Carnitine Plasma Levels and Fatigue in Children/Adolescents Receiving Cisplatin, Ifosfamide, or Doxorubicin

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Summary: Fatigue is the most frequent symptom experienced by children/adolescents with cancer. One mechanism contributing to cancer-related fatigue involves abnormalities in adenosine triphosphate synthesis caused by carnitine deficiency. The purpose of this study was to examine fatigue and carnitine in children/adolescents before and after ifosfamide, cisplatin, or doxorubicin chemotherapy. Sixty-seven patients from 2 children's cancer centers participated. Fatigue and carnitine measures were obtained before chemotherapy and a week later. Newly diagnosed children/adolescents had significantly higher free ($P = 0.018$) and total carnitine levels ($P = 0.017$) compared with those who received prior chemotherapy. There was a significant increase in free and total carnitine levels after treatment for patients receiving doxorubicin than patients receiving cisplatin or ifosfamide. Increased fatigue and decreased carnitine were significantly correlated a week after chemotherapy in children/adolescents who had received prior chemotherapy. Increased carnitine in newly diagnosed patients is likely associated with rapid tissue release into the bloodstream, replacing carnitine lost by chemotherapy metabolism. Decreased carnitine and increased fatigue occurred after 1 to 2 courses of chemotherapy. This study provides support for a relationship between carnitine and fatigue in children/adolescents with cancer.

Key Words: fatigue, carnitine, childhood cancer, chemotherapy

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Fatigue is now recognized as the most frequent symptom experienced by children and adolescents with cancer.[1–5] Children and adolescents describe fatigue as a distressing, pervasive symptom with physical, mental, and emotional components characterized by a lack of energy. The experience of fatigue differs by developmental level with the school age child emphasizing the physical sensation of fatigue whereas adolescents experience mental tiredness that alternates and at times merges with the physical sensation of fatigue.[6–9] Researchers have identified that biologic perspectives need to be incorporated into pediatric cancer symptom research.[10] A biologic mechanism thought to contribute to cancer-related fatigue involves abnormalities in adenosine triphosphate synthesis.[11–13] A deficiency of carnitine, a key micro-nutrient in adenosine triphosphate synthesis, is depleted by some chemotherapy agents. The specific aim of this study was to examine the influence of carnitine plasma levels on fatigue in children and adolescents before and after receiving ifosfamide, doxorubicin, or cisplatin chemotherapy.

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CARNITINE AND CANCER TREATMENT

Carnitine is a micronutrient used by the body to transport long chain fatty acids to the mitochondria in cells where fatty acids are converted to adenosine triphosphate.[14] Fatty acid metabolism is a major source of muscular energy and deficiencies in carnitine are manifested as low energy levels and muscular weakness.[15] If the blood glucose is low, glucagon and epinephrine mobilize the signal that energy is needed from fat storage. Fatty acids are released from the adipocytes and then flow into muscle cells to be oxidized for energy. Once in the muscle cell, fatty acids are combined with coenzyme-A to form fatty acyl-CoA. The fatty acid is carried to the mitochondria where β-oxidation takes place. Carnitine is required to carry the fatty acid across the inner mitochondrial membrane. Fatty acid first detaches from coenzyme-A and attaches to carnitine. The fatty acyl-carnitine (AC) complex then crosses the mitochondrial membrane. Inside the mitochondria, the reverse reaction takes place. The fatty acyl-CoA is reformed and free carnitine (FC) is released. FC can pass back across the membrane to be reused.[14] Carnitine also transports fatty acids back out of the mitochondria that accumulate as a result of normal and abnormal metabolism.[14] Carnitine homeostasis is maintained by absorption, synthesis, and renal reabsorption.[16]

Recent research suggests that some anticancer drugs (doxorubicin, ifosfamide, and cisplatin) interfere with the carnitine network.[17–19] Cisplatin can cause reduction in glomerular filtration and tubular damage. Carnitine is absorbed in the body proximal to the tubular level and patients receiving cisplatin may have an increased loss of carnitine through the kidney.[14] The metabolic pathways of ifosfamide, leads to formation of chloroacetyl-CoA with a decrease in CoASH levels, an activator of energy-providing systems.[14] Carnitine binds to the chloracetyl-CoA and detoxifies it, resulting in chloro-acteyl-carnitine being excreted in the urine. This detoxification results in a secondary deficiency of carnitine in patients receiving ifosfamide.[14] Doxorubicin influences the carnitine system by decreasing heart concentration of FC, free fatty acid oxidation, creatine phosphate, and protein synthesis and oxygen uptake.[20–22]

