroma cells, and the immune system, leading to the release of cytokines and other systemic mediators (6,7). Such interaction impacts in the host, generating variable symptoms that depend on the target organs or tissues (a hypothesis also supported by others) (8,9). A practical corollary of our hypothesis is that a therapeutic intervention intended to control the underlying common pathophysiology, rather than to a particular symptom, has more chances to positively impact the performance status and eventually the survival.

Experimental animal models (10–18) and clinical studies (19–22) have suggested that cytokine and eicosanoid-mediated events may be implicated in these alterations (23–26). Eicosanoids are members of a large and important family of cellular mediators (27) that modulate the effects of all kinds of hormonal, immunological, and nervous signals as well as of environmental influences (17). Two of the major families of eicosanoids (i.e., prostanoids and eicosatetraenoic acids and leukotrienes) are the products of 2 different enzymes [cyclooxygenases (COX) and lipoxygenases (LOX), respectively] preferentially from a common precursor [i.e., arachidonic acid (AA)]. Feeding fish oil results in partial replacement of AA in cell membranes by eicosapentaenoic acid (EPA). This leads to decreased production of AA-derived mediators through several mechanisms including less substrate availability, less enzyme availability (by decreasing the expression of COX-2 and LOX-5), and competitive antagonism (between EPA and AA) (26). These actions account for the antiinflammatory effect of n-3 fatty acids derived from fish oil. In fact, studies in patients with cancer showed that oral fish oil supplementation can be effective in ameliorating the weight loss and some other inflammation-related symptoms (5). Although some authors have described a dose relationship for fish oil and therapeutic gain, the poor compliance with the intake of the fish oil capsules limits its use in the clinical practice in patients with advanced cancer.

We envisaged that a better way to obtain the maximal therapeutic gain from fish oil without compromising compliance could be through combination with COX inhibitors.

For many years, dual COX inhibitors showed some efficacy to control particular features of a systemic, persistent, low-grade inflammatory response in animal tumor models (10,28–30) and patients with advanced cancer (31–33). Along this line of thought, more recently, our group (4) has been shown that more specific inhibition of the COX-2 isoform is feasible and possibly useful in ameliorating systemic inflammation in patients with lung cancer when celecoxib was combined with a progestagen.

The aim of this study was to test the hypothesis that by modulating systemic inflammation through an eicosanoid-targeted approach, some of the symptoms of the SIMS could be controlled.

Patients and Methods

Study Cohort

The study was carried out in a cohort of patients with advanced non-small cell lung cancer (NSCLC) and evidence of a SIMS. The tumor-node-metastasis classification from the International Union Against Cancer was usedfor staging

lung cancer. Tumor burden was assessed after the histological diagnosis by computer axial tomography of the chest and abdomen for primary and lung, hepatic, or suprarenal metastasis and the most valuable image techniques for other metastatic localization. Patients with either stage IV from presentation or systemically progressed-disease (from stage IIIb) were included; therefore, all patients had active disease at the time of study entry. A total of 8 patients in the first subset of 12 (67%) and 14 patients in the second subset of 24 (58%) did not receive any antineoplastic treatment. They were either not eligible due to poor performance status or the patient refused the proposed treatment. The remaining patients (14/36) received a broad range of palliative treatments including surgery (3/14), radiotherapy (14/14), and platinum-based chemotherapy (6/14). Patients did not have surgery, radiotherapy, or chemotherapy at least 4 wk before entering or during the study period.

SIMS was defined as the presence of cachexia (more than 10% weight loss), anorexia (visual analogue scale more than 5/10), performance status (Eastern Cooperative Oncology Group) equal or more than 2, plus evidence of an acute phase protein response [APPR; C-reactive protein (C-RP) more than 10 μg/ml].

The exclusion criteria were 1) treatment with corticosteroids, androgens, nonsteroidal antiinflammatory drugs other than the study drugs, or appetite stimulants within the past month; 2) use of tube feeding or parenteral nutrition; 3) moderate or severe dysphagia; 4) obvious functional obstruction to food intake; 5) ascites or clinically and/or ultrasound evident fluid retention; 6) severe endocrine abnormalities, diabetes mellitus, and manifest infection; 7) antecedent thrombopathy and/or hemopathies; and 8) known allergy to sulfa drugs.

The study was approved by the institutional research and ethic committees. All the patients submitted a written consent.

