

Phase I Clinical Study of Fish Oil Fatty Acid Capsules for Patients with Cancer Cachexia: Cancer and Leukemia Group B Study 9473¹

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ABSTRACT

The purpose of this study was to determine the maximum tolerated dose and dose-limiting toxicities of fish oil fatty acid capsules containing ω -3 fatty acid ethyl esters. Twenty-two patients with neoplastic disease not amenable to curative therapy who had lost 2% of body weight over a previous 1 month time period were given an escalating dose of fish oil fatty acids. The maximum tolerated dose was found to be 0.3 g/kg per day of this preparation. This means

that a 70-kg patient can generally tolerate up to 21 1-g capsules/day containing 13.1 g of eicosapentaenoic acid + docosahexaenoic acid, the two major ω -3 fatty acids. Dose-limiting toxicity was gastrointestinal, mainly diarrhea, and a poorly described toxicity designated as "unable to tolerate in esophagus or stomach." A patient with chronic lymphocytic leukemia taking the fish oil provided an unusual opportunity to perform a detailed biochemical study of the effect of fish oil capsules on the lipids of malignant cells at several sequential time points in treatment. Studies of the malignant lymphocytes, serum, and whole blood of this one patient revealed an increase in eicosapentaenoic acid, the major component of the fish oil capsules, during fish oil capsule treatment. This study provides a scientific basis for the selection of ω -3 fatty acid doses for future studies in cancer. The maximum tolerated dose found is considerably higher than anticipated from published studies of many human diseases. The observation of a modification of the lipids of leukemic cells, serum, and blood in a patient with chronic leukemia provides a biochemical basis for a possible effect of fish oil supplements on cancer cachexia and tumor growth.

INTRODUCTION

There is growing interest in the ingestion of fish oils that contain ω -3 fatty acids in the treatment of the often devastating cachexia associated with cancer and AIDS (1, 2). In animals bearing a murine colon adenocarcinoma, EPA³ (20:5 ω 3), one of the important fish oil ω -3 fatty acids, has been shown to inhibit cancer cachexia (3). The cachectic animals have decreased protein synthesis and increased degradation of skeletal muscle. After treatment with EPA, protein degradation was reduced (4). Diets in which 50% of total energy was provided as fish oil also reversed tumor-associated weight loss in rats with an experimental prostate tumor (5). There is evidence that tumor-associated cachexia is mediated by a specific factor. A sulfated glycoprotein isolated from mice with malignant tumors can induce weight loss when injected into healthy mice (6). Furthermore, the factor has been identified in the urine of patients with cancer cachexia but not from noncachectic cancer patients or from patients with weight loss attributable to other causes. Fish oil might modulate the synthesis or activity of this factor. In a small clinical study, 18 patients with pancreatic cancer received fish oil capsules [equivalent to EPA 2 g/day and DHA (22:6 ω 3) 1.3 g/day], and there was reversal of weight loss in 14 of 18 patients (7).

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³The abbreviations used are: EPA, eicosapentaenoic acid (20:5 ω 3); DHA, docosahexaenoic acid (22:6 ω 3); MTD, maximum tolerated dose; CALGB, Cancer and Leukemia Group B.

It has been established that ω -3 fatty acids, such as EPA and DHA, can inhibit the growth of experimental tumors in tissue culture and in animals, including xenografts of human tumors in nude mice (8, 9). In the MAC 16 tumor experimental animal model, treatment with EPA was associated with a decrease in tumor volume as compared with animals treated with cyclophosphamide or 5-fluorouracil (3). There is little information from clinical trials about the inhibition of human tumors by ω -3 fatty acids. However, it is known that the fatty acid composition of experimental tumors can be modified by supplementing the diets of tumor-bearing animals with various fatty acids (10). If the same is possible for human tumors, this would provide a rationale for a direct effect of dietary fatty acids on tumors in addition to whatever effect they have on tumor-related cachexia.

