Glutamine Supplementation in Cancer Patients Receiving Bone Marrow Transplantation and High Dose Chemotherapy[1,2]

Thomas R. Ziegler[3]

Department of Medicine, Division of Endocrinology and Metabolism, Emory University School of Medicine, Atlanta, GA 30322

ABSTRACT Glutamine supplementation of enteral and parenteral nutrition support has received increased attention in the research community over the past decade. Glutamine may become a conditionally essential nutrient during certain catabolic states, including after bone marrow transplantation (BMT). The administration of enteral or parenteral glutamine seems safe and also potentially efficacious in some patient groups undergoing intensive treatment for cancer. Studies indicate that adjunctive glutamine treatment may improve nitrogen retention, decrease clinical infection and length of hospital stay and reduce the incidence and severity of mucositis after BMT and high dose chemotherapy. Although not all studies demonstrate benefit, there are sufficient positive data to suggest that this nutrient should be considered in the metabolic support of many individuals undergoing the catabolic process of marrow transplantation. Given the available data, randomized, double-blind, controlled clinical trials of glutamine-enriched nutrition in patients receiving BMT and high dose chemotherapy protocols are indicated to further define the utility of this amino acid as adjunctive therapy. Studies of glutamine nutrition combined with current combinations of cytoreductive agents and hematopoietic growth factors in BMT will be particularly pertinent. J. Nutr. 131: 2578S-2584S, 2001.

KEY WORDS: • *glutamine* • *bone marrow transplantation* • *chemotherapy*

The use of bone marrow transplantation (BMT)[4] in medical treatment of adult and pediatric patients has increased dramatically during the past decade (Slavin 2000, Saba et al. 2000, Mogul 2000). Patients with leukemias or lymphomas now routinely receive high dose chemotherapy ± total body irradiation (TBI) to eradicate malignant cells, followed by BMT to support the ablated host hematopoietic system. BMT is also being increasingly studied in patients with testicular cancer and other solid tumors, multiple myeloma, sickle cell disease, genetic disorders and even as adjunctive treatment in solid organ transplantation (Slavin 2000, Saba et al. 2000, Mogul 2000). BMT may be allogeneic, in which cells for transplant are derived from human leukocyte antigen-matched donors, or autologous, in which cells for transplant are obtained from the patient. Some centers obtain cells for transplant directly from bone marrow biopsies, but the most commonly used method is ex vivo mobilization of stem cells from peripheral blood using growth factors, such as granulocyte/macrophage colony stimulating factor (Slavin 2000, Saba et al. 2000, Mogul 2000). Colony stimulating factors are now routinely used to increase neutrophil recovery in BMT regimens (Slavin 2000).

A feature of most BMT protocols for malignancy is administration of very high doses of chemotherapy (usually including cyclophosphamide, bulsulfan and epoposide) with or without TBI. These ablative regimens commonly cause gastrointestinal complications, including nausea, vomiting, inflammation of the oral and esophageal mucosa (mucositis), abdominal pain and diarrhea (Blijlevens et al. 2000). Recently, nonmyeloablative stem cell allogeneic transplantation (NST) has become a popular form of BMT (Slavin 2000). In these protocols, relatively low doses of chemotherapy and TBI are used in a strategy of adoptive immunotherapy involving induction of host-vs.-graft transplantation tolerance with infusion of donor T lymphocytes. The low doses of cytotoxic therapy are associated with much lower rates of infectious, gastrointestinal and other adverse effects. NST will likely be increasingly used to treat nonmalignant diseases in which replacement of host hematopoietic cells is indicated (e.g., genetic and autoimmune disorders, induction of organ allograft tolerance) (Slavin 2000). However, in malignant disease, the efficacy of NST remains to be defined and high dose cytotoxic therapy remains the standard of care for BMT in such patients.