In a phase I/II, open label clinical trial of adults with advance cancer and carnitine deficiency, the maximally

tolerated dose of L-carnitine supplementation was 3000 mg/d. Fatigue improved and no patient experienced significant side effects or toxicities.[23] In an Italian study, 50 patients, who experienced fatigue and had low plasma carnitine levels while receiving cisplatin or ifosfamide, were treated with a daily dose of 4 g of L-carnitine and reported improved fatigue.[17] Recently, Cruciani and others found decreased fatigue and improved functional well-being in 29 adults with advanced cancer after carnitine supplementation.[23] A phase III randomized clinical trial has recently completed enrollment of adults with invasive cancer who have moderate to severe fatigue to determine if L-carnitine replacement improves fatigue.[24]

Only 1 study evaluated serum carnitine levels in children. A group of 51 children with cancer, aged 3 to 16 years had similar carnitine levels at diagnosis compared with healthy controls. However, at month 3 of treatment, children with cancer had a significant decrease in levels ($P = 0.004$) and levels were significantly lower than the healthy controls ($P = 0.02$).[25] To our knowledge, no studies exist that evaluate fatigue and carnitine deficiencies in children and adolescents with cancer.

METHODS

Study Population

This study was part of a larger funded project evaluating the influence of the symptom cluster of fatigue, nausea/vomiting, and sleep disturbances on performance status, mood, and behavior in children and adolescents receiving chemotherapy. The sample included 67 children and adolescents between 7 and 18 years of age (mean age of 12.3 y), from 2 children's cancer centers who were receiving their first or second course of cisplatin, doxorubicin or ifosfamide chemotherapy.

Study Procedures

Children and adolescents completed fatigue instruments on the first day of ifosfamide, doxorubicin or cisplatin therapy and approximately 1 week later. Separate fatigue instruments were used for children and adolescents that are specifically designed to reflect the nature of cancer-related fatigue and to assess the multidimensional aspects of fatigue in the 2 developmentally specific age groups. A plasma carnitine level was drawn at the same time the fatigue score was obtained.

Fatigue Measurements

The Childhood Fatigue Scale (CFS) was used in children 7 to 12 years of age. The CFS is a 14-item questionnaire and asks the child about their experience of any fatigue-related symptoms during the past week. The child is asked to rate how much fatigue bothers him or her on a 4-point Likert scale ranging from "Not at all" to "A lot." Higher scores correspond to greater amounts of experienced fatigue. Reliability and construct validity was previously established in a population of 149 children receiving chemotherapy.[9]

The Adolescent Fatigue Scale was used in adolescents 13 to 18 years of age and is a 14-item self-report scale developed to measure fatigue experienced in the past week. Items describe the intensity of fatigue on a 4-point Likert-type scale. Intensity ratings range from 0 (no fatigue symptoms) to 56 (high fatigue). Instrument reliability and construct validity as well as the ability to measure change over time was tested in 64 adolescents who completed the scale at 2 to 4 data points as a subject in 1 of the 4 studies.[26]

Carnitine Plasma Levels

Carnitine plasma levels were obtained on the day chemotherapy was to be given before the infusion started and repeated after chemotherapy with an average of 9.5 days (range, 7-25 d) between carnitine plasma samples. FC and total carnitine (TC) was measured by tandem mass spectrometry and AC was calculated as the difference between TC and FC. All specimens were evaluated at the Mayo Medical Laboratories of Minnesota. Carnitine was measured in blood plasma using tandem mass spectrometry (MS/MS) stable isotope dilution analysis. FC is a measure of L-carnitine available for transporting fatty acids into the mitochondria. TC is L-carnitine plus AC; the waste product after the body has used L-carnitine. Carnitine deficiency is defined biochemically as abnormally low plasma levels of FC. Carnitine levels are usually quoted as the ratio of AC (TC minus FC) to the FC (ie, the L-carnitine); it is reported as the AC/FC ratio.[27]

Statistical Considerations

Paired t test analyses were performed to evaluate whether a change occurred in carnitine levels before and after chemotherapy treatment. Analysis of variance was used to determine if there was a difference among the 3 chemotherapy drugs (ifosfamide, cisplatin, and doxorubicin) in carnitine levels before and after chemotherapy. To evaluate the influence of carnitine levels on fatigue during childhood cancer treatment, correlation analysis was performed. Fatigue scores were analyzed separately for children and adolescents. Data were analyzed using SPSS 16.0.1, Windows Release.

