Original Article

Comparative study among glutamine, acetyl-L-carnitine, vitamin-E and methylcobalamine for treatment of paclitaxel-induced peripheral neuropathy

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ABSTRACT

Context: One of the major toxicity of paclitaxel is peripheral neuropathy. Sensory components are affected more than motor and autonomic dysfunction. **Aims:** Acetyl-L-carnitine (ALC), methylcobalamine, vitamin E and glutamine have been used in various trials against placebos. With head on trials among these four drugs missing, this randomized study was conducted to compare the efficacy in relieving symptoms of paclitaxel induced peripheral neuropathy. **Settings and Design:** This single institutional, prospective, multi-arm, randomized study was conducted as per Helsinki protocol and with local ethical committee clearances. **Materials and Methods:** Patients of carcinomas of lung, breast and ovary recruited, would receive paclitaxel 175 mg/m^2 intravenous as 1st or 2nd line drug. They underwent randomization to any of four treatment arms: Arm A (vitamin E 400 mg OD day 1 of the cycle to 1 month after completion of clinical trial [CT]); Arm B (ALC 250 mg OD from day 1 to day 7 in each cycle of CT); Arm C (glutamine 10 mg TDS from day 2 to day 5 in each cycle) and Arm D (methylcobalamine 500 µg TDS from day 1 of the first cycle to 1 month after completion of CT). All drugs were started at the onset of symptoms. CTCAE v 4.02 was used for assessments. **Statistical Analysis Used:** Changes in scores for sensory, motor and pain symptoms over the study period were compared using repeated measures of General Linear Model of SPSS version 17. **Results:** 22, 24, 21 and 23 patients were eligible for analysis in four arms. Vitamin E was producing comparable relief as methylcobalamine of peripheral neuropathy. Both vitamin E and methylcobalamine was superior to glutamine and ALC in relieving sensory, motor and pain symptoms. Glutamine and ALC had comparable effects. **Conclusions:** All four drugs were effective in the alleviation of symptoms with vitamin E and methylcobalaine more effective than glutamine and ALC in control of symptoms of paclitaxel induced peripheral neuropathy.

Key words: Acetyl-L-carnitine, glutamine, methylcobalamine, paclitaxel, peripheral neuropathy, vitamin-E

INTRODUCTION

Paclitaxel has gained wide acceptance in the treatment of breast, ovary, head-neck Kaposi sarcomas and lung carcinomas.[1-4] One of the major toxicities of paclitaxel is peripheral neuropathy, contributed largely by antimictrotubule activity of the drug.[5] Though exact mechanisms still remain elusive, the microtubules stabilization causes dysfunctional microtubules in dorsal root ganglia, axons and Schwann cells resulting in abnormal neurite outgrowth and neuronal death contributing to the peripheral neuropathy.[6] The most common initial symptoms include numbness, tingling and burning pain in a stocking-and-glove distribution, affecting lower limbs more than the upper limbs. Perioral numbness has also been described.[7] Symptoms are typically symmetric and length dependent but may be asymmetrical at the onset and then progress in a symmetrical pattern.[8] Because paclitaxel and docetaxel remains important components of cancer chemotherapy armament, efforts are made either to prevent or treat peripheral neuropathy. Various drugs ranging from vitamin supplements to anti-epileptics to steroids and

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amifostine have been used along with analgesics for control of symptoms.

Vitamin E and methylcobalamine are already approved for treatment of neuropathy due to various causes and are available in different combinations with anti-epileptics as first line drugs to treat chemotherapy induced peripheral neuropathy (CIPN).[9-12] Acetyl-L-carnitine (ALC) has been studied with positive effects to diminish sign-symptoms of paclitaxel induced neuropathy.[13-15] Glutamine known to up-regulate nerve growth factor mRNA, has shown to reduce neuropathy.[16-18]

ALC, methylcobalamine, vitamin E and glutamine have been used in various trials against placebos. With head on trials among these four drugs missing, this randomized study was conducted to compare the efficacy in relieving symptoms of paclitaxel induced peripheral neuropathy.

