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Efficacy of L-carnitine administration on fatigue, nutritional status, oxidative stress, and related quality of life in 12 advanced cancer patients undergoing anticancer therapy

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Abstract

Objective: Fatigue is a multidimensional symptom that is described in terms of perceived energy, mental capacity, and psychological status: it can impair daily functioning and lead to negative effects on quality of life. It is one of the most common side effects of chemotherapy and radiotherapy. In recent studies, L-carnitine (LC) supplementation has been demonstrated to be able to improve fatigue symptoms in patients with cancer.

Methods: In the present study we tested the efficacy and safety of LC supplementation in a population of patients who had advanced cancer and developed fatigue, high blood levels of reactive oxygen species, or both. As outcome measures we evaluated fatigue and quality of life in relation to oxidative stress, nutritional status, and laboratory variables, mainly levels of reactive oxygen species, glutathione peroxidase, and proinflammatory cytokines. From March to July 2004, 12 patients who had advanced tumors (50% at stage IV) at different sites were enrolled (male-to-female ratio 2:10, mean age 60 y, range 42–73). Patients were only slightly anemic (hemoglobin 10.9 g/dL) and hemoglobin levels did not change after treatment. LC was administered orally at 6 g/d for 4 wk. All patients underwent antineoplastic treatment during LC supplementation.

Results: Fatigue, as measured by the Multidimensional Fatigue Symptom Inventory—Short Form, decreased significantly, particularly for the General and Physical scales, and for quality of life in each subscale of quality of life in relation to oxidative stress. Nutritional variables (lean body mass and appetite) increased significantly after LC supplementation. Levels of reactive oxygen species decreased and glutathione peroxidase increased but not significantly. Proinflammatory cytokines did not change significantly.

Conclusion: Improvement of symptoms with respect to fatigue and quality of life in relation to oxidative stress may be explained mainly by an increase in lean body mass, which may be considered the most important nutritional or functional parameter in assessing the cachectic state of patients. In this view, fatigue with related symptoms can well be considered an important constituent of cancer-related anorexia cachexia syndrome.

Keywords: Cancer-related fatigue; L-carnitine; Lean body mass; Oxidative stress; Quality of life

Introduction

Patients with cancer commonly report a lack of energy during the course of their disease and treatment, which they describe as "fatigue" [1]. Fatigue is a subjective sensation with physical, cognitive, and emotional features of expres-

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sion [2]. The National Comprehensive Cancer Network Fatigue Practice Guideline Panel defined fatigue as "an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning" [3]. Cancer-related fatigue criteria have been proposed for the *International Classification of Disease, 10th Revision, Clinical Modification* [4].

Fatigue is a multidimensional symptom and can be described in terms of perceived energy, mental capacity, and psychological status [5,6]; it can impair daily functioning and lead to negative effects on quality of life (QoL) [7,8], self-care capabilities [9], and desire to continue treatment [10]. Fatigue may be caused by the disease, antineoplastic therapies, and/or a broad range of physical and psychological comorbidities.

Fatigue may represent a final common pathway to which many factors may contribute [10–12]; therefore, its pathophysiology is multifactorial. Suggested mechanisms include an imbalance in energy metabolism due to increased energy requirement (e.g., due to tumor growth, infection, fever, or surgery) and decreased availability of metabolic substrates (e.g., due to anorexia, nausea, or vomiting leading to poor nutrition), an abnormal production of substances that impair metabolic homeostasis or normal muscle functioning (e.g., cytokines [13] and proteolysis-inducing factor), anemia, or hypoxemia. Other suggested mechanisms refer fatigue to the pathophysiology of sleep disorders and major depression. There is no clear evidence favoring any of these mechanisms in a specific patient, and further research is needed [6].

Fatigue is a major problem for patients with advanced cancer [14]. Several studies have shown a correlation between fatigue and different modalities of cancer therapy [15,16]. Fatigue is one of the most common side effects of chemotherapy and radiotherapy; 65% to 100% of patients who undergo radiotherapy [17,18] and 82% to 96% of those who receive chemotherapy [19,20] develop fatigue during treatment.

Only recently has fatigue been included among the most important symptoms in cancer patients, and its evaluation is still not routinely included among the symptoms attributable to the toxicity of chemotherapy [21].

Cancer-related anorexia/cachexia syndrome (CACS) and oxidative stress (OS) are two of the most important features in patients with advanced cancer. Cachexia is present in 80% of terminally ill patients with cancer [22–24], in about 50% of patients who undergo antineoplastic therapies [1,25], and in 2% to 3% of patients who receive adjuvant chemotherapy [26]. CACS is a characteristic clinical picture of anorexia, tissue wasting, loss of body weight accompanied by decreases in muscle mass and adipose tissue, and poor performance status that often precedes death [27,28]; fatigue is also a significant component of this syndrome.

