L-Carnitine Supplementation for the Management of Fatigue in Patients With Cancer: An Eastern Cooperative Oncology Group Phase III, Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Purpose

L-carnitine, a popular complementary and alternative medicine product, is used by patients with cancer for the treatment of fatigue, the most commonly reported symptom in this patient population. The purpose of this study was to determine the efficacy of L-carnitine supplementation as a treatment for fatigue in patients with cancer.

Patients and Methods

In this double-blind, placebo-controlled trial, patients with invasive malignancies and fatigue were randomly assigned to either 2 g/d of L-carnitine oral supplementation or matching placebo. The primary end point was the change in average daily fatigue from baseline to week 4 using the Brief Fatigue Inventory (BFI).

Results

Three hundred seventy-six patients were randomly assigned to treatment with L-carnitine supplementation or placebo. L-carnitine supplementation resulted in significant carnitine plasma level increase by week 4. The primary outcome, fatigue, measured using the BFI, improved in both arms compared with baseline (L-carnitine: -0.96 , 95% CI, -1.32 to -0.60 ; placebo: -1.11 , 95% CI -1.44 to -0.78). There were no statistically significant differences between arms ($P = .57$). Secondary outcomes, including fatigue measured by the Functional Assessment of Chronic Illness Therapy–Fatigue instrument, depression, and pain, did not show significant difference between arms. A separate analysis of patients who were carnitine-deficient at baseline did not show statistically significant improvement in fatigue or other outcomes after L-carnitine supplementation.

Conclusion

Four weeks of 2 g of L-carnitine supplementation did not improve fatigue in patients with invasive malignancies and good performance status.

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INTRODUCTION

The National Center for Health Statistics conducted a survey of research in complementary and alternative medicine (CAM) showing that, of \$2.2 trillion total US health care spending in 2007, out-of-pocket expenditure for CAM was \$33.9 billion.¹ Considering that most CAM products are unregulated, there is a need for high level-of-evidence studies to establish the efficacy and safety of these products. L-carnitine is a popular supplement used for fatigue.

The biologic rationale for supplementation of carnitine is related to energy metabolism. The production of energy by the cell is dependent on three substrates: glucose, fatty acids, and amino acids. Glucose can be rapidly mobilized and is the pre-

ferred substrate for energy production, but fatty acids are more efficient because they produce more adenosine triphosphate per molecule. Fatty acids are stored in adipose tissue and have a carbon chain with variable lengths: short, medium, and long. Once in the mitochondrion, they become substrates of β -oxidation and produce a number of adenosine triphosphate molecules that are proportional to the length of the number of carbons in their chain. Hence the fatty acids with the longest chain (long chain fatty acids) are the most efficient substrates.

In contrast to fatty acids with short or medium carbon chains, long-chain fatty acids cannot penetrate the mitochondrion without a carrier. The translocation of the long-chain fatty acids is catalyzed by enzymatic complexes, which require the

micronutrient carnitine.² In the absence of carnitine, long-chain fatty acids cannot enter the mitochondrion, and energy production is compromised.³ Carnitine can also downregulate pro-cachectic cytokines, and it is speculated that this could further alter the biology and improve anorexia and cachexia in patients with cancer.⁴

Adults⁴ and children⁵ with chronic illnesses are prone to carnitine deficiency as a result of decreased intake, increased utilization, or increased elimination. In adults, open-label studies suggest that L-carnitine supplementation may improve fatigue in patients with cancer with carnitine deficiency secondary to chemotherapy and may improve fatigue, sleep, and mood.^{6,7}

L-carnitine supplementation has been pursued for the treatment of fatigue in some populations, such as those with advanced cancer, liver disease, and cachexia. We reported in a post hoc analysis of a preliminary randomized double-blind placebo controlled study in terminally ill patients with poor level of function and carnitine deficiency that 1 g twice daily of L-carnitine supplementation could improve fatigue symptoms.^{7,8} To further explore this observation and expand it to a broader cancer patient population, we conducted a phase III, randomized, double-blind, placebo-controlled clinical trial in patients with cancer with fatigue.