Study Characteristics

A total of 67 patients were enrolled in this study. There were 38 (56.7%) males and 29 (43.3%) females with a mean age of 12.3 years (range, 7-18 y). Thirty-two (47.8%) children/adolescents were white, 24 (35.8%) Hispanic, 8 (11.9%) African American, and 3 (4.5%) were Asian/Pacific Islander. Twenty-seven (40.3%) patients received doxorubicin, 21 (31.3%) ifosfamide, and 19 (28.4%) cisplatin. The study drugs were standardized mg/m^2 pediatric doses. Total doses received were ifosfamide (4000-17,500 mg/m^2, M = 9000 mg/m^2), cisplatin (75-200 mg/m^2, M = 100 mg/m^2), and doxorubicin (25-120 mg/m^2, M = 60 mg/m^2). Thirty-three (49.3%) patients had received 1 to 2 courses of cisplatin, ifosfamide, or doxorubicin before the study. For 20 patients (29.9%), this was their first course of chemotherapy. Fourteen patients (20.8%) had chemotherapy previously but had not received cisplatin, ifosfamide, or doxorubicin as part of their treatment. Twenty-nine (43.3%) patients were diagnosed with leukemia/lymphoma and 38 (56.7%) of the patients had solid tumors. Patient demographics are summarized in Table 1.

Carnitine Changes Before and a Week After Chemotherapy

To examine whether a change in carnitine levels occurred 1 week after ifosfamide, cisplatin, and doxorubicin chemotherapy, paired t test analyses were performed. For the entire cohort, there was a significant increase in the mean FC level from the measure before chemotherapy

TABLE 1. Patient Demographics by Prior Chemotherapy

	Prior Chemotherapy	No Prior Chemotherapy	Total
Sex			
Male	27 (57.4)	11 (55.0)	38 (56.7)
Female	20 (42.6)	9 (45.0)	29 (43.3)
Age			
7-12 y (Children)	25 (53.2)	10 (50.0)	35 (52.2)
13-18 y (Adolescents)	22 (46.8)	10 (50.0)	32 (47.8)
Race			
White	22 (46.8)	10 (50.0)	32 (47.8)
Hispanic	18 (38.3)	6 (30.0)	24 (35.8)
African American	5 (10.6)	3 (15.0)	8 (11.9)
Asian/Pacific Islander	2 (4.3)	1 (5.0)	3 (4.5)
Drug treatment			
Cisplatin	9 (19.1)	10 (50.0)	19 (28.4)
Doxorubicin	17 (36.2)	10 (50.0)	27 (40.3)
Ifosfamide	21 (44.7)	0 (0.0)	21 (31.3)
Prior study drug	33 (70.2)	0 (0.0)	33 (49.3)
No prior chemotherapy	0 (0.0)	20 (100.0)	20 (29.9)
Diagnosis			
Solid tumor	27 (57.4)	11 (55.0)	38 (56.7)
Leukemia/ Lymphoma	20 (42.6)	9 (45.0)	29 (43.3)

(M = 41.27, SD = 13.4), to the measure a week after chemotherapy (M = 45.33, SD = 15.3), $t(65) = -2.697$, $P = 0.009$. The mean TC level also increased significantly from the prechemotherapy measure (M = 47.61, SD = 14.4) to a week after chemotherapy (M = 51.58, SD = 16.3), $t(65) = -2.562$, $P = 0.013$ (Table 2).

Carnitine in Newly Diagnosed and Prior Treated Children/Adolescents

FC and TC levels of newly diagnosed children and adolescents receiving their first course of chemotherapy were compared with those who had received prior chemotherapy. This comparison revealed that newly diagnosed patients had a more significant increase in FC [$t(64) = 2.425$, $P = 0.018$] and TC levels [$t(64) = 2.442$, $P = 0.017$] a week after chemotherapy compared with those who had prior therapy.