The adverse gastrointestinal effects with BMT regimens often markedly decrease ad libitum oral food intake for up to several weeks (Biron et al. 2000, Blijlevens et al. 2000, Ziegler

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[3] To whom correspondence should be addressed. E-mail: tzieg01@emory.edu

[4] Abbreviations used: 5-FU, 5-fluorouracil; BMT, bone marrow transplantation; GSH, plasma glutathione; NST, nonmyeloablative stem cell allogeneic transplantation; PN, parenteral nutrition; TBI, total body irradiation.

et al. 1992, Jonas et al. 2000). High dose chemotherapy and TBI also induce protein catabolism, disruption of the gastrointestinal mucosa, marked immunosuppression and oxidative stress (Blijlevens et al. 2000, Ziegler et al. 1992, Jonas et al. 2000, Szeluga et al. 1987, Durken et al. 1995). Frequent infections and graft-vs.-host disease may directly cause gut mucosal inflammation and ulceration and, thus, interfere with spontaneous nutrient intake and/or increase nutrient requirements and losses (Iqbal et al. 2000). These observations provide the basis for the common prescription of parenteral nutrition (PN) or oral nutrient supplements in patients undergoing BMT. Unfortunately, the efficacy of nutrition therapy to support BMT patients remains unclear (Blijlevens et al. 2000, Ziegler et al. 1992, Weisdorf et al. 1987, Klein and Koretz 1994), due in part to a paucity of well-designed, randomized clinical trials in this field and the rapid evolution of chemotherapy and growth factor regimens in BMT. This latter fact has made controlled clinical trials of nutrition support in BMT difficult to perform and often impractical in many academic medical centers. Furthermore, clinical nutrition studies performed several years ago may not be applicable to present BMT treatment regimes. Thus, it is not surprising that policies for administration of specialized nutrition vary widely among BMT centers worldwide.

In a recent study, we found that use of conventional PN in patients undergoing BMT for hematologic malignancies did not prevent a serial decline in systemic antioxidant status [plasma glutathione (GSH) redox capacity and α-tocopherol concentrations] (Jonas et al. 2000). In fact, patients receiving standard PN demonstrated lower plasma GSH and α-tocopherol levels than those receiving intravenous micronutrients alone (Jonas et al. 2000). These and other data (Klein and Koretz 1994) strongly suggest that new strategies are needed to improve the efficacy of conventional nutrition support in cancer patients undergoing BMT or high dose chemotherapy for hematologic or solid tumors. Use of glutamine-supplemented nutrition has received increasing attention in basic, translational and clinical research (Souba 1993, Ziegler et al. 1997, 2000a and 2000b, Darmaun 2000, Griffiths 1999). This review will summarize the available clinical literature on adjunctive use of glutamine supplementation in patients undergoing BMT and high dose chemotherapy.

Glutamine supplementation in animal models and clinical trials in noncancer patients

Although glutamine is a classical nonessential amino acid, studies in animal models and emerging clinical trials suggest that glutamine requirements increase during certain catabolic states (Souba 1993, Ziegler et al. 1997) (**Table 1**). Glutamine is a critical substrate in many key metabolic processes, including interorgan nitrogen transfer, protein and nucleic acid synthesis, gluconeogenesis and acid-base homeostasis. Glutamine is also used as a major fuel and/or substrate by intestinal mucosal cells and by lymphocytes and other immune cells (Souba 1993, Ziegler et al. 1997).

TABLE 1

Beneficial effects of glutamine-supplemented nutrition in animal models relevant to BMT

- Improved nitrogen retention, plasma and skeletal muscle glutamine concentration
- Increased gut mucosal growth and repair after parenteral nutrition, chemotherapy, irradiation sepsis, colitis
- Decreased gut-origin bacteremia and endotoxemia in models of catabolic stress
- Improved plasma and tissue glutathione levels after chemotherapy, irradiation, sepsis, colitis, gut ischemia/reperfusion, acetominophen toxicity
- Enhanced systemic and tissue-associated immune cell number and function

The model of conditional glutamine deficiency during stress is supported by > 100 published animal studies showing benefits of enteral or parenteral glutamine supplementation. Although some studies show no apparent benefit, glutamine supplementation of PN, enteral diets or drinking water improves animal survival, decreases infectious morbidity and enhances gut mucosal repair in models of chemotherapy and irradiation, sepsis and inflammation (reviewed in Ziegler et al. 2000a). Glutamine-enriched nutrition attenuates depletion of the key antioxidant GSH in plasma, liver and gut after chemotherapy, sepsis, and gut ischemia/reperfusion and upregulates systemic and tissue immune function in animals (Souba 1993, Ziegler et al. 1997, 2000a, Darmaun 2000).

