Original Article

Safety, Tolerability and Symptom Outcomes Associated with L-Carnitine Supplementation in Patients with Cancer, Fatigue, and Carnitine Deficiency: A Phase I/II Study

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Abstract

Carnitine deficiency is among the many metabolic disturbances that may contribute to fatigue in patients with cancer. Administration of exogenous L-carnitine may hold promise as a treatment for this common symptom. Little is known about L-carnitine safety, tolerability, and dose-response in patients with cancer. We conducted a Phase I/II open-label trial to assess the safety and tolerability of exogenous L-carnitine and clarify the safe dose range associated with symptom effects for future controlled trials. Adult patients with advanced cancer, carnitine deficiency (free carnitine <35 for males or <25 $\mu M/L$ for females, or acyl/free carnitine ratio >0.4), moderate to severe fatigue, and a Karnofsky Performance Status (KPS) score ≥ 50 were entered by groups of at least three into a standard maximum tolerated dose design. Each successive group received a higher dose of L-carnitine (250, 750, 1250, 1750, 2250, 2750, 3000 mg/day, respectively), administered in two daily doses for 7 days. To compare symptom outcomes before and after supplementation, patients completed validated measures of fatigue (Brief Fatigue Inventory [BFI]), depressed mood (Center for Epidemiologic Studies Depression Scale [CES-D]), quality of sleep (Epworth Sleeplessness Scale [ESS]), and KPS at baseline and 1 week later. Of the 38 patients screened for carnitine levels, 29 were deficient (76%). Twenty-seven patients participated ("intention to treat, ITT") (17 males, 10 females), and 21 completed the study ("completers"); 17 of these patients ("responders," mean $\pm$ [SD] age $= 57.9 \pm 15$) had increased carnitine levels at the end of the supplementation period. The highest dose achieved was 3000 mg/day. No patient experienced significant side effects and no toxicities were noted. Analysis of all the patients accrued (ITT, n $= 27$) showed a total carnitine increase from 32.8 ± 10 to 54.3 ± 23 $\mu M/L$ ($P < 0.001$) and free carnitine increase from 26.8 ± 8 to 44.1 ± 17 $\mu M/L$ ($P < 0.001$).

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BFI decreased significantly, from 66 ± 12 to 39.7 ± 26 (P < 0.001); ESS decreased from 12.9 ± 12 to 9 ± 6 (P = 0.001); and CES-D decreased from 29.2 ± 12 to 19 ± 12 (P < 0.001). A separate analysis of the 17 "responders" showed a dose-response relationship for total- (r = 0.54, P = 0.03), free-carnitine (r = 0.56, P = 0.02) levels, and fatigue (BFI) scores (r = −0.61, P = 0.01). These findings suggest that L-carnitine may be safely administered at doses up to 3000 mg/day and that positive effects may be more likely at relatively higher doses in this range. This study provides the basis for the design of future placebo-controlled studies of L-carnitine supplementation for cancer-related fatigue. J Pain Symptom Manage 2006;32:551−559.

Key Words
L-carnitine deficiency, L-carnitine supplementation, cancer-related fatigue

Introduction

Fatigue is extremely prevalent in the cancer population, particularly among those with advanced illness.[1−4] The underlying causes for fatigue are multifactorial and include the disease itself, antineoplastic therapies, and diverse comorbidities such as anemia, poor nutrition, deconditioning, mood disorders, centrally acting drugs, and varied endocrine and metabolic abnormalities.