PATIENTS AND METHODS

Study Design

The primary objective of this randomized, placebo-controlled trial was to investigate the effectiveness of 4 weeks of L-carnitine supplementation on fatigue in patients with invasive cancer, assessed by change in scores for average fatigue from baseline to week 4 using the Brief Fatigue Inventory (BFI). Secondary outcome measures were overall fatigue (assessed by Functional Assessment of Chronic Illness Therapy–Fatigue [FACIT-F]), mood, pain, and performance status. Eligible patients were being treated or observed as outpatients and had moderate to severe fatigue, defined as a response of “somewhat,” “quite a bit,” or “very much” to the FACIT-F question “I feel fatigued.”

Patients were stratified according to sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS; 0, 1 v 2, 3) and currently receiving chemotherapy (yes v no). Twenty-four sites associated with ECOG accrued patients for the study. Eligibility criteria included 18 years of age or older and hemoglobin ≥ 9 g/dL taken ≤ 4 weeks before registration. Exclusion criteria included intake of carnitine, history of seizures, brain metastasis, nausea more than grade 1, and severely compromised renal, liver, or respiratory function. The study included a double-blind, placebo-controlled treatment phase followed by a 4-week open-label phase during which all patients received L-carnitine supplementation. The institutional review board of each participating institution approved the protocol.

Patients were randomly assigned using permuted blocks within strata, with dynamic balancing within main institutions, to receive 1 g of oral liquid L-carnitine or placebo twice daily for 4 weeks. Randomization was conducted using ECOG’s computerized randomization system. Treatment codes were known only to a senior information systems manager and were conveyed to the statistician at the times of interim and final analyses. L-carnitine was a standardized commercial preparation of 10 g of levocarnitine inert salt in 100-mL solution (provided by Sigma Tau Pharmaceuticals, Gaithersburg, MD). Study drug was shipped in coded vials to site pharmacies and was dispensed in blinded fashion to study teams for distribution to care providers and patients. Placebo vials were colored so that placebo matched L-carnitine in appearance. For weeks 5 to 8, all patients received L-carnitine in the same fashion.

The self-report measures were composed of four validated instruments that assess fatigue, mood, pain, and performance status that were completed at baseline, week 4, and week 8. The Brief Fatigue Inventory (BFI) is a nine-item

scale validated in the cancer population for the assessment of fatigue severity and impact on function.⁹ The study’s primary end point was the difference between arms in change in average fatigue from baseline to week 4 on this instrument. The Brief Pain Inventory (BPI) is a validated scale to assess pain, with the mean of the four severity items (range, 0 to 10) used as a measure of severity and the mean of the seven interference items used to measure pain interference.¹⁰ The Center for Epidemiologic Studies Depression Scale (CES-D) is a 20-item scale (range, 0 to 60) that was used to assess depression. Scores ≥ 16 indicate a potentially significant level of depression.¹¹ Finally, the FACIT-F is a 13-item scale where lower scores correspond to worse fatigue. This was used as an alternative questionnaire to assess overall fatigue.¹²

The ECOG performance status scale, where 0 is the best and 5 the lowest level of performance, was used by clinicians to screen patients at baseline and as a secondary outcome.¹³ All adverse events were graded according to the Common Terminology Criteria for Adverse Events (version 3).

Blood samples were collected at baseline, week 4, and week 8. Analysis of plasma carnitine and acylcarnitine levels was performed at the Mayo Clinic Central Laboratory for Clinical Trials. Carnitine-deficient patients were defined as those having acylcarnitine to total carnitine ratio more than 0.4 $\mu\text{mol/L}$ or free carnitine (FC) less than 35 $\mu\text{mol/L}$ (male patients) and FC less than 25 $\mu\text{mol/L}$ (female patients) at baseline. After the March 2006 amendment incorporating cytokine studies, serum samples were collected from consenting patients at baseline and week 4.

Statistical Design

The study was designed to detect a difference of 0.5 standard deviation (SD) in the change (baseline to week 4) of average fatigue between the two arms, with 85% power, assuming an inpatient correlation of 0.5, using a Wilcoxon-Mann-Whitney test with a two-sided type I error of 5%. One interim efficacy analysis was planned at 50% information, but no futility analyses were planned. The study was amended to include correlative studies of pro-inflammatory cytokines and triglycerides, and target accrual was raised to 286 patients to permit this addition (data to be included in further reports). This increased the statistical power to 95% for the previously described primary end point analysis.

