VOLUME 24 · NUMBER 21 · JULY 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Double-Blind, Placebo-Controlled, Randomized Study of Eicosapentaenoic Acid Diester in Patients With Cancer Cachexia

Kenneth C.H. Fearon, Matthew D. Barber, Alastair G. Moses, Sam H. Ahmedzai, Gillian S. Taylor, Michael J. Tisdale, and Gordon D. Murray

From the Department of Clinical and Surgical Sciences (Surgery), Royal Infirmary; Public Health Sciences, Edinburgh University Medical School, Edinburgh; Academic Unit of Supportive Care, The University of Sheffield, Royal Hallamshire Hospital, Sheffield; and the Pharmaceuticals Sciences Institute, CRC Nutritional Biochemistry Research Group Aston University, Aston Triangle, Birmingham, United Kingdom.

Submitted October 13, 2005; accepted May 4, 2006.

Supported by Scotia Pharmaceuticals, United Kingdom.

Presented in part at the European Society of Parenteral and Enteral Nutrition in Brussels, Belgium 2005.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to Kenneth C.H. Fearon, MD, Department of Clinical and Surgical Sciences (Surgery), The Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA United Kingdom; e-mail: k.fearon@ed.ac.uk.

0732-183X/06/2421-3401/$20.00

DOI: 10.1200/JCO.2005.04.5724

ABSTRACT

Purpose
Eicosapentaenoic acid (EPA) has been proposed to have specific anticachectic effects. This trial compared EPA diethyl ester with placebo in cachectic cancer patients for effects on weight and lean body mass.

Patients and Methods
Five hundred eighteen weight-losing patients with advanced gastrointestinal or lung cancer were studied in a multicenter, double-blind, placebo controlled trial. Patients were randomly assigned to receive a novel preparation of pure EPA at a dose of 2 g or 4 g daily or placebo (2g EPA, n = 175; 4 g EPA, n = 172; placebo, n = 171). Patients were assessed at 4 weeks and 8 weeks.

Results
The groups were well balanced at baseline. Mean weight loss at baseline was 18% (n = 518). Over the 8-week treatment period, both intention-to-treat analysis and per protocol analysis revealed no statistically significant improvements in survival, weight, or other nutritional variables. There was, however, a trend in favor of EPA with analysis of the primary end point, weight, at 8 weeks showing a borderline, nonsignificant treatment effect ($P = .066$). Relative to placebo, mean weight increased by 1.2 kg with 2 g EPA (95% CI, 0 kg to 2.3 kg) and by 0.3 kg with 4g EPA (−0.9 kg to 1.5 kg).

Conclusion
The results indicate no statistically significant benefit from single agent EPA in the treatment of cancer cachexia. Future studies should concentrate on other agents or combination regimens.

J Clin Oncol 24:3401-3407. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Cachexia is a major contributor to the morbidity and mortality of patients with advanced cancer.[1,2] The syndrome of cachexia appears to result from a variety of metabolic changes characterized by relative hypermetabolism, an acute-phase protein response, and a failure of anabolism compounded by inadequate food intake.[3] The mediators of this process are produced by both the tumor and the body in response to the tumor. Potential mediators include tumor necrosis factor, interleukin-1, interleukin-6, neuroendocrine hormones, and proteolysis inducing factor.[4] While conventional nutritional supplements have been shown to increase caloric intake, cachexia is not reversed fully,[5] and this is probably due to the presence of the aforementioned metabolic abnormalities.