Within the newly diagnosed children/adolescents cohort, there were significantly higher FC [$t(19) = -3.608$, $P = 0.002$] and TC levels [$t(19) = -3.451$, $P = 0.003$] a week after chemotherapy. Within the cohort who had received prior treatment, there was no significant difference in TC or FC levels before and after chemotherapy.

Carnitine Change in Children/Adolescents With Study Drug Exposure

Before enrollment in this study, over half the patients (50.7%) had never received the study drugs: cisplatin, doxorubicin, or ifosfamide (Table 3). Two-way analysis of variance (ANOVA) tests were conducted to evaluate the change in FC and TC levels before chemotherapy and a week later by the 3 study drugs (cisplatin, ifosfamide, and doxorubicin) and by 2 patient groups (those who had no study drug exposure compared with those who had received 1 of the 3 drugs). There was a significant increase in carnitine levels (both FC and TC) for patients who had no prior study drug exposure compared with patients who had previously received the study drug. The ANOVA revealed a significant main effect for FC [$F(1,60) = 6.71$, $P = 0.012$] and TC [$F(1,60) = 6.09$, $P = 0.016$] in patients who had previously received a study drug compared with those who had no exposure. There was a significant main effect among the study drugs for both FC [$F(2,60) = 4.27$, $P = 0.018$] and TC [$F(2,60) = 4.31$, $P = 0.018$].

Follow-up tests were conducted to evaluate pairwise differences among the means for the study drugs. The Bonferroni procedure was used to control for the Type I error across the pairwise comparisons. There was a change in FC levels before chemotherapy and a week later for patients who received doxorubicin. Patients who received doxorubicin experienced a significant increase in FC levels compared with patients treated with cisplatin ($P = 0.035$) or ifosfamide ($P = 0.003$). Similar results were shown for TC levels with a significant increase for patients receiving doxorubicin compared with cisplatin ($P = 0.039$) and ifosfamide ($P = 0.002$). There was no significant difference in FC or TC levels between patients treated with cisplatin versus ifosfamide. There was no significant interaction between the study drugs and prior drug exposure versus no study drug exposure for either the FC or TC levels.

Mean values of FC and TC levels by drug and by prior drug exposure are presented in Table 3. All patients who had received the study drug before enrollment experienced decreased FC and TC levels a week after chemotherapy. Patients who received cisplatin, doxorubicin, or ifosfamide for the first time demonstrated increased FC and TC levels a week after chemotherapy (Figs. 1, 2).

Carnitine and Fatigue

Pearson correlation coefficients were used to assess the relationship between fatigue and carnitine levels a week after chemotherapy. In the cohort of adolescents who have received prior chemotherapy, there was a significant negative correlation between fatigue and FC levels ($r = -0.530$; $P = 0.016$) and fatigue and TC levels ($r = -0.457$; $P = 0.043$) a week after chemotherapy. At this measurement

TABLE 2. Carnitine Results Before Chemotherapy and 1 Week Later

	Before Chemotherapy Mean (SD)	One Week Later Mean (SD)	*t*	*P*
Free Carnitine (FC)	41.27 (13.4)	45.33 (15.3)	−2.697	0.009*
Acyl-carnitine (AC)	6.33 (3.0)	6.24 (3.2)	0.201	0.842
AC/FC Ratio	0.16 (0.09)	0.15 (0.10)	1.143	0.257
Total Carnitine	47.61 (14.4)	51.58 (16.3)	−2.562	0.013*

*Significant at $P < 0.05$ level for paired *t* test analysis.

TABLE 3. Mean Free and Total Carnitine Levels by Prior Study Drug Exposure

	Prior Study Drug		No Prior Study Drug		All Patients	
	Free	Total	Free	Total	Free	Total
Cisplatin						
Before chemotherapy	58.00	64.71	48.17	55.25	51.79	58.74
One week after chemotherapy	49.57	56.57	55.58	62.50	53.37	60.32
Ifosfamide						
Before chemotherapy	37.61	43.28	46.00	52.33	38.81	44.57
One week after Chemotherapy	37.17	42.00	43.33	50.67	38.05	43.24
Doxorubicin						
Before chemotherapy	36.00	42.00	35.39	41.89	35.58	41.92
One week after chemotherapy	38.50	45.75	48.58	54.74	45.49	52.07
Total						
Before chemotherapy	41.55	47.52	41.00	47.70	41.27	47.61
One week after chemotherapy	40.12	46.00	50.59	57.12	45.33	51.58

point, adolescents who experienced higher fatigue levels also had lower TC and FC levels. All adolescents who had received doxorubicin had increased fatigue and decreased FC levels ($r = -0.652$, $P = 0.041$) a week later, regardless of whether they had prior exposure to the agent.