MATERIALS AND METHODS

This single institutional, prospective, open-label, comparative, interventional, non-crossover, multi-arm, randomized study was conducted as per Helsinki protocol and with local ethical committee clearances. Patients recruited for study would require histology proven evidence of carcinomas of lung, breast and ovary and would be treated with 1st line or 2nd line chemotherapeutic drugs. All patients receiving paclitaxel either as first line or second line chemotherapeutic drug, either as a single agent or in combinations and with baseline clinical evaluation negative for any existing peripheral neuropathy were eligible for inclusion in the study. When paclitaxel is administered as second like drug, the exact details of previous chemotherapeutic agents would be necessary. Those who have already received platinum, vincristine would be included provided no peripheral neuropathy is detected at the time of enrollment. Patients with co-morbidities like diabetes, autoimmune diseases which include lupus, rheumatoid arthritis, kidney disease, liver disease and thyroid (hypothyroidism, tested pre-enrollment by thyroid-stimulating hormone, T4, T3) and with infections like hepatitis C and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV)/AIDS (all patients would undergo laboratory confirmation for shingles, hepatitis B, C and HIV/AIDS [at any Voluntary Confidential Counselling and Testing Centre, India,] prior to inclusion in study), spinal cord injuries, peripheral vascular disorders known to be associated with peripheral neuropathy would not be included in the study. Patients with uncontrolled diabetes or compromised cardiac function or any other major organ dysfunctions, other than cancer, which would require curtailment of full doses of paclitaxel at 175 mg/m^2, 3 weekly regimens, would be excluded from the study.

The selected patients underwent computer generated randomization to any of four treatment arms: Arm A (vitamin E: 400 mg. OD from day 1 of the first cycle to 1 month after completion of chemotherapy); Arm B (ALC): 250 mg. OD from day 1 to day 7 in each cycle of chemotherapy); Arm C (glutamine): 10 mg. TDS from day 2 to day 5 in each cycle and Arm D (methylcobalamine): 500 μg TDS from day 1 of the first cycle to 1 month after completion of chemotherapy. Patients were advised pre-medications as applicable for intravenous (IV) paclitaxel and non-steroidal anti-inflammatory drugs (NSAIDS) and opioids were avoided. The clinical assessments for motor, sensory and pain components of peripheral neuropathy were done using the Common Terminology Criteria for Adverse Events, version 4.02 [CTCAE v4.02, Sept. 15, 2009]. The evaluations for peripheral neuropathy were started at the time when the individual first received the 1st dose of paclitaxel, thereafter prior to each cycle of chemotherapy or earlier if required, followed by assessments at monthly intervals post-treatment. The nerve function tests were not advocated during the evaluation. However, in patients in whom muscle weakness was suspected, comprehensive neurological checkup including electromyography and nerve conduction velocity test were done at specialized neurological tertiary care center.

Statistical analysis

Those patients receiving < 4 cycles of paclitaxel or any dose curtailments were excluded from the analysis. The categorical variables were computed as frequency or actual count and compared using Chi-square test. The means of numerical data were described as, mean ± standard error and compared using analysis of variance. All analysis were two-tailed and statistical significance was accepted for a calculated $P < 0.05$. The changes in scores for sensory, motor and pain symptoms over the study period were compared using repeated measures of General Linear Model of Statistical Package for the Social Sciences (released 2008, SPSS Statistics for Windows, version 17, Chicago, SPSS Inc).

RESULTS

Baseline profiles analysis

Between August, 2012 and September 2013, 160 patients were recruited for study and randomized into four groups. Using the CONSORT 2010 flow chart only 22, 24, 21 and 23 patients were eligible for analysis in four arms glutamine, ALC, vitamin E and methylcobalamine arms, respectively. The baseline profile comparisons have been highlighted in Table 1.

Onset of syndromes

The onset of symptoms were 17.79 ± 12.43 (5-57) days for sensory, 22.98 ± 14.99 (5-56) days for motor and

18.50 ± 14.01 (5-58) days for pain [Table 2]. 67.8% of patients developed sensory symptoms after 1st cycle of clinical trial (CT) while motor symptoms developed in 51.1% patients and pain symptoms in 70% patients after 1st cycle CT. The pain symptoms were major complains as paclitaxel is known to cause bodyache, myalgia which were quite indistinguishable to patients from conventional pain symptoms of peripheral neuropathy.