Micronutrient deficiencies may be among the nutritional and metabolic disorders that influence the development of fatigue.[5−7] Carnitine, a micronutrient involved in the production of energy at the cellular level, is commonly deficient in chronically ill patients and has been considered a candidate molecule potentially responsible for some cases of cancer-related fatigue. Winter et al. reported that 53% of patients with chronic illness had carnitine deficiency,[8] a finding confirmed in a survey of cancer patients age matched to normal controls.[9] Esteban-Cruciani et al. identified carnitine deficiency in a high proportion of pediatric patients with chronic illness, including acquired immune deficiency syndrome and cancer.[10,11]

Carnitine deficiency may predispose to chronic fatigue by impairing utilization of long chain fatty acids in energy metabolism. Long chain fatty acids are the preferred source of energy by muscle and cardiac cells because they have a high yield of adenosine triphosphate (ATP), their consumption does not compromise other cellular functions, and they can be stored in large quantities. Carnitine is required to translocate long chain fatty acid substrate into the cell, where it is metabolized to release energy.[12,13]

Patient with cancer are at risk for carnitine deficiency due to decreased oral intake and increased renal losses. Concerns that L-carnitine supplementation could accelerate cancer progression or interfere with some chemotherapies have not been confirmed in preclinical studies.[14,15] The hypothesis that L-carnitine treatment could improve cancer-related fatigue or lead to other positive outcomes deserves further evaluation. The first step in this process is to assess safety and tolerability of clinically relevant doses of L-carnitine while better defining a dose range associated with symptom effects for future controlled trials. These aims were pursued through a Phase I/II open-label trial in a population with advanced cancer. A preliminary analysis of some of these data was reported previously.[14]

Methods

This was an open-label Phase I/II clinical trial of L-carnitine supplementation in carnitine-deficient patients with advanced cancer. It was designed to 1) evaluate safety and tolerability through a maximum tolerated dose, and 2) clarify a safe dose range that could be tested in future controlled efficacy trials. The protocol and consent form were approved by the Institutional Review Board at Beth Israel Medical Center, New York.

The study population comprised adult patients with advanced cancer under the care of Beth Israel Medical Center's Continuum

Hospice Care/The Jacob Perlow Hospice or the Cancer Center. Eligible patients had moderate to severe fatigue, a Karnofsky Performance Status (KPS) score ≥50, and carnitine deficiency. For the purposes of the study, carnitine deficiency was defined as free carnitine <35 μM/L for males or <25 μM/L for females (normal range 35–67 and 25–55, respectively), or an acyl-carnitine ratio (total carnitine minus free carnitine/free carnitine) >0.4. Patients with hemoglobin levels <9 g/dL were excluded, with two exceptions for compassionate reasons. Other exclusion criteria were an increased risk of seizure or heart failure, current treatment with chemotherapy, radiation therapy, or recombinant erythropoietin; and renal insufficiency (blood urea nitrogen (BUN) or creatinine more than two times the upper normal range).

A standard maximum tolerated dose design was used. Three patients were assigned to successive dose groups, starting at 250 mg/day and increasing in each group by 500 mg/day to a maximum dose target of 3000 mg/day. Carnitine was prepared by our institutional pharmacy at a concentration of 1 g/mL. In each group, an open-label L-carnitine was administered in two daily doses for 7 days (Fig. 1). At the end of the 7-day period, patients were allowed to continue with L-carnitine supplementation at the discretion of their primary physicians.

At the screening visit, medical history and physical examination were performed and blood was sampled for plasma carnitine determination, complete blood count, electrolytes, liver function and renal function tests, thyroid function tests, vitamin B12 and folate levels, and ferritin level. Plasma carnitine was measured by standard laboratory methods. Self-report instruments for selected symptoms were completed (see below). Patients who met eligibility criteria, including carnitine deficiency, began treatment with the study drug. Instructions on storage conditions, preservation, and disposition of any unused drug were provided to the patient.

During the week of L-carnitine treatment, the patient was contacted by the research staff at least every other day. At each contact, the patient was asked an open-ended question about side effects or other problems. After 7 days, they were reevaluated, asked to complete the self-report measures, and repeat blood drawing for plasma carnitine determinations, complete blood count, and electrolytes.

Patients who did not complete 1 week of L-carnitine supplementation were replaced. They underwent a termination visit, which included an examination and repeat laboratory screening.