Glutamine has become one of the most intensively studied nutrients in clinical nutrition trials. At least 20 randomized, blinded, controlled clinical studies of glutamine-enriched enteral nutrition or PN have been published in adult and pediatric patients; most, but not all, of these studies indicate beneficial metabolic and/or clinical effects (Ziegler et al. 2000a, 2000b, Darmaun 2000, Griffiths 1999). Clinical benefits demonstrated in noncancer intensive care unit and postoperative patients include improved nitrogen balance, decreased length of hospital stay, improved immune functions and reduced hospital costs, while decreased infection rates in trauma patients and in neonates requiring intensive care have been demonstrated (Ziegler et al. 2000a, 2000b, Darmaun 2000, Griffiths 1999). Glutamine-induced regulation of human immune cell number and function has been summarized recently (Wilmore and Shabert 1998, Ziegler and Daignault 2000) (**Table 2**).

Administration of intravenous glutamine in bmt

The initial clinical safety and efficacy data on glutamine-enriched PN in BMT patients were published in the early 1990s (Ziegler et al. 1992, 1990, Scheltinga et al. 1991, Young et al. 1993, McBurney et al. 1994). In the first trial, the clinical safety and dose response of glutamine-containing PN was performed in healthy adults and patients undergoing allogenic BMT (Ziegler et al. 1990). This pilot study was followed by a double-blind, randomized, controlled trial in a group of 45 clinically patients undergoing allogeneic BMT for hematologic malignancies (leukemia and lymphomas) (Ziegler et al. 1992). Patients received standard glutamine-free PN per usual protocols (n = 21) or isocaloric, isonitrogenous, glutamine-supplemented PN (n = 24) designed to provide estimated requirements for energy and protein and supplemented with L-glutamine (0.57 g·kg·d). L-glutamine provided ~40% of total amino acid intake in the trial.

After multidrug chemotherapy and TBI, PN was started on the day after BMT. Plasma glutamine levels rose ≈40% with glutamine-enriched PN, but plasma glutamate, ammonia and pyroglutamic acid levels were unaltered; no adverse clinical or significant biochemical effects were noted. Daily nitrogen balance performed in the initial 23 patients between d 4 and 11 post-BMT was significantly improved with glutamine supplementation (glutamine, -1.4 ± 0.5 g/d vs. control, -4.2 ± 1.2 g/d; P = 0.002) (Ziegler et al. 1992). A significant reduction in 7-d net nitrogen loss and in urinary excretion of 3-methyl-

TABLE 2

Glutamine regulation of human immune cells

- Important fuel/substrate for lymphocytes and macrophages in vitro
- Enhances in vitro bacterial killing by neutrophils and monocytes
- Upregulates in vitro intracellular reactive oxygen species generation in neutrophils and monocytes and intracellular glutathione in lymphocytes
- Increases blood T lymphocyte recovery post-BMT
- Increases postoperative blood lymphocyte levels
- Attenuates decrease in blood lymphocytes and enhances blastogenesis after chemo/irradiation

histidine occurred with glutamine administration (**Fig. 1**). This later finding suggests that L-glutamine diminished the rate of skeletal muscle myofibrillar protein breakdown as a mechanism for the protein-anabolic effect (Ziegler et al. 1992).

This randomized, controlled trial also demonstrated improved clinical outcomes with glutamine supplementation. The incidence of total positive microbial cultures was significantly decreased in the glutamine group, without a change in fever, antibiotic usage or oral mucositis scores. Significantly more standard PN-treated patients developed one or more positive throat (86% vs. 54%, $P < 0.05$) and stool cultures (75% vs. 42%, $P < 0.05$). Significantly fewer glutamine-treated patients developed clinical infection (3 vs. 9, $P = 0.041$); the length of hospital stay was also significantly decreased (29 + 1 d vs. with 36 + 2 d; $P = 0.017$; **Fig. 2**) (Ziegler et al. 1992). In a subgroup of these study patients, physiological benefits from the use of glutamine supplementation were demonstrated. These included the attenuation of extracellular fluid expansion (Scheltinga et al. 1991), improvement in mood scores (Young et al. 1993) and enhanced recovery of circulating lymphocytes (Ziegler et al. 1998). The number of circulating total lymphocytes, T lymphocytes, T helper (CD-4), and T suppressor (CD-8) cells was increased with glutamine supplementation. No change was observed in total leukocyte or neutrophil engraftment; thus, glutamine seemed to predominantly influence lymphocyte metabolism in the postallogeneic BMT period (Ziegler et al. 1998). The decrease in hospital length of stay and in-hospital medical care costs in this trial translated to a reduction in hospital charges of $21,095 per patient in glutamine-supplemented subjects