In addition to decreased food intake, important abnormalities in carbohydrate, protein, and lipid biochemistry and metabolism and changes in energy metabolism have been observed in patients with cancer, which may account for CACS. Abnormalities in protein metabolism are increased protein turnover, loss of skeletal muscle, and increased gluconeogenesis from amino acids. Loss of skeletal muscle proteins occurs through increased rate of skeletal muscle protein breakdown and a decrease in the rate of muscle protein synthesis. Fatigue may be therefore a consequence of the loss of protein reserves in skeletal muscle.

Cancer-related anorexia/cachexia syndrome may result from circulating factors produced by the tumor or by the host immune system in response to the tumor, such as cytokines released by lymphocytes and/or monocytes or macrophages [29]. Several proinflammatory cytokines, including interleukin-1, interleukin-6, tumor necrosis factor-α, interferon-α, and interferon-γ, are involved in the pathogenesis of cachexia associated with human cancer [30,31].

Several mechanisms may lead to OS in patients with cancer. The first mechanism is the deranged energy metabolism, which may account for symptoms such as anorexia/cachexia, nausea, and vomiting that prevent a normal nutrition and thus a normal supply of nutrients that leads eventually to accumulation of free radicals that are known as reactive oxygen species (ROS) [29]. The second mechanism is a non-specific long-term activation of the host immune system with an excessive production of proinflammatory cytokines, which may in turn increase production of ROS [32]. A third mechanism may be the result of the use of antineoplastic drugs; many of them, particularly alkylating agents and cisplatin, can produce an excess of ROS and thus lead to OS [33].

Carnitine, a trimethylated amino acid roughly similar in structure to choline, is a cofactor required for transformation of the free long-chain fatty acids into acyl-carnitines and for their subsequent transport into the mitochondrial matrix, where they undergo β-oxidation for cell energy production. Mitochondrial fatty acid oxidation is the primary fuel source for heart and skeletal muscles, thus indicating the importance of this nutrient for proper function in these tissues [34]. Fatty acids in cytoplasm are transformed to long-chain acyl-coenzyme A (CoA) and transferred into the mitochondrial matrix by the action of three carnitine-dependent enzymes to produce acetyl-CoA through the β-oxidation pathway. The relation between CoA and carnitine is pivotal for energy metabolism. CoA is required for β-oxidation, for the metabolism of several amino acids, for pyruvate dehydrogenase, and thus for tricarboxylic acid cycle. The pyruvate dehydrogenase complex, the key irreversible rate-limiting step in carbohydrate oxidation, is modulated by the intramitochondrial ratio of acetyl-CoA to CoA. An increased ratio results in inhibition of pyruvate dehydrogenase activity; carnitine, by converting acetyl-CoA into acetylcarnitine, removes a powerful inhibitor of pyruvate dehydrogenase. Thus, the activity of L-carnitine (LC) in the modulation of the intramitochondrial ratio of acetyl-CoA to CoA affects glucose oxidation. The resulting increased access to the

citric acid cycle leads to an increased availability of adenosine triphosphate and Nicotinamide adenine dinucleotide (NADH)/reduced 1,5-dihydroflavin adenine dinucleotide ($FADH_2$) production. Carnitine also has important mitochondrial detoxification properties [35,36]. Impairment of mitochondrial energy production and β-oxidation and decreased detoxification lead to critical metabolic inefficiency and mitochondrial dysfunction.

A decrease in fatigue with LC supplementation in patients with cancer has been demonstrated in recent studies [37,38].

The present study tested the efficacy and safety of LC supplementation in 12 patients who had advanced cancer and developed fatigue, high levels of ROS, or both. As outcome measures we evaluated fatigue and OS-related QoL (QoL-OS), nutritional status and laboratory variables, mainly ROS levels, glutathione peroxidase, and proinflammatory cytokines.

Materials and methods

Patients

Patients who had advanced solid tumors and reported fatigue every day or nearly every day in the week before study entry and/or had high levels of ROS were considered eligible for study.

The inclusion criteria were histologic evidence of advanced solid tumor; development of fatigue, high levels of ROS, or both; and concurrent anticancer treatment. The exclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status score greater than 2, insulin-dependent diabetes mellitus, and pregnancy.

Treatment plan

Based on current knowledge of carnitine use, its metabolism, and treatment of deficiency, a high daily oral dose (6 g) fractionated in three single doses (2 g each) of LC for 4 wk was selected for the present study. Total dosage was spaced throughout the day and during or after the three mains meals.

