

Reduction of Paclitaxel-induced Peripheral Neuropathy with Glutamine¹

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ABSTRACT

Purpose: Dose-limiting toxicity of many newer chemotherapeutic agents is peripheral neuropathy. Prior attempts to reduce this side effect have been unsuccessful. We report on the possible successful reduction of peripheral neuropathy with glutamine administration after high-dose paclitaxel.

Experimental Design: Patients entered a high-dose chemotherapy protocol in which the first high-dose cycle was paclitaxel at 825 mg/m² given over 24 h. The first cohort of patients did not receive glutamine, and the second cohort of patients received glutamine at 10 g orally three times a day for 4 days starting 24 h after completion of paclitaxel. Neurological assessment was performed at baseline, and at least 2 weeks after paclitaxel, and consisted of a complete neurological exam and nerve conduction studies.

Results: There were paired pre- and post-paclitaxel evaluations on 33 patients who did not receive glutamine and 12 patients who did. The median interval between pre- and post-exams was 32 days. For patients who received glutamine, there was a statistically significant reduction in the severity of peripheral neuropathy as measured by development of moderate to severe dysesthesias and numbness in the fingers and toes ($P < 0.05$). The degree and incidence of motor weakness was reduced (56 versus 25%; $P = 0.04$) as well as deterioration in gait (85 versus 45%; $P = 0.016$) and

interference with activities of daily living (85 versus 27%; $P = 0.001$). Moderate to severe paresthesias in the fingers and toes were also reduced (55 versus 42% and 64 versus 50%, respectively), although this value was not statistically significant. All of these toxicities were reversible over time.

Conclusions: Glutamine may reduce the severity of peripheral neuropathy associated with high-dose paclitaxel; however, results from randomized, placebo-controlled clinical trials will be needed to fully assess its impact, if any. Trials are currently ongoing to assess its efficacy for standard-dose paclitaxel in breast cancer and other tumors for which peripheral neuropathy is the dose-limiting toxicity.

INTRODUCTION

Peripheral neuropathy is a common side effect of a wide variety of cancer chemotherapeutic agents. The mechanisms of this neuropathy are usually attributed to microtubule disruption (taxanes, *Vinca* alkaloids) or a direct toxic effect (platinum compounds). Dose-limiting peripheral neuropathy is most often observed in the setting of advanced cancer necessitating a change in therapy while the patient is still actively responding to the agent. Even when alternative schedules are used (shorter versus longer infusion) peripheral neuropathy \geq grade 2, as evidenced by moderate motor and sensory symptoms, is noted in up to 30% of patients receiving paclitaxel (1, 2). The options of stopping treatment early or dose reducing are equally undesirable in the advanced disease setting but may have greater implications in the adjuvant setting because taxanes may become part of the standard treatment of node-positive breast cancer. In the adjuvant setting, the potential for affecting larger numbers of patients increases, because it is estimated that at least 56,000 patients will be considered for adjuvant taxane use for node-positive disease (30% of all breast cancers). If the node-negative trials reveal an advantage with adjuvant taxanes, then, potentially, the number of patients affected by peripheral neuropathy will widen considerably.

Paclitaxel has a broad spectrum of activity against a wide variety of neoplasms, including breast, ovary, lung, and gastrointestinal tumors. It is generally well tolerated with dose-limiting neutropenia and peripheral neuropathy after multiple cycles.

The neuropathy, generally a sensory polyneuropathy affecting large fibers, can also lead to cranial nerve palsies, motor weakness, and autonomic dysfunction (3, 4).

Several avenues have been explored to ameliorate the neurotoxicity associated with paclitaxel, including the use of nonsteroidal anti-inflammatory agents, corticosteroids, and amifostine; and these treatments have been uniformly unsuccessful (5, 6). Recently, Savarese *et al.* (7) reported the successful reduction of paclitaxel-associated myalgias and arthralgias by glutamine in five patients treated with paclitaxel doses ranging from 175 to 200 mg/m². All of the patients had debilitating paclitaxel-associated myalgias/arthralgias associated with their

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Table 1 Clinical trials using glutamine to prevent toxicity from chemotherapy

Author (Ref.)	n ^a	Chemotherapy	Glutamine dose (po)	Results
Rubio (10)	9	MTX ^b	0.5 g/kg/day	No mucositis seen
Skubitz (19)	14	varied	4 g BID × 28 days	Decreased stomatitis
Savarese (7)	5	paclitaxel ^c	10 g TID × 4 days	Prevention of myalgias/arthralgias
Ohkuno (16)	66	5FU	4 g BID × 14 days	No difference in mucositis from controls

^a n, number of patients; MTX, methotrexate; BID, twice a day; 5 FU, 5-fluorouracil.