Eicosapentaenoic acid (EPA) has been shown to have anti-inflammatory properties including down-regulation of both proinflammatory cytokine production and the acute phase protein response in both healthy individuals and cancer patients.[6,7] EPA has also been shown to inhibit the development of cancer cachexia in mice bearing the MAC-16 tumor (methylhydrazine-induced adenocarcinoma of the colon, 16th cell line).[8] The activity of EPA in this context has been ascribed to inhibition of activation of the ubiquitin proteasome pathway by proteolysis-inducing factor.[9] In tumor-bearing rats, n-3 fatty acids have been shown to improve food intake, restore normal eating pattern, delay the onset of anorexia, tumor appearance, and growth, and prevent body weight loss.[10]

Short-term (2 weeks) administration of fish oil to cachectic cancer patients has been shown to be of no benefit.[11] However, uncontrolled studies of either a mixed fish oil preparation providing approximately 2 g per day EPA or a pure EPA preparation providing 6 g per day EPA have reported weight stabilization in cachectic pancreatic cancer patients when treated over

a period of 8 weeks.[12,13] In contrast, a phase II study of concentrated fish oil capsules (providing 4.7 g EPA and 2.8 g docosahexaenoic acid) demonstrated an overall median weight loss of 0.8 kg over 1.2 months in a heterogeneous group of cachectic cancer patients.[14] Although weight change was not examined, a controlled study of a mixed fish oil preparation (18 g per day) plus vitamin E demonstrated a modest survival benefit in a heterogeneous group of 60 cancer patients.[15] Two large, phase III trials of fish oil in combination with an oral nutritional supplement have shown no clear benefit (in terms of body weight or lean body mass) beyond either the nutritional supplement on its own[16] or in comparison with megestrol acetate.[17] No survival benefit was noted in either trial.

This study aimed to examine the effects of two doses (2 g per day and 4 g per day) of a 95% pure EPA diester against placebo over a period of at least 8 weeks on the process of cachexia in a randomized study.

PATIENTS AND METHODS

Overview

The protocol received multicenter research ethics committee approval. Written informed consent was obtained from all patients. Procedures followed were in accordance with International Committee for Harmonisation, Good Clinical Practices, and the Helsinki Declaration. A total of 61 primary treatment centers in four different countries participated in the trial.

Eligibility Criteria

Patients were recruited with a clinical diagnosis of gastrointestinal and lung cancer (radiological/histological/cytological confirmation) between the ages of 18 and 80 years with 5% or more loss of preillness stable weight. Patients had a life expectancy of 2 months or longer and a Karnofsky performance status of 70 or higher.

Exclusion Criteria

Patients receiving ongoing antineoplastic therapy (including chemotherapy) were excluded from the trial. In addition, patients were excluded if they had undergone major surgery, chemotherapy, or radiotherapy in the previous 4 weeks, had current or incipient dysphagia/obstruction to the GI tract, concomitant treatment with fish oil supplementation, systemic steroid therapy, nystatin, or metronidazole. Nonsteroidal anti-inflammatory drug (NSAID) use was recorded.

Follow-Up

Survival (from random assignment) was monitored continuously and the following variables were measured at 4-weekly intervals for 24 weeks: body weight, body composition, C-reactive protein, albumin, appetite, physical

Table 1. Baseline Characteristics of Patients Recruited Onto Study

Characteristic	No. of Patients					
	Placebo		2 g EPA		4 g EPA	
	No.	%	No.	%	No.	%
Sex						
Male	123		117		115	
Female	48		58		57	
Type of cancer						
Upper GI cancer	67		73		58	
Lower GI cancer	29		25		29	
Lung cancer	73		76		82	
Unclassified GI cancer	2		1		3	
Taking NSAIDS (%)	33	19	35	20	29	17
Usual weight (kg)						
Median	73.5		73.0		73.0	
Range	44.4 to 168.0		47.0 to 123.8		45.4 to 115.0	
Weight (kg)						
Median	58.8		59.8		59.5	
Range	29.9 to 120.6		29.5 to 114.3		37.5 to 100.0	
Percentage weight loss						
Median	17.8		17.9		16.3	
Range	2.6 to 44.6		12.0 to 55.6		3.8 to 42.6	
Body mass index (kg/m^2)						
Median	20.9		20.9		21.4	
Range	11.3 to 33.3		12.8 to 38.6		13.9 to 35.9	
Lean body mass (kg)						
Median	44.6		45.3		44.9	
Range	24.7 to 74.9		25.0 to 71.4		26.3 to 65.2	
Percentage of patients with elevated C-reactive protein (> 10 mg/L)	11		12		8	
Karnofsky performance status						
Median	80		80		70	
Range	70 to 100		70 to 100		70 to 90	
EORTC physical functioning (out of 100)						
Median	60		53		67	
Range	0 to 100		0 to 100		0 to 100	
EORTC global health						
Median	50		46		50	
Range	0 to 100		0 to 100		0 to 100	