Study design

Enrolled patients were evaluated at baseline (t0), after 2 wk (t1), and after 4 wk (t2) of LC supplementation for fatigue, QoL, and nutritional/functional and laboratory variables.

After baseline evaluation, patients started treatment with 2 g of an oral LC solution (Carnitene, Sigma Tau, Rome, Italy) three times daily for 4 wk.

Outcome measures

Fatigue (as measured by the Multidimensional Fatigue Symptom Inventory—Short Form [MFSI-SF]) [39,40], QoL-OS (QoL focused on symptoms of OS) by QoL-OS questionnaire, and global health status by the EQ-5D visual analog scale ($EQ\text{-}5D_{VAS}$), nutritional/functional status (lean body mass [LBM] and body impedance by bioelectric impedance analyzer, appetite by VAS, and grip strength by dynamometer) and laboratory variables (ROS, glutathione peroxidase, and proinflammatory cytokines C-reactive protein and hemoglobin) were assessed at t0, t1, and t2.

All instruments used in this study have been validated except for the QoL-OS questionnaire.

Fatigue assessment

Fatigue assessment was performed with the Italian version of the MFSI-SF QoL questionnaire [39,40]. The MSFI-SF, a self-administered questionnaire, consists of 30 items designed to assess the multidimensional nature of fatigue. The patients indicate to what extent they have experienced each symptom during the preceding 1-wk period on a five-point scale rating from 0 (not at all) to 4 (extremely).

The MFSI-SF consists of five subscales and each subscale includes six items: General scale, Physical scale, Emotional scale, Mental scale, and Vigor scale. The first four MFSI-SF subscale scores (general, physical, emotional, and mental fatigue) are added, and the Vigor scale score is subtracted to generate the total fatigue score. The highest MFSI-SF scores are associated with higher levels of fatigue.

QoL assessment

The QoL assessment focused on evaluation of the QoL-OS questionnaire; it is a multidimensional QoL tool developed at our institution to assess those dimensions of life in patients who have cancer that are mostly related to fatigue and OS. It consists of two parts. Part A consists of 37 items and each question is scored on a five-point scale from 0 (not at all) to 4 (very much). For an internal control, for some items the highest score corresponds to the best QoL; to calculate the score of these items, the actual score is subtracted from 4. The maximum score of part A corresponding to the worst QoL reaches 148. It investigates QoL over a 7-d period and is designed for patient self-administration or an interview format.

The QoL-OS consists of five subscales: Functional scale (three items), Physical scale (eight items), Emotional scale (three items), Social and Family scale (six items), and Fatigue scale (17 items).

Part B is a tool that is administered only at study entry and was developed to investigate a patient's food intake and estimate antioxidant nutritional deficiencies and nutritionally imbalanced. It refers most specifically to the intake of antioxidants through alimentary sources, an unbalanced diet (high consumption of known oxidant agents, saturated fatty acids from animal sources, fried foods, and alcohol), and

Table 1
Patient clinical characteristics*

Patients enrolled	12
Patients evaluable	12
Male/female	2/10
Age (y)	
Mean ± standard deviation	60 ± 9
Range	42–73
Tumor site	
Head and neck	3 (25)
Breast	2 (16.7)
Ovary	4 (33.4)
Uterine sarcoma	1 (8.3)
Stomach	1 (8.3)
Pleura	1 (8.3)
Stage	
IV	11 (91.7)
III	1 (8.3)
ECOG PS	
0	3 (25)
1	3 (25)
2	6 (50)
Concomitant chemotherapy	10 (83.3)
Disease state at baseline	
NED	1 (8.3)
SD	2 (16.7)
PD	9 (75.0)

ECOG PS, Eastern Cooperative Oncology Group performance status; NED, no evidence of disease; PD, progression of disease; SD, stable disease.

* Data are presented as numbers (%) of patients.

water/saline intake. Moreover, part B includes two items that investigate smoking habits and symptoms related to active and passive smoking. The maximum score of part B that corresponds to the most imbalanced diet reaches 73.

Moreover, we evaluated a patient's perceived global health status by the EQ-5D$_{VAS}$, a VAS that ranges from 0 to 100, in which 100 corresponds to the best imaginable health status and 0 to the worst.

Nutritional/functional assessment

The nutritional/functional variables assessed were LBM and impedance, appetite, and grip strength. LBM and impedance measurements were carried out with a bioelectric impedance analyzer (Bodystat 1500, Bodystat Ltd., Isle of Man, United Kingdom) using the standard four-electrode arrangement at 800 mA and 50 kHz. Body composition data analyzed by bioelectrical impedance analyzer are derived from correlations of resistance and reactance. During measurement with a bioelectrical impedance analyzer, the subject lies supine with arms and legs angled outward so that the medial surfaces of the limbs do not touch each other. For conventional whole-body measurement, electrodes are placed between the hand and the foot of the dominant side.

