



**Emerging Evidence of the Effectiveness
of Glutamine as a Protectant Against
Semisynthetic
TAXOL[®] (paclitaxel) Injection-Induced
Myalgia/Arthralgia and Neurotoxicity**

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Semisynthetic TAXOL[®] (paclitaxel) Injection-Associated Toxicities and Current Clinical Management

Neuropathy can be a dose-limiting toxicity of TAXOL chemotherapy.¹ The neurologic symptoms produced by TAXOL are predominantly sensory neuropathies in the feet and hands, characterized by numbness, dysesthesia, and paresthesias.² Grade 2/3 neuropathies occur in approximately 20% to 40% of patients and usually occur after multiple cycles.³ Although the mechanism by which TAXOL induces neuropathy is not well understood, electrophysiological data suggest that axonal degeneration and demyelination are involved.² TAXOL-induced neuropathy may be more pronounced with shorter infusion schedules than with longer schedules.⁴ Agents that have been investigated in both animal models and in humans for the treatment of TAXOL-induced neuropathy include antihistamines,⁵ amitriptyline,⁶ amifostine,⁷ nerve growth factor,^{8,9} pyridoxine, carbamazepine,^{10,11} and the ACTH analog, ORG 2766.¹²

Transient myalgias and/or arthralgias are commonly observed in patients following treatment with TAXOL, usually occurring 2 to 3 days after treatment and resolving within 5 to 6 days.^{6,13} The incidence and severity of arthralgias and myalgias appear to correlate with TAXOL dose,¹³⁻¹⁵ with doses of > 190 mg/m² being associated with more frequent and severe arthralgias and myalgias.¹ A variety of agents have been used to treat arthralgias and myalgias associated with TAXOL therapy, including nonsteroidal antiinflammatory drugs,^{16,17} corticosteroids,^{16,18} antihistamines,⁵ and anticonvulsants.¹⁹

Evidence Supporting Investigation of Glutamine as a Neuroprotectant in Cancer

Physiological Importance of Glutamine

Glutamine is the most abundant amino acid in the blood, comprising 50% of free amino acids in the body.²⁰ Glutamine is a source of precursor nitrogen for the synthesis of RNA, DNA,²¹ and some neurotransmitters.²² Glutamine plays a vital role in several physiologic functions, including the transfer of nitrogen between tissues, and the regulation of glycogen synthesis.²³

Although traditionally considered to be a nonessential amino acid, evidence that glutamine deficiency may occur as a result of conditions such as extreme physical exertion, trauma, and sepsis has led to the reclassification of glutamine as a conditionally essential nutrient. Daily consumption of glutamine is typically less than 10 g. However, loss of glutamine as a result of certain stress states may increase the requirement for glutamine to 20 to 40 g per day.²²

Chemoprotective Effects

Neuroprotectant activity of glutamate was demonstrated in experiments conducted in rats, in which glutamate ameliorated both sensory and motor neuropathy associated with vincristine administration.²⁴ Experiments suggesting that glutamate has potential protectant activity against neurotoxicity induced by vinblastine and vincristine (which, like semisynthetic TAXOL® [paclitaxel] Injection, act by binding to tubulin) provided a rationale for conducting animal studies evaluating glutamine as a protectant against TAXOL-induced neurotoxicity.^{25,26} Boyle and coworkers²⁷ evaluated the use of glutamate to protect against TAXOL-induced neurotoxicity in Dark Agouti rats (n = 12). When TAXOL, 9 mg/kg, was administered intraperitoneally twice weekly to rats, 100% of the animals developed gait disturbances. Addition of glutamate, 500 mg/kg/d, to their drinking water delayed the onset of all signs of neuropathy, and allowed the rats to tolerate a significantly higher cumulative dose of TAXOL. As reported by these investigators in separate studies, glutamate supplementation did not interfere with the cytotoxicity of TAXOL against a Dark Agouti rat adenocarcinoma (DAMA) grown

subcutaneously. The investigators concluded that glutamate, in this animal model, appears to be an effective neuroprotectant that does not interfere with the antitumor activity of semisynthetic TAXOL® (paclitaxel) Injection.²⁷