Abbreviations: EPA, eicosapentaenoic acid; GI, gastrointestinal; NSAIDS, nonsteroidal anti-inflammatory drug; EORTC, European Organisation for Research and Treatment of Cancer.

functioning, and Karnofsky performance status. All adverse events were assessed by a medical practitioner and classified according to the Cancer and Leukemia Group B Expanded Common Toxicity Criteria in particular noting potential relationship to study medication.

Patients were randomly assigned to one of three interventions: either 2 g EPA 95% diester per day, 4 g EPA diester per day, or placebo. Patients were requested to take the relevant dose as two capsules twice daily for a period of 8 weeks. Patients surviving beyond 8 weeks were offered EPA diester on a compassionate use, open label basis. Self-reported capsule intake was used to determine patient compliance.

Stratification and Random Assignment

Random assignment was performed via random number tables by a third party with minimization based on trial center, type of cancer (lung or gastrointestinal), NSAID use (beyond 75 mg aspirin dose), and method of diagnosis (clinical or histological).

Sample Size Calculations

A sample size of 81 patients per treatment group at week 8 was calculated to have an 80% power to detect a body weight difference of 2 kg or more. This assumed a common standard deviation of 4.5 kg based on the cachexia intervention trial on a similar patient population undertaken by Simons et al.[18]

Weight and Body Composition

Patients were weighed on spring balance scales (Tanita Solar Powered Scale model 1618; Tanita, Uxbridge, United Kingdom) without shoes and wearing light clothing.

Body composition was measured using a Bodystat 1500 bioelectrical impedence analyser (Bodystat Douglas, United Kingdom). All assessments were made with the patient supine and limbs apart. Electrodes were placed over the wrist and ankle joints and metacarpal and metatarsal heads. Repeat measurements were performed using the same pair of limbs. Resistance was measured at 200 Hz. Values for total body water were derived using equations validated in a similar patient group.[19] Lean body mass was calculated assuming that lean tissue contains 73% water.[20]

Performance Status and Quality of Life

Patients completed the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 version 3.0.[21] The question relating to appetite was used to determine appetite changes throughout the course of the study. The questions related to physical functioning were used to determine the mobility and independence of patients. Karnofsky performance status was noted at each visit.[22]

EPA Diethylester and Placebo Capsules

The EPA and placebo were provided as 1 g soft gelatin capsules supplied by Scotia Pharmaceuticals (Scotia House, Stirling, United Kingdom). The EPA diester was manufactured from fish oil derivatives and consisted of at least 95% propane diol diester compound formed with EPA at both ester linkages. The EPA diester oil was formulated with propyl gallate as an antioxidant. The placebo capsules contained medium chain triglyceride, which was also blended with the diester oil to allow blinding of the different doses to be achieved.

Statistics

Two populations were determined for the efficacy analysis: an intention-to-treat population containing all those with details of survival or body weight postbaseline who consumed at least one dose of study medication; and a per-protocol population who provided baseline and week 8 body weight measurements, were at least 80% compliant (based on capsule count), and who did not take steroids between baseline and week 8.

The primary end point was defined as change in body weight between baseline and week 8. Secondary end points were survival from random assignment and changes in lean body mass, quality of life variables, performance status, and C-reactive protein between baseline and week 8.

Differences between groups were studied by analysis of covariance. Differences from placebo at week 4 and week 8 are presented as mean and 95% CI. *P* value of less than .05 was used to denote statistical significance.