Appetite was measured by a self-assessment numerical rating scale of 0 to 10, with 0 indicating absolutely no appetite and 10 indicating extremely good appetite.

The grip strength test was measured with a dynamometer (Jamar hand dynamometer; Jamar, Chicago, IL). Patients were asked to sit comfortably with shoulders adducted and elbow flexed at 90 degrees and to squeeze the hand at maximum strength. Each test was repeated three times.

Laboratory variables

Blood levels of ROS were determined with the FORT test. Radical species that are produced by the reaction are directly proportional to the quantity of lipid peroxides present in the sample and interact with an additive (phenylenediamine derivative) that forms a radical molecule that can be evaluated with spectrophotometry at 505 nm (Form CR 2000, Callegari, Parma, Italy). Results are expressed as FORT units, where 1 FORT unit corresponds to 0.26 mg/L of H_2O_2 [41]. Erythrocytic glutathione peroxidase was measured by photometer using a commercially available kit (Ransod, Randox Laboratory, Crumlin, United Kingdom).

Proinflammatory cytokines (interleukin-6, interleukin-1, and tumor necrosis factor-α) were evaluated by enzyme-linked immunosorbent assay using monoclonal antibodies for two different epitopes of the cytokine molecules. Absorbance of the sample was analyzed by spectrophotometry at 450 nm.

Serum leptin levels were determined with an enzyme-linked immunosorbent assay using a monoclonal antibody specific for human leptin. Absorbance was measured by spectrophotometry at 450 ± 10 nm. More details about these techniques have been reported in our previous studies [42,43].

Safety

Assessment of toxicity was performed according to the National Cancer Institute's Common Toxicity Criteria (NCI-CTC; version 2.0, final January 30, 1998, revised by the NCI on March 23, 1998).

Statistical analysis

In the present study, values are reported as mean ± standard deviation. Differences among t0, t1, and t2 treat-

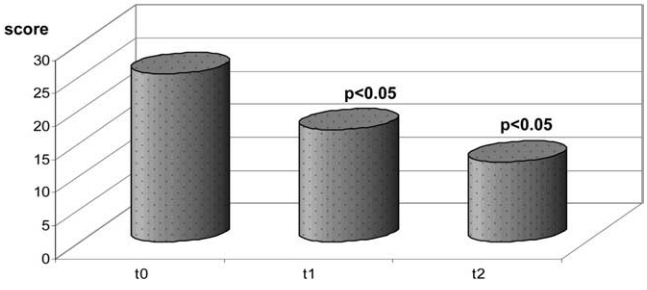

Fig. 1. Histograms represent the mean scores of the Multidimensional Fatigue Symptom Inventory—Short Form questionnaire. The difference between mean values of the score at baseline (t0) versus that at 2 wk (t1) and 4 wk (t2) of treatment with L-carnitine supplementation was statistically significant ($P < 0.05$ and $P < 0.001$, respectively).

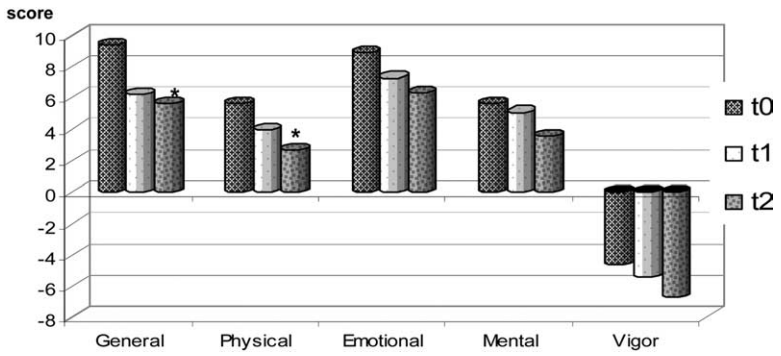

Fig. 2. Histograms represent the mean scores of the Multidimensional Fatigue Symptom Inventory—Short Form questionnaire subscales. Evaluation of the General, Physical, Emotional, Mental, and Vigor subscales showed a statistically significant difference between baseline (t0) and 4 wk (t2) of treatment only for the General scale ($P < 0.05$) and the Physical scale ($P < 0.05$). *$P < 0.05$. t2, 2 wk of treatment.

ment values were assessed with two-tailed Student's *t* test for paired data. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

From March to July 2004, 12 patients were enrolled in the present study (male-to-female ratio, 2:10; mean age, 60 y; range, 42–73); their clinical characteristics are listed in Table 1. The most represented sites concerned gynecologic cancer (five patients). All patients had locally advanced or metastatic disease (91.7% at stage IV). Performance status was an ECOG performance status of 2 in 50% of patients and an ECOG performance status of 1 in 25% of patients. All patients were non-smokers.