Safety and tolerability were assessed from the reports of side effects during telephone contacts, the findings on the evaluation by the investigator before and after treatment with study drug, and the results of the laboratory screening. If the patient reported any side effect associated with treatment, the research coordinator obtained additional detail, including onset, course, relationship to the dose, and severity. Every report was to be discussed with the principal investigator. If a severe adverse effect believed to be related to the study medication occurred, the study was planned for termination without advancing to the next patient; if moderate adverse effects believed to be related to the study medication occurred in two of the three patients at any dose level, the study also would be terminated without proceeding to the next dose. As described below, the study drug was well tolerated and none of these procedures were implemented.

The self-report measures completed at baseline and 1 week later comprised validated instruments that assess fatigue, mood, sleep, and performance status. These instruments included 1) the Brief Fatigue Inventory (BFI),[15] a 9-item scale validated in the cancer population for the assessment of fatigue severity and impact on function; the Center for Epidemiologic Studies Depression Scale (CES-D),[16] a widely-used 20-item measure of depressed mood; and the Epworth Sleeplessness Scale (ESS),[17] an 8-item scale that validly measures quality of sleep. In addition, the investigator recorded a score on the KPS scale,[18] a well-known, observer-rated measure of overall performance status, at baseline and after 1 week of study drug administration.

Statistical Analysis

Descriptive statistics are presented as mean ± SD for normally distributed variables (e.g., age), as median (minimum, maximum) for skewed data (e.g., thyroid-stimulating hormone or TSH), and as frequency (%) for categorical variables (e.g., ethnicity). Descriptive statistics for L-carnitine and other study

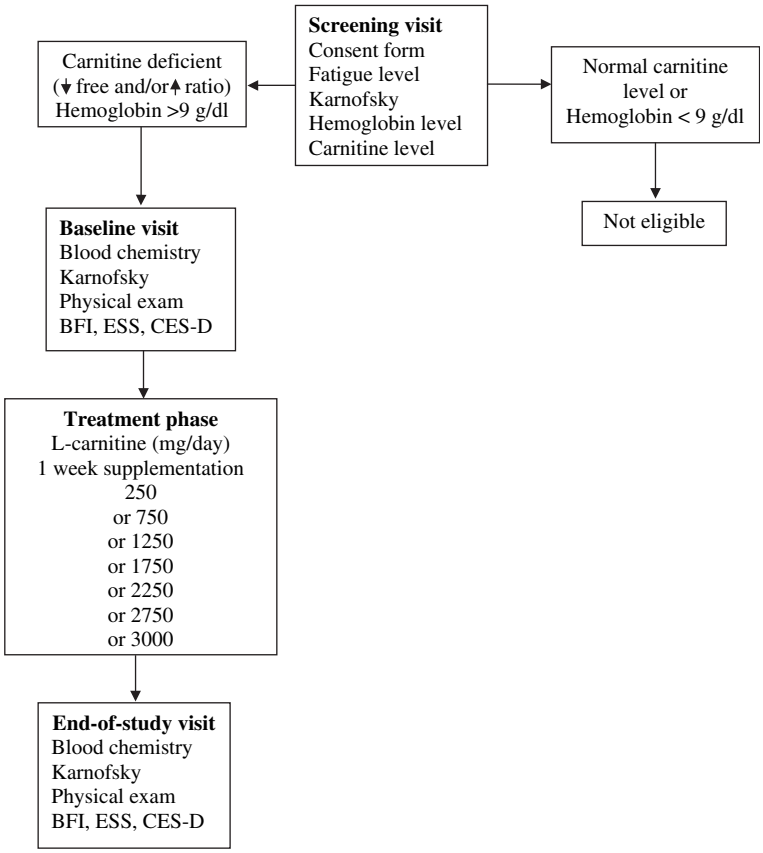

Fig. 1. Schema.

outcomes are presented as mean ± SD to allow comparison with other studies. All patients were included in the review of side effects and safety data. Prepost comparisons were done using either a Student's paired *t*-test or a Wilcoxon nonparametric test for paired data, where appropriate. Tests for possible differences in response for males and females were done using repeated measures ANOVA with a time × gender interaction. Separate analyses were performed on the entire sample and on a subgroup of completers who finished 1 week of supplementation and provided interpretable data. Dose response was measured by the Pearson correlation between the L-carnitine dose level that the patient received and outcome measure after 1 week. All analyses were carried out using SPSS 13.0 (SPSS Inc., Chicago).