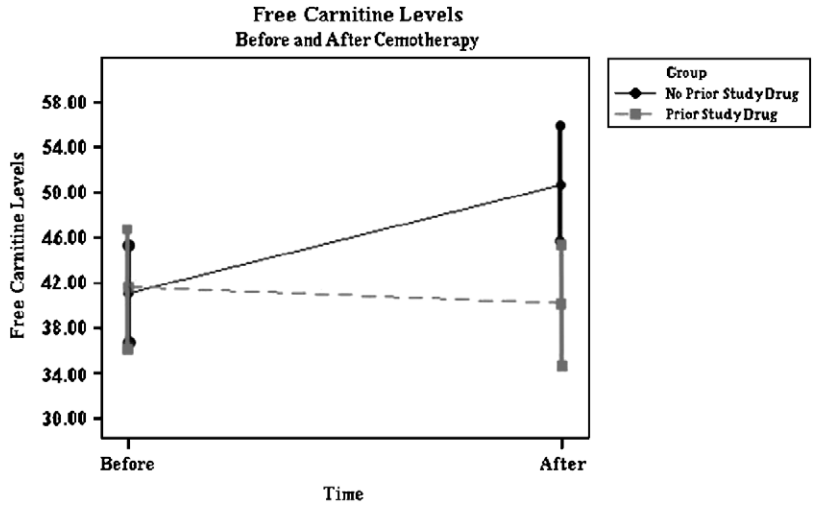
For children 12 years of age and under who had no exposure to any of the study drugs but had received prior chemotherapy (n = 6), there was a significant correlation between fatigue and FC ($r = 0.841$, $P = 0.036$) and TC ($r = 0.812$, $P = 0.049$) levels a week after chemotherapy. For this group of children when fatigue was higher, total and free carnitine levels were higher.

LIMITATIONS

Although the literature suggests doxorubicin, ifosfamide, and cisplatin interfere with carnitine excretion and production, it is possible that nausea, vomiting, and anorexia associated with these chemotherapy agents may decrease oral intake of foods high in carnitine that could influence carnitine levels. Only 1 published study evaluated carnitine in children with cancer and found no significant relationship between carnitine levels and nutritional status either at diagnosis or 3 months later.[25] Researchers concluded that inadequate intake of carnitine was not responsible for the decreased levels and suggested that findings were due to metabolic changes during chemotherapy treatment and/or from the neoplastic process itself. Another limitation is that fatigue and carnitine measures were only collected a week apart. It is not known how carnitine levels and fatigue changed over time.

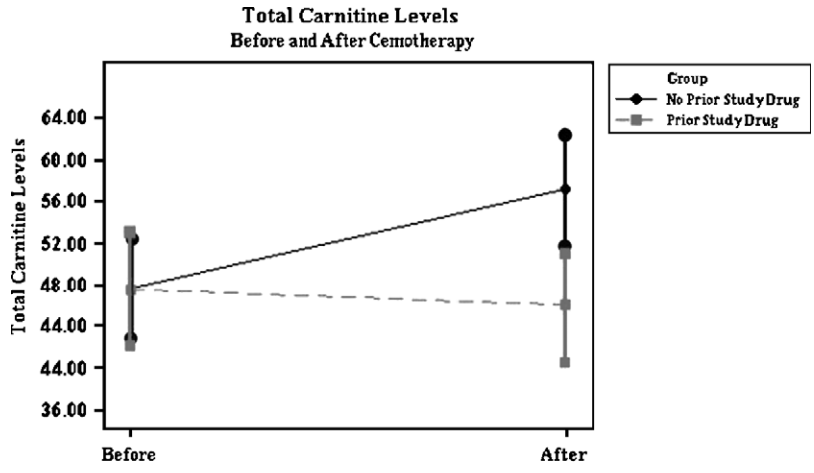
DISCUSSION

Fatigue is a distressing and pervasive symptom experienced by children and adolescents with cancer that has a physical component described as a "lack of energy during treatment."[2,3,6,7,28] Carnitine, a key essential nutrient, has an important role in how muscles metabolize energy.[14] Studies indicate that several anticancer drugs interfere with the carnitine network,[14] resulting in a less efficient aerobic muscle metabolism. Other researchers found that carnitine