O’Brien-Fleming upper and lower boundaries computed using the Lan-DeMets¹⁴ method were used to guide the interim efficacy analysis of change in average fatigue between the two arms. The corresponding nominal critical value and nominal significance for the interim analysis at 50% information (143 eligible patients) were 2.96 and 0.003, respectively. The corresponding nominal critical value and nominal significance for the final analysis (286 eligible patients) were 1.98 and 0.049, respectively. Because of unusually brisk accrual, a large number of patients were consented near the end of the trial, and these patients were permitted to register. Final accrual was 376 patients.

Statistical Analysis

The Wilcoxon-Mann-Whitney test was used to compare score changes from baseline to week 4 between the carnitine and placebo arms. Fisher’s exact test was used to assess the relationship between categorical covariates/responses. Kaplan-Meier estimates were used for survival distributions, and stratified log-rank tests were used to test for differences in survival between the two arms. Mixed-effects repeated measures models were used to explore quality of life (QOL) score changes over time. All models were built assuming an unstructured covariance matrix, and all parameter estimates were obtained under restricted maximum likelihood. First, a full model including a time-by-treatment interaction term (5 df) was evaluated to determine whether there was a difference in the pattern of change over time attributable to treatment. Generalized linear models were used to model the associations between time and treatment and the proportion of patients with severe fatigue or significant depression. A binomial distribution and logit link function were assumed, and the Wald test was used to test the time-by-treatment interaction. In the absence of a statistically significant interaction, a reduced model without the interaction term was used to make inferences about differences between time points or between arms.

Fig 1. Patient disposition. QOL, quality of life.

RESULTS

The CONSORT diagram in Figure 1 summarizes patient disposition, and Table 1 shows patient demographics and disease characteristics at baseline. There were no differences between arms for any of the factors and characteristics. Patient QOL form compliance is shown in Appendix Table A1 (online only). Proportions at baseline, week 4, and week 8 for carnitine and placebo arms were 95.2% and 96.2%, 68.3% and 79.6%, and 74.7% and 70.4%, respectively. The most common reason for noncompletion of QOL forms was patient refusal. Appendix Table A2 (online only) shows the prevalence of severe fatigue, significant depression, significant pain (defined as a score of ≥ 5 on any BPI item or being on analgesics at baseline), and carnitine deficiency by arm and time point.

L-Carnitine Supplementation and Carnitine Serum Levels

The group receiving L-carnitine during the blinded phase had a greater increase in total L-carnitine levels between baseline and the end

of the blinded phase (Table 2). In the L-carnitine group, mean total carnitine increased from 46.3 $\mu\text{M/L}$ (95% CI, 44.1 to 48.4 $\mu\text{M/L}$) to 66.2 $\mu\text{M/L}$ (95% CI, 62.4 to 69.9 $\mu\text{M/L}$), whereas in the placebo group, mean total carnitine increased nominally from 43.6 $\mu\text{M/L}$ (95% CI, 41.4 to 45.7 $\mu\text{M/L}$) to 43.7 $\mu\text{M/L}$ (95% CI, 40.7 to 46.7 $\mu\text{M/L}$; $P = .004$).

The proportion of patients with carnitine deficiency on the two arms was similar at baseline (34% and 32%). At week 4, one third of the patients randomly assigned to placebo were carnitine-deficient, compared with 11% of those randomly assigned to carnitine ($P \leq .001$). By week 8, after open-label carnitine supplementation had been instituted for the patients randomly assigned to placebo, there were again no significant differences between arms in the proportion of patients with carnitine deficiency (13.5% and 11.5%).

Primary End Point

The primary end point was the difference between arms in change in BFI from baseline to week 4 (Table 3). Fatigue improved in

