

# Prevention of chemotherapy and radiation toxicity with glutamine

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*Goals of the work.* Malignancy produces a state of physiologic stress that is characterized by a relative deficiency of glutamine, a condition that is further exacerbated by the effects of cancer treatment. Glutamine deficiency may impact on normal tissue tolerance to antitumor treatment, and may lead to dose reductions and compromised treatment outcome. Providing supplemental glutamine during cancer treatment has the potential to abrogate treatment-related toxicity. We reviewed the available data on the use of glutamine to decrease the incidence and severity of adverse effects due to chemotherapy and/or radiation in cancer patients.

*Methods.* We performed a search of the MEDLINE database during the time period 1980–2003, and reviewed the English language literature of both human and animal studies pertaining to the use of glutamine in subjects with cancer. We also manually searched the bibliographies of published articles for relevant references.

*Main results.* The available evidence suggests that glutamine supplementation may decrease the incidence and/or severity of chemotherapy-associated mucositis, irinotecan-associated diarrhea, paclitaxel-induced neuropathy, hepatic veno-occlusive disease in the setting of high dose chemotherapy and stem cell transplantation, and the cardiotoxicity that accompanies anthracycline use. Oral glutamine supplementation may enhance the therapeutic index by protecting normal tissues from, and sensitizing tumor cells to chemotherapy and radiation-related injury.

*Conclusions.* The role of glutamine in the prevention of chemotherapy and radiation-induced toxicity is evolving. Glutamine supplementation is inexpensive and it may reduce the incidence of gastrointestinal, neurologic, and possibly cardiac complications of cancer therapy. Further studies, particularly placebo-controlled phase III trials, are needed to define its role in chemotherapy-induced toxicity.

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**Key words:** Glutamine; chemotherapy; radiation; cancer; chemoprotectant.

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## INTRODUCTION

Glutamine is a neutral amino acid that acts as a substrate for nucleotide synthesis in most dividing cells. It is the most abundant amino acid in free blood, and constitutes 60% of the total free amino acid pool in skeletal muscle (1). Glutamine is a “nitrogen rich” amino acid, containing two amine

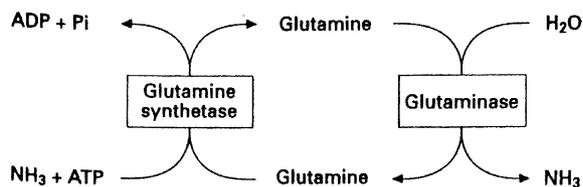
groups per molecule. This characteristic underlies its critical role as a nitrogen transporter, providing precursor nitrogen for the synthesis of purines and pyrimidines. The significance of glutamine to metabolic homeostasis becomes evident during periods of stress, when it becomes a conditionally essential amino acid (2).

In patients with cancer, marked glutamine depletion develops over time; cancer cachexia is marked by massive depletion of skeletal muscle glutamine. This can have a negative impact on the function of host tissues that are dependent upon adequate stores of glutamine for optimal functioning (e.g., intestinal epithelial cells (3–5) and lymphocytes (6)). Furthermore, the extent of normal tissue damage from radiation or chemotherapy may be influenced by the presence of adequate tissue glutamine stores. Both of these facts support a possible therapeutic role for glutamine in the prevention of host normal tissue toxicity during cancer treatment.

We will review the pertinent biology and metabolism of glutamine, discuss its role in the normal function of the immune system and the gastrointestinal (GI) tract, and explore the available data on the use of supplemental glutamine to prevent specific toxicities related to radiation or chemotherapy. The use of supplemental glutamine in the setting of sepsis is not considered here.

## BIOLOGY AND METABOLISM OF GLUTAMINE

Glutamine metabolism is regulated by two principal enzymes, glutaminase and glutamine synthetase (Figure 1). Glutaminase hydrolyzes glutamine to ammonia and glutamate, a process that is central to total body nitrogen exchange; high glutaminase activity is characteristic of many rapidly dividing cells (7). Glutamine synthetase catalyzes the synthesis of glutamine from glutamate and ammonia, which, *in vivo*, occurs primarily in skeletal muscle and brain (8). Most tissues are either predominantly glutamine consumers, having relatively high glutaminase ac-



**Figure 1** Actions of the two key enzymes, glutamine synthetase and glutaminase in glutamine metabolism. ADP, adenosine 5'-diphosphate; ATP, adenosine 5'-triphosphate; NH<sub>3</sub>, ammonia; Pi, phosphate. (Reprinted from Hall, JC, *et al.* Glutamine. *Br J Surg* 1996; **83**: 305.)

tivity, or glutamine producers with high glutamine synthetase activity.