Trial Design

A pilot study was performed to determine the maximum tolerable dose for fish oil capsules. An acceptable compliance for the randomized trial was set up in 90% or higher. Patients were asked to return the untaken doses and to complete a specially designed form. Four consecutive groups of 3 patients each were treated with a total of 15, 12, 9, or 6 g of fish oil capsules. All patients received their capsules tid. Treatments were administered for 1 wk at the end of which the compliance was calculated.

A subsequent controlled study was carried out to determine the efficacy of fish oil versus fish oil plus celecoxib in the management of systemic symptoms. As the maximum tolerable dose was determined to be 6 g of fish oil (2 g every 8 h or tid); for the compared part of the study, patients were randomly assigned to receive either fish oil, 2 g tid, plus placebo capsules bid or fish oil, 2 g tid, plus celecoxib 200 mg bid. Treatments were administered for 6 wk.

Treatments

Celecoxib (Microsules y Bernabo SA, Buenos Aires, Argentina) and placebo were prepared as 200 mg capsules. Fish oil capsules were purchased from the market and consisted of 1-g soft gels containing about 18% of EPA and 12% docosahexaenoic acid (DHA; Spectrum Organic Products, Inc., Petaluma, CA). Fish oil capsules were formulated with natural tocopherols as antioxidant.

Eicosanoids exhibit pleiotropic effects on hemostasis and by partially altering the relative proportion of anti and procoagulant eicosanoids, n-3 fatty acids, and /or COX-2 inhibitors (34,35) and can increase the already high prothrombotic risk of advanced cancer patients (36). To prevent a higher increase of the thrombotic risk, all patients in both groups received aspirin at 75 mg per day.

All patients in both groups received oral food supplementation with a preparation providing 1.52 kcal/ml and containing approximately 56.4% carbohydrates (40% corn syrup, 35% maltodextrin, and 25% sucrose), 14.6% proteins (80% calcium caseinate and 20% soy protein), and 29% fat (50% canola, 27% corn, and 23% sunflower oils). The prescribed caloric intake of this food supplement was equivalent to a 20% of the basal metabolic rate (BMR) at resting and was calculated at the start of the treatment.

Nutritional and Symptomatic Assessment

Baseline and weekly measurements of Karnofsky's performance score (KPS), appetite, nausea, fatigue, weight, fat mass (FM), lean mass (LM), total body water (TBW), caloric intake and handgrip (HG) were taken by the same researcher. HG value, as indication of muscle strength, was calculated as the average of the best of 3 trials for each hand. For patients with known functional impairment (tumor invasion of the brachial plexus or pathological fracture, for instance), only the values from the functional hand were considered.

Appetite, nausea, and fatigue were assessed using a numerical rating scale (0–10). Number of patients with clinically significant early satiety and taste change were recorded at baseline and after treatment.

FM (kg), LM (kg), and TBW (liters) were calculated by a body composition analyzer that measures bioelectrical impedance (BIA; BF 906, Maltron International Limited, Rayleigh, Essex, UK).

Caloric intake was measured considering the daily intake of food and nutritional supplement. A meal advice (regarding size portions and basic components) was given to a patient's relative by a nutritionist to maintain a caloric intake similar to the BMR estimated by BIA analysis. During previous sessions, a patient's relative was trained to perform the amount estimation (in ml) of nutritional supplement intake and fill out a form. At each weekly medical visit, the information was translated into calories using food tables and the information provided by the manufacturers.

Compliance with medication, incidence of side effects, and incidence of coagulopathies were recorded in each scheduled and unscheduled medical visit.

Blood Chemistry

Venous blood samples were taken before breakfast at baseline and weekly for measurement of albumin, total protein, hemoglobin, total and differential white blood cell count, sodium, potassium, ionic calcium, creatinine, urea, total and direct bilirubin, aspartate amino transaminase, alanine amino transaminase, lactate dehydrogenase, gamma glutamil transpeptidase, alkaline phosphatase, and C-RP.

Statistics

The Wilcoxon's signed rank test was used to compare (pre–post) the intensity of nausea, appetite, and fatigue. The paired *t*-test was used to compare (pre–post) body weight change, C-RP levels, and HG values as well as other continue variables. Mann–Whitney or *T* test were used to compare between treatment groups, parametric and nonparametric distributed variables, respectively.

Values are presented as mean with the 95% confidence interval or median with the range for nonparametric distributions.

Unless otherwise noted, the *P* values cited were 2-sided, and *P* values less than 0.05 were judged as statistically significant. All calculations were done with the statistics program Statistix version 7.0 (Analytical Software, 2000, Tallahassee, FL).