In Phase II clinical trials of patients with neoplastic diseases, it is customary to give the drugs at the MTD because favorable effects may be small and would be undetected at less than highest possible dose. However, we were not able to identify in the literature a Phase I trial of normal subjects or patients that would allow us to select a proper maximum dose for fish oil fatty acids. Therefore, we carried out this Phase I trial using a fish oil capsule obtained from the NIH that can be administered easily as a dietary supplement and does not require the patient to be hospitalized or to ingest oily liquid. In addition, the capsules do not require special storage conditions.

PATIENTS AND METHODS

Patients. Patients ≥ 18 years of age with a histological/cytological diagnosis of cancer not amenable to curative treatment were eligible for this CALGB limited institution study if they had a weight loss of $\geq 2\%$ of body weight within the 1-month period prior to enrollment. All patients had adequate renal (creatinine and BUN < 1.5 times the upper limit of normal), liver (serum bilirubin level < 1.5 times and aspartate aminotransferase and alkaline phosphatase < 3 times the upper limit of normal) and bone marrow (granulocytes $> 1000/\mu\text{l}$, hemoglobin > 8 g/dl, and platelet count $> 75,000/\mu\text{l}$) function. They were also required to have a free or total thyroxine within normal limits. Patients were excluded if they were taking steroids, dronabinol, megestrol acetate, diuretics, or had gastrointestinal obstruction, life expectancy < 2 months, pregnancy, edema, ascites, congestive heart failure, metabolic disorder, uncontrolled infection, radiation, chemotherapy or major surgery within 3 weeks (6 weeks for nitrosoureas), brain tumors or brain metastasis, or performance status of 3 or 4. All patients gave written informed consent. During the study, patients had examinations that included a history, weight without shoes, performance status, complete blood count, creatinine, blood urea nitrogen, alkaline phosphatase, aspartate aminotransferase, total protein and albumin every 2 weeks, and physical examination, electrolytes, calcium, uric acid, glucose, prealbumin, and 24-h urine creatinine every 4 weeks. In addition to these studies, a measurement of height, chest X-ray, and urinalysis was done prior to the study.

Treatment Plan and Dose-Escalation Rules. Patients were entered in groups of two starting at 0.1 g/kg per day, a low dose known from cardiovascular studies to be tolerated without

significant side effects. Capsules were taken in two divided doses, one with or after breakfast and one with or after lunch. In this study, individual patients were eligible to be escalated to the next dose level as soon as they had completed at least 2 weeks of therapy with no grade 3 toxicity and could be escalated again after another 2 weeks if they had no toxicity. Although this is not a classical design (doses for an individual patient in a Phase I trial are usually not escalated), the absence of life-threatening or cumulative toxicity anticipated for ω -3 fatty acids made this approach safe. This also makes it possible that all patients will be given their best chance of getting a response, a criticism of the classical design in Phase I trials (11). After two patients had been accrued at each step, there was a brief suspension until at least one patient had taken that dose for 2 weeks. If tolerated without unacceptable toxicity, then patients were entered at the next consecutive step. When a toxic event (grade 3 or higher) was encountered and the MTD was suspected of being reached, then additional patients were studied at the next lower dose. Escalation was continued in cohorts of two until there was a toxic event observed. If only one patient of the two experienced an event, then three patients were added to the cohort. In general, we deescalated if $> 50\%$ of patients at a dose level experienced toxicity. We escalated if $< 25\%$ of patients in a cohort experienced toxicity. If between 25% and 50% inclusive of patients on a cohort experienced a toxic event, we continued to add to that cohort. Within a given patient who experienced toxicity, the capsules were stopped until the toxicity, *e.g.*, diarrhea, disappeared; then the highest previously tolerated dose was restarted. If the diarrhea recurred, then the patient was removed from study. If the investigator suspected that the side effect was not attributable to the ω -3 fatty acids, then reescalation was allowed, using the same rules as initial escalation. The treatment was continued for a minimum of 2 months. The use of analgesics, antiemetics, and antiarrhea medications was not routinely given as prophylaxis but was allowed if clinically indicated. The non-life-threatening nature of the toxicities allowed some latitude in testing toleration of a specific dose. If a dose was not tolerated, the protocol allowed reinstitution of capsules at a lower dose after a brief discontinuation. If a dose was not tolerated on one occasion but later tolerated without difficulty, or *vice versa*, then the observation that occurred last was considered definitive in the determination of MTD, although a dose-limiting toxicity was recorded. For this study, the MTD was defined as the highest dose level at which no more than one-third of the patients treated, including patients escalated from a lower dose, experienced grade 3 or greater toxicity.