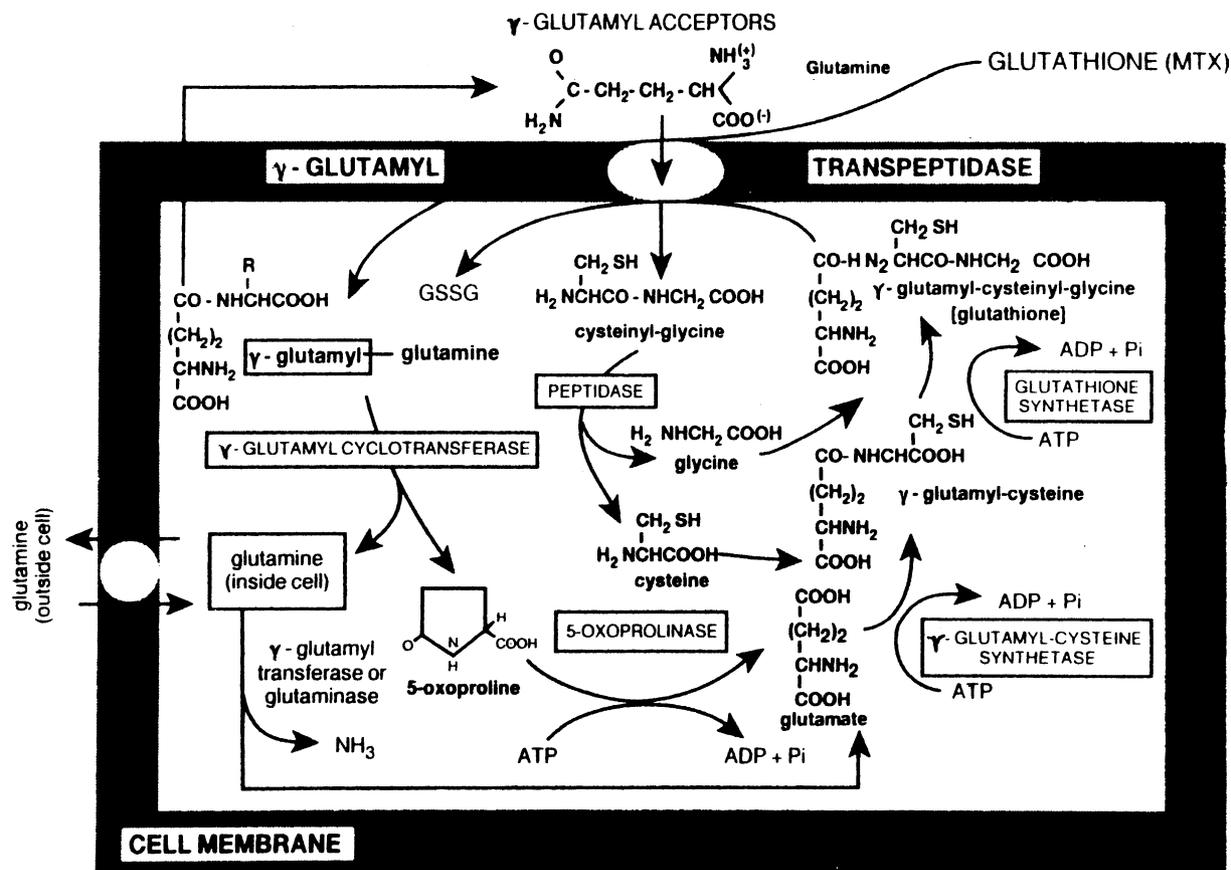
Enterocytes play a major role in glutamine metabolism. Glutamine is the primary oxidative fuel for the gut epithelium, and is necessary for the maintenance of intestinal structure in normal and stressed states. It has trophic effects on the bowel mucosa (3,5,9). Glutamine uptake and metabolism by the small bowel accelerates during states of catabolic stress (10–12). This additional glutamine is derived from skeletal muscle, which releases glutamine during periods of increased metabolic demand (13,14).

## GLUTAMINE AND GLUTATHIONE

Glutathione (GSH), a byproduct of glutamine metabolism, protects against oxidant injury in normal tissues. The gut is a major organ of GSH synthesis, which can be increased three-fold by the provision of supplemental glutamine (15). In the presence of oxidative stress, glutamine is rate limiting for GSH synthesis (16).

The GSH concentration in tumor cells is 5 to 50-fold higher than in noncancer cells (17), and high levels of GSH mediate resistance to chemotherapy and radiation (18–20). In normal tissues, toxicity due to radiation and chemotherapy is magnified when GSH stores are depleted, an effect that may be reversed by the administration of supplemental glutamine (21). In contrast, glutamine supplementation appears to *decrease* intratumoral GSH stores, an effect that may preserve tumor response to cytotoxic therapy (21–24). These data suggest that glutamine may enhance the selectivity of antitumor drugs by protecting normal tissues from, and possibly sensitizing tumor cells to chemotherapy-related injury. The net result could be an improvement in the therapeutic index.