Results

Compliance Study

We exclusively evaluated 12 patients for compliance. Patients were assigned 1 of the 4 treatment groups (15-, 12-, 9- or 6-g dose, fractionated every 8 h). For patients assigned to 15 and 12 doses, the overall compliance was very poor, and unsatisfactory for patients receiving the 9-g dose (Fig. 2). The causes of no compliance were nausea (100%), vomiting (92%), satiety (75%), and fish-smelling breath and perspiration (75%). The maximum tolerable dose was calculated to be around 2 capsules tid (6 g of fish oil per day); in consequence, this dose was used for the randomized trail. None of the patients included in the pilot study were included in the randomized trial.

Randomized Study

Of 24 patients with NSCLC and SIMS approached for the randomized trial, 2 were excluded (both were taking medication conflicting with this study), and 22 were included in the study and randomized according to a random number generator (1:1 rate). A total of 12 patients received fish-oil capsules plus placebo, and 10 patients received fish-oil capsules plus celecoxib. Flowchart of the patients is shown in the Fig. 3. The clinical characteristics of the patients are given in Table 1.

After 6 wk of treatment, patients receiving fish oil + placebo showed significantly more appetite, less fatigue, and lower C-RP values than their respective baselines values (Table 2). A similar therapeutic gain was noted with the patients receiving fish oil + celecoxib, but additionally in these patients, their body weight and HG scores were significantly higher after the treatment compared to baseline values (Table 2). Fat mass and lean mass showed a tendency to improve after 6 wk of treatment in patients receiving fish oil + celecoxib. These patients gained lean and fat mass, whereas patients who received fish oil + placebo continued to lose fat and lean mass. No other symptom, body measure, or chemical value changed significantly in any of the groups.

Comparing both groups, patients receiving fish oil + celecoxib showed significantly lower C-PR levels and higher HG scores and body weight than patients receiving fish oil + placebo. There were no other significant differences between groups.

There were significant correlations (Spearman rank) between change in (Δ) fatigue and Δ HG ($r = –0.49$, $P = 0.019$), Δ fatigue and Δ fat mass ($r = –0.48$, $P = 0.025$), Δ fatigue and lean mass ($r = –0.43$, $P = 0.046$), Δ body weight and Δ appetite ($r = 0.43$, $P = 0.047$), Δ body weight

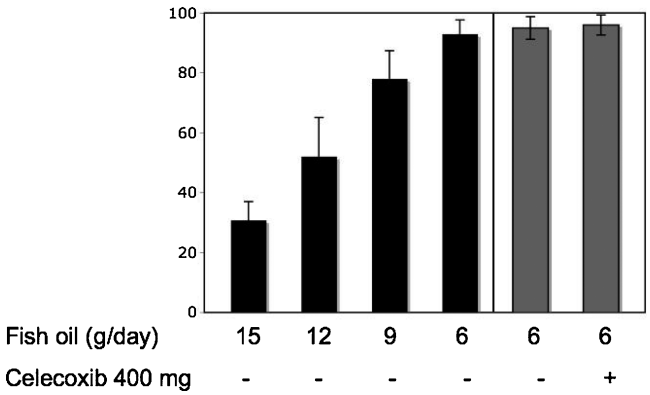

Figure 2. Compliance (as percentage of the planned dose) of the patients treated with several doses of fish oil (black bars) and compliance of the patients in the randomized trial (grey bars).

Table 1. Characteristics of the Patients at Randomization[a]

Characteristic	Fish Oil ($n = 12$)	Fish Oil + Celecoxib ($n = 10$)
Sex (male/female)	9/3	8/2
Age, yr (range)	61 (44–83)	64 (44–90)
Performance status		
50–60%	5 (42%)	6 (60%)
70–80%	7 (58%)	4 (40%)
Body weight (kg)	62.8 (±9.7)	60.1 (±8.2)
Fat mass (kg)	25.8 (±4.4)	24 (±6.2)
Lean mass (kg)	37 (±15)	36.1 (±15.3)
Body water (l)	29.4 (± 8)	30.2 (±8.6)
Handgrip	27 (±7.8)	21.2 (±7.1)
Appetite, median (range)	4 (0–5)	4 (0–6)
Fatigue, median (range)	6.5 (3–10)	7.5 (3–10)
C-reactive protein (μg/ml)	33 (±17.8)	38 (± 22.3)

a: All values are mean ±95% confidence interval unless noted.