Table 1. Patient Demographics and Disease Characteristics at Baseline

Characteristic	Carnitine (n = 189)		Placebo (n = 187)	
	No.	%	No.	%
Sex				
Male	78	41.8	79	42.3
Female	111	58.2	108	57.7
Race				
White	176	93.1	177	94.7
Black	6	3.2	7	3.7
Asian	2	1.1	0	0.0
Native American	1	0.5	0	0.0
Unknown	4	2.1	3	1.6
Ethnicity				
Non-Hispanic or Latino	155	82.0	154	82.4
Hispanic or Latino	1	0.5	4	2.1
Institution refused	1	0.5	1	0.5
Unknown	32	17.0	28	15.0
Metastatic disease	114	60.3	98	52.4
Performance status				
0	53	28.0	64	34.2
1	110	58.2	90	48.1
2	20	10.6	30	16.1
3	6	3.2	1	0.5
Unknown	0	0.0	2	1.1
Current treatment				
Current radiotherapy	33	17.5	35	18.7
Current chemotherapy	154	81.5	146	78.1
No concurrent therapy	27	14.3	28	15.1
Medication				
Psychostimulants	4	2.1	6	3.2
Analgesics	84	44.4	63	33.7
Antidepressants	54	28.6	52	27.8

Table 2. L-Carnitine Supplementation and Carnitine Serum Levels

Visit	Carnitine			Placebo		
	No.	Mean	SD	No.	Mean	SD
Acetylcarnitine						
Baseline	172	11.35	6.62	172	10.68	5.96
Week 4	132	16.05	7.71	133	10.08	4.05
Week 8	111	17.88	9.90	113	16.09	12.78
Total carnitine						
Baseline	173	46.28	14.42	172	43.56	14.09
Week 4	133	66.18	21.83	132	43.70	17.67
Week 8	111	70.07	23.41	113	65.58	25.56
Free carnitine						
Baseline	173	37.20	11.39	172	35.10	11.91
Week 4	133	52.97	17.40	132	43.70	17.67
Week 8	111	55.31	16.79	113	52.16	17.33
Ratio = (total – free)/free						
Baseline	173	0.25	0.11	172	0.26	0.26
Week 4	133	0.25	0.11	132	0.25	0.11
Week 8	111	0.26	0.12	113	0.25	0.11

NOTE. The number of carnitine-deficient patients was defined as those having acetylcarnitine ratio > 0.4 $\mu\text{mol/L}$ or free carnitine < 35 $\mu\text{mol/L}$ (male patients) and free carnitine < 25 $\mu\text{mol/L}$ (female patients) at that visit.

both arms compared with baseline (L-carnitine: -0.96 , 95% CI -1.32 to -0.60 ; placebo: -1.11 , 95% CI -1.44 to -0.78). The Z-transformed Wilcoxon-Mann-Whitney test statistic for the difference between arms, approximately 0.075 points, is -0.58 ($P = .57$). The one-point improvement represents a statistically significant improvement from baseline on both arms (Wilcoxon signed rank $P < .001$). Cronbach α values for the BFI at each visit were greater than 0.92 and were very similar between treatment arms (data not shown). Thus the BFI seems to be a reliable measure of fatigue in this patient population. Inpatient Pearson correlation coefficients among time points by treatment arm for BFI scores did not show significant differences between arms.

Secondary End Points

We assessed the effect of L-carnitine supplementation on fatigue using the FACIT-F instrument, depression, and pain. None of the outcomes were significantly different when the L-carnitine arm was compared with the placebo arm (fatigue $P = .64$; depression $P = .93$, pain severity $P = .61$, and pain interference $P = .75$). From the reduced model, there was a decrease in the proportion of patients with severe fatigue, depression, or pain over time on both arms ($P < .001$), but there were no differences between arms. The time-by-treatment interactions for all instruments were not statistically significant, indicating that patterns of change were similar for the two arms.

Changes in Performance Status

Performance status did not show significant change when the two arms were compared. The percentage of patients who improved, remained stable, or declined were 14.2% and 17.5%, 66.5% and 70.0%, and 19.4% and 12.5% at 4 weeks ($P = .13$), and 18.0% and 18.1%, 61.5% and 64.6%, and 20.5% and 17.3% at 8 weeks ($P = .63$) for the carnitine and placebo arms, respectively. When performance status in patients with carnitine deficiency at baseline was compared with the rest of the patients, the differences were also not significant. The percentage of patients who improved, remained stable, or declined were 16.7% and 19.1%, 66.7% and 19.1%, 66.7% and 72.3%, and 16.7% and 8.5% at 4 weeks ($P = .36$), and 18.4% and 20.6%, 52.6% and 55.9%, and 28.9% and 23.5% at 8 weeks ($P = .68$) for the carnitine and placebo arms, respectively.