There are several possible explanations for the dichotomy in GSH metabolism in tumor and host tissues. One possibility is that local increases in glutamate concentration inhibit GSH transport into tumor mitochondria, but not the mitochondria of normal cells (24). Another hypothesis is that glutamine downregulates tumor GSH metabolism while at the same time upregulating the production of GSH in normal tissues (21). Normally, intracellular GSH production requires the enzyme oxoprolinase, which catalyzes the formation of  $\gamma$ -glutamyl-glutamine dipeptide, the immediate precursor of GSH (Figure 2). Tumor cells have a relatively more acidic intracellular environment compared to normal cells, thus inactivating the pH-sensitive oxoprolinase. In normal cells, this block can be overcome by



**Figure 2** Proposed mechanism for increased host and decreased tumor intracellular glutathione (GSH) levels in the presence of glutamine. In normal host tissues, the metabolism of glutamine to GSH requires the 5-oxoprolinase enzyme. If the enzyme is blocked by an acidic environment, it can be bypassed by an alternate since excess glutamine upregulates the enzyme  $\gamma$ -glutamyl transferase. The more acidic environment of tumor cells inhibits the oxoprolinase, and this block cannot be bypassed because the tumor cannot upregulate the enzyme  $\gamma$ -glutamyl transferase. (Reprinted from Klimberg, VS, *et al.* Glutamine, cancer and its therapy. *Am J Surg* 1996;172:418.)

providing excess glutamine, which acts as a  $\gamma$ -glutamyl acceptor, forming  $\gamma$ -glutamyl-glutamine dipeptide and upregulating the enzyme  $\gamma$ -glutamyl transferase (glutaminase). In contrast, these enzymes cannot be upregulated in the tumor cells, and the net result is that intracellular GSH levels are depleted in tumor but not in normal tissue (16). This hypothesis is supported by data showing that tumors containing high levels of  $\gamma$ -glutamyl transferase are more resistant to cytotoxic chemotherapy (25).

## DIETARY GLUTAMINE AND GLUTAMINE SUPPLEMENTATION

Traditional Western diets taken by mouth usually contain less than 10g of glutamine per day. However, during periods of severe metabolic stress or catabolic insult, 20 to 40g may be required to maintain homeostasis. The safety of glutamine supplementation at these levels was shown in one dose-response study, in which no evidence of clin-

ical toxicity or generation of toxic metabolites was observed at doses up to 0.3 g/kg; nitrogen retention was optimally enhanced when glutamine was administered at a dose of 0.57 g/kg per day (26). Whole blood concentrations rose in proportion to the orally administered glutamine load, with levels peaking 30 to 45 min after glutamine ingestion, and declining steadily to the normal range with 1.5 to 6 h, depending on the dose. Administration of oral glutamine resulted in a dose-dependent increase in the concentrations of several amino acids that are known products of glutamine metabolism (e.g., alanine, citrulline, and arginine). With short-term intravenous infusions elimination followed a two-compartment model, with a rapid initial phase ( $t_{1/2}$   $12 \pm 2$  min) and a longer terminal disappearance phase ( $t_{1/2}$   $67 \pm 11$  min). The volume of distribution following intravenous administration was similar to the distribution of the extracellular fluid compartment; it was significantly less than that derived from oral studies (210 mL/kg *versus* 512 to 1254 mL/kg).

Supplemental glutamine can be administered enterally or parenterally. Although glutamine is

similarly metabolized whether it enters the gut mucosal cells across the brush border from the lumen, or across the basolateral cell membrane from the arterial blood (27,28), enteral administration appears to provide an enhanced gut protective effect (29). Ready to use enteral supplements are not routinely supplemented with glutamine because of instability of glutamine solutions. Standard pills or capsules are expensive and contain very small amounts of glutamine (500 to 1000 mg) relative to the daily dosages shown to be effective (30 g). Powdered glutamine is the supplement of choice because it is cost effective, easy to use, well absorbed, and well tolerated (26,30,31). Glutamine powder is virtually tasteless and can be mixed into any beverage or soft/moist food or dissolved in water and flushed into a feeding tube. Daily oral glutamine doses are best divided throughout the day to increase enterocyte contact.

There may be clinical settings in which oral supplemental glutamine is relatively contraindicated. In patients with hyperammonemia and hepatic encephalopathy, glutamine doses may need to be reduced or eliminated because intestinal glutamine catabolism is responsible for approximately 50% of the ammonia released into the portal vein (32). There are no published data on the need for dose reduction in patients with renal insufficiency.

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## DOES GLUTAMINE STIMULATE TUMOR GROWTH?

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*In vitro* evidence of the dependence of tumor growth on glutamine has deterred its use in patients with cancer (33). Glutamine is a principal fuel for rapidly proliferating tumors, and host glutamine stores are inversely related to tumor growth, leading some to describe tumors as glutamine traps, contributing to host depletion of glutamine stores and cancer-related cachexia (34,35). However, multiple studies

have failed to show stimulation of malignant growth in tumor-bearing hosts supplemented with glutamine (3,36–38). In fact, accumulating *in vivo* evidence suggests that supplemental glutamine may actually decrease tumor growth, possibly by upregulating various aspects of the immune system (Figure 3) (31,36,37,39–41).