The sensory symptoms

The significant *P* value showed an effect of time on the sensory symptoms (within-subjects effect) reflected by the repeated measures, Pillai's Trace multivariate *F* (24.927, $P < 0.001$). With a significant Mauchly's test of Sphericity, ($P < 0.001$), the Greenhouse-Geisser correction was also statistically significant, ($F = 14.376$, $P < 0.001$) [Figure 1a and Table 3a]. Even though the sensory symptoms of peripheral neuropathy were significantly reduced around 6 months post (after completion of) CT, the exact cause cannot be accounted for this delayed effect as no placebo was used as control. But when comparing among the different arms, the repeated measures with a Greenhouse-Geisser correction determined that the change in mean sensory scores at any point among the treatment arms were not statistically significant ($F = 1.824$, $P = 0.115$). However, the post-doc least significant difference (LSD) analysis showed that vitamin E was producing comparable effects as methylcobalamine ($P = 0.446$) but was superior to glutamine ($P < 0.001$) and ALC ($P = 0.002$). Methylcobalamine was superior to glutamine ($P = 0.001$) and ALC (0.013).

Table 1: Baseline profiles comparisons

Baseline parameters	Groups				*P* value
	Glutamine	ALC	Vitamin E	Methylcobalamine	
Age (in years) (mean±SE)	54.9±1.1	53.7±1.0	51.7±1.0	56.5±1.2	0.224
Sex					
Female	9	10	11	10	0.878
Male	13	14	10	13	
ECOG performance status					
0	2	2	3	5	0.708
1	17	20	13	15	
2	3	2	5	3	
Cancer sites					
Breast	6	3	4	4	0.771
Lung	13	17	11	14	
Ovary	3	4	6	5	
Stage[$]					
II	3	1	1	2	0.667
III	16	18	18	17	
IV	3	5	2	4	
Total number of CT cycles					
4	7	8	5	5	0.559
5	4	2	0	3	
6	11	14	16	15	
CT regimens**					
1	16	21	17	19	0.663
2	6	3	4	4	
Paclitaxel dose/cycle (mg) (mean±SE)	252.3±10.6	255.3±1.8	253.5±2.4	252.7±2.6	0.804

[$]Irrespective of cancer subsite specific, **CT regimens: Regimen 1-Paclitaxel+carboplatin, Regimen 2-Paclitaxel+doxorubicin+cyclophosphamide, SE: Standard error, ECOG: Eastern co-operative oncology group, CT: Clinical trial, ALC: Acetyl-L-carnitine

Table 2: Onset of relief (in days) after initiation of intervention drugs

Parameters	Groups	Mean	SE	95% CI for mean (bound)		*P* value
				Lower	Upper	
Sensory	Glutamine	4.9545	0.49006	3.9354	5.9737	<0.001
	ALC	5.7500	0.50809	4.6989	6.8011	
	Vitamin E	8.2381	0.65794	6.8657	9.6105	
	Methylcobalamin	5.6087	0.53620	4.4967	6.7207	
Motor	Glutamine	4.9545	0.49006	3.9354	5.9737	<0.001
	ALC	5.7500	0.43924	4.8414	6.6586	
	Vitamin E	8.3810	0.69856	6.9238	9.8381	
	Methylcobalamin	5.7826	0.56567	4.6095	6.9557	
Pain	Glutamine	4.6818	0.55200	3.5339	5.8298	<0.001
	ALC	6.1250	0.49017	5.1110	7.1390	
	Vitamin E	8.7143	0.51706	7.6357	9.7928	
	Methylcobalamin	6.2609	0.55956	5.1004	7.4213	

SE: Standard error, CI: Confidence interval, ALC: Acetyl-L-carnitine

Glutamine and ALC had comparable effects on sensory symptoms alleviation ($P = 0.412$).

The motor symptoms

The Greenhouse-Geisser correction for comparison of motor symptoms was statistically significant over the study period, ($F = 23.792$, $P < 0.001$). When comparing among the different arms, the repeated measures with a Greenhouse-Geisser correction determined that the mean motor scores at any point among the treatment arms were statistically significant (F = 2.267, $P = 0.045$) [Figure 1b and Table 3b]. However, the post-doc LSD analysis showed that vitamin E was producing comparable effects in the alleviation of motor symptoms as methylcobalamine ($P = 0.227$), but was superior to glutamine (<0.001) and ALC (<0.001). Methylcobalamine was superior to glutamine (<0.001) and ALC (<0.001). Glutamine and ALC had comparable effects on motor symptoms alleviation ($P = 0.988$).