^b Escalating dose methotrexate from 40 to 100 mg/m².

^c Paclitaxel-containing regimen.

first cycle of therapy. For subsequent cycles, they received glutamine (10 g p.o. t.i.d.)³ for 4 days starting 24 h after the completion of paclitaxel. No patient had a recrudescence of symptoms while on glutamine (7).

Glutamine is a neutral gluconeogenic nonessential amino acid stored primarily in skeletal muscle (75%) and liver (25%); (8). Among its many functions, glutamine serves as the primary carrier of nitrogen between tissues; it is also the main energy source for rapidly proliferating cells such as intestinal epithelium, activated lymphocytes (9), and fibroblasts (8). Glutamine is depleted in stress states such as major surgery, sepsis, and cancer (8). It is also essential for maintenance of gut epithelium for patients on total parenteral nutrition as its omission hastens villous atrophy (9).

Preclinical data suggest that glutamine supplementation does not augment tumor cell growth and may augment response to chemotherapy (10–13). Clinical studies have assessed the efficacy of glutamine with different doses and schedules to prevent gastrointestinal toxicity (mucositis, diarrhea) in patients receiving a variety of chemotherapy agents or radiation therapy (Ref. 10, 14–19; Table 1).

The efficacy of high-dose chemotherapy with stem cell support in breast cancer is currently being studied in the United States and Europe. Although the benefit is still undetermined, numerous pilot studies incorporate high doses of newer drugs such as paclitaxel into some of the more common regimens. There is laboratory evidence of a dose-concentration effect of paclitaxel in MCA-4 transplanted tumors in C3Hf/Kam mice that supports a dose-concentration/response effect in breast cancer (20, 21), although only a modest dose-response effect has been observed in the clinical setting (22). We 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, we noted a severe but reversible sensory polyneuropathy at doses of paclitaxel ≥ 725 mg/m²; and in 5 of 18 patients, transient motor weakness was observed, which led to the designation of 825 mg/m² as the Phase II dose (23). The neuropathy was reversible, although at varying rates. In an attempt to ameliorate the neuropathy from this dose of paclitaxel, we incorporated oral glutamine administration after paclitaxel after the initial report by Savarese *et al.* (7).

MATERIALS AND METHODS

Patients with histologically documented stage 4 breast cancer were eligible for participation in this study if their disease had responded (partial or complete response) to conventional dose chemotherapy. Patients were excluded if they had central nervous system metastases, prior progression while on a taxane, compromised organ function, or a baseline neuropathy from chemotherapy that was disabling. All of the patients gave informed consent. This study was approved by the Institutional Review Board of Columbia University.

Treatment Plan

Mobilization. Peripheral blood hematopoietic progenitor cells were mobilized, harvested and cryopreserved using previously published techniques (24).

High-dose chemotherapy with stem cell support included: (a) intensification 1, paclitaxel. After standard premedication, paclitaxel at 825 mg/m² was administered as a continuous infusion over 24 h on day –4 prior to stem cell infusion; (b) intensification 2, melphalan. With recovery to an ANC $\geq 1000/\mu\text{l}$, and in the absence of platelet refractoriness or disease progression, patients received melphalan at 90 mg/m²/day for 2 consecutive days (180 mg/m² total) on days –2 and –1 prior to stem cell infusion; (c) intensification 3, CTCb. After recovery from intensification 2, patients were admitted for cyclophosphamide (6000 mg/m²), thiotepa (500 mg/m²), and carboplatin (800 mg/m²) over 96 h on days –7 to –4 prior to stem cell infusion. Mesna (7500 mg/m²; 1500 mg/m²/day) was administered by continuous infusion over 120 h. All of the cycles were also supported with G-CSF (5 $\mu\text{g/kg/day}$ s.c.) until the ANC $\geq 1000/\mu\text{l}$ for 2 consecutive days.

Glutamine

As of December 1998, patients enrolled in this study received glutamine (10 g p.o. t.i.d.) for 4 days, starting 24 h after the completion of paclitaxel (Cambridge Nutraceuticals, Cambridge MA).

Neurologic Evaluation

Patients entering the study were examined by a single reference neurologist (C. B.) at baseline and at least 2 weeks after the paclitaxel. One patient had paired exams conducted by a single neurologist at an outside institution. When possible, patients were also evaluated by nerve conduction studies prior to receiving paclitaxel and at a minimum of 2 weeks after completion of high-dose paclitaxel.