Toxicity Criteria. Toxicity was graded using CALGB Expanded Common Toxicity Criteria. The nature of the fatty acid therapy required the addition of two criteria that are not addressed in standard definitions: (a) oil in the stools noted visually by the patient accompanied by any extent of diarrhea was considered a dose-limiting toxicity because it is unacceptable to most patients and would limit later Phase II or III trials; and (b) there were patients who were "unable to tolerate the fatty acid in stomach or esophagus." This was sometimes described on the data sheets as "unable to swallow pill" or "difficulty taking the pills." It was considered grade 3 for purposes of estimating a meaningful MTD if the symptoms led to $\geq 50\%$

reduction in number of capsules tolerated or discontinuation of the fatty acid.

Content and Characteristics of Capsules. The soft gelatin capsules of fish oil ω -3 ethyl esters were obtained from the NIH/National Oceanic and Atmospheric Administration, Biomedical Test Material Program, National Marine Fisheries Service, Southeast Fisheries Science Center, Charleston Laboratory, Charleston, SC. The capsules were assayed by the National Marine Fisheries Service, and a typical lot contained the following: 378 mg/g EPA; 249 mg/g DHA; 728 mg/g total ω 3 fatty acids; 35 mg/g total ω 6 fatty acids; 0.15% total free fatty acids; 2.7 mg/g cholesterol; antioxidants (0.9 mg/g α -tocopherol; 0.9 mg/g γ -tocopherol; and 0.02% tertiary butylhydroquinone); trace metals (arsenic, cadmium, mercury, lead, and selenium), each <0.2 μ g/g. Peroxide value was 3.3 mEq/kg. The major fatty acids were 378 mg/g EPA (20:5 ω 3); 249 mg/g DHA (22:6 ω 3); 66 mg/g 18:4 ω 3; 59 mg/g 16:3 ω 4; 18 mg/g 20:4 ω 6; 16 mg/g 22:5 ω 3; 14 mg/g 21:5 ω 3. The ω -3 concentrate capsules are large and about the size of a sulfamethoxazole/trimethoprim double-strength tablet USP. They were shipped at room temperature and then stored by the institutions and patients at refrigerator temperatures in closed bottles (shelf life is at least 1 year; National Marine Fisheries data).

Fatty Acid Composition Case Study. A detailed biochemical study of the malignant and normal blood components of one patient with chronic lymphocytic leukemia taking 0.2 g/kg/day was performed. Whole blood anticoagulated with EDTA was extracted with CHCl_3 - CH_3OH , 2:1 (v/v). A mononuclear fraction was isolated using a Histopaque-1077 (Sigma Diagnostics, St. Louis, MO) gradient. This gradient interface fraction studied was 96–99% lymphocytes. The fatty acid composition was determined using gas chromatography as described previously (12, 13). Briefly, after alkaline hydrolysis, fatty acids in the saponifiable fraction were methylated, and the methyl esters were separated by gas-liquid chromatography. Mole percentages of various fatty acids were calculated on the basis of actual amounts of fatty acids determined from integrated peak areas on chromatograms, an internal standard, and respective molecular weights of fatty acid methyl esters.

RESULTS

Patient Demographics. Twenty-five patients were entered in this Phase I trial. Twenty-two of the 25 were evaluable for toxicity. The three patients who were not evaluable took no capsules because of rapid progression of disease (one patient) or withdrawal of consent before starting the study (two patients). The characteristics of the patients are shown in Table 1. Noteworthy is the median age of 64, and the fact that a majority had performance status of 1. Almost 60% of patients had lung or pancreas cancer, and all but 14% had been treated with some type of anticancer therapy for their tumor in the past. The median baseline weight was 62 kg.