Effects on Tumor Growth and Drug Uptake

Nutritional supplements that augment or improve cell function are used cautiously in cancer treatment, because of the possibility of preferential use of such nutrients by tumors or interactions with chemotherapy drugs.²⁸ To date, no preclinical studies have demonstrated stimulatory effects of glutamine supplementation on tumors. Also, administration of oral glutamine in rats was shown to preferentially increase retention of methotrexate in tumor tissue over that in normal host tissue.²⁹

Clinical Evidence

Tolerability and Drug Interactions

There have been many trials investigating glutamine as an antimucositis and anti-diarrheal agent, with mixed results. In these studies with various chemotherapeutic agents, glutamine supplementation was reported to have no adverse effects. In a study of 28 patients being treated with 5-fluorouracil and folinic acid for gastrointestinal cancer, oral glutamine had no significant effect on oral mucositis, but was reported by the investigators to be well tolerated with no apparent adverse effects.³⁰ Glutamine-supplemented total parenteral nutrition did not ameliorate chemotherapy-induced toxicity in a placebo-controlled pilot study of patients (n = 5; 20 treatment cycles) with hematologic malignancies. However, no side effects or allergic reactions were noted and, furthermore, the treatment was associated with weight gain.^{31,32} Glutamine was also not associated with toxicity in a phase I trial of patients (n = 9) with inflammatory breast cancer treated with methotrexate.²⁹

Likewise, though glutamine did not reduce the incidence of doxifluridine-induced diarrhea in a double-blind randomized study of patients (n = 65) with advanced breast cancer, the study investigators concluded that glutamine did not lessen tumor response to chemotherapy.³²

Efficacy Results

Savarese and colleagues reported results obtained in 5 patients using glutamine to alleviate semisynthetic TAXOL® (paclitaxel) Injection-induced myalgias and arthralgias. These patients received TAXOL at 175 to 200 mg/m² over 1 to 3 hours, alone or in combination; symptoms of severe myalgia or arthralgia occurred within 24 to 36 hours after the initial dose in all 5 patients. When the same patients were given glutamine 10 g 3 times daily beginning 24 hours after the second TAXOL cycle, no myalgia or arthralgia was reported; and 2 of the 5 patients received further doses of TAXOL without recurrence of symptoms.³³

Beneficial effects of glutamine in patients undergoing chemotherapy have been noted. In a pilot study of 12 patients, a suspension of L-glutamine 4 g, administered as swish and swallow twice daily, significantly reduced the severity of chemotherapy-induced stomatitis.³⁴ Similarly, in a placebo-controlled study of 24 patients undergoing chemotherapy, oral glutamine (2 g/m² bid) taken during and after chemotherapy significantly reduced both the duration and severity of stomatitis.³⁵

In one study (n = 13), in patients with advanced esophageal cancer undergoing radiochemotherapy, glutamine supplements were shown to protect immune and gut barrier function in patients, reducing gut permeability.³⁶ Beneficial effects of glutamine supplementation have also been reported in patients following surgery, radiation treatment, or bone marrow transplantations, or in patients suffering from injury, sepsis, or burns.²¹

Glutamine for Semisynthetic TAXOL® (paclitaxel) Injection-Related Neuropathy, Myalgia, and Arthralgia: The New York Presbyterian Hospital—Columbia Campus Experience

We recently conducted a phase II study in women with responding metastatic breast cancer treated with high-dose chemotherapy plus stem cell support. TAXOL was used in the first cycle of high-dose chemotherapy. Forty-five women received 3 cycles of high-dose chemotherapy alone; the final 12 women were selected to receive glutamine after the high-dose TAXOL. Patients with preexisting > grade 2 neuropathy were excluded from the study, although many patients had sensory neuropathy and mild paresthesias upon entry. Patients in both groups (ie, receiving or not receiving glutamine) were well balanced for pretreatment level of peripheral neuropathy.²⁸