Effect of L-Carnitine Supplementation on Fatigue in Carnitine-Deficient Patients

Patients who were carnitine-deficient at randomization did not show a statistically significant improvement in fatigue scores or secondary outcomes when compared with patients who were not deficient at accrual. Patients in both arms experienced improvement in fatigue, regardless of carnitine deficiency status. Table 4 gives the mean difference in BFI scores from baseline to week 4 for patients who were carnitine-deficient and non-carnitine-deficient at baseline, by treatment arm. Both groups experienced approximately a one-point improvement, regardless of treatment (Wilcoxon sign rank $P < .01$ for all subsets). Carnitine-deficient patients in both arms had statistically significant reductions in fatigue over time.

Subgroup Analysis

We looked at changes from baseline on the primary end point (fatigue as assessed by BFI) and the secondary end points of fatigue as assessed by FACIT-F, mood, and pain within subsets defined by sex, race, severity of fatigue, and carnitine deficiency status. There was no

Table 3. Effect of L-Carnitine Supplementation on the Primary End Point Fatigue From Baseline to Week 4

Subgroup	Carnitine			Placebo			Test Statistic*	P
	No.	Mean	SD	No.	Mean	SD		
Sex								
Male	62	−0.74	2.36	57	−0.99	1.86	−0.79	.43
Female	83	−1.13	2.05	81	−1.20	2.03	−0.16	.88
Race								
White	132	−1.08	2.20	132	−1.15	1.96	0.17	.86
Nonwhite	9	−0.10	1.82	5	−0.09	1.92	−0.13	.89
White non-Hispanic	109	−1.09	2.18	108	−1.11	1.96	−0.09	.93
Other†	32	−0.79	2.24	29	−1.14	2.00	−0.46	.64
Fatigue level								
Mild fatigue‡	43	−0.29	2.21	45	−0.72	1.88	0.32	.75
Severe fatigue	101	−1.26	2.13	93	−1.30	1.97	−0.51	.61
Carnitine-deficient at baseline								
Yes	46	−1.03	2.27	38	−1.33	2.12	−0.54	.59
No	96	−0.95	2.20	94	−1.06	1.90	−0.38	.70
Overall	145	−0.96	2.19	138	−1.11	1.95	−0.58	.57

Abbreviation: SD, standard deviation.

*Z-transformed Wilcoxon-Mann-Whitney test statistic.

†Not white non-Hispanic.

‡Defined as score < 7 for “fatigue worst” item on Brief Fatigue Inventory.

evidence that these variables moderated the effect of treatment assignment on the end points.

There was consistent improvement from baseline to week 4 among patients randomly assigned to both arms. We also examined the impact of depression on fatigue, as patients with significant depression were not excluded in this study. A post hoc analysis comparing the effect of L-carnitine supplementation on patients with fatigue alone (primary fatigue) versus patients with fatigue pain and depression (secondary fatigue) did not show significant differences (Table 5).

Toxicity and Adverse Effects

Events with missing treatment attribution were considered possibly related to treatment. Toxicities of all attributions and those con-

sidered possibly, probably, or definitely treatment-related are shown in Appendix Tables A3 and A4 (online only). There were few high-grade, treatment-related toxicities. There were three patients with reportable grade 5 events: one was death owing to disease progression, unrelated to treatment; in another patient, the cause of death was possibly related to treatment; for the third, cause of death was considered probably caused by disease progression and unrelated to treatment. In addition to these events, there were 11 deaths owing to disease within 30 days of treatment. Four other patients died within 30 days of the end of treatment: one developed multiorgan failure related to disease progression; another developed infectious colitis, considered unrelated to treatment; the third developed pleural effusion,

Table 4. Effect of L-Carnitine Supplementation on Fatigue Scores in Carnitine-Deficient Patients

Visit	Carnitine			Placebo		
	No.	Mean	SD	No.	Mean	SD
BFI, average						
Baseline	58	6.04	1.86	52	6.10	2.10
Week 4	14	4.18	2.44	42	5.56	2.22
Week 8	14	3.29	2.24	12	4.48	2.25
BFI, worst						
Baseline	58	7.52	2.03	52	7.19	2.42
Week 4	14	5.57	2.77	42	7.19	2.19
Week 8	14	5.00	2.75	12	5.58	2.54
FACIT-F						
Baseline	58	19.83	8.10	53	18.83	8.34
Week 4	14	28.36	12.58	42	20.12	10.32
Week 8	15	31.40	9.21	12	23.67	11.24

NOTE. Number of carnitine-deficient patients were defined as those having acetylcarnitine ratio > 0.4 $\mu\text{mol/L}$ or free carnitine < 35 $\mu\text{mol/L}$ (male patients) and free carnitine < 25 $\mu\text{mol/L}$ (female patients) at that visit.