RESULTS

Baseline characteristics of patients are shown in Table 1. Overall 518 patients were recruited, 355 men and 163 women. Median age was 67 years (range, 31 to 85). Two hundred thirty-one patients had lung cancer, 198 patients had upper gastrointestinal cancer, 83 patients had lower gastrointestinal cancer, and six patients had unclassified gastrointestinal cancer. In general, the three treatment groups were comparable for all variables. At baseline, patients had lost approximately 18% of their preillness body weight and had a BMI of about 21 kg/m^2 (indicating moderately severe undernutrition). Patients were well matched for Karnofsky performance score and quality of life variables. The values reflect a debilitated older group of patients with significant impairment of physical function and global health status.

The number of patients remaining in the study decreased by approximately 50% over 8 weeks. The reasons for sample attrition between baseline and the end of the 8 week study period are shown in Figure 1. Both the EPA and placebo capsules were well tolerated. Seventy-three percent of patients took more than 80% of prescribed capsules over the first 4 weeks (capsule count) and there were no statistically significant differences in this measure of compliance between the groups (placebo, 77%; 2 g EPA, 68%; 4 g EPA, 75%). There were no significant differences between the groups in the numbers of patients who experienced any adverse events (AEs; placebo, 704 AEs affecting 131 patients; 2 g EPA, 806 AEs affecting 143 patients; 4 g EPA, 687 AEs affecting 137 patients) or serious AEs (placebo, 100 serious AEs affecting 64 patients; 2 g EPA, 134 serious AEs affecting 67 patients; 4 g EPA, 99 serious AEs affecting 64 patients). None of the serious AEs were considered to be due to the EPA or placebo medication. Rather, the investigators concluded that they were due to disease progression.

A comparison with placebo for the main study end points in the intention-to-treat group of patients receiving either 2 g EPA or 4 g EPA per day is presented in Table 2. Analysis of covariance for weight between the three groups at 8 weeks was borderline nonsignificant ($P = .066$). When compared with the placebo group, the mean weight change for the group receiving 2 g EPA daily was an increase of 1.2 kg

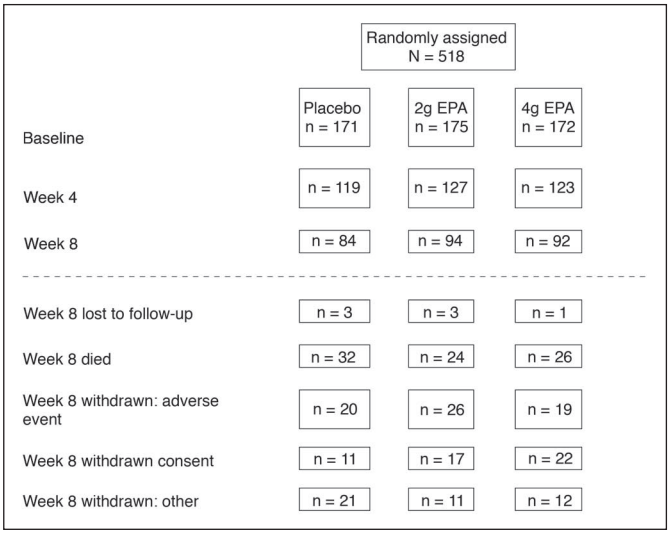

Fig 1. CONSORT diagram. EPA, eicosapentaenoic acid.

Table 2. Comparison With Placebo in the Intention-to-Treat Group of Cachectic Cancer Patients