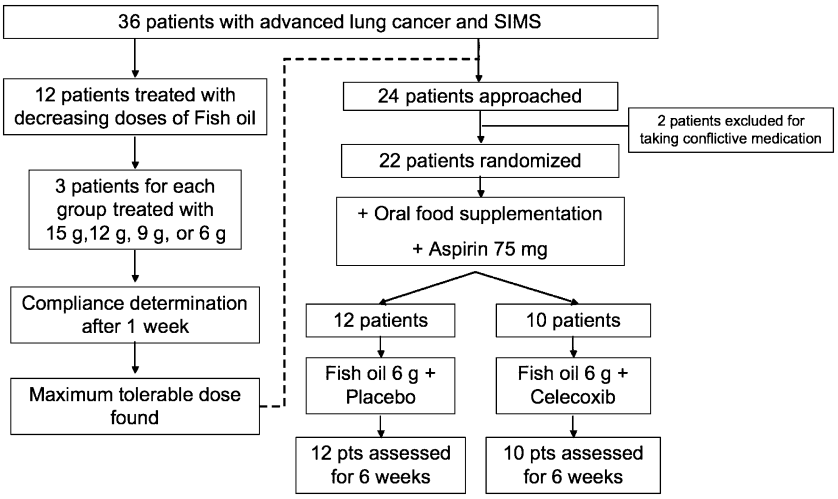

Figure 3. Flowchart of the patients during the study.

Table 2. Endpoints Comparison Between Groups After 6 Wk of Treatment

	Fish Oil ($n = 12$)	Fish Oil + Celecoxib ($n = 10$)	P Value
Compliance	96%	98%	NS
ΔBody weight (kg)	–1.4 (0.84)	1.5 (1.2)*	0.05
ΔFat mass (kg)	–0.6 (0.8)	1.2 (0.64)	NS
ΔLean Mass (kg)	–0.6 (0.67)	0.4 (0.6)	NS
ΔBody water (l)	0.4 (0.85)	0.3 (0.9)	NS
ΔHang grip	1.16 (0.3)	3.12 (0.98)*	0.002
ΔAppetite	3.8 (0.8)*	3.1 (1.2)*	NS
ΔFatigue	–3.5 (0.9)*	–3 (0.9)*	NS
ΔC-RP (μg/ml)	–6.7 (4.5)*	–21.3 (7)*	0.005

a: Abbreviations are as follows: NS, not significant; Δ, Difference between Week 6 and baseline; C-RP, C-reactive protein. Values are mean with SE in parentheses.

*, $P < 0.02$ compared to their respective baseline value.

and Δ fatigue ($r = –0.56$, $P = 0.007$), Δ body weight and Δ fat mass ($r = 0.47$, $P = 0.026$), Δ body weight and Δ lean mass ($r = 0.50$, $P = 0.017$), Δ body weight and Δ HG ($r = 0.47$, $P = 0.028$), Δ C-RP and Δ body weight ($r = –0.49$, $P = 0.016$), Δ C-RP and Δ fatigue ($r = 0.62$, $P = 0.024$), and Δ C-RP and Δ fat mass ($r = –0.48$, $P = 0.021$).

Compliance with the treatment was similar among groups (Fig. 2). No clinically evident coagulopathy or infections were detected in any patient during the study.

No clinically significant side effects were detected in any group.

Discussion

In this exploratory study, we evaluated the effect of celecoxib in addition to fish oil and oral nutritional supplementation in the management of some systemic syndromes in a homogenous group of patients with lung cancer. Systemic inflammation has been found in association with the majority of solid tumors, and up to 50% of patientsmay have evidence of APPR at the time of diagnosis (37). C-RP is a very sensitive positive biomarker of systemic inflammation and/or tissue damage. As a nonspecific marker, C-RP, in contrast to individual cytokine levels, can contribute powerfully to the monitoring of the response to treatment of systemic inflammation (38). Here we showed that a decrease in the C-RP levels relates to therapeutic gain as evidenced by the improvements in fatigue, weight loss, and fat mass.

In our study, fish oil alone was enough to increase the appetite and decrease the fatigue after 6 wk of treatment. Interestingly, this effect on fatigue (39) (or physical activity) (40) has also been reported by others. Together with the idea that the daily EPA intake appeared to be inversely associated with depressive symptoms in patients with lung cancer (41), it led to the hypothesis that the beneficial effects of EPA regarding physical activity (a multidimensional outcome) could be partially secondary to the amelioration of depression (42). It is noteworthy that in our study, the addition of celecoxib to fish oil not only improved fatigue but also muscle strength measured by HG. Additionally, although HG measurement has potential significant interpatient variability, we are showing here that could be an important and reliable tool for the longitudinal follow-up of the muscular function in these patients.