Chemotherapy administered to patients during the study consisted of platinum compounds (well-known potent inducers of OS), taxanes, ifosfamide, epirubicin, topotecan, 5-Fluorouracil, and vinca alkaloids; these drugs, to different extents, are able to induce or increase fatigue.

All 12 patients received the planned LC treatment without dose reduction and each patient completed the planned questionnaires and tests.

Assessment of fatigue

Mean MFSI-SF scores at t0, t1, and t2 were 25.40 ± 13.91, 16.93 ± 11.92, and 12.05 ± 12.56, respectively. The difference was statistically significant for t1 and t2 ($P < 0.05$ and $P < 0.001$, respectively; Fig. 1). Evaluation of the item subscales (General, Physical, Emotional, Mental, and Vigor) showed a statistically significant difference at t0 versus t2 only for the General scale ($P < 0.05$) and the Physical scale ($P < 0.05$; Fig. 2).

QoL assessment

QoL-OS evaluation

Mean part A QoL-OS scores at t0, t1, and t2 were 54.30 ± 20.3, 44.54 ± 12.7, and 36.80 ± 15.7, respectively. The difference was statistically significant at t0 versus t1 and t2 ($P < 0.05$ for both; Fig. 3). Evaluation of item subscales (Functional, Physical, Emotional, Social and Family, and Fatigue) showed a statistically significant difference ($P < 0.05$) between t0 and t2 in each subscale (Fig. 4).

The mean part B QoL-OS score was 32.55 ± 8.5 at t0, which corresponds to a slightly unbalanced diet. Obviously it did not make sense to make a comparison of this score at t1 and t2 because it is unlikely that patients will modify their food habits in such a short period.

EQ-5D$_{VAS}$ evaluation

Mean EQ-5D$_{VAS}$ scores at t0, t1, and t2 were 50.58 ± 6.6, 60.83 ± 12.5, and 73.33 ± 12.4, respectively. The difference was statistically significant at t0 versus t1 and t2 ($P < 0.05$ and $P < 0.001$, respectively; Fig. 5).

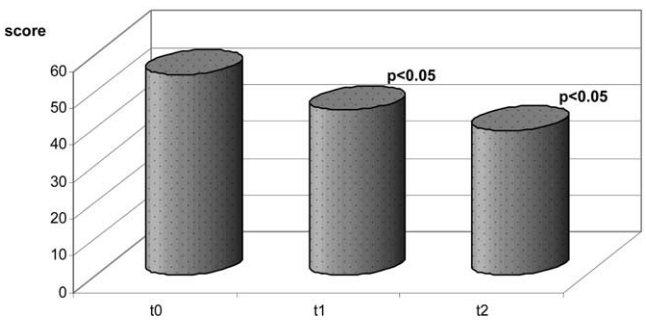

Fig. 3. Histograms represent mean scores of part A of the questionnaire on quality of life with a focus on oxidative stress. The difference between mean score at baseline (t0) and those at 2 wk (t1) and 4 wk (t2) of treatment with L-carnitine supplementation was statistically significant ($P < 0.05$ for both).

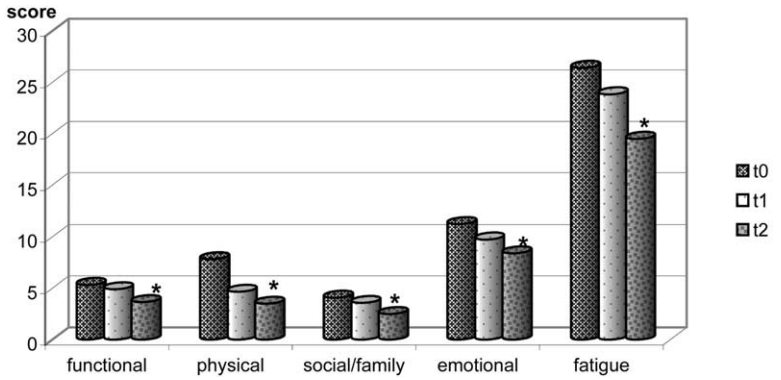

Fig. 4. Histograms represent mean scores of part A subscales of the questionnaire on quality of life with a focus on oxidative stress (Functional, Physical, Emotional, Social and Family, and Fatigue). Evaluation of the subscale scores showed a statistically significant difference between mean values at baseline (t0) versus 4 wk (t2) of treatment ($P < 0.05$) in each subscale. *$P < 0.05$

Nutritional/functional assessment

Body weights at t0, t1, and t2 were 61.01 ± 6.79, 61.23 ± 6.76, and 61.20 ± 6.93 kg, respectively. The difference was not statistically significant.

