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Original Article

Glutamine as a Neuroprotective Agent in High-dose Paclitaxel-induced Peripheral Neuropathy: A Clinical and Electrophysiologic Study

M. D. Stubblefield*†, L. T. Vahdat†, C. M. Balmaceda‡, A. B. Troxel§, C. S. Hesdorffer¶, C. L. Gooch‡

**Department of Neurology, Rehabilitation Service, Memorial Sloan-Kettering Cancer Center, New York City, NY, USA; †Weill Medical College of Cornell University, New York City, NY, USA; ‡Department of Neurology, Columbia University College of Physicians and Surgeons, New York City, NY, USA; §Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA, USA; ¶Division of Medical Oncology, Columbia University College of Physicians and Surgeons, New York City, NY, USA*

ABSTRACT:
Aims: The appearance of peripheral neuropathy is the dose-limiting toxicity in many chemotherapy protocols, and glutamine has been proposed as a potentially neuroprotective agent in patients receiving paclitaxel.
Materials and methods: In this non-randomised study, we assessed neurologic signs and symptoms, and changes in nerve-conduction studies in 46 consecutive patients given high-dose paclitaxel either with ($n = 17$) or without ($n = 29$) glutamine. Neurological assessments and electrodiagnostic studies were carried out at baseline and at least 2 weeks (median 32 days) after treatment.
Results: Patients who received glutamine 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 per cent change in the compound motor action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes after paclitaxel treatment was lower in the glutamine group, but this finding was not statistically significant in these small groups.
Conclusions: In this study, serial neurologic assessment of patient symptoms and signs seemed to be a better indicator of a possible glutamine effect than sensory- or motor-nerve-conduction studies. Prospective randomised trials are needed to clarify the effect of glutamine on paclitaxel and other types of chemotherapy-induced neuropathy. Stubblefield, M. D. *et al*. (2005). *Clinical Oncology* **17,** 271–276

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Introduction

Peripheral neuropathy is a frequent dose-limiting toxicity of many active chemotherapeutic agents [1,2], and is characterised by numbness, tingling, paresthesias, dysaesthesias, pain or weakness. These symptoms can interfere with the usual activities of daily living, and can be a significant source of distress to patients.

There are several approaches to managing the symptoms of chemotherapy-induced peripheral neuropathy. Paresthesias, dysaesthesias and neuropathic pain can often be controlled pharmacologically with agents such as gabapentin [3], tramadol hydrochloride [4] or tricyclic antidepressants [5]. Physical and occupational therapy may help strengthen weakened muscles. Often, a dose reduction, an increase in the length of the treatment interval (e.g. from 3 to 4 weeks) or discontinuation of chemotherapy is required to prevent more severe nerve injury. However, these approaches could potentially decrease either disease-free or overall survival in people with advanced disease [6]. If maintenance of a threshold dose or a dose–response relationship is important, or if a minimum number of chemotherapy cycles are required for cure, overall survival might be negatively affected by the limitations imposed by this dose-related toxicity. Various interventions designed to limit neurotoxicity have been studied, but none have yet been proven to be effective.

Paclitaxel is an antineoplastic agent used extensively in the treatment of breast cancer. Although it is generally well tolerated, it can cause dose-limiting neutropenia and dose-limiting peripheral neuropathy, producing moderate symptoms in up to 30% of patients [7,8]. This is typically a predominately sensory polyneuropathy affecting the large

Author for correspondence: Michael D. Stubblefield, Rehabilitation Service, Memorial Sloan-Kettering Cancer Center, Rehabilitation Service, 1275 York Ave, New York City, NY 10021, USA. Tel: +1-212-639-7835; Fax: +1-646-422-2356; E-mail: stubblem@mskcc.org

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nerve fibres, although cranial nerve palsies, motor weakness and autonomic dysfunction can also be seen [9,10].

Attempts to mitigate the neurotoxic effects of paclitaxel with non-steroidal anti-inflammatory agents, corticosteroids and amifostine have not been successful [11,12]. In 1998, Savarese *et al.* [13] reported the successful use of oral glutamine to treat paclitaxel-associated myalgias and arthralgias in a group of five patients. These patients had been treated with paclitaxel at doses ranging from 175 to 200 mg/m^2, and experienced debilitating paclitaxel-associated myalgias and arthralgias with their first dose of treatment. Each of the patients was given glutamine (10 g orally three times a day) for 4 days starting 24 h after completing paclitaxel therapy. None of these patients had a recurrence of these symptoms while on glutamine. Glutamine supplementation does not seem to augment tumour-cell growth, but may enhance response to chemotherapy [14–17].