Current literature is uncertain as to the role of fish oil in cachexia and management of other systemic syndromes. For many reasons, populations and endpoints tend not to be comparable among studies. Accordingly, fish oil and/or n-3 fatty acids studies have yielded conflicting results in cancer patients. Uncontrolled studies carried out in populations of advanced pancreatic cancer patients with either fish oil (containing approximately 2 g per day of EPA and 1.5 g per day of DHA) (43) or pure EPA (44) (escalating dose with 6 g per day of maintaining dose) have reported weight gain or stabilization over a 4-wk period (with weight stabilization over the 12-wk study period) (44). Interestingly, only in the study in which patients received fish oil, the acute phase protein production was significantly reduced (43). In a trial of

high-dose fish oil capsules (39) (about 0.15 g per kg of body weight) for patients with advanced cancer and weight loss, only a small subset of patients had weight stabilization or weight gain. There was correlation between time receiving treatment and weight gain for the patients who were able to tolerate the capsules in a 4-wk period. Many patients experienced gastrointestinal side effects (as much as 30% of the enrolled patients withdrew because of this), and compliance emerged as a major issue. Also, in a short-term study of fish oil supplementation (45), compliance was a problem in the majority of the patients because of the side-effects of the capsules. Gastrointestinal side effects of fish oil (including nausea, altered taste, excessive belching, vomiting, diarrhea, and dyspepsia) can be so frequent and severe enough to overcome the potential beneficial effects of EPA and DHA. A trial comparing EPA alone, megestrol alone, or EPA plus megestrol (46), showed that despite patients in all treatment groups increased their total body weight, those receiving megestrol alone experienced more weight gain than EPA alone or EPA plus megestrol. Even though a dose–effect relationship was suggested in many studies, a recent clinical study (47) that evaluated placebo versus EPA 2 g versus EPA 4 g partially challenged this concept. This study showed that compared with weight at baseline, patients receiving placebo lost a mean of 0.7 kg over 8 wk, whereas those receiving 2 g EPA gained a median of 0.4 kg, and whereas those receiving 4 g EPA lost a median of 0.4 kg ($P = 0.066$). Moreover, physical function improved by 7% compared with placebo in those receiving 2 g EPA ($P = 0.04$) and fell by around 5% in those receiving 4 g EPA. The reason for the lack of overall benefit for a higher dose of EPA was not clear to the authors, but apparently noncompliance was ruled out. In a large study in cachectic patients with pancreatic cancer (48), fish oil plus oral nutritional supplement did not provide therapeutic advantage over nutritional supplement alone. However, dose-response analysis suggests that if taken in sufficient quantity, only the fish-oil-supplemented oral nutrition results in net gain of weight, lean tissue, and improved quality of life (48). Many attempts have been made to maximize the compliance with the treatment; most of them have relied on putting as much omega-3 fatty acid as possible into each capsule so that the number of capsules taken is reduced. Considering the mechanism of action proposed for the omega-3 fatty acids in systemic inflammation and the limited, if any, benefit of this approach, we decided to combine a tolerable dose of fish oil with a drug that could synergize in providing antiinflammatory effect without increasing the gastrointestinal symptoms. We have previously shown that celecoxib 400 mg per day (in combination with oral nutritional supplementation and medroxyprogesterone) is safe and potentially effective in controlling systemic symptoms (including cachexia) by creating a host-favorable cytokine pattern in patients with advanced lung cancer (4). We are showing now that the addition of celecoxib to fish oil improves the control of the APPR, total body weight, and muscle strength. Additionally, the nutritional supplementation, as also some studies suggested (48), could be relevant for the efficacy of fish oil in ameliorating inflammation and vice versa. We used intensive oral nutritional support for our patients in both groups to maximize the pharmacological effects of fish oil.

In conclusion, this study shows that by modulating the eicosanoid metabolism using a combination of n-3 fatty acids and COX-2 inhibitor, some of the signs and symptoms associated with a SIMS could be ameliorated. This study provides the basis to conduct future larger trials intended to validate the clinical efficacy of fish oil plus COX-2 inhibitors in advanced cancer patients.

Acknowledgments and Notes

The work was done at the Translational Research Unit and Internal Medicine Department of the Angel H. Roffo Cancer Institute, University of Buenos Aires, Buenos Aires, Argentina. Celecoxib was a gift from Microsules y Bernabo SA, Buenos Aires, Argentina. Address correspondence to Leandro Cerchietti, M.D., Albert Einstein College of Medicine. 1300 Morris Park Avenue, Chanin 302-A, Bronx, NY 10461. Phone: 718-430-4239. FAX: 718-430-8567. E-mail: lcerchie@aecom.yu.edu.

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