Results

Six hundred fifty-nine patients were screened for the study. Eighty-five were eligible and 27 signed informed consent. Of the patients screened, 193 (29%) were too ill, 142 (22%) were undergoing either chemotherapy or radiation therapy, 71 (11%) were cognitively impaired, 52 (8%) had brain tumor, and 39 (6%) were not sufficiently fluent in English (Table 1). Of the 58 eligible patients who elected not to participate, the majority indicated that they were interested in trials aimed at treating their condition and were less interested in symptom management studies. Two patients with hemoglobin below 9 g/dL (7.2 and 8.4, respectively) asked to participate and were permitted to do so for compassionate reasons.

The intention-to-treat (ITT) group ($n = 27$) received at least one dose of L-carnitine (Table 2). The age of the group was 59.7 ± 14 (mean ± SD), with 10 (37%) females and 16 (59%) Caucasian. The most common cancer diagnoses were breast (22%), colorectal (15%), lung (15%), prostate (15%), and head and neck (11%). Most patients reported severe fatigue (70%). Baseline B12, folate,

Table 1
Patients Considered for Participation

Total Patients Considered	659	100%
Not eligible	574	87
Too ill (KPS ≤50)	193	29
Chemo/radiation therapy	142	22
Impaired mental status	71	11
Brain tumor	52	8
Language barrier	39	6
Could not give consent	19	3
Not fatigued	19	3
Cardiac failure	13	2
Recombinant erythropoietin	13	2
Renal insufficiency	13	2
Eligible	85	13%
Refused consent	47	7
Normal carnitine level	9	1
Did not start study	2	<1
Discontinued from study	6	<1
Per protocol nonresponders	4	<1
Per protocol responders	17	2

ferritin, T4, and TSH were normal in most patients (Table 2). Elevations in B12 and folate levels were recorded in 5 patients and 14 patients, respectively, due to vitamin supplementation. Ferritin was abnormal in one patient, and T4 was below the laboratory threshold for normal values in one.

Of the 27 patients who began the study, 6 were discontinued and 21 completed a full week of dosing and provided interpretable data. The reasons for discontinuation included hospitalization requiring changes in medications ($n=2$), severe deterioration ($n=3$) and a protocol violation ($n=1$). Patients who did not complete the 1 week of dosing were replaced (Fig. 2).

Seven groups of 3–6 patients each received L-carnitine supplementation for 1 week to end with three completers per group. Dose escalation proceeded through all dose levels (250, 750, 1250, 1750, 2250, 2750, and 3000 mg/day, respectively) (Fig. 1). Two patients reported mild nausea related to the study drug. There were no other reported side effects.

In the entire sample (ITT, $n=27$), there was a significant increase in all carnitine-associated laboratory measurements between baseline and postdosing (Table 3). The mean ± SD total carnitine (μM/L) rose from 32.8 ± 10 to 54.3 ± 23 ($P<0.001$), while mean-free carnitine (μM/L) also increased significantly, from 26.8 ± 8 to 44.1 ± 17 ($P<0.001$). Analysis by gender showed that baseline mean ± SD for women was 26.2 ± 4 μM/L and 21.2 ± 3 μM/L