Toxicity. No life-threatening toxicity (grade 4 or 5) was expected for this natural fatty acid, and none was observed. There was no hematological toxicity. The dose-limiting toxicities (defined as grade 3 or greater) are shown in Table 2, and all were gastrointestinal. There were three instances of grade 3 diarrhea and oil in stools at doses of 0.35, 0.35, and 0.5 g/kg/

Table 1 Characteristics of the patients entered in the trial

Total patients entered	25
Evaluable patients	22 ^a
Median age \pm SD, years	64 \pm 13 (range, 34–76)
Gender (male/female)	12/10 (55%/45%)
ECOG ^b performance score (%)	
0	3 (13.6%)
1	13 (59.1%)
2	6 (27.3%)
Diagnoses (%)	
Lung cancer	9 (40.5%)
Pancreas cancer	4 (18.0%)
Cervical cancer	2 (9.0%)
Sarcoma	1 (4.5%)
Rectal cancer	1 (4.5%)
Breast cancer	1 (4.5%)
Hepatocellular carcinoma	1 (4.5%)
Renal cell carcinoma	1 (4.5%)
Chronic lymphocytic leukemia	1 (4.5%)
Neuroendocrine cancer	1 (4.5%)
Prior chemotherapy	14 (64%)
Prior other therapy ^c	5 (23%)
No prior therapy	3 (14%)

^a Three patients were entered but received no ω -3 capsules because of withdrawal of consent or rapid progression of disease.

^b ECOG, Eastern Cooperative Oncology Group.

^c Includes radiation therapy and immunotherapy.

day. There was one additional occurrence accompanied by fecal incontinence at a lower dose of 0.15 g/kg/day, but that patient later tolerated the dose without incontinence, diarrhea, or oil in the stools. Three patients experienced grade 3 diarrhea with or without abdominal cramping at 0.2, 0.45, and 0.5 g/kg/day, one patient experienced nausea/vomiting at 0.25 g/kg/day, and three patients were “unable to tolerate the capsules in stomach or esophagus,” at 0.3, 0.35, and 0.4 g/kg/day.

Table 3 shows the non-dose-limiting toxicities. These included (in order of frequency) excessive belching, fish taste in mouth, fish taste of food, smell of fish on their own body, flatulence, and smell of fish on the body of others. For none of these toxicities did there seem to be a clear dose-response relationship, and none required a change in dose.

Dose Reductions and Treatment Delays. Dose reductions were necessary in four instances (three patients) at the dose levels of 0.5, 0.45, 0.2, and 0.15 g/kg/day; all were attributable to diarrhea. No appreciable treatment delays were recorded.

Recommended Dose for Phase II Trials (MTD). There was one dose-limiting grade 3 toxicity at each of the doses of 0.15, 0.2, 0.25, and 0.3 g/kg/day (the patient suffering diarrhea and incontinence of oil at 0.15 g/kg per day was later able to tolerate that dose without toxicity). At doses of 0.35 g/kg/day and above, at least one-third of patients suffered a dose-limiting toxicity. Therefore, the MTD was considered to be 0.3 g/kg/day because only one of seven patients had a dose-limiting toxicity at that dose, and three of six suffered one at the next higher dose. The eight patients entered at the three highest dose levels are explained by the fact that many patients developed delayed side effects after other patients had been escalated or accrued to levels higher than the MTD. In addition, there was a great variability in the ability of patients to tolerate the fatty acid capsules; therefore, some patients tolerated the capsules well