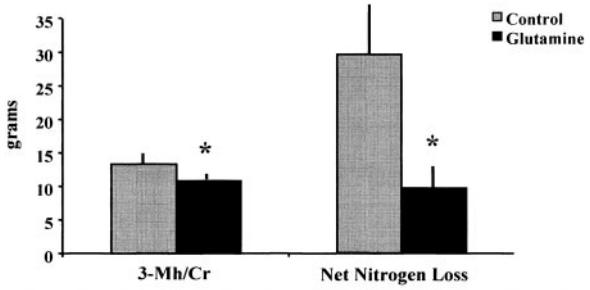

FIGURE 1 Protein-anabolic effects of L-glutamine-supplemented PN after allogeneic BMT. Adult patients undergoing allogeneic BMT for hematologic malignancies received standard glutamine-free PN (control) or isocaloric, isonitrogenous, PN providing L-glutamine (0.57 g/kg per day). Nitrogen balance was performed between d 4 and 11 post-BMT. Net nitrogen losses and urinary 3-methylhistidine excretion, corrected for creatinine (3-Mh/Cr), were determined. *$P < 0.04$ control vs. glutamine-supplemented. Data from Ziegler et al. 1992.

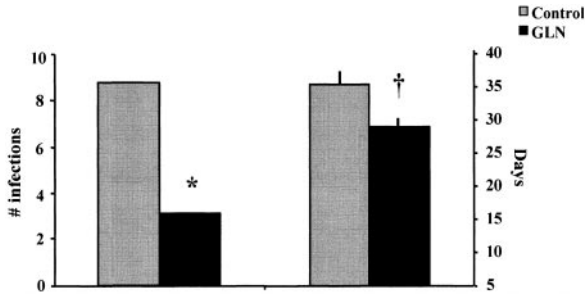

FIGURE 2 L-glutamine-supplemented PN improves clinical outcomes after allogeneic BMT. Adult patients undergoing allogeneic BMT for hematologic malignancies received standard glutamine-free PN (control) or isocaloric, isonitrogenous, PN providing L-glutamine (0.57 g/kg per day) for an average of 28 ± 1 and 26 ± 2 d after BMT. The incidence of documented clinical infections and hospital length of stay was determined. *$P < 0.05$ and †$P < 0.02$ control vs. glutamine-supplemented. Data from Ziegler et al. 1992.

compared with patients who received standard PN therapy (McBurney et al. 1994). This reduction in the cost of hospital care is consistent with results of subsequent studies on glutamine-enriched nutrition in postoperative adults and critically ill adult and pediatric patients (Ziegler et al. 2000b, Mertes et al. 2000, Jones et al. 1999, Dallas et al. 1998, Griffiths et al. 1997).

In another double-blind, randomized trial, Schloerb and Amare (1993) studied 29 patients receiving similar glutamine-free or glutamine-supplemented PN after allogeneic or autologous BMT for hematologic cancer or solid tumors. PN was given for ≈30 d in each group and no adverse effects related to glutamine administration were noted. Glutamine-supplemented PN did not affect the incidence of mucositis, fever, neutrophil engraftment, clinical infections or microbial colonization; antibiotic requirements and mortality were also similar between groups. In the subset of patients receiving allogeneic BMT, significantly more control subjects than glutamine subjects had bacteremia ($P < 0.05$). In addition, the change in total body water during hospitalization was significantly less with glutamine (control + 3.1 ± 1.5 vs. glutamine −3.4 ± 1.3 L; $P < 0.05$). As demonstrated in the previous trial (Ziegler et al. 1992), administration of glutamine-supplemented PN significantly decreased the length of hospital stay in this more heterogeneous group of BMT patients (33 ± 2 d vs. 27 ± 1 d, $P < 0.05$) (Schloerb and Amare 1993). The patient populations investigated, clinical conditions and cancer treatment protocols were different in these initial studies (Ziegler et al. 1992, Schloerb and Amare 1993), which may have influenced the effect of glutamine on infection rates. Although glutamine supplementation seems to upregulate lymphocyte recovery after BMT (Ziegler et al. 1998), the incidence of acute graft-vs.-host disease was not increased in these studies. Importantly, both investigations were carried out in patients before the advent of routine growth factor use; the current use of granulocyte/macrophage colony stimulating factor in the post-transplant period has significantly decreased neutropenia and the incidence of infection in BMT patients.