Table 2
Demographic and Clinical Characteristics

Variable	All Patients (ITT) ($n=27$)	Responders ($n=17$)
Age	59.7 ± 14.4	57.9 ± 14.9
Female	10 (37%)	8 (47%)
Ethnicity		
White	16 (59%)	9 (53%)
Black	4 (15%)	3 (18%)
Hispanic	6 (22%)	4 (24%)
Asian	1 (4%)	1 (6%)
Cancer Diagnosis		
Bladder	1 (4%)	—
Breast	6 (22%)	5 (29%)
Colon/rectum	4 (15%)	3 (18%)
Head and neck	3 (11%)	3 (18%)
Leukemia	2 (7%)	1 (6%)
Lung	4 (15%)	1 (6%)
Prostate	4 (15%)	2 (12%)
Other	3 (11%)	2 (12%)
Level of fatigue		
Moderate	8 (30%)	6 (35%)
Severe	19 (70%)	11 (65%)
B12 (pg/mL)	502 (184, 1177)	622 (184, 1177)
Folate (ng/mL)	18.8 ± 6.6	21.3 ± 5.5
TSH (mIU/L)	1.8 (0.42, 29.2)	1.8 (0.95, 29.2)
T4 (μg/dL)	8.5 ± 2.8	8.5 ± 2.6
Ferritin (ng/mL)	118.9 (0.8, 1154.4)	97.6 (0.8, 607.5)
Dose of L-carnitine (mg/day)		
250	3 (11%)	1 (6%)
750	4 (15%)	3 (18%)
1250	3 (11%)	2 (12%)
1750	6 (22%)	3 (18%)
2250	3 (11%)	3 (18%)
2750	4 (15%)	2 (12%)
3000	4 (15%)	3 (18%)

for total and free L-carnitine, while men showed baseline values of 38.8 ± 12 μM/L and 31.7 ± 7 μM/L, respectively (Table 4). Women and men showed comparable significant increases in total- and free-carnitine levels: to 51.2 ± 27 μM/L and 41.8 ± 19 μM/L, respectively, in women (both P-values = 0.01), and to 62.0 ± 18 μM/L and 51.2 ± 14 μM/L, respectively, in men (both P-values = 0.008).

There was a small but statistically significant decline in hemoglobin, from 12.2 ± 2.1 g/dL to 12.0 ± 1.8 g/dL ($P=0.03$). The significant difference is primarily due to a statistical artifact. There was a very high correlation between baseline hemoglobin and hemoglobin after 1 week, $r=0.91$ ($P<0.001$). Since the error variance in a paired sample comparison is calculated by subtracting the amount of covariance shared by the samples, a very high correlation can reduce the error variance to the point that clinically nonsignificant differences yield statistical significance.

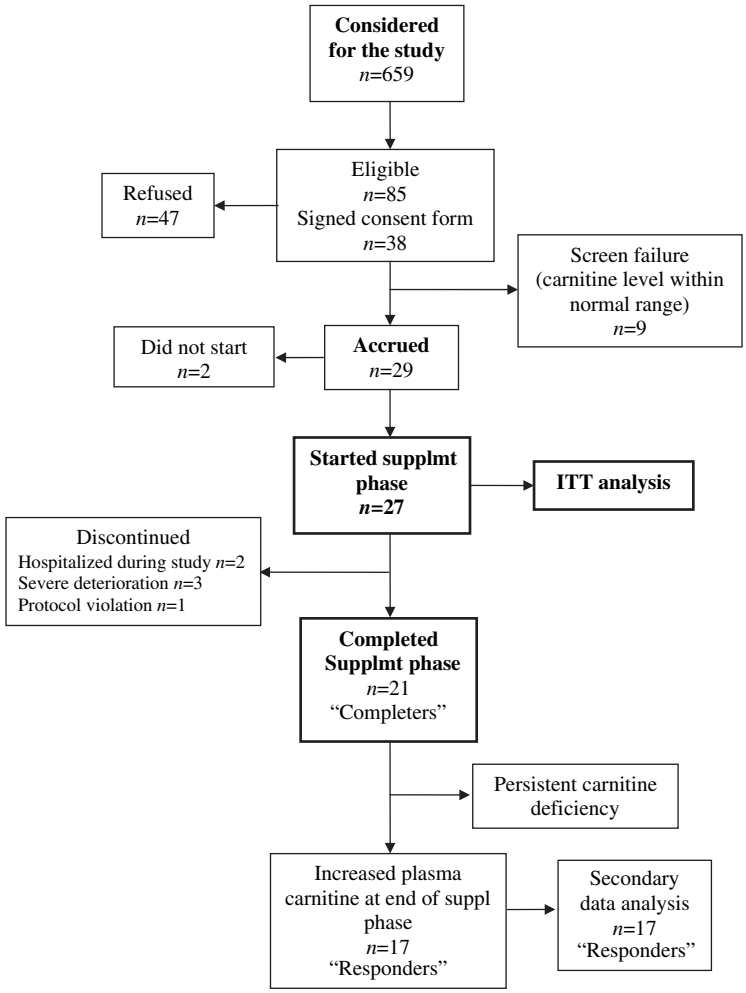

Fig. 2. Patient disposition.