Table 2 Dose-limiting toxicity of fish oil ethyl ester soft gelatin capsules

Dose level (g/kg/day)	No. of patients		DLT event
	Entered	DLT ^a	
0.10	2	0	
0.15	3	1 (33%) ^b	Grade 3 diarrhea/fecal incontinence of oil
0.20	4	1 (25%)	Grade 3 diarrhea/cramping
0.25	7	1 (14%)	Grade 3 nausea/vomiting
0.30^c	7	1 (14%)	Unable to tolerate in stomach/esophagus ^d
0.35	6	3 (50%)	Oily stools/diarrhea; oily stools/diarrhea; Unable to tolerate in stomach/esophagus
0.40	3	1 (33%)	Unable to tolerate in stomach/esophagus
0.45	3	1 (33%)	Grade 3 diarrhea/fecal incontinence
0.50	2	2 (100%)	Grade 3 diarrhea Grade 3 diarrhea/oily stools

^a Dose-limiting toxicity.

^b Patient later tolerated same dose without toxicity.

^c Maximal tolerated dose in **bold**.

^d Defined in "Patients and Methods."

Table 3 Non-dose limiting (grades 1 and 2) toxicities of fish oil ethyl ester soft gelatin capsules^a

Dose, g/kg/day	N ^b	Abnormal taste of food	Abnormal taste in mouth	Abnormal body smell		Belching	Flatulence	Other	Description of other
				Patient	Others				
0.10	2							1	Difficulty swallowing
0.15	3		1			2	1	2	Incontinent of oil; cramping
0.20	4					1			
0.25	7	1	2	2	1	2	2	2	Nausea/vomiting Nausea/vomiting
0.30	7	3	5 ^c	1		5	3	0	
0.35	6	1		1	1	1	1	3	Constipated, passage of orange stools; diarrhea; constipation
0.40	3					1		2	Dry mouth; bloating
0.45	3		1	1	1	2	1	1	Soft stools and vomiting
0.50	2	1	1	1	1	1	1		
Total		6	10	6	4	15	9	11	

^a Shown are number of patients who experienced ω -3 fatty acid-specific toxicities less than grade 3 by the actual dose given.

^b Total patients at dose level.

^c Fishy for some patients.

and were escalated rapidly. At the MTD of 0.3 g/kg/day of ω -3 concentrate capsules, a 70-kg patient would take 21 1-g capsules each day and thereby would ingest 7.9 g of EPA, 5.2 g of DHA, and 15.3 g of total ω -3 fatty acids each day. This dose is among the highest in the literature for ω -3 fatty acids given as capsules for any disease. The mean duration of therapy was 49 days (median, 27 days). The longest time of therapy was 150 days.

Response Data and Survival. Weight change was measured as the weight at the time of last follow-up from baseline. A linear regression model was used to test whether time on treatment predicts weight change. Weight change was significantly associated with time on treatment ($P = 0.028$). The least-squares fitted line for weight change was: weight (kg) = $-3.137 + 0.053 \times$ time (days). This indicates that after the patients are on treatment for 2 months, no weight loss would be expected. The median time of survival was 134 days.

Modification of Fatty Acid Composition. The malignant lymphocytes, serum, and whole blood of a 76-year-old man with chronic lymphocytic leukemia who had been on the capsules for 31 days and again when off therapy were studied. On the day of the "on-therapy" study, his white blood count was

34,000/ μ l with 81% lymphocytes, and on the day of the "off-therapy" study, his white blood count was 29,300/ μ l with 79% lymphocytes. There was a considerable difference in the fatty acid composition of the leukemic cells while on therapy. The percentage of EPA in malignant lymphocytes, the major ω -3 contained in the capsules, was almost 3-fold higher during supplementation (Fig. 1). Surprisingly, the DHA was not increased during ingestion of the capsules (on therapy, 4.0 ± 0.2 mole %; off Therapy, $5.6 \pm <0.1$). This lack of change is similar to neutrophils of normal subjects taking ω -3 capsules, which demonstrated an increase in EPA but not DHA (14). Similarly, ingestion of the capsules in our study did not appreciably change the total ω -3 fatty acids of the lymphocytes (data not shown).