Lymphocytes, including natural killer (NK) cells, depend upon adequate supplies of glutamine to proliferate in response to an antigenic challenge. Supplemental glutamine enhances NK cell-mediated tumor cell lysis, and this is associated with decreases in tumor volume (6,36,42,43). The relationship between tumor growth, NK cell activity, and GSH was studied in a rat breast cancer model, in which equal numbers of Fisher 344 rats with breast cancer xenografts were fed either supplemental glutamine or placebo (isonitrogenous amounts of Freamine) for seven weeks, then sacrificed (43). Compared to placebo, the glutamine supplemented group had higher measured NK cell activity, higher blood levels of GSH and nearly one-half the tumor volume.

Oral glutamine also appears to exert a local immunostimulatory effect, increasing intestinal T-cell counts after 10 days of therapy in animal models (44). This local effect may be relevant to the preservation of gut integrity by glutamine (see below).

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## GLUTAMINE SUPPLEMENTATION AND THE GASTROINTESTINAL TRACT

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Glutamine mediates several important protective influences on the GI tract. In animal models, increases in gut permeability, a marker of severe illness in hosts undergoing catabolic stress (45), can be prevented with parenteral or enteral glutamine (46). Furthermore, oral glutamine supplementation supports GI mucosal growth, thereby preventing atrophy of the intestinal mucosa in patients receiving total parenteral nutrition (TPN) (5,47). Finally, glu-

Upregulation of antitumor immunity

    Lymphocyte proliferation

    Enhancement of NK cell-mediated tumor lysis

    Local immunostimulatory effect in gastrointestinal tract

Depletion of intratumoral glutathione stores, potentially preserving cytotoxic antitumor tumor response

Increases glutathione stores in normal tissue, providing protection from treatment-related toxicity

**Figure 3** Potentially favorable influences of glutamine in patients with malignant tumors.

tamine enhances nutrient transport and facilitates the enteral absorption of electrolytes in animals with experimental diarrhea (48).

The protective effect of glutamine on the GI tract might be attributable to induction of heat shock proteins (HSPs), particularly HSP 72 (49). HSP 72 is part of a natural defense mechanism, called the "stress response" that is induced in response to a variety of cell stressors. *In vitro*, glutamine enhances cell survival in response to a variety of stressful stimuli via induction of HSP 72 (50), an effect that was significantly blunted when the HSP 72 gene was blocked via anti-sense inhibition (51). The induction of gut HSP 72 (and other heat shock proteins) by glutamine has now been demonstrated in an *in vivo* model (52) and *in vivo* gut protection studies related to HSP 72 are currently underway.

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#### Glutamine supplementation to protect against radiation-related toxicity

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##### *Glutamine supplementation and radiation therapy of the gastrointestinal tract*

Radiation enteritis is a significant clinical problem in patients receiving ionizing radiation directed to the abdomen or pelvis. The mucosal injuries described in such patients include destruction of crypt cells, decrease in villus height, and ulceration and necrosis of the gastrointestinal epithelium (53). Resulting acute symptoms may include abdominal pain, bloody diarrhea, malabsorption, and in some cases, bacterial translocation due to altered gut permeability (54). Potential late complications include strictures, obstruction, perforation, and fistula formation.

In animal models, glutamine supplementation before or after whole abdominal irradiation appears to inhibit bacterial translocation and decreases the likelihood of both acute and chronic toxic radiation effects on the lower intestine (9,55–57). However, these benefits have not been realized in patients undergoing radiation therapy of the abdomen or pelvis. The inability of low doses of supplemental glutamine to influence acute radiation toxicity was shown in a randomized trial of 129 patients receiving pelvic radiotherapy who were randomly assigned to glutamine (4g orally twice daily) or placebo (58). There were no significant differences in the incidence, amount, or maximum severity of diarrhea.

##### *Glutamine prevention of radiation-induced mucositis*

Very limited data suggest a possible protective effect of oral glutamine in radiation-induced muco-

stitis. In one randomized trial of 17 patients who were receiving radiation for head and neck cancer, those who were randomized to oral glutamine (2g swished for 3 min, four times daily during radiation) had a significantly shorter duration of objective mucositis, less severe maximum grade of mucositis, and less subjective grade three or worse mucositis than did the placebo group (59).

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#### Glutamine in patients receiving standard dose chemotherapy

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Cytotoxic chemotherapy often produces GI tract epithelial injury, with resultant mucositis, and/or enterocolitis. Depending upon the specific drug, the severity of these effects may force a reduction in dose, which in some clinical situations (e.g., adjuvant therapy for resected colorectal cancer), could compromise the positive impact of treatment on survival. Beneficial effects of supplemental glutamine during chemotherapy have been recognized (60,61). In animal studies, oral glutamine enhances the antitumor effect of methotrexate while simultaneously decreasing host morbidity and mortality (21,23,61,62). Some have hypothesized that glutamine increases the proportion of polyglutamated methotrexate, improving intratumoral retention (23,62), while others attribute the improved therapeutic ratio to alterations in GSH metabolism as described above (21).