The first cycle of high-dose chemotherapy in our study consisted of TAXOL given 825 mg/m² as a continuous infusion over 24 hours. After a 3-day washout period, patients received peripheral stem cell infusion and were managed as outpatients. Approximately 3 weeks later, patients received a second cycle of chemotherapy: melphalan at 180 mg/m², given over 2 days on an outpatient basis. On the third day of this cycle, patients received peripheral blood stem cells and were then followed as outpatients. The final cycle of chemotherapy was CTCB (STAMP V), which required a 2.5 to 3 week hospital stay and which comprised total doses of cyclophosphamide 6 g/m², thiotepa 500 mg/m², and carboplatin 800 mg/m² administered over 4 days. After a 2-day washout period, patients received peripheral stem cells and remained hospitalized until blood count recovery, typically 8 to 10 days following stem cell infusion.²⁸ Glutamine was given 10 g orally, 3 times daily, starting 24 hours after cessation of the TAXOL chemotherapy (according to the dosage schedule suggested by Savarese and colleagues) to 12 patients. A single neurologist examined these patients before and after they received TAXOL.^{28,33}

We have found that high-dose TAXOL therapy was usually associated with the development of transient grade 3 sensory neuropathy, and motor weakness, which interfered with patients' activities of daily living (ADL). In the past we typically prescribed gabapentin and analgesics for neuropathy, arthralgias, and myalgias.²⁸

An analysis of the data revealed that patients who received glutamine experienced less acute sensory and motor neurologic impairment than those who did not receive glutamine. Physical examination showed that patients who received glutamine had less frequent development of moderate to severe dysesthesias and numbness in the fingers and toes than patients who did not receive glutamine. Glutamine also reduced the amount of transient motor weakness, interference with ADLs, and gait disturbance. Myalgias also appeared to be reduced in the glutamine group compared with the nonglutamine group.²⁸

Based on these observations in this pilot trial, we conclude that glutamine appears to be effective in reducing the incidence and severity of semisynthetic TAXOL® (paclitaxel) Injection-induced neuropathies.

Randomized Studies of Glutamine in Cancer

Randomized trials investigating the role of glutamine in ameliorating chemotherapy-induced adverse effects are ongoing (see Table 1).

Table 1. Ongoing Trials Incorporating Glutamine

Study	Treatment	Accrual Goal
Savarese et al Phase II ^{37,38}	Neoadjuvant semisynthetic TAXOL® (paclitaxel) Injection 50 mg/m ² /wk, 3-h IV with RT (50.4 Gy in 28 fractions) and G 10 g PO tid beginning 3 d before the 1st d of radiation therapy, continuing until 2 wk following the completion of radiation therapy	24
Mayo Clinic MC99C2 Randomized Phase III ³⁹	<i>Arm A:</i> TAXOL* d 1 G 10 g PO tid, d 1-5 TAXOL* d 22 Placebo PO tid, d 1-5 <i>Arm B:</i> TAXOL* d 1 Placebo PO tid, d 1-5 TAXOL* d 22 G 10 g PO, tid d 1-5	72

IV = intravenously; RT = radiotherapy; G = glutamine; PO = orally; ECOG PS = Eastern Cooperative Oncology Group performance status; CT = chemotherapy.

*TAXOL doses not reported.

Patients

Confirmed primary adenocarcinoma of the rectum;
no metastatic disease; ECOG PS 0-2;
no prior CT, RT, or immunotherapy

Objectives

Evaluate safety of semisynthetic TAXOL® (paclitaxel) Injection,
glutamine, and RT

History of cancer of any histology; ≥ 1 prior course of
TAXOL q 3 wk that caused myalgias or arthralgias

To assess the effect of oral G compared with placebo in
preventing TAXOL-associated myalgia/arthralgia; to assess
the toxicity related to glutamine use when given to prevent
or alleviate TAXOL-associated myalgia/arthralgia

Summary

Peripheral neuropathy remains a dose-limiting toxicity of standard and high-dose semisynthetic TAXOL® (paclitaxel) Injection chemotherapy. Myalgia and arthralgia are other side effects associated with TAXOL use.⁶ Emerging evidence suggests that glutamine supplementation may be an effective way of ameliorating these side effects.

In preclinical studies, glutamate was shown to delay the onset of neuropathy.²⁷ Clinical data from 5 patients with cancer suggested that glutamine was effective in preventing TAXOL-associated myalgia and arthralgia.³³ In my personal experience, I have seen glutamine lessen symptoms of neuropathy in a subset of patients with metastatic breast cancer enrolled in a phase II study responding to high-dose TAXOL chemotherapy.²⁸ The results of ongoing randomized clinical trials will assist in defining the role of glutamine in the clinical management of TAXOL-associated side effects.

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