Table 3a: Sensory scoring during the study period

Time	Groups	Mean	SE	95% CI for mean (bound)	
				Lower	Upper
After 3 cycles	Glutamine	1.09	0.160	0.76	1.42
	ALC	1.42	0.158	1.09	1.74
	Vitamin E	2.05	0.185	1.66	2.44
	Methylcobalamin	1.65	0.149	1.34	1.96
After 6 cycles	Glutamine	1.00	0.218	0.54	1.46
	ALC	1.19	0.225	0.72	1.66
	Vitamin E	2.00	0.198	1.58	2.42
	Methylcobalamin	1.90	0.206	1.48	2.33
At 6 months post-CT	Glutamine	0.58	0.176	0.21	0.95
	ALC	0.65	0.167	0.30	1.00
	Vitamin E	1.72	0.177	1.35	2.10
	Methylcobalamin	1.60	0.245	1.09	2.11

SE: Standard error, CI: Confidence interval, ALC: Acetyl-L-carnitine, CT: Clinical trial

Table 3b: Motor scoring during the study period

Time	Groups	Mean	SE	95% CI for mean (bound)	
				Lower	Upper
After 3 cycles	Glutamine	0.91	0.146	0.61	1.21
	ALC	1.00	0.147	0.69	1.31
	Vitamin E	2.00	0.145	1.70	2.30
	Methylcobalamine	1.57	0.176	1.20	1.93
After 6 cycles	Glutamine	0.67	0.144	0.37	0.97
	ALC	0.62	0.129	0.35	0.89
	Vitamin E	1.84	0.175	1.47	2.21
	Methylcobalamine	1.73	0.164	1.39	2.07
At 6 months post-CT	Glutamine	0.32	0.110	0.09	0.55
	ALC	0.20	0.092	0.01	0.39
	Vitamin E	1.39	0.143	1.09	1.69
	Methylcobalamine	1.40	0.152	1.08	1.72

SE: Standard error, CI: Confidence interval, ALC: Acetyl-L-carnitine, CT: Clinical trial

Table 3c: Pain scoring during the study period

Time	Groups	Mean	SE	95% CI for mean (bound)	
				Lower	Upper
After 3 cycles	Glutamine	0.27	0.097	0.07	0.47
	ALC	0.67	0.115	0.43	0.91
	Vitamin E	1.75	0.176	1.38	2.12
	Methylcobalamine	1.83	0.136	1.54	2.11
After 6 cycles	Glutamine	0.62	0.109	0.39	0.85
	ALC	0.48	0.131	0.20	0.75
	Vitamin E	1.79	0.196	1.38	2.20
	Methylcobalamine	2.05	0.167	1.70	2.39
At 6 months post-CT	Glutamine	0.26	0.104	0.05	0.48
	ALC	0.10	0.069	−0.04	0.24
	Vitamin E	1.33	0.181	0.95	1.71
	Methylcobalamine	1.30	0.147	0.99	1.61

SE: Standard error, CI: Confidence interval, ALC: Acetyl-L-carnitine, CT: Clinical trial

The pain symptoms

The repeated measures analysis using Pillai's Trace multivariate correction for changes of pain symptoms were statistically significant over the study period, (F = 38.002, P < 0.001). When comparing among the different arms, the Pillai's Trace showed that the mean pain scores at any point among the treatment arms were statistically significant (F = 3.358, P = 0.004) [Figure 1c and Table 3c]. However, the post-doc LSD analysis showed that vitamin E was producing comparable effects in the alleviation of pain symptoms as methylcobalamine but was superior to glutamine (P < 0.001) and ALC (P < 0.001). Methylcobalamine was superior to glutamine (P < 0.001) and ALC (P < 0.001). Glutamine and ALC had comparable effects on pain symptoms alleviation (P = 0.781).