	Patients				
	2 g EPA		4 g EPA		
Intention-to-Treat	Mean	95% CI	Mean	95% CI	*P*
Weight 4 wk (kg)	0.1	−0.6 to 0.8	0.2	−0.6 to 0.9	.88
Weight 8 wk (kg)	1.2	0.0 to 2.3	0.3	−0.9 to 1.5	.066
Lean body mass 4 wk (kg)	−0.4	−1.6 to 0.8	−0.3	−1.6 to 0.9	.75
Lean body mass 8 wk (kg)	0.9	−0.3 to 2.0	−0.1	−1.3 to 1.1	.14
Albumin 4 wk (g/L)	0.4	−0.6 to 1.4	0.7	−0.4 to 1.7	.40
Albumin 8 wk (g/L)	0.3	−1.3 to 1.9	0.8	−0.9 to 2.4	.59
KPS 4 wk (/100)	1.1	−2.1 to 4.4	1.4	−1.9 to 4.7	.60
KPS 8 wk (/100)	0.4	−3.6 to 4.5	1.3	−2.7 to 5.4	.76
Physical functioning* 4 wk (/100)	4.3	−1.4 to 10.0	−0.8	−6.5 to 4.9	.10
Physical functioning* 8 wk (/100)	4.3	−2.4 to 11.0	−3.4	−10.1 to 3.4	.040
Weakness* 4 wk (/100)	−8.7	−16.9 to-0.5	−2.8	−11.0 to 5.5	.057
Weakness* 8 wk (/100)	−9.5	−19.5 to 0.6	0.3	−9.8 to 10.4	.050
Appetite* 4 wk (/100)	−3.4	−12.5 to 5.7	−3.3	−12.4 to 5.9	.65
Appetite* 8 wk (/100)	−6.6	−17.6 to 4.5	−1.2	−12.3 to 9.9	.38
Nausea* 4 wk (/100)	0.5	−7.5 to 8.6	−0.7	−8.7 to 7.4	.95
Nausea* 8 wk (/100)	−2.1	−12.2 to 8.1	0.9	−9.2 to 11.0	.8
Vomiting* 4 wk (/100)	1.6	−5.3 to 8.6	3.7	−3.3 to 10.6	.5
Vomiting* 8 wk (/100)	1.7	−6.5 to 9.9	0.9	−7.3 to 9.2	.9
Diarrhea* 4 wk (/100)	3.0	−2.9 to 8.9	2.0	−3.9 to 8.0	.52
Diarrhea* 8 wk (/100)	4.4	−2.4 to 11.2	5.3	−1.6 to 12.1	.19

NOTE. Significance tests are presented for the analysis of covariance comparing the three treatment groups.
Abbreviations: EPA, eicosapentaenoic acid; wk, week; KPS, Karnofsky performance score.
*As documented by the patients using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 version 3.0.

(95% CI, 0.0 kg to 2.3 kg). For the group receiving 4 g EPA daily the mean weight change was an increase of 0.3 kg (−0.9 kg to 1.5 kg). These changes (and those at 4 weeks) are shown in Figure 2. Compared with weight at baseline, patients receiving placebo lost a mean of 0.7 kg over 8 weeks. Those receiving 2 g EPA daily gained a median of 0.4 kg and those receiving 4 g EPA lost a median of 0.4 kg.

Analysis of covariance for lean body mass between the three groups in the intention-to-treat analysis at 8 weeks (Table 2) gave a nonsignificant result ($P = .14$). When compared with the placebo group, the mean change in lean body mass for the group receiving 2 g EPA daily was an increase of 0.9 kg (95% CI, −0.3 kg to 2.0 kg). For the group receiving 4 g EPA daily, the mean change in lean body mass was a decrease of 0.1 kg (−1.3 kg to 1.1 kg). These changes (and those at 4 weeks) are shown in Figure 2. Compared with lean body mass at baseline, patients receiving placebo lost a mean of 0.3 kg over 8 weeks. Those receiving 2 g EPA daily gained a median of 0.6 kg and those receiving 4 g EPA lost a median of 0.4 kg. In the per-protocol group changes were similar in scale, but there were no statistically significant differences.