Lean body mass values at t0, t1, and t2 were 38.0 ± 7.36, 39.74 ± 7.62, and 40.39 ± 8.55 kg, respectively. LBM increased significantly at t1 and t2 versus t0 ($P = 0.001$ and $P < 0.05$, respectively; Fig. 6). Impedances at t0, t1, and t2 were 595.25 ± 90.40, 532.73 ± 56.95, and 518.00 ± 57.36 Ω, respectively. The difference was statistically significant at t0 versus t1 and t2 ($P < 0.05$, for both).

Appetite at t0 was 4.75 ± 2.59 and increased significantly at t1 (6.16 ± 2.4, $P < 0.05$) and t2 (6.83 ± 1.9, $P = 0.001$) versus t0 (Fig. 7).

Mean grip strength at t0 was 24.38 ± 7.5 kg. Subsequent evaluations showed a non-significant worsening at t1 and t2.

Laboratory variables

The level of ROS at t0 was 475.8 ± 109.12 FORT units and was significantly higher than in controls. Values at t1 and t2 were 456.7 ± 147.5 and 415.2 ± 125.96 FORT units, respectively; these decreases versus t0 were not significant (Fig. 8).

Glutathione peroxidase activity at t0 was 9208 ± 3048.8 U/L and was not significantly different from that in controls. Values at t1 and t2 were 8724 ± 1438.7 and 9890 ± 3004.1 U/L, respectively. The difference was not significant for t1 and t2 versus t0.

Levels of proinflammatory cytokines interleukin-1β, interleukin-6, and tumor necrosis factor-α at t0 were not significantly different from those in controls and showed no significant changes at t1 and t2 versus t0.

Levels of C-reactive protein at t0, t1, and t2 were 0.97 ± 0.68, 0.73 ± 0.50, and 0.59 ± 0.51 ng/mL, respectively. The decrease was statistically significant for t1 and t2 ($P = 0.05$ for both) versus t0.

Mean hemoglobin levels at t0, t1, and t2 were 10.88 ± 1.01, 10, 69 ± 0.97, and 10. 98 ± 1.17 g/dL, and the difference was not statistically significant.

Safety

According to the NCI-CTC, no toxicity of any grade was observed that could not attributable to concomitant chemotherapy. No adverse events possibly related to LC were reported for any patient. Treatment was well tolerated by all patients and no patient had to discontinue treatment.

Discussion

Patients who have cancer are especially at risk for carnitine deficiency and its prevalence self-reported symptoms of fatigue by these patients is extremely high (>80%) [37]. They frequently present with decreased caloric intake and increased metabolic requirements. In addition, numerous drugs can interfere with the absorption, synthesis, and excretion of carnitine. In particular, chemotherapy with ifosfamide and cisplatin-based agents may result in increased urinary excretion and serum carnitine deficiency because

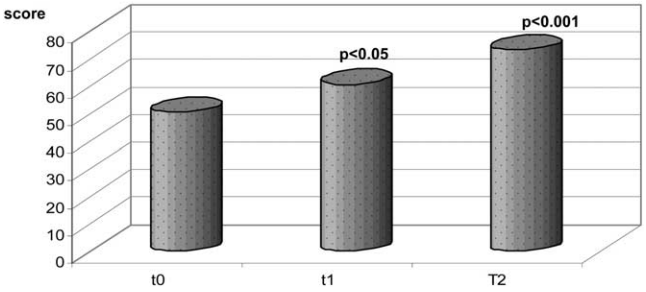

Fig. 5. Histograms represent mean scores of the EQ-5D visual analog scale. The difference between the mean score at baseline (t0) and after 2 wk (t1) and 4 wk (t2) of treatment with L-carnitine supplementation was statistically significant for t1 and t2 versus t0 ($P < 0.05$ and $P < 0.001$, respectively).

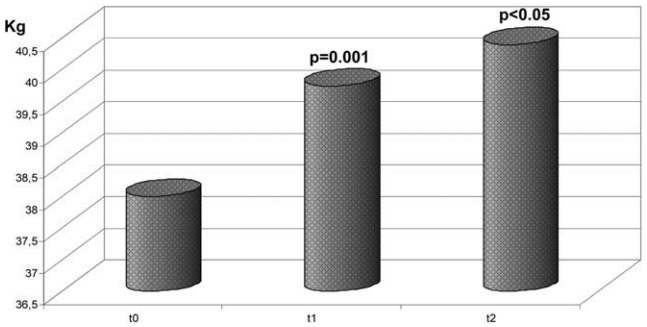

Fig. 6. Histograms represent mean lean body masses (kilograms). The difference between baseline (t0) and after 2 wk (t1) and 4 wk (t2) of treatment was statistically significant for t1 and t2 versus t0 ($P = 0.001$ and $P < 0.05$, respectively).

they compete with carnitine reabsorption at the proximal convoluted tubule [37].