##### *Chemotherapy-related mucositis*

Mucositis is a common toxicity of cancer chemotherapy, and attributed to direct damage to the mucosal epithelial cells. Despite the frequency of this side effect, and its significance in terms of quality of life, relatively few treatments have been shown to be of benefit in reducing the severity or duration of mouth pain. Oral cryotherapy is modestly useful for patients receiving bolus 5-fluorouracil (5-FU)-containing regimens (63–65), while preemptive systemic administration of granulocyte-macrophage colony-stimulating factor (GM-CSF) (66,67) and mouthwash formulations of GM-CSF (68) have a modest beneficial impact in selected patients. The benefit of topical antimicrobials and protective agents (e.g., sucralfate) has been difficult to prove.

It is rational to hypothesize that oral mucosa may be afforded the same benefit as intestinal epithelium from oral glutamine supplementation. However, simply providing glutamine systemically does not appear to alter the incidence of clinically apparent mucositis. As an example, multiple studies have failed to demonstrate a protective effect on either

oral mucositis or esophagitis by parenteral administration of glutamine (47,69–71).

In contrast, topical application of glutamine, which increases local contact with the oral mucosa, may provide benefit, but not for all chemotherapy agents (Table 1) (72–75). In particular, there appears to be no significant benefit for patients receiving 5-FU, although in one of these studies, all patients received oral cryotherapy before the swish and swallow treatment, perhaps blunting the beneficial effects of oral glutamine (73).

The variability of these results may also reflect the importance of glutamine dose in preventing chemotherapy-induced mucositis. One of us has noted significant benefit from higher doses of glutamine (0.25 g/kg per day divided into three doses) in a swish and swallow preparation administered in a sweet syrup for a number of pediatric patients who had severe mucositis after multiple courses of chemotherapy. (P Wischmeyer, unpublished observations, April, 2000).

#### *Glutamine and prevention of chemotherapy-related diarrhea*

Diarrhea is a common complication of chemotherapy; it can have profound effects on the patient's quality of life, may be life-threatening, and may have a negative impact on the chemotherapy regimen by forcing either treatment delays or dose reductions. Reducing or delaying the administration of the next cycle of chemotherapy in response to dose limiting toxicity may decrease efficacy.

Under normal conditions, intestinal fluids remain in homeostasis, maintaining a balance between fluid secretion and absorption. Alteration of this balance, by either increased secretion or reduced absorption,

leads to diarrhea. Chemotherapeutic agents such as 5-FU can cause diarrhea by directly damaging the intestinal epithelium. The resulting denuded mucosa has increased permeability, and is unable to absorb fluid (76–78).

Opioid agonists (e.g., loperamide, diphenoxylate, or tincture of opium) are standard treatments for chemotherapy-induced diarrhea. These agents act by slowing GI peristalsis, reducing secretions, diminishing the defecation reflex, and increasing sphincter tone. General guidelines for treatment and prevention of chemotherapy-induced diarrhea have been published (79).

Agents that protect the GI tract epithelium from toxic damage may also decrease the incidence and/or severity of chemotherapy-induced diarrhea. As noted above, glutamine mediates several important protective influences on the GI tract; benefit may be dependent upon apical (luminal) rather than basolateral (systemic) exposure (29).

The initial suggestion of benefit from glutamine came from an observational study of 11 children with acute myelogenous leukemia undergoing induction chemotherapy along with oral glutamine (6 g PO three times daily) were compared to 22 unsupplemented children who were concurrently treated but not randomly assigned (Table 2) (80). Although the overall incidence of diarrhea was no different, the glutamine supplemented patients had a significantly shorter duration of diarrhea, and a lesser incidence of > 6 stools per day.

Subsequent literature reports on the protective effect of oral glutamine in patients receiving chemotherapy have been mixed (Table 2). In particular, conflicting data have been published regarding the protective benefit of glutamine in patients receiving

**TABLE 1** Glutamine for chemotherapy-induced mucositis

Study	n	Glutamine dose, route	Chemotherapy agent(s)	Outcome
Skubitz, 1996 (72)	14	2 g/m <sup>2</sup> , topical	Variety of regimens containing doxorubicin, etoposide, ifosfamide, carboplatin	Significant decrease in grade and duration of mucositis
Anderson, 1998 (74)	24	Cycle 1 (nonsupplemented) versus Cycle 2 (supplemented) 2 g/m <sup>2</sup> , topical versus topical glycine (placebo)	Variety of regimens containing doxorubicin, ifosfamide, methotrexate, etoposide	Improved quality of life during glutamine-supplemented cycle Significant decrease (4.5 days) in duration and severity of mouth pain Significant decrease (4 days) in number of days of restricted oral intake
Jebb, 1994 (75)	28	16 g per day, by mouth versus placebo	Bolus 5-fluorouracil	No benefit
Okuno, 1999 (73)	134	4 g twice daily, by mouth versus placebo	Variety of fluorouracil-based regimens	No benefit