Abbreviations: BFI, Brief Fatigue Inventory; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; SD, standard deviation.

Table 5. Baseline Fatigue and Change From Baseline for Patients on Each Arm, by Category (primary fatigue or secondary cause) With Significant Pain and Depression as Opposed to Primary Fatigue

Fatigue	Arm A, L-Carnitine		Arm B, Placebo	
	Pain or Depression	Primary Fatigue	Pain or Depression	Primary Fatigue
Baseline fatigue				
No.	138	43	129	49
Mean	7.51	6.02	7.49	6.24
Standard deviation	2.02	2.14	2.13	2.55
Change from baseline				
No.	113	32	102	36
Mean	−1.09	−0.46	−1.33	−0.50
Standard deviation	2.09	2.52	1.95	1.87

NOTE. Patients with either significant pain (defined as a score of ≥ 5 on any of the Brief Fatigue Inventory pain items or taking analgesics for pain) or depression (defined as a score of ≥ 16 on the Center for Epidemiologic Studies Depression Scale) were considered to have secondary fatigue, whereas patients free of both of these conditions were considered to have primary fatigue.

probably related to lung metastases; the fourth experienced multiorgan failure as a result of infection. The rate of grade 5 serious adverse events did not differ by treatment arm (Fisher's exact $P = .64$).

DISCUSSION

This is the largest clinical trial to date studying the effect of L-carnitine supplementation on patients with invasive malignancy and fatigue. In this phase III, randomized, double-blind, placebo-controlled study, we observed that 1 g twice daily of oral L-carnitine supplementation for 4 weeks does not improve fatigue, depression, or pain in patients with cancer. None of the outcomes showed a significant improvement when the treatment arm and placebo arms were compared, but both showed significant improvement when compared with baseline scores, suggesting a large placebo effect. A separate analysis in patients who were carnitine-deficient at baseline also showed improvement in the treatment and placebo arms as compared with baseline scores and did not show statistically significant improvement between the study arms. Similar results were observed when the data were examined according to retention of patients receiving L-carnitine or by a responders analysis.

This negative study has several important limitations. The 25% to 30% failure to complete the assessments weakens the conclusions of the study, as we do not know whether those subjects who did not complete the assessments experienced improvement or on the contrary were more fatigued. This percentage of missing follow-up assessments, however, is within the range reported by others in studies that have symptoms as primary outcomes. Also, whereas our preliminary study was conducted in patients with carnitine deficiency at baseline, only 30% of the current study's subjects had carnitine deficiency, and this factor may be important. Moreover, the dose and duration of L-carnitine supplementation and patient population selected for this study are different from those of some other studies that showed positive results. There are studies in cachectic patients that showed fatigue improvement at higher doses in combination with other supplements.^{15,16} Finally, depression and pain

are common among patients with advanced cancer and could confound the fatigue analysis. In our study, patients with significant depression were not excluded. However, a post hoc analysis comparing the effect of L-carnitine supplementation on patients with fatigue alone (primary fatigue) versus patients with fatigue pain and depression (secondary fatigue) did not show significant differences (Table 5).

Overall, there was a biologic rationale for L-carnitine supplementation to treat cancer fatigue based on preliminary data in patients with cancer. This trial was conducted successfully, and these data help establish the prevalence of carnitine deficiency (33%) in ambulatory patients with cancer. The active form of carnitine (measured by acetyl-L-carnitine levels in the plasma) was increased with L-carnitine supplementation, with good tolerance of the treatment. We found that this particular approach for L-carnitine supplementation lacks efficacy in treating cancer fatigue in this patient population. Futility analyses ought to be incorporated in the design of future fatigue trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Ricardo A. Cruciani, Judith Manola, David Cella, Michael J. Fisch

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Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

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