Glutamine is a neutral gluconeogenic non-essential amino acid. It is stored in skeletal muscle (75%) and the liver (25%) [18], and serves as the primary carrier of nitrogen between tissues. It is a major energy source for rapidly proliferating cells, such as intestinal epithelial cells, activated lymphocytes and fibroblast. Glutamine can be depleted by major surgery, sepsis, cancer and other stress states, and its omission may contribute to villous atrophy in patients on total parenteral nutrition [19].

In the mid to late 1990s, the Stem Cell Transplant Group at the Columbia-Presbyterian Medical Center conducted a series of sequential high-dose chemotherapy trials in which high-dose paclitaxel was the first of three high-dose cycles. In the phase I trial, a severe but reversible sensory polyneuropathy at paclitaxel doses of 725 mg/m^2 or over was observed. Five out of 18 patients had transient motor weakness, which led to the designation of 825 mg/m^2 as the phase II dose [20]. In the phase II trial, the neuropathy was reversible, although at varying rates [6]. On the basis of the initial report by Savarese *et al.* [13] that glutamine might reduce paclitaxel-induced myalgias, and in an attempt to ameliorate the myalgias associated with this high dose of paclitaxel, we gave oral glutamine after paclitaxel to all patients enrolled in this trial after January 1999. The present non-randomised study compares patients treated with glutamine after January 1999 with those patients treated without glutamine before this date.

We reported that glutamine may reduce some of the signs and symptoms of paclitaxel neuropathy in a previous study [21]. In this report, we analysed the neurologic signs and symptoms, and the neuronal function using nerve-conduction studies in patients on paclitaxel with and without glutamine, to determine whether electrophysiologic testing might prove a more sensitive indicator of glutamine effect, toxic neuronal injury, or both.

Methods

Patients with histologically documented stage IV breast cancer were eligible for participation in this sequential high-dose chemotherapy trial, in which high-dose paclitaxel was the first of three high-dose cycles if patients had responded (partial or complete response) to conventional dose chemotherapy. Patients were excluded if they had central nervous system metastases before progression while on a taxane, compromised organ function or a baseline neuropathy from chemotherapy that was disabling. All patients gave informed consent. This study was approved by the Institutional Review Board of Columbia University. Administration of glutamine was not randomised. All patients enrolled into the high-dose paclitaxel study before January 1999 were not given glutamine, and all those enrolled after this date were given glutamine.

Treatment Plan

Peripheral blood haematopoietic progenitor cells were mobilised, harvested and cryopreserved using standard techniques [12].

High-dose chemotherapy with stem-cell support included (1) intensification 1 (paclitaxel): after standard premedication, paclitaxel at 825 mg/m^2 was given as a continuous infusion over 24 h on day 4 before stem-cell infusion; (2) intensification 2 (melphalan): this cycle was given after recovery to an absolute neutrophil count of 1000/μL or over, and in the absence of platelet refractoriness or disease progression. Patients received melphalan 180 mg/m^2 total (90 mg/m^2/day for two consecutive days) on days −2 and −1 before stem-cell infusion; (2) intensification 3 (cyclophosphamide thiotepa carboplatin): after recovery from intensification 2, patients were admitted for cyclophosphamide 6000 mg/m^2, thiotepa 500 mg/m^2 and carboplatin 800 mg/m^2 over 96 h on days −7 to −4 before stem-cell infusion. Mesna 7500 mg/m^2 (1500 mg/m^2/day) was given by continuous infusion over 120 h. All cycles were also supported with granulocyte colony-stimulating factor (5 μg/kg/day subcutaneously) until the absolute neutrophil count was equal to or greater than 1000/μL for two consecutive days.

Glutamine

Patients enrolled in this study after January 1999 received glutamine 10 g orally three times a day for 4 days, starting 24 h after completing paclitaxel. (Cambridge Nutraceuticals, Cambridge, MA). Patients enrolled before this date did not receive glutamine.

Neurologic Evaluation

A single reference neurologist (CB) examined all patients at baseline and at least 2 weeks (median 32 days) after giving paclitaxel. One patient had paired exams conducted by a single neurologist at an outside institution. Previous neurological assessments were not blinded to the examiner.