**TABLE 2** Glutamine for protection from chemotherapy-related diarrhea

Study	n	Glutamine dose, route	Chemotherapy agent(s)	Outcome
Muscaritoli, 1997 (80)	11 supplemented  22 unsupplemented  (nonrandomized)	6 g three times daily, by mouth <i>versus</i> unsupplemented	Induction chemotherapy, AML	No difference in overall incidence of diarrhea  Significant decrease in duration of diarrhea (7 <i>versus</i> 12 days, $p = 0.05$ ) Significant decrease in number of days of >6 stools/day (0/5 <i>versus</i> 6/9, $p = 0.03$ )
Decker-Baumann <i>et al.</i> , 1999 (71)	24	0.4 g/kg per day, IV <i>versus</i> no treatment	Leucovorin-modulated 5-fluorouracil	Significant reduction in histologically demonstrated mucositis and villus height/crypt ratio. No difference in incidence or severity of diarrhea
Bozzetti, 1997 (81)	65	30 g per day, by mouth <i>versus</i> no treatment	Doxifluridine	No difference in incidence or severity of diarrhea
Daniele, 2001 (82)	70	18 g/day by mouth for 20 of every 30 days <i>versus</i> placebo	Leucovorin-modulated 5-FU	Decrease in duration of diarrhea (1.9 <i>versus</i> 4.5 days, $p = 0.09$ ) Significant decrease in number of loperamide tablets taken during first cycle of treatment (0.4 <i>versus</i> 2.6, $p = 0.002$ )
Savarese, 2000 (92)	5	30 g daily, by mouth	Irinotecan	Dose reescalation possible after glutamine supplementation in 5/5

fluorinated pyrimidines, one of the most important classes of drugs causing chemotherapy-induced diarrhea (Table 2) (71,81,82). Thus, the influence of glutamine supplementation on chemotherapy-related diarrhea remains a matter questionable.

#### *Glutamine and irinotecan-induced diarrhea*

Irinotecan is an important drug for the management of metastatic colorectal cancer, but frequently, diarrhea is dose-limiting (83–85). Early diarrhea, observed within 24 h of irinotecan, is cholinergically mediated (86), while late diarrhea appears to be multifactorial, with contributions from dysmotility, secretory factors, and a direct toxic effect of the drug or its metabolite, SN38, on the intestinal mucosa (86,87). The onset and duration of late irinotecan-associated diarrhea varies with the dosing schedule, and older age is a risk factor for severe diarrhea (83,88).

Intensive loperamide treatment reduces the incidence of severe diarrhea in patients receiving irinotecan (89). Although no randomized studies of loperamide in this setting have been performed, the use of an intensive loperamide regimen decreased the incidence of grade 3 to 4 diarrhea from 56 to 9%

in one study of patients treated on a weekly schedule (90).

Glutamine enhances nutrient transport and facilitates the enteral absorption of electrolytes in animals with experimental diarrhea (48,91), an effect which may be germane to the management of post-irinotecan diarrhea. Our preliminary experience in five patients who developed dose-limiting diarrhea during irinotecan treatment supports a role for oral glutamine in alleviating late irinotecan-related diarrhea (Table 2) (92). Of the five patients who required dose reduction because of diarrhea, all were able to reescalate their dose when glutamine supplementation was instituted using Glutamine Enriched Antioxidant Formula, 10 Gm. (Cambridge Nutraceuticals, Boston MA), starting the morning of irinotecan treatment, and administered every 8 h thereafter for 48 h following each dose.

A larger prospective study is underway to confirm these initial findings. Interestingly, a recent report suggests that thalidomide, a glutamic acid derivative with antiangiogenic and immunomodulatory properties, may also be beneficial in the abrogation of dose-limiting GI toxic effects of irinotecan (93).

## GLUTAMINE SUPPLEMENTATION IN PATIENTS UNDERGOING HIGH DOSE CHEMOTHERAPY AND BONE MARROW TRANSPLANTATION

Glutamine supplementation has been extensively studied in patients hematopoietic stem cell or bone marrow transplantation (BMT). Although its potential benefits in this setting are multiple, results of clinical studies have been conflicting (Table 3) (94).

### Glutamine and prevention of mucositis in patients receiving high dose chemotherapy

Mucositis may be particularly severe in patients receiving high dose chemotherapy and stem cell transplantation, and oral glutamine has shown benefit in some (95,96) but not all (97,98,104) studies (Table 3).

### Prevention of gut atrophy in BMT patients receiving total parenteral nutrition

Animals sustained on parenteral nutrition develop atrophy of the gut, an effect that may be prevented by

glutamine supplementation (99,100). As noted above, glutamine and glutamic acid (its immediate precursor) are not constituents of commercially available parenteral nutrition solutions due to concerns about stability at room temperature and the resulting generation of ammonia and pyroglutamic acid (8).