A third double-blind, randomized trial has been reported, but only in abstract form (Poynton et al. 1995). Fifty unselected BMT patients received 50 g/d of dipeptide glycyl-glutamine intravenously vs. parenteral infusion of isonitrogenous mixed nonessential amino acids in clinically matched patients. The study solutions were begun 1 d before chemotherapy induction and continued until hospital discharge or

post-BMT d 30. There was a significant improvement in self-reported lower gastrointestinal symptoms (e.g., diarrhea and abdominal pain) with glutamine ($P = 0.015$). The lactulose: mannitol urinary excretion ratio, a measure of small intestinal permeability, was also improved with glutamine ($P = 0.04$) and there were fewer fever days ($P = 0.01$) and less episodes of fever ($P = 0.029$) in the glutamine group (Poynton et al. 1995). Critical review of this latter study will be possible only after publication of the full manuscript.

Glutamine and bmt-associated veno-occlusive disease

After high dose chemotherapy for BMT, patients may develop a form of hepatic failure known as veno-occlusive disease that is due to subendothelial swelling and narrowing of the central hepatic veins, with subsequent liver outflow obstruction (Wilmore et al. 1999, Brown et al. 1998). Veno-occlusive disease is frequently lethal and seems to be related, at least in part, to oxygen-free radical-mediated liver injury and depletion of antioxidants, including GSH (Brown et al. 1998). Glutamine seems to be rate limiting for the production of hepatic and intestinal GSH during catabolic stress (Ziegler et al. 2000a, Rouse et al. 1995). Furthermore, standard glutamine-free PN itself may have prooxidative effects and contribute to GSH depletion by mechanisms that remain unclear (Jonas et al. 2000, Jonas and Ziegler 1998). Two reported case studies suggest that the administration of intravenous + oral L-glutamine (Nattakom et al. 1995) or intravenous alanyl-glutamine dipeptide (Goringe et al. 1998) in combination with oral vitamin E diminishes signs and symptoms of veno-occlusive disease after BMT. In a double-blind prospective study, clinically matched BMT patients received either 50 g/d of dipeptide glycyl-glutamine intravenously or infusion of isonitrogenous mixed nonessential amino acids from the start of conditioning to discharge from the transplant unit (Brown et al. 1998). Patients in the glutamine dipeptide group demonstrated significantly preserved plasma protein C and albumin levels, suggestive of preserved hepatic function and a decreased risk of veno-occlusive disease (Brown et al. 1998). Additional studies are needed to determine whether glutamine and vitamin E prophylaxis (or treatment with other antioxidants) reduce the incidence of post-BMT veno-occlusive disease.

Use of oral glutamine in bmt

Two recent prospective, randomized, double-blind studies have evaluated clinical effects of oral L-glutamine in patients receiving BMT. Schloerb and Skikne (1999) studied a group of 43 patients with hematologic malignancies receiving either autologous or allogeneic BMT and 23 with solid malignancies receiving autologous BMT. Patients were randomized to either oral glutamine ($n = 35$) or glycine ($n = 31$) at a dose of 10 g three times daily. If PN became necessary, patients in the oral glutamine group received PN supplemented with L-glutamine (0.57 g·kg·d) and control subjects receivied isonitrogeneous, isocaloric glutamine-free PN. Hospital deaths ($n = 14$) were unrelated to study group assignment. Respective comparisons were performed in patients undergoing allogeneic or autologous BMT for hematologic cancer and subjects with solid tumors undergoing autologous BMT. There were no significant differences between study groups in hospital length of stay, days on PN, neutrophil recovery, incidence of positive blood cultures and sepsis, diarrhea severity or incidence/severity of mucositis. In the patients with hematologic malignancy, a possible reduction in need for PN and a clear suggestion of improved long-term survival ($P = 0.0572$) were associated with glutamine administration. Otherwise, combined oral and parenteral glutamine seemed to be of limited benefit for patients having autologous or allogeneic BMT for hematologic or solid malignancies.