³ The abbreviations used are: t.i.d., three times a day; ADL, activity/activities of daily living.

Table 2 Baseline assessment: number of patients with symptoms of peripheral neuropathy

Variable	Without glutamine <i>n</i> = 33		With glutamine <i>n</i> = 12		<i>P</i>
	None/ Mild	Moderate/ Severe	None/ Mild	Moderate/ Severe	
Dysesthesias					
Fingers	33	0	11	1	NS ^a
Toes	33	0	12	0	NS
Numbness					
Fingers	33	0	12	0	NS
Toes	33	0	12	0	NS
Paresthesias					
Fingers	30	3	12	0	NS
Toes	32	1	12	0	NS

^a NS, nonsignificant.

Neurology Exam

A detailed neurological 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 assure that all of the data points were collected on all of the patients. Questions assessing symptoms (paresthesias, dysesthesias, numbness) were queried separately for fingers and toes and were graded as mild, moderate, or severe as well as to whether there was any interference with function. Signs (reflexes, vibration sense, pin prick, and proprioception) were assessed in upper and lower extremities as well. Cerebellar function, gait, and motor weakness were also evaluated. This baseline assessment was conducted prior to, and at a follow-up exam at least 2 weeks after, initiating paclitaxel. Most patients were reassessed prior to the second high-dose cycle of chemotherapy. At that visit, a medication history was obtained (if applicable) and if the patient had increasing or decreasing medication requirements.

Nerve Conduction Studies

When possible, nerve conduction studies were performed. Serial motor conduction studies were performed in four nerves: median, ulnar, peroneal, and tibial. Motor responses were recorded using 2-mm diameter platinum surface electrodes placed over the motor point and the reference placed over a distal, electrically inactive site. Distal motor latency, segmental velocity, and baseline to peak amplitude were measured. Serial sensory nerve conduction studies were performed in three nerves: median, ulnar, and sural. Segmental sensory velocity and peak-to-peak amplitude were measured for each nerve.

Statistics

Data analysis was conducted using frequency tables and Pearson and Mantel-Haenszel χ^2 tests. All of the tests were conducted at the 0.05 significance level. Because of the small sample size and the pilot nature of the data, no statistical adjustments for the multiplicity of tests was used.

RESULTS

Paired pre- and post-paclitaxel evaluations are available in 33 patients who did not receive glutamine and 12 patients that

Table 3 Baseline assessment: number of patients with signs of peripheral neuropathy

Variable	Without glutamine <i>n</i> = 33		With glutamine <i>n</i> = 12		<i>P</i>
	Normal	Abnormal	Normal	Abnormal	
Reflexes	19	14	9	3	NS ^a
Motor weakness	33	0	12	0	NS
Vibration sense					
Toes	25	8	10	2	NS
Ankle	32	1	11	1	NS

^a NS, not significant.

Table 4 Evaluation of acute peripheral neuropathy symptoms after paclitaxel

Moderate-to-severe symptoms	Without glutamine <i>n</i> = 33 (%)	With glutamine <i>n</i> = 12 (%)	<i>P</i>
Dysesthesias			
Fingers	13 (40)	1 (8)	0.047
Toes	14 (42)	1 (8)	0.04
Numbness			
Fingers	24 (73)	4 (33)	0.016
Toes	27 (82)	5 (42)	0.009
Paresthesias			
Fingers	18 (56)	5 (42)	NS ^a
Toes	21 (64)	6 (50)	NS

^a NS, not significant.

received glutamine. The median number of days between evaluations was 33 days for the glutamine group and 30 days for the nonglutamine group.

Of the 45 patients with paired assessments, 39 also had paired nerve conduction studies (28 in the nonglutamine and 11 in the glutamine group). Both of the groups were well balanced for pretreatment peripheral neuropathy as shown in Tables 2 and 3.

Symptoms. Patients who received glutamine had fewer symptoms than those who did not receive glutamine (Table 4). For those who received glutamine, only 8% had moderate-to-severe dysesthesias in their fingers or toes compared with at least 40% of patients who did not receive glutamine. In addition, the frequency of moderate-to-severe numbness was observed less often in the glutamine than in the non-glutamine group for both fingers and toes ($P = 0.016$ and 0.009 , respectively). Moderate-to-severe paresthesias were also observed less frequently in the glutamine group, although this value is not statistically significant. These symptoms in both groups were reversible.