Other outcome measures showed improvement (Table 4). BFI decreased significantly, from 66.1 ± 12 to 39.7 ± 26 ($P < 0.001$); ESS decreased from 12.9 ± 7 to 9 ± 6 ($P = 0.001$), and CES-D decreased from 29.2 ± 12 to 19 ± 12 ($P < 0.001$). Median KPS remained unchanged at 70, with three patients decreasing in performance level and four increasing. There were significant correlations between dose level and final total carnitine ($r = 0.58$, $P = 0.002$) and free carnitine ($r = 0.55$, $P = 0.004$) but not between dose level and any of the outcome instruments.

When only the "responders" (increase in carnitine levels after 1 week supplementation) were analyzed ($n = 17$) in addition to a dose response for total- ($r = 0.54$, $P = 0.03$) and free-carnitine levels ($r = 0.56$, $P = 0.02$), a dose-response relationship was also observed for fatigue (BFI scores) ($r = -0.61$, $P = 0.01$) (Fig. 3). No such relationship was observed for other outcomes (KPS, [$r = -0.31$, $P = 0.23$]; CES-D, [-0.27, $P = 0.29$]; ESS, [$r = 0.09$, $P = 0.74$]). The "responders" were representative of the entire sample. The mean $\pm$ SD age was 57.9 ± 15, eight were female (47%), and nine were Caucasian (53%). Distribution of cancer diagnoses was also similar to the entire sample. In this group of patients, the mean $\pm$ SD total carnitine increased significantly from 32.9 ± 11 to 56.9 ± 23 ($P < 0.001$), and free carnitine increased from 26.8 ± 8 to 46.8 ± 17 μM/L ($P < 0.001$). There were no significant changes in hemoglobin levels. Mean $\pm$ SD BFI decreased from 62.6 ± 12 at baseline to 38.1 ± 21 after 1 week ($P < 0.001$). Mean $\pm$ SD CES-D decreased from 28.6 ± 14 to 17.2 ± 10

Table 3
Pre- and Post Carnitine Plasma Values of All Patients Accrued in the Study (ITT Group)

		1 Week of L-Carnitine Supplementation							
				Carnitine Levels					
		Hgb		Pre			Post		
Gender		Pre	Post	Free	Tot	Ratio	Free	Tot	Ratio
1	F	15.5	14.1	24	33	0.38	32	36	0.13
2	F	13.4	13.5	19	26	0.37	28	35	0.25
3	F	13.8	12.8	23	28	0.22	33	38	0.15
4	F	11.1	11.1	18	23	0.28	38	51	0.34
5	F	14.5	13.6	11	12	0.09	19	26	0.37
6	F	9.4	10.3	22	27	0.23	57	68	0.19
7	F	11.1	11.6	25	29	0.16	39	42	0.08
8	F	9.5	10.2	17	21	0.24	82	111	0.35
9	F	12.1	11.3	26	28	0.08	37	45	0.22
10	F	11.4	12.2	22	23	0.05	25	29	0.16
11	M	13.1	13.5	31	37	0.19	29	34	0.17
12	M	4.8	14.9	26	32	0.23	23	28	0.22
13	M	13.6	12.9	25	33	0.32	38	51	0.34
14	M	11.5	10.2	29	35	0.21	—	—	—
15	M	12	11.7	30	34	0.13	38	44	0.16
16	M	7.2	7.6	18	28	0.56	52	83	0.6
17	M	8.4	8.6	34	37	0.09	41	50	0.22
18	M	11.1	10.1	25	35	0.4	25	27	0.08
19	M	11.2	10.9	28	33	0.18	39	45	0.15
20	M	11.3	10	30	37	0.23	52	63	0.21
21	M	15.4	15.3	36	44	0.22	42	47	0.12
22	M	14	13.7	27	31	0.15	78	92	0.18
23	M	11.8	11.5	35	39	0.11	78	92	0.18
24	M	13	10.4	35	47	0.34	47	58	0.23
25	M	10.9	11.1	48	68	0.42	65	90	0.38
26	M	15.3	14.5	35	39	0.11	50	60	0.2
27	M	13.2	13.4	26	30	0.15	59	66	0.12