In the second recent trial of oral glutamine, Coghlin-Dickson et al. (2000) organized a prospective, randomized, double-blind trial in 58 matched adult patients with leukemia or lymphoma receiving autologous or allogeneic BMT. Subjects received 30 g/d of L-glutamine or sucrose (placebo) daily, beginning at the initiation of chemotherapy/TBI and continuing until hospital discharge or d 28 post-BMT. Mucositis, diarrhea, PN use and clinical outcomes were major endpoints. Amino acid intake was similar between groups (control, 0.25 g·kg·d vs. glutamine, 0.29 g·kg·d) and was well tolerated clinically and biochemically. No significant difference in neutrophil engraftment, oral mucositis, diarrhea, PN use, length of stay, disease relapse or survival occurred between groups.

Effect of glutamine supplementation on mucositis after high dose chemotherapy

Mucositis or inflammation of the oral mucosa is a common, painful and dose-limiting complication associated with high dose chemotherapy that has served as a clinical endpoint in a variety of studies in BMT or with chemotherapy alone. The management of oral mucositis and inflammation that affects esophageal, gastric, small bowel and colonic mucosa is controversial and optimal treatments are still not clarified. Therapies in practice and under investigation are directed at the inflammatory, epithelial, ulcerative and healing phases of mucositis. These include cryotherapy, cytoprotection (prostaglandin E_2, antioxidants) epithelial cell protective factors (e.g., keratinocyte growth factor), agents that accelerate epithelial restoration (sucralfate, growth factors), antiseptics and antibiotics (Blijlevens et al. 2000, Rosenthal et al. 2000, Biron et al. 2000).

In the four randomized, controlled trials outlined above (Ziegler et al. 1992, Schloerb and Amare 1993, Schloerb and Skikne 1999, Coghlin-Dickson et al. 2000), and in an additional controlled trial (Jebb et al. 1995), intravenous and/or oral L-glutamine trials did not influence incidence or severity of mucositis after BMT. However, additional studies indicate the potential benefit of oral glutamine as a method to decrease mucositis after BMT. Anderson et al. (1998a) published a large, randomized, double-blind clinical trial that evaluated effects of oral L-glutamine in 193 pediatric and adult patients receiving allogeneic or autologous BMT. The subjects were matched for diagnosis, demographics and BMT regimen; the majority of study subjects had hematologous malignancies but 32% had solid tumors and 9% were transplanted for inherited diseases. The patients were given either oral L-glutamine or glycine at a dose of 1.0 g·m^2·dose as a swish-and-swallow mouthwash four times daily. Subjects were randomized to receive the amino acid mouthwashes from hospital admission (before conditioning) until 28 d post-BMT.

In patients undergoing autologous BMT ($n = 87$), glutamine use was associated with significantly less mouth pain and less difficulty eating and decreased opiate requirements (Anderson et al. 1998a). For example, the number of patients not requiring morphine for pain was significantly greater in the glutamine group than in the control group (53% vs. 31%, $P = 0.04$). When morphine was given, the duration of administration was ~50% less in the glutamine group than in the control group (5 vs. 10 d, $P = 0.005$). Because these effects were not observed in all subgroups (e.g., matched donors and

unrelated donors), the response to glutamine may have been related to the different consolidation regimens used. There were no differences between groups in graft-vs.-host disease or the incidence of infections; however, seven viral infections developed in placebo patients vs. none in those receiving glutamine (Anderson et al. 1998a). Furthermore, in autologous BMT patients, glutamine use was associated with a significant improvement in the 28-d survival rate (100.0% vs. 92.6% survival, $P = 0.006$), but this difference that was no longer statistically significant at 100 d post-transplant (87.2% vs. 80.9% survival, $P = 0.18$) (Anderson et al. 1998a).

In a recent retrospective analysis of 21 consecutive patients receiving high dose paclitaxel and melphalan as the preparative regimen for autologous BMT for metastatic breast cancer, L-glutamine suspension was given as a swish-and-swallow every 4 h around the clock starting on d −7 before BMT (total dose of 24 g/d) (Cockerham et al. 2000). The group that was given oral glutamine demonstrated significantly fewer days of mucositis, a lower maximum grade of mucositis and required fewer days of parenteral morphine for oral pain relief.