Signs. The results are presented in Table 5. Vibration sense was less often reduced in the toes of those patients who received glutamine ($P = 0.04$). Less motor weakness was also observed in patients who received glutamine (3) as compared with patients in the nonglutamine group (19), which is illustrated in Table 6. A transient deterioration in gait, which can be described as an ataxic-type gait, was observed in 28 (85%) of 33 of the patients who did not receive glutamine compared with 5 (45%) of 11 patients who did receive glutamine (Fig. 1). Reflexes were less often affected in the glutamine group; however,

Table 5 Evaluation of acute peripheral neuropathy signs after paclitaxel

Variable	Without glutamine <i>n</i> = 33		With glutamine <i>n</i> = 12		<i>P</i>
	Normal	Abnormal	Normal	Abnormal	
Reflexes	6	27	4	8	NS ^a
Vibration sense					
Toes	2	31	10	2	0.04
Ankle	20	13	11	1	NS

^a NS, not significant.

Table 6 Evaluation of motor function after paclitaxel

	Without glutamine <i>n</i> = 33	With glutamine <i>n</i> = 12	<i>P</i>
Any motor weakness	19 (58%)	3 (25%)	0.04
Extensor hallucis longus	11	3	
Anterior tibialis	5	0	
Foot drop	3	0	

this value was not reduced in a significant manner with glutamine. For patients without any sensory deficits at baseline, glutamine more often limited the post-paclitaxel sensory deficits (to pinprick) only to the toes, compared with patients who did not receive glutamine (73 versus 22%; $P = 0.02$). In the upper extremities, more patients who received glutamine remained at baseline (normal) than those who did not (48 versus 17%; $P = 0.08$). All of the above abnormalities were also reversible over time.

ADL. Interference with ADL was seen for the majority (86%) of patients who did not receive glutamine compared with those who received glutamine (27%; Fig. 2). This transient interference with function consisted mainly with manipulating buttons, opening jars, and other measures of fine motor coordination.

Nerve Conduction Studies. There were statistically significant decrements in the amplitude and conduction velocity of the motor (peroneal, tibial, median, and ulnar) and sensory (median, ulnar, and sural) nerves from baseline in both of the groups, and glutamine did not appear to exert a protective effect.

DISCUSSION

Dose-limiting toxicity of many cancer chemotherapeutic agents is peripheral neuropathy. Our data suggest that peripheral neuropathy may be reduced with the addition of glutamine in patients receiving high-dose paclitaxel as the first part of a tandem high-dose chemotherapy regimen. Glutamine appeared to reduce both the incidence and severity of symptoms previously observed with this dose. In addition, some of the signs of peripheral neuropathy were also reduced (vibration sense at the toes, interference with ADLs, gait, sensory deficits to pinprick) in patients who received glutamine compared with those who did not. Because a large proportion (38%) of the patients entered this trial with abnormal reflexes, it is not surprising that this parameter did not show any difference between the two groups.

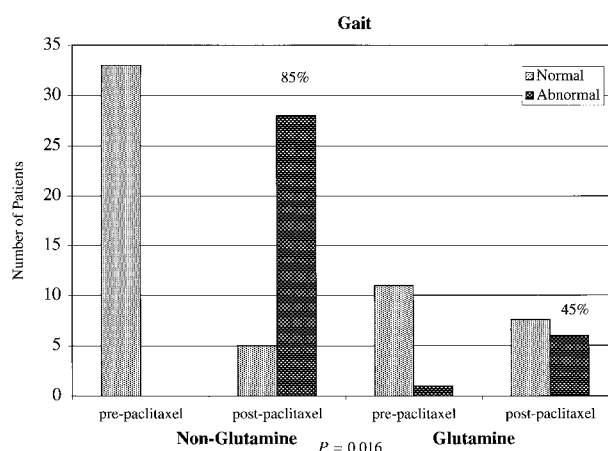


Fig. 1 Gait evaluated pre- and postpaclitaxel in the glutamine and nonglutamine groups.

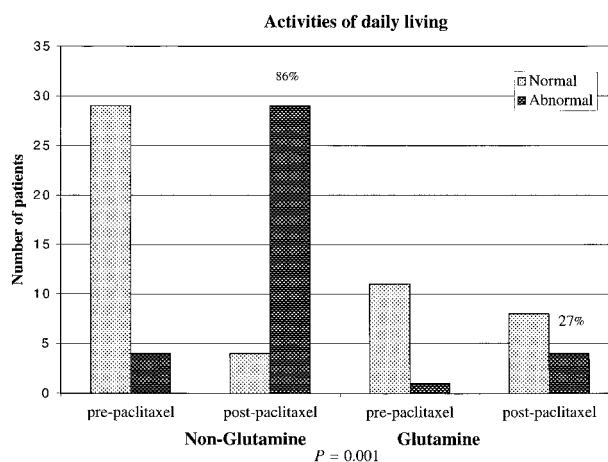


Fig. 2 ADL evaluated pre- and postpaclitaxel in the glutamine and nonglutamine groups.