There was an \sim 4-fold increase in EPA in the serum after 1 month on treatment as compared when the patient was not taking the capsules (Fig. 1). Likewise, the percentage of total ω -3 fatty acids in the serum was 96–98% higher when taking the fish oil (data not shown). The values for the whole blood during treatment showed a higher EPA (Fig. 1), and total ω -3 fatty acids (data not shown) compared with the day he was off

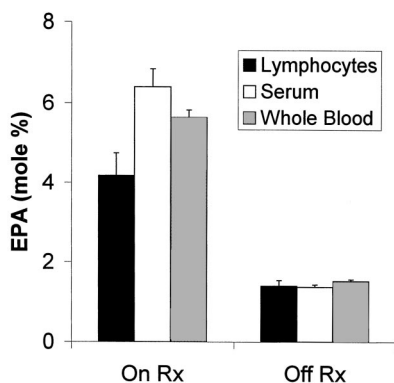


Fig. 1 EPA composition of blood components. Blood from a patient with chronic lymphocytic leukemia was obtained on therapy day 31 (studies on day 54 were similar) and again 2 months after completion of therapy. The blood was anticoagulated with EDTA, and the components were separated. The lymphocytes were purified using a Histopaque-1077 (Sigma Diagnostics, St. Louis, MO) gradient. The lymphocyte fraction was 96–99% lymphocytes. The fatty acid composition was determined using gas chromatography. Shown are mole % of EPA (SD) in 3–6 replicates.

therapy. Samples were also obtained after almost 2 months of fish oil ingestion (treatment day 54), and the fatty acid composition data were similar to those of treatment day 31.

DISCUSSION

This study establishes the MTD of 0.3 g/kg/day for ω -3 fatty acids given in capsule form to patients with advanced cancer. The dose determined in this study is now being used in a Phase II CALGB study to determine whether these unsaturated fatty acids can ameliorate cancer cachexia and/or tumor growth. It is generally thought for cytotoxic agents that it is necessary to use the highest possible dose at or near the MTD in oncological studies to identify the maximum effect. We believe that this may apply as well to the use of fish oil fatty acids in cancer cachexia. In animal studies, high doses of fish oils were required to ameliorate weight loss of animals bearing experimental tumors. For example, weight loss was reduced by 25% in mice with transplantable murine colon adenocarcinoma on a 5% fish oil diet, but a 50% fish oil diet was required to show statistical significance (3). In another study of the same tumor, 5 g/kg of EPA were required to obtain complete reversal of weight loss (15). However, the requirements in humans may be quite different and to properly test the ability of these fatty acids to ameliorate tumor cachexia in humans, we thought it necessary to use maximum doses possible. We were unable to find published Phase I data that could be applied to cachexic cancer patients.

There have been only limited previous studies of ω -3 fatty acids in terminal cancer patients. Wigmore *et al.* (7) performed a dose escalation study on 18 patients with unresectable pancreatic cancer who received 2–16 capsules per day. They found that patients tolerated a median number of 12 Max-EPA fish oil capsules/day (2.2 g of EPA + 1.4 g of DHA per day) and had no serious toxicity. However, 25% had steatorrhea, and some patients received pancreatic enzyme supplements. A number of patients had taste aberrations or transient diarrhea. Gogos *et al.*

(16) studied immune response and survival in patients with advanced solid tumors who were randomized to Max-EPA capsules or placebo. They found no toxicity of the fish oil except for mild abdominal discomfort and transient diarrhea, but they gave a dose of 3.06 g of EPA and 2.07 g of DHA per day, which is less than half of the dose for a 70-kg person using the MTD of our study. In a study of the fish oil antitumor response of 12 patients with metastatic breast cancer reported in abstract form, the investigators found no untoward side effects except unpleasant taste (17). That study used a dose of fatty acids (3.6 g of EPA and 2.4 g of DHA daily), also well below our MTD. All three studies used Max-EPA capsules, which contain less than half the ω -3 fatty acids (17% EPA and 12% DHA) as in the capsules used in our study. In this regard, to properly compare the doses of fish oil fatty acids given in various studies, it is necessary to compare the amount of actual EPA, DPA, and other ω -3 fatty acids taken. It is misleading to compare based on number of “1 gram” fish oil capsules taken because the capsules contain widely varying amounts of ω -3 fatty acids.