Parenteral glutamine supplementation has been extensively studied in BMT recipients receiving chronic TPN. Three studies indicate that patients receiving TPN with glutamine had a significantly shorter hospital stay compared with those receiving standard parenteral nutrition (47,70,101), while two of these also indicated a reduced incidence of positive blood cultures (Table 3) (47,70). However, in one trial examining oral glutamine supplementation, there was only a suggestion of decreased need for TPN and possibly improved long term survival in those patients who received supplemental glutamine (102). Thus, the impact of glutamine supplementation to prevent gut atrophy in patients undergoing BMT remains controversial.

### Glutamine and hepatic veno-occlusive disease in patients receiving high dose therapy and stem cell transplantation

Veno-occlusive disease (VOD) of the liver is a frequent and serious complication of BMT. Although

**TABLE 3** Randomized trials of glutamine in patients receiving high dose chemotherapy/hematopoietic cell transplantation

Study	n	Glutamine dose, route	Type of transplant	Outcome
Anderson, 1998 (96)	193	1 g/m <sup>2</sup> four times daily, by mouth versus placebo (glycine)	Autologous, allogeneic	Significant decrease in mouth pain and opiate use in patients undergoing autologous transplant only
Canovas, 2001 (97)	NR	20 g daily, by mouth versus placebo (dextrinomaltose supplement)	Autologous	No significant difference in number of days requiring parenteral nutrition (TPN), or the incidence/severity of gastrointestinal toxicity
Ziegler, 1992 (47)	45	0.57 g/kg daily, IV versus placebo (isocaloric, isonitrogenous glutamine-free formula)	Allogeneic	Significant decrease in infection and colonization rates
Schloerb, 1993 (70)	29	TPN with glutamine versus TPN without glutamine	Allogeneic, autologous	Significantly shorter length of hospital stay (LOS, 29 versus 36 days, p = 0.017)
Schloerb, 1999 (102)	66	30 g/day, by mouth versus placebo (glycine)	Allogeneic, autologous	No difference in incidence of positive bacterial cultures, clinical infections, or mortality Six day shorter LOS No difference in LOS, days requiring TPN, culture positivity, sepsis, mucositis, or diarrhea Minimal decrease in need for TPN, ? long-term survival benefit

the pathophysiology is incompletely understood, VOD is thought to be caused by injury to the central veins of the liver with deposition of fibrinogen. The progressive venous occlusion contributes to structural damage of the liver, accompanied by a procoagulant state (103,104). During this time, maintenance of adequate tissue glutathione levels may be important. In a randomized study of 34 patients undergoing this therapy, parenteral glutamine was shown to prevent the decrease in protein C levels and preserve albumin levels, markers of hepatic injury (101). These data suggest that glutamine may preserve hepatic function following BMT.

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#### GLUTAMINE AND PREVENTION OF PACLITAXEL-RELATED MYALGIAS/ ARTHRALGIAS, AND CHEMOTHERAPY- INDUCED NEUROPATHY

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Paclitaxel has become an integral component of chemotherapy regimens for many solid tumors, including breast, lung, and ovarian cancer. Paclitaxel binds to tubulin and promotes microtubule polymerization (105,106). Microtubules play an important role in the development and maintenance of neurons (107,108). Thus, it is not surprising that this agent is associated with neurotoxicity.

Paclitaxel causes a predominantly sensory distal neuropathy, although motor neuropathy has been described in patients receiving higher doses (109). Neurotoxicity is dose-related, cumulative, and is most frequent and severe at doses of 250 mg/m<sup>2</sup> or greater, administered every three weeks (110). Neuropathy appears to be less frequent with 3- and 1-h infusion schedules compared to 24 h infusions, and with weekly as compared with every three week dosing schedules. However, these schedules still induce significant neuropathy in a significant number of patients. As an example, in a phase II study of weekly paclitaxel administered at 175 mg/m<sup>2</sup> for advanced breast cancer, the incidence of grade 3 or 4 neuropathy was 44% (111). A similar schedule of single agent paclitaxel with a slightly lower dose (150 mg/m<sup>2</sup> per week) in patients with lung cancer resulted in a 28% incidence of grade 2 or 3 neuropathy (112).

Preliminary animal studies suggest that glutamine may prevent neurotoxicity caused by administration of vincristine, paclitaxel, or cisplatin (113,114). Boyle studied the influence of dietary glutamine supplementation in a rat model of cytotoxic neuropathy, randomly assigning the animals receiving paclitaxel or cisplatin to get drug alone or with 500 mg/kg/day glutamate in drinking water

(113). End points in this study included measurement of gait disturbance and rota-rod performance (motor function) and tail-flick threshold (sensory function). He found a significant delay to onset of gait disturbance (6 to 7 weeks *versus* 2 to 3 weeks) in rats treated with paclitaxel and glutamine *versus* paclitaxel alone. In the glutamine-supplemented groups, tail flick and rota-rod scores did not worsen with treatment, and higher mean doses of chemotherapy could be administered.