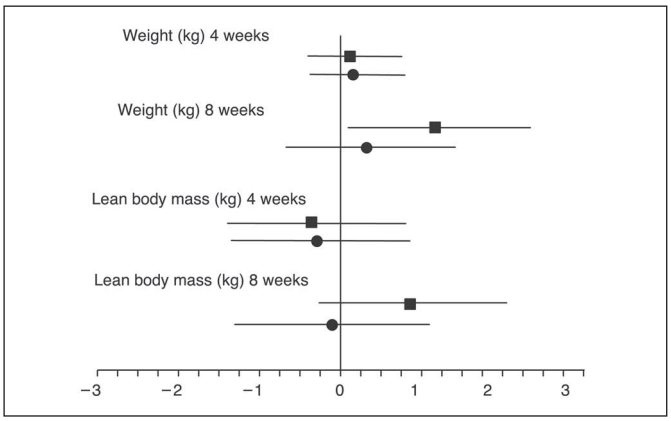

Fig 2. Comparison of experimental groups to placebo at 4 weeks and 8 weeks for weight and lean body mass in the intention-to-treat group. (■) 2 g EPA; (●) 4 g EPA. Figure presents mean and 95% CI.

There was a statistically significant difference in physical function at 8 weeks between the study groups and those receiving placebo. Physical function improved by approximately 7% compared with placebo in those receiving 2 g EPA ($P = .04$) and fell by around 5% in those receiving 4 g EPA. There was also a trend toward a difference in levels of self-reported weakness between the study groups and those receiving placebo. Weakness tended to decrease in the 2 g EPA group at 4 weeks and 8 weeks, whereas there was little change in the 4 g EPA group. There were no differences between groups for C-reactive protein, albumin, Karnofsky performance status, or appetite at any time point in either the intention-to-treat or per-protocol groups.

The influence of the patient's type of cancer on the response to EPA is shown in Table 3. Overall, the weight of patients with gastrointestinal cancer who received EPA increased significantly compared with placebo. In contrast, the weight of those patients with lung cancer showed no significant response. However, there was no proof that these two subgroups were responding differently to EPA because a test of interaction was not significant ($P = .155$).

Median survival from baseline of patients receiving placebo was 140 days (95% CI, 104 to 176). Patients receiving 2 g EPA had a median survival of 155 days (95% CI, 136 days to 173 days) and those

Table 3. Change in Weight (kg) From Baseline to Week 8 When Compared With Placebo

Type of Cancer	No. of Patients	2 g EPA		4 g EPA		P
		Mean	95% CI	Mean	95% CI	
GI	98	1.9	0.2 to 3.5	1.3	−0.4 to 3.0	.044
Lung	158	0.5	−1.1 to 2.2	−0.7	−2.3 to 0.9	.230

NOTE. Test of interaction, $P = .155$.
Abbreviations: EPA, eicosapentaenoic acid; GI, gastrointestinal.

receiving 4 g EPA had a median survival of 142 days (95% CI, 106 days to 177 days; $P = .75$). Survival curves are shown in Figure 3.

DISCUSSION

This large, multicenter study examined the effect of a novel diester preparation of EPA in cachectic cancer patients. Overall, no statistically significant effects of treatment on the primary end point of weight were observed. However, over an 8-week period those patients receiving 2 g of EPA had weight gain of around 1 kg compared with placebo. The CIs were consistent with a clinically relevant treatment effect for EPA at this dose. There was also a modest improvement in physical function in those receiving 2 g EPA. The 4 g EPA preparation had no effect on weight. There were no other obvious differences in nutritional or quality of life measures as a result of EPA diester administration.

Previous phase I/II trials have reported similarly a median increase in weight of 2 kg over 7 weeks[23] and an increase in physical function[24] when EPA (as marine tryglycerides) was given at a dose of approximately 2 g per day and combined with a high-protein, high-calorie oral nutritional supplement. However, two large, randomized trials[16,17] of the same combination regimen either failed to reach a similar dose of EPA (1.4 g per day) or did not document the dose and showed equivalence to the non-EPA containing arms of the studies. In one of these trials,[16] plasma EPA level was measured at 4 weeks and 8 weeks and there was a clear dose response in relation to improved lean body mass up to the maximum dose of 2.2 g EPA per day. Together these data suggest an optimum net dose of EPA as marine triglycerides to be at least 2 g per day when given in combination with oral nutritional supplements.