We opted to use the glutamine source cited in the original report because it is unknown whether all glutamine preparations are equivalent. The product that we used did not contain antioxidants because of unknown potential interactions with chemotherapy.

The ability to reproducibly quantify peripheral neuropathy is challenging (25, 26). The level of symptoms, or signs on physical exam, is not always predictive of whether or not ADLs are affected, and it is the ADL that patients often consider the most important parameter. In this study, ADL were much less affected in those patients who received glutamine. A debate continues in the neurological literature as to whether nerve conduction studies are useful in objectively assessing peripheral neuropathy (27–30). In this study we found that while amplitudes and conduction velocities usually deteriorated, glutamine did not exert the protective effect mirrored in the physical exam. However, the ability to detect small or moderate differences in nerve conduction velocity or amplitude is limited by our small sample size and, hence, must be interpreted cautiously.

Whereas this was not a randomized trial, the entry criteria were identical for all of the patients entering this trial as was the degree of prior therapy with neurotoxic drugs. Statistical analysis reveals that all of the pretreatment parameters were well balanced between the glutamine and nonglutamine groups. Solely quantifying the amount of taxane or *Vinca* alkaloid that was received prior to entering the study, to compare both groups, is unreliable for matching these two groups because the neurotoxicity profile observed may vary widely, depending on the chemotherapy schedule as well as the interpatient variability. In addition, all of the patients except one were examined by a single reference neurologist (C. B.).

A major limitation of this study is that it was not placebo controlled, and significant placebo-effects have been described across a variety of studies (31). Because there are a number of ongoing randomized placebo-controlled studies of the effect of glutamine on myalgias and arthralgias after standard-dose paclitaxel (Drs. Loprinzi and Grauwels, Mayo Clinic) and on peripheral neuropathy (L. V., Columbia University), this issue will be addressed in the near future.

In contrast to other parameters, the grading of myalgias was not collected prospectively, and retrospective chart reviews were performed. The average symptoms of myalgias and arthralgias were mild or absent in patients who received glutamine and were moderate to severe in patients who did not receive glutamine after paclitaxel administration.

The potential role of glutamine as a neuroprotectant may be better understood based on the current proposed mechanism for the development of peripheral neuropathy. Dr. DeSantis *et al.* (32) assessed circulating nerve growth factor levels in 23 patients undergoing chemotherapy with neurotoxic agents. As peripheral neuropathy worsened, serum levels of nerve growth factor declined (32). Glutamine is known to up-regulate nerve growth factor mRNA in an animal model (33); therefore, this may be a plausible mechanism for the benefit from glutamine. To test this hypothesis, we are currently measuring levels of nerve growth factor in the banked serum of these patients. The other possibility is that glutamine may alter the perception of pain in the cerebral cortex. Glutamine functions as a precursor amino acid for excitatory neurotransmitters such as glutamate and γ aminobutyric acid (GABA) (34). This glutamate/glutamine cycle is highly compartmentalized and subject to a complex transport mechanism across the blood-brain barrier (35). Glutamine is taken up into astrocytes, where it is converted to glutamate by glutamine synthetase and released into the synapse. However, all of the glutamate is not used in a neurotransmitter capacity but is also used to satisfy neuronal energy requirements. It has also been hypothesized that high systemic levels of glutamine may down-regulate the conversion of glutamine to the excitatory neuropeptide, glutamate, which may also account for the reduced symptoms observed in patients who received glutamine (36).

One concern is that glutamine might protect the tumor from the cytotoxic effects of chemotherapy. In this small series, we have not noted any decrease in response rate or increase in the relapse rate. Furthermore, we did not note any change in paclitaxel pharmacokinetics with glutamine administration (data not

shown) and unpublished data generated by Pharmaceutical Research Institute in mice confirm our observation.⁴

As clinicians who treat patients on a daily basis are aware, managing the toxicity of commonly used drugs is an ongoing challenge in optimally caring for our patients.

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⁴ Terry Dugan, Ph.D., personal communication.

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