Dodson et al. [44] observed a significant decrease in LC level in 23 patients with cancer compared with 13 healthy aged-matched controls. Cruciani et al. [37] observed that 67% of adult patients who had cancer and fatigue and resided in a hospice had carnitine deficiency.

Graziano et al. [38] treated 50 patients who had cancer and underwent cisplatin- or ifosfamide-based chemotherapy with 4 mg/d of LC for 7 d; after 1 wk, fatigue (as assessed by the Functional Assessment of Cancer Therapy—Fatigue questionnaire) was significantly ameliorated in 45 patients. In a subsequent study, Cruciani et al. [37] found an increase in total carnitine, decreased fatigue symptom (as measured by the Brief Fatigue Inventory), and improved mood and quality of sleep after 1 wk of LC supplementation (from 250 to 1750 mg/d) in 13 untreated patients who had cancer and self-reported moderate to severe fatigue for at least 1 wk before accrual.

Among patients who did not have cancer, Pistone et al. [45] treated 84 elderly subjects who developed fatigue after light physical activity with 2 g of LC twice daily (4 g/d) and found significant decreases in physical and mental fatigue (as measured with Wessely and Powell scores) and an increase in total muscle mass. Among patients who had end-stage renal disease, Brass et al. [46] treated 122 patients with 10 to 40 mg/kg of intravenous LC and found decreased fatigue and preserved exercise capacity.

The primary aim of the present study was to test the efficacy and safety of LC supplementation in patients who had advanced cancer and experienced fatigue, had high levels of ROS, or both. The results demonstrated that fatigue decreased significantly (specifically, the General and Physical scales), QoL-OS decreased (all subscales of the QoL-OS questionnaire), and EQ-$5D_{VAS}$ increased (which expresses a global subjectively perceived health status). Moreover, we observed a significant increase in patient LBM (and appetite), which may be considered the most important nutritional/functional parameter in assessing the cachectic state of patients; the decrease in LBM is the most important nutritional symptom present in CACS. The loss of LBM is due to several factors such as derangements in energy and specifically protein muscle metabolism, proteolysis-inducing factor, and other factors that induce muscle proteolysis also through the ubiquitin-proteasome pathway, thus leading to muscle atrophy.

It is worth noting that in one of our recently published studies, we demonstrated that an innovative treatment approach, including a pharmaconutritional support containing Eicosapentaenoic acid (EPA), Medroxyprogesterone Acetate (MPA), and antioxidants such as polyphenols plus cyclooxygenase-2 inhibitor celecoxib, is effective in inducing a significant increase in LBM, an improvement in QoL, and a decrease in proinflammatory cytokines and ROS levels [29].

Therefore, fatigue, which is the most commonly reported symptom in patients with cancer, has a profound effect on a patient's QoL [47] and previously referred primarily to psychological disturbances, depression, sleep or mood disturbances currently should be considered, to a large extent, a direct consequence of loss of muscle mass (i.e., LBM) and thus of all underlying metabolic and functional disturbances. In this view, fatigue with related symptoms can well be considered an important, or considerable, constituent of CACS.

Proof that fatigue is not primarily a psychological symptom that is isolated from CACS is that pharmacologic measures, such as corticosteroids [48], psychostimulants such as methylphenidate [49] and modafinil [50], aimed at modifying the psychological status of patients have proved to be poorly effective, with significant side effects [51]. Moreover, symptomatic measures such as education and counseling have not been demonstrated to be effective, whereas exercise is the non-pharmacologic intervention for fatigue that has the strongest evidence of therapeutic benefit [52].