	No Prior Study Drug Mean (95% CI)	Prior Study Drug Mean (95% CI)
Before Chemotherapy	41.00 (36.67 - 45.33)	41.55 (36.36 - 46.73)
One Week after Chemotherapy	50.59 (45.49 - 55.60)	40.12 (34.89 - 45.35)

FIGURE 1. Free carnitine levels (mean and 95% CI) for patients before and one week after receiving chemotherapy.



	No Prior Study Drug Mean (95% CI)	Prior Study Drug Mean (95% CI)
Before Chemotherapy	47.70 (42.88 - 52.51)	47.52 (42.05 - 52.98)
One Week after Chemotherapy	57.12 (51.71 - 62.59)	46.00 (40.53 - 51.47)

FIGURE 2. Total carnitine levels (mean and 95% CI) for patients before and one week after receiving chemotherapy.

plasma levels decrease in children over the course of cancer treatment but its relationship to fatigue remained unknown.[25] To our knowledge this is the first pediatric study to evaluate the effect cancer chemotherapy has on carnitine and this nutrient's relationship to fatigue in children and adolescents being treated for cancer. A major strength of this study is the inclusion of newly diagnosed patients compared with patients on treatment. Also patients who had no prior exposure to 1 of the 3 study agents were compared with those who had previously received 1 to 2 course of one of the agents.

In this study, carnitine increased in newly diagnosed cancer patients a week after their first course of chemotherapy. FC and TC levels also increased a week after ifosfamide, cisplatin, or doxorubicin chemotherapy in patients who had no previous exposure to one of these agents. Patients who had been receiving chemotherapy and have previously had 1 to 2 courses with one of the study agents had decreased carnitine levels a week after receiving one of the study drugs. This study supports an initial increase in carnitine in new patients associated with rapid tissue release into the bloodstream to replace carnitine lost by chemotherapy metabolism. This finding is supported by observations of others[29] that carnitine may be released from tissues into the bloodstream to replace carnitine loss through renal excretion. This results in an initial increase in plasma carnitine levels after initial chemotherapy. Carnitine may increase due to the rapid release into the bloodstream and then decrease over time with repeated exposure to chemotherapy. Our study supports this rationale with increased carnitine levels in patients receiving one of the study agents for the first time compared with decreased carnitine levels in patients who had previous exposure to chemotherapy and to one of the study agents. Findings from our study provide support that carnitine deficiency develops during treatment with cisplatin, ifosfamide, or doxorubicin. This deficiency can occur within 3 cycles of these agents.

Patients who received doxorubicin experienced significantly higher carnitine levels compared with patients treated with one of the other agents. Researchers have found acute and chronic effects of anthracyclines on fatty acid oxidation, in part due to depletion of L-carnitine.[20–22] Doxorubicin's influence on FC and TC after chemotherapy was much more pronounced compared with ifosfamide or cisplatin and warrants further investigation.

Children and adolescents who had received prior chemotherapy experienced increased fatigue in the presence of decreased carnitine levels. In this study, doxorubicin impacted fatigue more than the other 2 study drugs; all adolescents who received doxorubicin experienced increased fatigue and lower carnitine levels. This finding raises concern that doxorubicin increases the risk for carnitine deficiency as well as increased symptom distress and should be the focus of future research.

In adults with cancer, clinical trials have been completed to identify the maximally tolerated dose of L-carnitine and to evaluate its efficacy.[23,24,30] The pediatric oral dosage for a primary carnitine deficiency is 50 to 100 mg/kg/d divided 2 to 3 times per day with a maximum dose of 3 g/d.[31] In animal models, however, carnitine has been shown to be a modulator of the glucocorticoid[32] receptor; glucocorticoids are used in the treatment of leukemia and lymphoma. Before carnitine supplementation can be considered, interactions with corticosteroids used in cancer treatment must be explored. Longitudinal measurement of carnitine levels is also needed to provide further insight into the trajectory of carnitine plasma levels. Further research is needed to understand the relationship between carnitine and fatigue in children and adolescents with cancer.

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