A detailed neurologic history was obtained, including possible risk factors for the development of peripheral neuropathy (diabetes, alcohol abuse or prior history of

neurotoxic chemotherapy or neuropathy). A peripheral neuropathy assessment instrument was used to facilitate and standardise data collection. Questions assessing the symptom of numbness were queried separately for fingers and toes. Each symptom was graded as absent (0), mild (1), moderate (2) or severe (3). Signs including reflexes, strength and vibration sense were assessed in the lower extremities. This baseline assessment was conducted before and at a follow-up exam at least 2 weeks after starting paclitaxel. Reflexes and vibration were graded as normal (0), decreased (1) or absent (2). Strength in the lower extremities was graded as normal (0), extensor hallucis longus weakness (1), tibialis anterior weakness (2) or foot drop (3). Most patients were re-assessed before the second high-dose cycle of chemotherapy. At that visit, a medication history was obtained (if applicable), and an assessment made of whether the patient had increasing or decreasing medication requirements.

Nerve-conduction Studies

All patients evaluated by nerve-conduction studies were evaluated before receiving paclitaxel and at a minimum of 2 weeks (median 32 days) after completing high-dose paclitaxel. Previous electrophysiological assessments were not blinded. Motor and sensory responses were recorded using standardised equipment and techniques. Serial motor nerve conduction studies were carried out on the median, ulnar, peroneal and tibial nerves. Distal latency, baseline to peak compound muscle action potential (CMAP) amplitude, and segmental conduction velocity, were recorded for each nerve. Sensory-nerve-conduction studies were carried out on the median, ulnar and sural nerves. Onset distal latency, conduction velocity, and peak-to-peak amplitude of the sensory nerve action potential (SNAP) were recorded for each nerve.

Statistical Analysis

The variables of primary interest were the changes over time (pre-treatment vs post-treatment) in the motor- and sensory-nerve amplitudes as recorded in the nerve-conduction studies, physical-examination findings (changes in reflexes, strength and vibration) and symptoms (changes in finger and toe numbness). We considered absolute changes in the variables over time and dichotomous indicators of failure (achieving the worst possible score at the post-treatment test). These were compared between treatment groups using t-tests for continuous variables, and Fisher's exact test and the Mantel–Haenszel trend test for categorical variables. Two-sided tests were conducted and a P value of 0.05 was used to determine significance. We used Spearman correlation coefficients to assess correlation of various variables of interest.

Results

The average elapsed time between the pre-paclitaxel clinical and electrodiagnostic evaluation and the post-paclitaxel clinical and electrodiagnostic evaluation was 40 days for all patients, 39 days for patients in the no-glutamine group and 44 days for patients in the glutamine group.

Paired pre- and post-paclitaxel electrodiagnostic evaluations were available in a total of 46 patients (Table 1), including 29 in the control group and 17 in the glutamine group. Complete nerve-conduction study data, including paired CMAP and SNAP amplitudes, are available for all 29 patients in the control group. Paired median and tibial nerve CMAP amplitude data are available for 14 out of 17 patients in the glutamine group and paired ulnar and peroneal CMAP amplitude data are available for 13 out of 17 patients in the glutamine group. Paired SNAP amplitude data are available for all 17 of the patients in the glutamine group.

Paired pre-and post-paclitaxel clinical evaluations of signs (reflexes, strength and vibratory sense) and symptoms (finger numbness and toe numbness) of neuropathy are available on 36 out of the 46 patients enrolled in the study (Table 2). This includes 24 out of 29 patients in the control group and 12 out of 17 patients in glutamine group.

Electrodiagnostic Studies

The per cent changes of the average CMAP and SNAP amplitudes after paclitaxel treatment for both the control group and the glutamine group are shown in Table 1. The per cent loss of the average CMAP amplitude was more pronounced in the control group than the glutamine group for all nerves tested. The per cent difference between the average of the control group and glutamine group after paclitaxel was most evident in the tibial (14%) and peroneal (9%) nerves, respectively. Per cent change of the average SNAP amplitude was more pronounced in the control group than the glutamine group for the median and ulnar nerves, and more pronounced in the glutamine group than the control group for the sural nerves. The per cent changes in the average CMAP and SNAP amplitudes

Table 1 – Per cent change of the average compound muscle action potential and sensory nerve action potential amplitude after paclitaxel treatment (median 32 days after initial assessment)

	Control (%)	*n*	Glutamine (%)	*n*	Difference (%)	*P* value
CMAP						
Median nerve	25	29	22	14	−3	0.87
Ulnar nerve	15	29	5	13	−5	0.16
Peroneal nerve	80	29	71	13	−9	0.76
Tibial nerve	39	29	25	14	−14	0.15
SNAP						
Median nerve	54	29	44	17	−10	0.50
Ulnar nerve	54	29	39	17	−15	0.35
Sural nerve	36	29	43	17	+12	0.83

CMAP, compound muscle action potential; SNAP, sensory nerve action potential.