However, anemia, commonly considered the main cause of fatigue in patients with cancer, has been demonstrated to be not always involved; The patients included in the study by Graziano et al. [38] were not at all

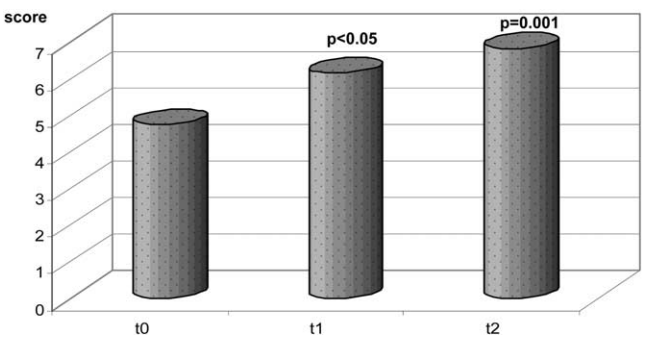

Fig. 7. Histograms represent mean appetite scores on a visual analog scale. Appetite increased significantly after 2 wk (t1; 6.16 ± 2.4, $P < 0.05$) and 4 wk (t2; 6.83 ± 1.9, $P = 0.001$) of treatment with L-carnitine supplementation versus baseline (t0).

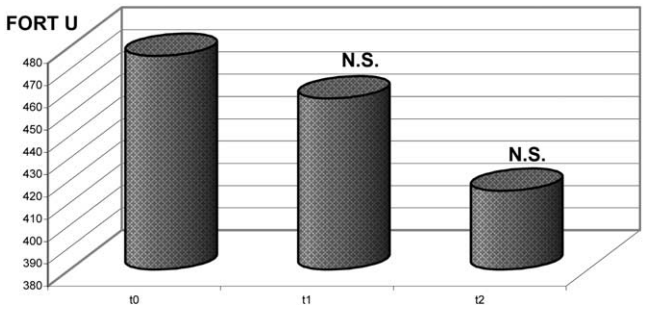

Fig. 8. Histograms represent mean levels of reactive oxygen species (FORT units). The difference between levels at baseline (t0) and at 2 wk (t1) and 4 wk (t2) of treatment was not statistically significant (N.S.).

anemic (hemoglobin ≥13 g/dL) and those included in our study were only slightly anemic. Hemoglobin levels at baseline were 10.9 g/dL and these values remained unchanged during treatment.

Several fatigue assessment tools exist [51]; they include functional capacity tests, subjective assessment during function, and objective and subjective assessments of function. Subjective fatigue rating is the most clinically relevant assessment tool. Multidimensional fatigue assessment, which incorporates multiple characteristics and manifestations of fatigue and its effect on function, is more informative than the measurement of fatigue severity alone but is more time consuming to administer [6]. Examples are the Functional Assessment of Cancer Therapy—Fatigue Scale [53], the Piper Fatigue Self Report Scale [54], the Brief Fatigue Inventory [55], and the MFSI [39–40]. Among these, the MFSI appears to be sensitive to fatigue because it accurately discriminates patients with cancer from control subjects and between patients with different levels of performance status. The MFSI may be useful in identifying patterns of fatigue within individual patients and across treatment modalities. Such specificity may allow the clinician to develop, implement, and evaluate interventions that are targeted at different patterns of fatigue. Because the measure is keyed to a 1-wk time frame, it may be useful during the course of cancer treatment [56]. On the basis of these specific characteristics, we have selected the MSFI-SF as the most adequate instrument for fatigue assessment.

The results observed on the QoL-OS questionnaire and its subscales (fatigue symptoms) were in accordance with those found on MSFI-SF.

Concerning the results of the QoL-OS questionnaire part B, the mean score at baseline corresponds to a slightly imbalanced diet with respect to antioxidant versus prooxidant content in favor of a prooxidant. The aim of this study, which was only 1 mo, was not to change food habits. Such an aim could only make sense within a preventive intervention trial over a much longer period.

Reactive oxygen species levels decreased, although not significantly, during the study. By increasing the amount of acetyl-CoA and enhancing the citric acid cycle, LC may induce increased NADH/$FADH_2$ production and thus positively influence cell redox status by decreasing ROS production and enhancing their scavenging. An explanation for the lack of a significant decrease in ROS in the present study may be the concomitant chemotherapy administered to patients, which may have contributed to maintenance of a high rate of ROS production or the too short duration of LC treatment.

Serum levels of proinflammatory cytokines did not change significantly during the study, although baseline levels were not significantly different from those in controls. We deliberately enrolled patients without overt cachexia, so high levels of proinflammatory cytokines, in keeping with the findings of many of our previous studies [42,43,57], should have not been expected.

Concerning the possibility that LC supplementation accelerates cancer progression or interferes with the chemotherapeutic effect of certain agents, the current evidence suggests that LC does not have either effect [38,58].

Further studies should investigate in more depth the effect of LC supplementation on more detailed metabolic indexes, laboratory parameters, and significant clinical outcomes.

Although the reported results are interesting, the present study should be regarded with some caution due to the limited number of patients and that it is an open-label, non-randomized study. We are currently carrying out a randomized phase III study with an innovative treatment to assess the role of LC for the treatment of CACS and fatigue in patients with cancer.

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