The ratio is calculated as the difference between total (T)−free carnitine (F) divided by free carnitine ($T–F/F$). The median (min, max) total carnitine rose from 33 (12, 68) to 48.5 (26, 111) ($P<0.001$) and the median free carnitine also increased significantly, from 26 (11, 48) to 39 (19, 82) ($P<0.001$). Women had total- and free-carnitine levels of 40 (26, 111) and 35 (19, 82), respectively (ratio 0.20 [0.08, 0.37]), and men had total- and free-carnitine levels of 54.5 (27, 92) and 44.5 (23, 78), respectively (ratio 0.19 [0.08, 0.60]).

($P=0.001$), and mean ± SD ESS decreased from 12.5 ± 6 to 9.1 ± 5 ($P=0.003$). None of these patients experienced a decline in performance status and KPS increased in four of them ($P=0.05$).

After 1 week of supplementation, patients were given the opportunity to continue. All patients but two requested that the treatment continue.

Discussion

The safety and tolerability of L-carnitine supplementation at doses that could be clinically relevant in cancer patients have not been established. The findings from this study indicate that supplementation is very well tolerated up to doses of 3000 mg/day. Only two patients experienced nausea that was not severe enough to require the discontinuation from the study. Studies to determine the possibility of side effects in patients undergoing supplementation for longer periods of time need to be conducted.

Although responses were variable, L-carnitine supplementation usually increased plasma carnitine-associated laboratory measurements. Carnitine supplementation for 1 week increased the carnitine levels in 85% of the patients, a finding that is consistent with those reported by Graziano et al.[19] There was a moderately strong relationship between dose and rise in serum concentrations.

Most of the patients who received L-carnitine experienced improved fatigue, mood, and sleep. The improvement in fatigue was dose dependent within the subgroup that received 7 days of supplementation and experienced a rise in carnitine-associated laboratory values ("responders"). These changes in subjective effects, which suggest that L-carnitine

Table 4
Carnitine Plasma Levels and Symptom Outcomes in the Intention-to-Treat and Responder Groups

	All Patients (ITT, $n=27$)			Responders ($n=17$)		
Variable	Pre	Post	*P*-Value	Pre	Post	*P*-Value
Carnitine (μM/L)						
Total	32.8 ± 10	54.3 ± 23	<0.001	32.9 ± 11	56.9 ± 23	<0.001
Free	26.8 ± 8	44.1 ± 17	<0.001	26.8 ± 8	46.8 ± 17	<0.001
Hgb (g/dL)	12.2 ± 2	12.0 ± 2	0.03	12.5 ± 2	12.6 ± 2	0.36
BFI	66.1 ± 12	39.7 ± 26	<0.001	62.6 ± 12	38.1 ± 21	<0.001
ESS	12.9 ± 7	9.0 ± 6	0.001	12.5 ± 6	9.1 ± 5	0.003
CES-D	29.2 ± 12	19.0 ± 12	<0.001	28.6 ± 14	17.2 ± 10	0.001
KPS						
<50	—	3 (11%)	0.76	—	—	0.05
50	5 (19%)	3 (11%)		2 (12%)	1 (6%)	
60	7 (26%)	6 (22%)		4 (24%)	5 (2 9%)	
70	12 (44%)	8 (30%)		10 (59%)	7 (41%)	
80	3 (11%)	7 (26%)		1 (6%)	4 (24%)	