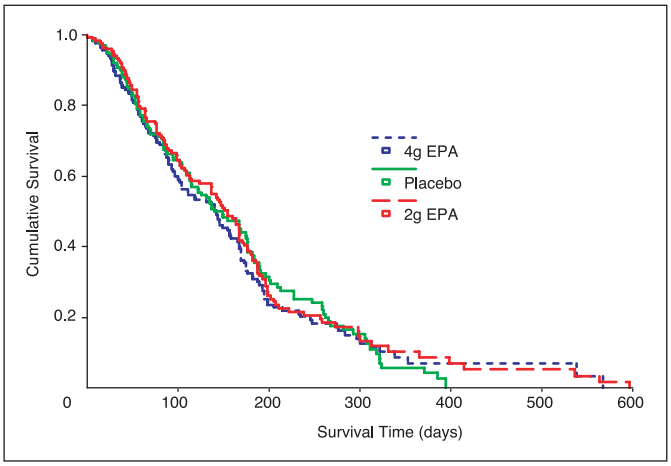

Fig 3. Survival of patients (intention-to-treat analysis) with cancer cachexia receiving eicosapentaenoic acid (EPA) preparations and placebo. No significant difference between groups (log-rank test $P = .75$).

In this study EPA was given alone and not in combination with oral nutritional supplements. There was no benefit observed with the 4 g EPA per day diethyl ester preparation but a potentially clinically relevant treatment effect with 2 g EPA per day. Thus, there was no evidence of a dose response beyond 2 g per day and if anything a suggestion of either a plateau or at worst a degree of deterioration with 4 g per day. This deterioration may have been due to a subclinical toxicity of the higher dose of EPA. It is not clear what the toxicity at 4 g per day EPA was and how this might have resulted in a net decline in weight. One explanation might be that the higher dose of EPA gave rise to nonspecific gastrointestinal adverse effects, which might have caused a relative net decline in food intake and hence nutritional status. However, in this study, self-reported levels of gastrointestinal symptoms were similar at 4 weeks and 8 weeks in the placebo, 2 g per day EPA and 4 g per day EPA groups (Table 2) thus suggesting that any adverse effects of 4 g per day EPA diester were relatively subtle.

An alternative explanation for the apparent lack of efficacy of 4 g EPA per day as a diethyl ester is that due to unobserved adverse effects patients took less of the prescribed capsules than at the 2 g dose. Against this, compliance at 4 weeks (> 80% capsules taken) was apparently similar between patients taking the 2 g EPA dose and those patients taking the 4 g EPA dose (68% and 75%, respectively; $P = .18$). It is possible that patients were not willing to reveal noncompliance and in this study plasma EPA levels were not measured as an objective measure of compliance. It may also be that the present preparation of EPA lacked efficacy due to ineffective hydrolysis of the ester or altered distribution in vivo. Finally, with regard to the apparent lack of overall benefit with a higher dose of EPA, it is important to recognize that this may simply reflect the play of chance in a heterogeneous population in relation to a marginal effect.

In this study patients with gastrointestinal cancer may have responded better compared with patients with lung cancer (Table 3). A possible explanation for this could be the differential expression of proinflammatory cytokines and other procachectic molecules in different cancer types. Heterogeneity has been shown at the level of the genotype for which polymorphisms of cytokine genes appear to influence survival in cancer patients with a high prevalence of cachexia.[25,26] Cytokine gene polymorphisms have also been suggested to affect the response of individuals to EPA supplementation.[27,28] Future trials may need to take account of such heterogeneity in their design. Furthermore, in this study, due to their advanced stage of disease and overall frailty patients did not receive ongoing systemic antineoplastic therapy. Future cachexia trials would likely benefit from studying a single tumor type with earlier stage disease, optimally receiving the same systemic therapy. Evaluating patients with better survival prospects would also reduce the potential problems with selective attrition whereby only the fittest patients reach the end of the study.