Limited clinical data in humans suggest a possible neuroprotective role for glutamine in women with metastatic breast cancer receiving high dose paclitaxel with autologous hematopoietic stem cell support (115). In this observational phase II study, paired pre- and post-paclitaxel neurologic evaluations were available in 45 patients who underwent high dose paclitaxel (825 mg/m<sup>2</sup> over 24 h), 12 of whom received oral glutamine (10 g tid for three days), starting 24 h after the completion of paclitaxel. Women receiving glutamine supplementation had a significant reduction in the severity of peripheral neuropathy as measured by severe dysesthesias and numbness in the fingers and toes. In addition, the degree and incidence of motor weakness was reduced (56 *versus* 25%) as was the incidence of gait deterioration during treatment (85 *versus* 45%) and interference with activities of daily living (85 *versus* 27%).

Preliminary experience suggested that oral glutamine could also prevent paclitaxel-induced myalgias and arthralgias (116). However, a randomized controlled trial comparing glutamine (30 g orally daily for five days) with placebo in 36 patients who developed paclitaxel-induced myalgias and/or arthralgias failed to demonstrate any significant reduction in either the incidence or severity of symptoms (117).

Taken together, these *in vitro* data and early clinical observations suggest a potential neuroprotective effect of glutamine in patients treated with paclitaxel. A significant limitation of the phase II trial reported above is the lack of a placebo control, and the extremely high doses of paclitaxel. At present, the benefit of glutamine for patients receiving standard dose paclitaxel is unknown. A prospective randomized evaluation of oral glutamine as a neuroprotectant in patients receiving weekly standard doses paclitaxel for lung and breast cancer is currently in progress. An important correlate of this study will be the effect of glutamine supplementation on circulating levels of nerve growth factor (NGF). Some data in cancer patients receiving neurotoxic chemotherapy agents (including taxanes) suggest a correlation between treatment-induced decline in NGF levels and the severity of neurotoxicity (118). In murine models, adminis-

tration of NGF is associated with inhibition of paclitaxel-induced neuropathy (119).

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## GLUTAMINE AND PROTECTION AGAINST ANTHRACYCLINE-INDUCED CARDIOTOXICITY

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Supplemental glutamine can effectively maintain cardiac GSH levels in animals given methotrexate or cyclophosphamide. In controlled studies, supplemental glutamine provided marked protection against cardiotoxicity and resulted in strikingly improved survival in rats given lethal and sublethal doses of cyclophosphamide (120). Only 20% of the glycine supplemented control group survived a 450 mg/kg dose of cyclophosphamide compared to 100% survival in the glutamine-supplemented group. The glutamine supplementation maintained normal cardiac GSH levels, presumably decreasing cardiotoxicity.

High dose doxorubicin therapy is limited by both acute and chronic cardiac toxicity. The most common chronic effect, a dose-related cardiomyopathy, is thought to result from doxorubicin-induced free radicals. Doxorubicin promotes free radical formation, elicits oxidative damage, decreases glutathione, and depletes superoxide dismutase in cardiac muscle (121–123). These molecules alter DNA, causing mitochondrial dysfunction, eliciting a cellular calcium overload, causing acute depression of glutathione levels, and inducing release of catecholamines (122,124).

Several maneuvers can be applied to decrease the incidence of cardiac toxicity, including weekly administration of doxorubicin rather than every 21 days (lower peak drug levels), or by the use of dexrazoxane, a derivative of EDTA (125). This agent may enhance mucositis and myelosuppression during treatment, and also has been reported in one study to alter antitumor efficacy (126). Animal data suggest that supplemental dietary glutamine may diminish doxorubicin-induced oxidative damage, and thus, cardiotoxicity through upregulation of cardiac GSH metabolism (127). A second potential mechanism by which glutamine may be protective to the myocardial cell is via induction of HSP. HSP 72 is known to be protective to the myocardium against hypoxic/ischemic injury. Induction of HSP 27 (another protective heat shock protein) has been shown to be protective against doxorubicin-induced cardiac injury (128). Glutamine also appears to be a potent inducer of myocardial HSP 72 in an *in vivo* rat model (52). Trials of glutamine protection via HSP 72/27 induction in the heart are currently underway. Finally, recent evidence indicates that glutamine can

preserve myocardial high energy phosphate levels and prevent accumulation of lactate following a variety of stress, including infection and ischemia/reperfusion injury (129,130).

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## CONCLUSIONS

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Glutamine is a molecule whose influence on body homeostasis is protean. States of physiologic stress, including those resulting from the treatment of malignant disease, are characterized by a relative deficiency of glutamine. Supplementation with this inexpensive dietary supplement may have an important role in the prevention of gastrointestinal, neurologic, and possibly cardiac complications of cancer therapy. These complications often negatively affect quality of life and may also lead to changes in therapy, which potentially alter efficacy. Glutamine may also improve the therapeutic index of both chemotherapy and radiation, increasing cytotoxicity while concurrently protecting against toxicity. Further study of glutamine supplementation in these areas is warranted. Placebo-controlled phase III studies are needed to evaluate the role of glutamine for prevention of paclitaxel-induced neurotoxicity, anthracycline-related cardiotoxicity, and for prevention of hepatic venoocclusive disease in patients undergoing hematopoietic cell transplantation.

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