DISCUSSION

Paclitaxel, discovered in a U.S. National Cancer Institute (NCI) Programme at Research Triangle Institute in 1967 was originally derived from the bark of western yew, *Taxus brevifolia*.[19] Today it is widely used in lung, breast, ovary, head-neck, gastro-intestinal carcinoma and Kaposi's sarcoma either as neo-adjuvant, concurrent or adjuvant therapy. However, neurotoxicity remains one of the most serious side-effects due to paclitaxel. Unlike the vinca alkaloids, paclitaxel stabilizes microtubule polymer and protects it from disassembly. Unusual microtubule aggregation results in demyelination and loss of axoplasmic transport.[6,8] At lower concentrations there is suppression of dynamics. At higher concentration, paclitaxel appears to act by suppressing microtubule detachment from centrosomes, a process normally activated during mitosis.[6,20] The inability of chromosomes to achieve a metaphase spindle configuration leads to mitotic block causing prolonged activation of mitotic check-point with subsequent triggering of apoptosis.[21-23] As a consequence, neurotoxicity may occur.

Neurotoxicity of paclitaxel is dose and infusion duration related.[24] A higher incidence of paclitaxel induced neuropathy has been reported when paclitaxel is infused over 3 h when compared to 24 h. One possible explanation is neuropathy may be related to peak blood concentration.[25,26] Although neuropathy is quite common at a dose of 175 mg/m^2, it occurs most frequently when dose of paclitaxel per administration exceeds 250 mg/m^2.[8,27,28] Severe neuropathy occurs when cumulative dose is >1400 mg/m^2.

Neurologic symptoms are observed in 27% of patients after the first course of treatment and 34-51% from course 2 to 10. The sensory components are affected most by paclitaxel followed motor neuropathy.[29] Autonomic neuropathy induced by paclitaxel is rare.[30] Peripheral neuropathy remains a dose related non-hematologic toxicity and requires discontinuation of the drug in individuals showing worsening of pre-existing neuropathy or newly developed symptoms. To avoid the discontinuation of paclitaxel several drugs have been tried either prophylactically or therapeutically. Use of corticosteroids and amifostine have been uniformly unsuccessful.[31,32] Following World Health Organization (WHO) analgesic ladder role of NSAIDS and opioids have been established beyond doubt but off course bringing along with them a host of drug related toxicities. To avoid these side-effects newer drugs have been tried ranging from neurotropic vitamin supplements to drugs associated with metabolism of the neuron. Notably among them are vitamin B12 methylcobalmine and vitamin E. Vitamin E in formulations have been established as drug in neuropathy. In the study on the small size of 31 patients with cancer treated with six courses of cumulative cisplatin, paclitaxel, or their combination regimens, 16 patients assigned to oral vitamin E at a daily dose of 600 mg/day had a lower incidence of neurotoxicity 4/16 (25%) versus no supplements 11/15 (73.3%), P = 0.019. Mean peripheral neuropathy scores were 3.4 ± 6.3 for patients of vitamin E arm and 11.5 ± 10.6