The purpose of intervention in cancer cachexia is to improve patients' quality (for example, physical function) and /or quantity of life. In this context nutritional status is used as a robust, but nonetheless surrogate, end point. This study was designed to detect a 2 kg difference in body weight in the EPA-supplemented groups compared with the controls. Although of marginal statistical significance, the mean weight of the patients who received 2 g EPA per

day over 8 weeks increased by 1.2 kg (95% CI, 0 kg to 2.3 kg). In the poor prognosis cancer types being studied here, where progressive and symptomatic weight loss is the norm,[29] stabilization of additional weight loss and even a small gain in weight of 1 kg to 2 kg, is likely to be clinically important to patients. Indeed in studies of nutritional intervention for undernourished patients with anorexia nervosa,[30] benign chronic gastrointestinal disease,[31] or pancreatic cancer,[24] an improvement in physical function (a key aspect of nutrition-dependent quality of life) has occurred ahead of weight gain or restoration of normal nutritional status.

The potential mechanisms of action of EPA in cachexia are diverse but include suppression of proinflammatory mediators such as cytokines and prostanoids.[32] NSAIDs have been shown to be of benefit in animal models[33] with some evidence for efficacy in human studies.[34,35,36] In this study patients were stratified for use of NSAIDs and there was no difference in the proportion of patients taking NSAIDs between groups at baseline (17% to 20%; Table 1). Compared with patients who received placebo, weight changes at 8 weeks in the subgroups who were taking both EPA and NSAIDs (2 g EPA, 1.8 kg; 4g EPA, −0.2kg) were not significantly different from the overall groups (Table 2). These findings provide no clear evidence in favor of a beneficial interaction between n-3 fatty acids and NSAIDs. However, patient numbers were small and this question would require further prospective evaluation.

The literature is currently uncertain as to the role of n-3 fatty acids in human cancer cachexia management. This study has shown no statistically significant improvement in survival, weight, or other nutritional variables. There was, however, a possible benefit at 2 g per day of EPA but it is clear that the optimum dose, formulation, route of administration, and target population remain yet to be defined. It also appears that the benefit of n-3 fatty acids by themselves is at best marginal and it may be that future studies should concentrate on other agents or combination regimens.

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Acknowledgment

The authors would like thank the personnel at Scotia Pharmaceuticals (Stirling, United Kingdom) involved in the study (Richard Bryce, MD, Elspeth Pyper, Helen Colquhoun, MD) and the investigators who contributed patients to the study (see online-only Appendix).

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Kenneth C.H. Fearon					Ross Products (A)	Scotia Pharmaceuticals (B); Ross Products (B)		
Sam H. Ahmedzai			Ark Therapeutics (B)		Janssen-Cilag (A)	Ark Therapeutics (B); Cephalon (A); Link Pharmaceuticals (A)		
Michael J. Tisdale						Ross Products (B)		

Dollar Amount Codes (A) < $10,000 (B) $10,000-99,999 (C) ≥ $100,000 (N/R) Not Required

Author Contributions

Conception and design: Kenneth C.H. Fearon, Matthew D. Barber, Michael J. Tisdale, Gordon D. Murray
Administrative support: Alastair G. Moses
Provision of study materials or patients: Alastair G. Moses, Sam H. Ahmedzai
Collection and assembly of data: Kenneth C.H. Fearon, Matthew D. Barber, Alastair G. Moses, Sam H. Ahmedzai
Data analysis and interpretation: Kenneth C.H. Fearon, Matthew D. Barber, Sam H. Ahmedzai, Gillian S. Taylor, Michael J. Tisdale, Gordon D. Murray
Manuscript writing: Kenneth C.H. Fearon, Matthew D. Barber, Sam H. Ahmedzai, Michael J. Tisdale, Gordon D. Murray
Final approval of manuscript: Kenneth C.H. Fearon, Matthew D. Barber, Alastair G. Moses, Sam H. Ahmedzai, Gillian S. Taylor, Michael J. Tisdale, Gordon D. Murray