Several studies have been published on effects of oral glutamine in non-BMT patients receiving chemotherapy alone, with mixed results. In a crossover study of patients receiving 5-fluorouracil (5-FU) and folinic acid for intestinal cancer, Jebb et al. (1994) found that oral glutamine (16 g/d) had no measurable effect on the incidence or severity of mucositis. In another study, patients receiving 5-FU-based chemotherapy regimens for various cancers were randomized, in a double-blind manner, to receive oral glutamine (4 g swish-and-swallow twice daily) for 14 d beginning on d 1 of chemotherapy (68 patients per group) (Okuno et al. 1999). Patients in both groups were also given oral cryotherapy before chemotherapy and were evaluated for mucositis by standard physicians' evaluation and by a self-report instrument. There were no significant differences or substantial trends in the mucositis scores between the two study arms (Okuno et al. 1999). Bozzetti et al. (1997) studied 65 patients with advanced breast cancer being treated with doxifluridine. Subjects received either L-glutamine orally (30 g/d) or maltodextrine for eight consecutive days during each interval before chemotherapy. There were no differences between groups in doxifluridine-induced diarrhea or tumor response.

In contrast to the results presented above, additional data indicate that glutamine administration can decrease gastrointestinal toxicity to chemotherapy in cancer patients (Anderson et al. 1998b, Muscaritoli et al. 1997, Daniele et al. 2001). In a double-blind, crossover study of 24 pediatric and adult patients receiving doxorubicine-based chemotherapy for solid tumors, Anderson et al. (1998b) found that twice-daily oral administration of glutamine (2.0 g/m^2 per dose) vs. glycine swish-and-swallow significantly decreased the duration of mucositis by 4.5 d and also the severity of oral pain. In an unblinded study of 14 patients with acute leukemia receiving high dose combination chemotherapy, oral glutamine given at a dose of 18 g/d begun 3 d before chemotherapy induction significantly decreased the duration and severity of diarrhea and requirements for antifungal agents (Muscaritoli et al. 1997). In a recently published study, Daniele et al. (2001) investigated 70 chemotherapy-naive patients with colorectal cancer randomly assigned to oral glutamine (18 g/d) or placebo before the first cycle of 5-FU and folinic acid, administered intravenously for 5 d. Treatment was continued for 15 consecutive days starting 5 d before chemotherapy. Serial urinary excretion D-xylose and cellobiose-mannitol after oral loads were measured as indices of intestinal absorption and permeability, respectively, and patients kept a daily diarrhea diary. Results showed that patients receiving oral glutamine had a significantly improved D-xylose absorption and decreased cellobiose-mannitol urinary excretion, indicating improved gut absorptive and barrier function compared with controls. Glutamine also significantly decreased the severity of diarrhea and the need for loperamide therapy for diarrhea. Thus, oral glutamine in this clinical setting had a protective effect on 5-FU-induced diarrhea and abnormal intestinal function after chemotherapy. Trials on effects of glutamine treatment in chemotherapy-induced mucositis and diarrhea are summarized in **Table 3**.

Effects of glutamine supplementation on outcomes in non-bmt chemotherapy patients

An earlier prospective, double-blind trial evaluated the efficacy of PN enriched in alanyl-glutamine dipeptide (40 g/d dipeptide, equivalent to 26 g glutamine) vs. matched control PN in non-BMT patients undergoing high dose chemotherapy for acute leukemia (Van Zaanen et al. 1994). Administration of GLN dipeptide did not improve clinical outcome, infection rates, use of antibiotics, mucositis, diarrhea or neutrophil engraftment. In patients undergoing high dose cispatin and 5-FU chemotherapy with mediastinal radiotherapy for esophageal cancer, orally administered glutamine (30 g/d) or isonitrogenous, glutamine-free intravenous mixed amino acids was given for 28 d after the initiation of therapy (Yoshida et al. 1998). The patients receiving oral glutamine demonstrated improved circulating lymphocyte number and function and decreased gut permeability over time (Yoshida et al. 1998). Decker-Baumann et al. (1999) recently published an unblinded prospective study in 24 patients with metastatic colon cancer undergoing serial 5-d infusions of high dose 5-FU. Intravenous glycyl-glutamine dipeptide (0.4 g/kg per day) was given to 12 patients, while the 12 controls received no additional treatment. Serial endoscopic studies of the gastric and

TABLE 3

Effects of glutamine supplementation on mucositis and diarrhea in cancer patients