Most previous therapeutic studies of ω -3 fatty acids in other diseases such as rheumatoid arthritis, coronary artery disease, kidney disease, hypertriglyceridemia, and hypertension have used a dose of ω -3 fatty acids below what we found to be the MTD for patients with advanced cancer. This low dose may have been chosen in part because of a low amount of ω -3 fatty acids in the capsules available. Max-EPA capsules or similar capsules used in many other studies contain about half as much ω -3 fatty acid per capsule compared with the capsules we used, which were 38% EPA and 25% DHA. However, some previous studies used doses equivalent to ours. Krokan *et al.* (18) gave fish oil capsules for a total dose of almost 12 g of EPA + DHA to a few normal subjects for 14 days, and there were no adverse effects. Many other studies that gave total ω -3 fatty acid doses equivalent to those of this study administered the fatty acids as an oil or emulsion rather than a capsule. For example, the reported studies which used similarly high doses (>10 g of EPA + DHA, the major ω -3 fatty acids in the preparations) given as oils found no adverse effects (19–21), which suggests that the ω -3 fatty acids might be better tolerated as oils as compared with capsules. Most other published studies of capsules used less total ω -3 fatty acids, usually considerably less. It is possible that a greater therapeutic effect would have been found in those studies if higher doses had been administered.

The MTD of natural fatty acid capsules may be influenced by several factors such as pancreatic function and the types and amounts of other fats taken in the concurrent diet. We have no evidence of pancreatic insufficiency in any of the study subjects; however, differences in the diet of the patients were likely. This may explain the difference of tolerability of some patients who could tolerate doses above the MTD, and those who had symptoms at doses considerably below the MTD.

It is known that the fatty acid composition of experimental animal tumors can be modified by supplementing the diets of tumor-bearing animals with various fatty acids (9, 10). Neutrophils of normal human subjects can be modified by ingesting capsules containing ω -3 fatty acids (14). Therefore, it seemed likely that human tumors can be modified if the patients take fish oil. However, there is limited information on the dietary modification of human tumors. We could not determine the fatty

acid composition of the tumors of most patients on this Phase I study because multiple biopsies of often difficult-to-access solid tumors would be required at times that there were no other clinical indications for the procedure. The multi-institutional nature of the study and cost involved in utilization of operating rooms (needle biopsy provides inadequate amounts of tissue) further precluded such a study. However, one patient with chronic lymphocytic leukemia offered a singular opportunity for obtaining malignant cells during and after the period of fish oil ingestion. In our biochemical case study, there was a considerable increase in the EPA of malignant lymphocytes obtained during the ingestion of fish oil capsules. Enrichment of the malignant cells with EPA, which is a highly polyunsaturated fatty acid, enhances susceptibility to oxidation, physical properties, membrane transport, and eicosanoid production (10, 22). Therefore, EPA enrichment has the potential to ameliorate cachexia in several ways, including decreased production of a possible mediator of cachexia. This also provides a biochemical rationale for a possible direct effect of fish oil ingestion on tumor growth kinetics. Taken together, the modification of tumor, serum, and whole blood provides a rational basis for a Phase II study of the effect of fish oil fatty acids on the cachexia of patients with advanced cancer.

In summary, we found that patients with advanced cancer can tolerate a large dose of the encapsulated fish oil with only minor side effects. Our data indicate that ingestion of the capsules is feasible for periods of time appropriate for the expected life span of cachectic cancer patients and sufficient to test the hypothesis of reversal of cachexia in a Phase II study. We identified a MTD that was higher than the doses used in previous studies of patients with cancer or other diseases in which fish oil capsules were used. This MTD of encapsulated fish oil is now being used in an ongoing Phase II CALGB cooperative group study of the effect of fish oil on cachexia and tumor growth. This dose may also be useful in the design of studies of patients with cardiac, renal, and rheumatic diseases to deliver a maximum fish oil dose to test therapeutic efficacy.

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