Table 2 – Baseline signs and symptoms of peripheral neuropathy

	Control ($n = 24$)	Glutamine ($n = 12$)
Reflexes		
Normal	14 (58%)	9 (75%)
Decreased	4 (17%)	2 (17%)
Absent	6 (25%)	1 (8%)
Strength		
Normal	24 (100%)	12 (100%)
EHL weakness	0	0
TA weakness	0	0
Foot drop	0	0
Vibratory sensation		
Normal	18 (75%)	10 (83%)
Decreased	5 (21%)	2 (17%)
Absent	1 (4%)	0
Finger numbness		
Absent	20 (83%)	10 (83%)
Mild	4 (17%)	2 (17%)
Moderate	0	0
Severe	0	0
Toe numbness		
Absent	20 (83%)	10 (83%)
Mild	4 (17%)	2 (17%)
Moderate	0	0
Severe	0	0

EHL, extensor hallucis longus; TA, tibialis anterior.

between the control and glutamine groups did not reach statistical significance for any of the nerves tested.

Signs

The changes in signs with paclitaxel treatment are presented in Table 3. Patients in the glutamine group ($n = 12$) were significantly less likely ($P = 0.02$) to experience weakness than patients in the control group ($n = 24$). None (0%) of the 12 patients in the glutamine group compared with seven out of 24 (29%) patients in the control group had a marked worsening of strength. Vibratory sensation was significantly less likely ($P = 0.04$) to be adversely affected in patients in the glutamine group than those in the control group. A worse or much worse vibratory sense was seen in 23 out of 24 (96%) of the patients in the control group compared with eight out 12 (67%) in the glutamine group after paclitaxel treatment. Lower-extremity reflexes were not more likely to be preserved in patients in the glutamine group compared with those in the control group ($P = 0.28$). Eleven (46%) patients in the control group had much worse reflexes after paclitaxel treatment compared with four (33%) in the glutamine group.

Symptoms

Symptom results are presented in Table 4. Patients in the glutamine group ($n = 12$) experienced significantly less toe numbness ($P = 0.004$) and less finger numbness ($P = 0.06$) than did patients in the control group ($n = 24$) after treatment with paclitaxel. Worse or much worse toe numbness was seen in 83% of the patients in the control group after paclitaxel treatment compared with 25% in the glutamine group. Worse or much worse finger numbness was seen in 71% of the patients in the control group after paclitaxel treatment compared with 25% in the glutamine group, although this did not meet statistical significance ($P = 0.06$).

Table 3 – Changes in signs with paclitaxel treatment (median 32 days after initial assessment)*

Reflexes ($P = 0.28$)		
Much worse	11 (46%)	4 (33%)
Worse	6 (25%)	2 (17%)
Unchanged	6 (25%)	5 (42%)
Improved	1 (4%)	1 (8%)
Strength ($P = 0.02$)		
Much worse	3 (12%)	0 (0%)
Worse	4 (17%)	0 (0%)
Slightly worse	8 (33%)	3 (25%)
Unchanged	9 (38%)	9 (75%)
Vibration ($P = 0.04$)		
Much worse	10 (42%)	3 (25%)
Worse	13 (54%)	5 (42%)
Unchanged	1 (4%)	3 (25%)
Improved	0 (0%)	1 (8%)

*Control ($n = 24$); glutamine ($n = 12$).