Responders were defined as those who showed increase in carnitine plasma levels after 1 week of L-carnitine supplementation.

supplementation in the dose range tested could provide meaningful clinical benefit, warrant evaluation in a randomized controlled trial. Of the 38 patients whom we screened for carnitine levels, 29 were deficient (76%) suggesting a higher prevalence of carnitine deficiency in patients with cancer than reported earlier.[9]

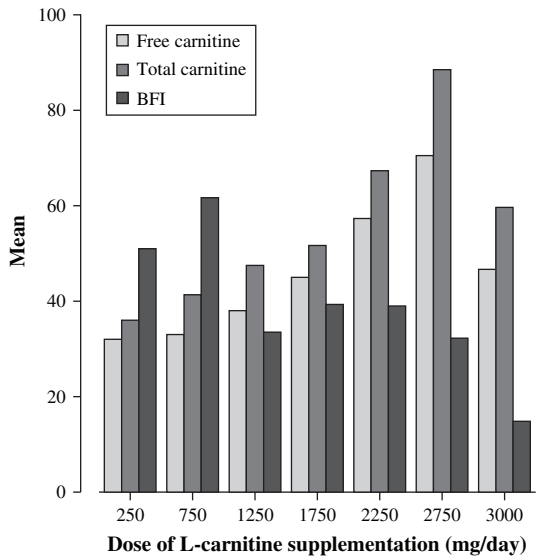

Fig. 3. Analysis of the 17 patients, who after 1-week supplementation, had increased serum carnitine levels ("responders"). Each bar represents a dosing group. There was significant dose response for total carnitine ($r=0.54$, $P=0.03$) and for free carnitine ($r=0.56$, $P=0.02$). Decrease in fatigue scores (BFI) also showed a significant dose response ($r=-0.61$, $P=0.01$).

Several important limitations of this trial deserve mention. A large number of cancer patients were screened to identify a small group of eligible patients. This effort illustrates the difficulties encountered in working with this patient population. Of the 85 patients who did qualify for the study, 47 (55%) elected not to participate. Given these factors, generalizability of the findings requires confirmation in additional trials. Assessment of side effects did not rely on validated measures and a range of potential safety measurements, such as repeated liver function tests, were not performed. These decisions were made to limit patient burden. Because the trial was an open-label and did not have a comparison group, a placebo effect cannot be excluded and the measurement of subjective effects should not be taken as valid on their own, but only as an indicator of endpoints that may be important in future controlled trials. The patients were taking carnitine in a liquid form at a concentration of 1 g/10 mL. The placebo effect could be magnified by the difference in the volume of drug that the different groups were taking. The lowest dose group was taking 2.5 mL three times a day while the highest group was taking 10 mL three times a day.

Notwithstanding these limitations, this study suggests that the prevalence of carnitine deficiency in patients with cancer may be higher than previously reported,[9] and that L-carnitine supplementation up to a dose of 3000 mg/day is well tolerated in patients with cancer.

Carnitine supplementation for 1 week increased the carnitine levels in 85% of the patients, and appeared to be associated with clinical benefit. Hence, 6 g/day dosing as proposed by Gramignano et al.[20] to treat fatigue in patients with cancer might not be necessary. However, the fact that these patients were receiving active chemotherapy or radiation therapy (we excluded those patients from our study) might justify the election of a higher dose to compensate for the carnitine deficiency induced by certain specific agents as previously shown by Graziano et al.[19] Hence, trials to define dosing over 3 g of L-carnitine supplementation to treat fatigue and other outcomes in patients with cancer need to be conducted. Since there was a dose-response improvement for fatigue among the responders, it seems that 3000 mg/day gave the highest benefit. However, it is possible that with a longer period of supplementation a beneficial effect could be obtained with lower doses.

These findings suggest a possible role of L-carnitine in the symptom management of patients with advanced cancer and fatigue and provide the bases for the design of future placebo-controlled supplementation studies in this population.

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