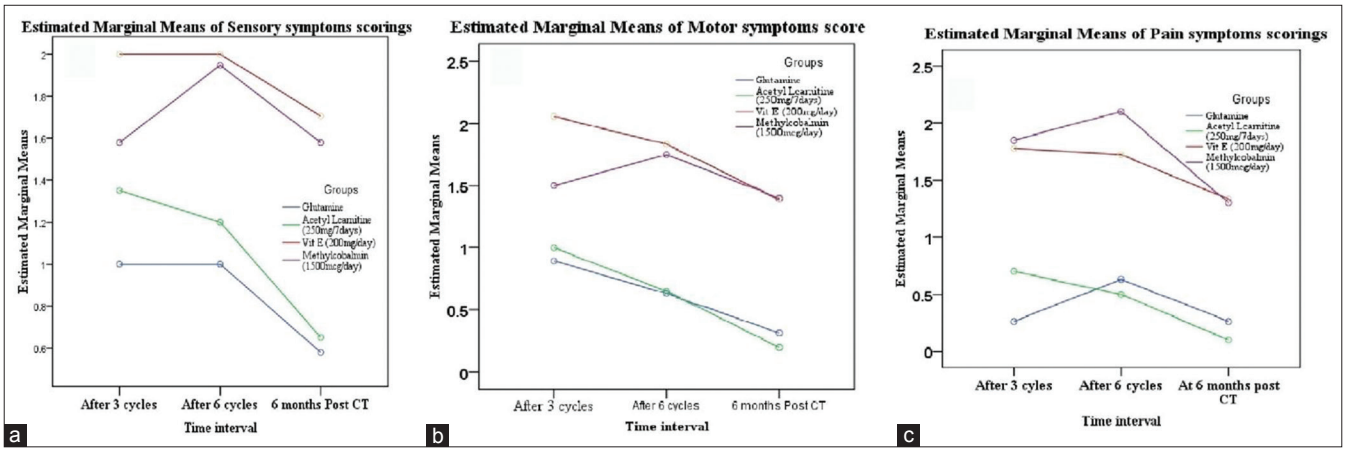

Figure 1: Changes in the sensory (a) motor (b) and pain (c) components of paclitaxel induced peripheral neuropathy brought about by the interventional drugs

for patients of no supplements arm ($P = 0.026$). The relative risk (RR) of developing neurotoxicity was significantly higher in case of control patients, RR = 0.34, 95% confidence interval = 0.14-0.84.[33]

In a retrospective analysis of 227 patients treated with paclitaxel, multivariate-ordered logistic regression analysis to examine the relationship between the severity of peripheral neuropathy and various predictive factors showed co-administration of vitamin B12 (odds ratio = 2.554) was significantly associated with reduction of or less serious peripheral neuropathy.[34]

Glutamine is a neutral gluconeogenic non-essential amino acid. Glutamine is known to up-regulate nerve growth factor mRNA. This may be a mechanism of action of glutamine to reduce neuropathy - according to De Santis *et al*. who showed circulating nerve growth factor declined in patients receiving chemotherapy with neurotoxic agents.[21] Savarese *et al*. in their study have reported successful reduction of paclitaxel-associated neuropathy by glutamine.[17] In trail on 46 patients of breast cancer treated with high-dose paclitaxel either with ($n = 17$) or without ($n = 29$) glutamine, glutamine receiving patients developed significantly less weakness ($P = 0.02$), less loss of vibratory sensation ($P = 0.04$) and less toe numbness ($P = 0.004$) than controls. The percent change in the compound motor action potential and sensory nerve action potential amplitudes after paclitaxel treatment was lower in the glutamine group, but this finding was not statistically significant in these small groups.[35]

ALC possesses both neuroprotective as well as neurotropic actions with positive actions on mitochondrial preservation which contributes to its usefulness in the treatment of drug induced peripheral neuropathy.[36] 27 patients with CIPN induced by cisplatin ($n = 5$), paclitaxel ($n = 11$), or a combination of these two drugs ($n = 11$) were enrolled in a pilot trial by Maestri *et al*. using IV ALC. Patients underwent IV infusion with 1 g ALC over 1-2 h for at least 10 days (range: 10-20 days). Of the 26 evaluable patients, 73% had at least 1 grade improvement on the WHO peripheral neuropathy scale.[15] 25 patients with established CIPN (20 taxane induced, five platinum-induced) were enrolled in another phase II trial of ALC, 1 g 3 times daily for 8 weeks. Participants included had ≥ grade 3 neuropathy (according to NCI-Common Toxicity Criteria, 1998) and were still receiving treatment with a neurotoxic chemotherapy, or they had ≥ grade 2 neuropathy for at least 3 months after discontinuing treatment with either drug. Of the 25 participants, 7 received neurotoxic chemotherapy during the study (6 = paclitaxel, 1 = vinorelbine) and 18 had residual CIPN of varying duration (3-35 months). Total neuropathy score improved significantly at 8 weeks in 23 out of 25 patients ($P = 0.0003$). One patient with a significantly worsening score was receiving vinorelbine. Symptomatic relief was also reported in all but the patient receiving vinorelbine. Amelioration of symptoms was independent of the type of chemotherapy that induced the neuropathy, or the duration of CIPN post-treatment.[37]

Our study showed that all four drugs were effective in the alleviation of symptoms, vitamin E and methylcobalaine are more effective than glutamine and ALC in control of sensory, motor and pain symptoms of paclitaxel induced peripheral neuropathy. However, the major limitations were small sample size and logistics problems associated with nerve conduction tests for all patients.

CONCLUSION

This study showed that vitamin E and methylcobalamine are both effective in control of sensory, motor and pain symptoms of paclitaxel induced peripheral neuropathy more than glutamine and ALC.

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