Discussion

The dose-limiting toxicity of many cancer chemotherapeutic agents is peripheral neuropathy. It is frequently a major detriment to quality of life in patients who have received and who are actively receiving neurotoxic chemotherapy. Few interventions can improve the symptoms and none can prevent it. Data from the present study suggest that many of

Table 4 – Changes in symptoms with paclitaxel treatment (median 32 days after initial assessment)*

Finger numbness ($P = 0.06$)		
Much worse	4 (17%)	1 (8%)
Worse	13 (54%)	2 (17%)
Slightly worse	4 (17%)	6 (50%)
Unchanged	2 (8%)	2 (17%)
Improved	1 (4%)	1 (8%)
Toe numbness ($P = 0.004$)		
Much worse	8 (33%)	1 (8%)
Worse	12 (50%)	2 (17%)
Slightly worse	2 (8%)	6 (50%)
Unchanged	2 (8%)	2 (17%)
Improved	0 (0%)	1 (8%)

*Control ($n = 24$); glutamine ($n = 12$).

the signs and symptoms of peripheral neuropathy can be reduced by the addition of glutamine (10 g orally three times a day for 4 days) for patients receiving high-dose paclitaxel as part of a tandem high-dose chemotherapy regimen.

The original intent glutamine administration was to attenuate the myalgias observed in patients treated with high-dose paclitaxel before January 1999. The possible reduction in peripheral neuropathy was an unanticipated observation. This study has limitations because it was not a randomised placebo-controlled trial; however, glutamine was shown to reduce the symptoms of toe numbness in patients who received high-dose paclitaxel. A trend toward reducing the symptoms of finger numbness was also seen. The signs of neuropathy, including changes in lower-extremity strength and vibratory sense, were also reduced in the glutamine group compared with the control group. As the lower-extremity strength of all patients enrolled in the study was considered normal at baseline, the preservation of strength seen in the glutamine group was particularly striking. In the control group, three (12%) of the patients developed complete foot drop, and four (17%) developed tibialis anterior weakness compared with none in the glutamine group. No difference in reflex changes was seen between the glutamine and control group. This is not surprising, as a large proportion (36%) of the patients enrolled in this trial had abnormal reflexes at baseline. The significance seen using the Mantel–Haenszel trend test for these measures was not as robust using the non-parametric Fisher's exact test, probably due to the relatively small sample size. In addition, the trend test has greater power for an alternative hypothesis of trend.

Although the per cent change in average CMAP was lower in the glutamine group than the control group for all nerves tested, this was not statistically significant. For SNAP amplitude, a larger average per cent loss was seen in the median and ulnar sensory nerves of the control group than in the glutamine group, but in the sural sensory nerve, a larger average per cent amplitude change was seen in the glutamine group than the control group. These fluctuations are most probably related to the innate variability of serial nerve conduction study parameters, particularly motor and sensory amplitudes, as the sample size in this study was too small to factor out such effects.

Motor amplitudes may vary by as much as 77% in the median nerve depending on where on the muscle the recording electrode is placed relative to the motor point [22]. This variability in CMAP amplitude does not seem to depend on examiner skill or experience but on subtle variations in electrode placement [23]. Electrophysiological recording of the sural nerve SNAP is also subject to marked variability, particularly between examiners. This is probably due to the variable course of the sural nerve in the calf and ankle as well as the lack of fixed landmarks for placement of both the stimulation and recording sites [24]. Lower-extremity oedema, muscle bulk, skin integrity, examiner skill and other factors may also affect recording of this nerve. These factors may also have contributed to the results seen for the sural nerve. The median and ulnar sensory nerves, on the other hand, have relatively fixed stimulating and recording sites, and are less affected by extraneous factors such as oedema and skin integrity.

In this study, serial neurologic assessment of patient symptoms and signs seemed to provide a more significant indicator of possible glutamine effect than sensory- or motor-nerve-conduction studies. This study is limited because it was not randomised or blinded. The major differences observed were also in more subjective, patient-reported sign and symptom parameters compared with objective electrophysiological data. This hypothesis-generating study needs confirmation in a larger, randomised study. Such a study is to begin shortly. It will enrol women with breast cancer who have a mild peripheral neuropathy from paclitaxel chemotherapy, and will be a randomised, placebo-controlled trial of glutamine to prevent or attenuate peripheral neuropathy. Several biological correlates will be collected, and it is hoped that additional information on the insight into the mechanism of paclitaxel peripheral neuropathy will be obtained from this clinical trial.

Although the mechanism of neuroprotection conferred by glutamine in paclitaxel neuropathy is unclear, some evidence suggests a correlation between treatment-induced reduction in nerve growth factor and severity of neurotoxicity. Administration of nerve growth factor in a murine model was associated with inhibition of toxic neuropathy [25]. The possible neuroprotective effect of glutamine in high-dose paclitaxel needs to be assessed for other chemotherapeutic agents. Any potential for glutamine in reversing neuropathy has not been assessed and also deserves investigation.

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