No effect
- Mucositis in BMT: IV L-GLN, 30–40 g/d (Ziegler et al. 1992, Schloerb and Amare 1993)
- Mucositis/diarrhea in BMT: oral L-GLN, 16 g/d (Jebb et al. 1995)
- Mucositis/diarrhea in BMT: oral L-GLN, 30 g/d ± IV L-GLN (Schloerb and Skikne 1999)
- Mucositis/diarrhea/oral food intake in BMT: oral L-GLN, 30 g/d (Coghlin-Dickson et al. 2000)
- Mucositis/diarrhea in acute leukemia chemotherapy: IV ALA-GLN, 26 g/d (Van Zaanen et al. 1994)
- Mucositis with 5-FU-based chemotherapy: oral L-GLN 8 g/d (Okuno et al. 1999)
- Mucositis with 5-FU-based chemotherapy: oral L-GLN 16 g/d (Jebb et al. 1994)
- Diarrhea in breast cancer + doxifluridine: oral L-GLN, 30 g/d (Bozzetti et al. 1997)

Beneficial effect
- Mucositis in autologous BMT: oral L-GLN, 4 g/m^2 per day (Anderson et al. 1998a)
- Mucositis in autologous BMT for breast cancer: oral L-GLN, 24 g/d (Cockerham et al. 2000)
- Diarrhea after high dose combined chemotherapy for leukemia: oral L-GLN, 18 g/d (Muscaritoli et al. 1997)
- Diarrhea and need for loperamide therapy after 5-FU therapy for colorectal cancer: oral L-GLN, 18 g/d (Daniele et al. 2001)

GLN = glutamine; IV = intravenous.

duodenal mucosa were performed after the first and third course of chemotherapy. There were no significant differences between groups in the incidence or severity of clinical adverse effects during the study. However, endoscopic visual analysis and histomorphology showed that subjects receiving intravenous glutamine dipeptide demonstrated significantly decreased inflammation and ulceration of the gastric and duodenal mucosa after the third course of chemotherapy and an improved duodenal villus height/crypt depth ratio as an index of gut mucosal integrity.

The administration of enteral or parenteral glutamine seems safe and potentially efficacious in patients undergoing BMT and high dose chemotherapy. Given the positive data to date, additional double-blind, controlled clinical trials of glutamine-enriched nutrition in patients receiving BMT and chemotherapy protocols are indicated to define the utility of this amino acid as adjunctive therapy. Studies of glutamine nutrition combined with novel combinations of cytoreductive agents and hematopoietic growth factors in BMT may be particularly pertinent.

The mechanisms of the beneficial glutamine actions observed in some studies of BMT and chemotherapy patients remain speculative. Glutamine supplementation exerts a number of effects that may be interrelated (Ziegler et al. 1992). For example, reduced protein breakdown rates may improve patient nitrogen retention. Improved resistance to colonization and decreased clinical infection may be related to a protein-sparing effect of glutamine combined with enhanced number/function of tissue-associated or circulating immune cells, maintenance of gut mucosal barrier defenses and/or improved tissue antioxidant GSH status (Ziegler et al. 2000a). Decreased mucositis observed in some studies may be related to cytoprotective or antioxidant effects of glutamine and/or use of this amino acid as an energy source for epithelial cells. Additional study is needed to define underlying mechanisms of glutamine action.

It is possible that glutamine is used as a growth factor or fuel for malignant cells or may alter pharmacokinetic interactions between malignant tumors and chemotherapeutic drugs (Wilmore et al. 1999). Thus, carefully planned pharmacological studies may need to be performed before administering large doses of glutamine that may have pharmacological effects on the patients receiving cytotoxic drugs. However, the available clinical data in cancer patients does not suggest that glutamine-supplemented nutrition enhances or induces tumor growth or worsens clinical outcomes. In fact, available data suggest that glutamine may improve clinical outcomes in some patients undergoing BMT (Ziegler et al. 1992, Wilmore and Shabert 1998, Schloerb and Skikne 1999, Anderson et al. 1998a). As noted above, glutamine treatment may increase plasma or tissue levels of the antioxidant GSH (Ziegler et al. 2000a). Antioxidant supplementation as a modality to protect normal tissue from injurious oxygen-free radicals has been approached with caution because of potential to reduce the therapeutic efficacy of cytotoxic regimens by upregulation of tumor antioxidants (Jonas et al. 2000). Therefore, further study of long-term outcomes with glutamine supplementation in cancer patients seems indicated to complement the primarily short-term safety data available to date. Although not all studies demonstrate benefits, sufficient positive data exist to suggest that glutamine supplementation should be considered in the design of clinical trials and in metabolic support of many individuals undergoing BMT for treatment of cancer.

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