Oral Glutamine Reduces the Duration and Severity of Stomatitis after Cytotoxic Cancer Chemotherapy

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BACKGROUND. Mouth sores and/or difficulty swallowing are common and painful consequences of cytotoxic chemotherapy for cancer. In previous studies oral glutamine was found to protect animals from the effects of whole abdominal radiation and methotrexate-induced enteritis. Glutamine also was found to reduce oral mucositis in a nonrandomized pilot study in humans. Therefore, the authors attempted to determine the efficacy of oral glutamine in a randomized, double blind, crossover trial in cancer patients receiving chemotherapy.

METHODS. Twenty-four patients (16 children and 8 adults) received glutamine or placebo (glycine) suspension (2 g amino acid/M^2/dose twice daily) to swish and swallow on days of chemotherapy administration and for at least 14 additional days. Patients completed a calendar indicating days of mouth pain associated with each chemotherapy course and the effect of mouth pain on oral intake.

RESULTS. Paired data indicated significant amelioration of stomatitis associated with glutamine administration after chemotherapy. The duration of mouth pain was 4.5 days less in chemotherapy courses in which glutamine supplementation was compared with placebo (Wilcoxon's signed rank test, $P = 0.0005$). The severity of oral pain also was reduced significantly when glutamine was provided with chemotherapy (the amount of days mucositis restricted oral intake to soft foods [≥Grade 2; Modified Eastern Cooperative Oncology Group grading system] was 4 days less with glutamine compared with placebo; Wilcoxon's signed rank test, $P = 0.002$).

CONCLUSIONS. Low dose oral glutamine supplementation during and after chemotherapy significantly reduced both the duration and severity of chemotherapy-associated stomatitis. Oral glutamine appears to be a simple and useful measure to increase the comfort of many patients at high risk of developing mouth sores as a consequence of intensive cancer chemotherapy. *Cancer* **1998;83:1433–9.**
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Cytotoxic cancer chemotherapy appears to be most effective against rapidly proliferating cells. As a consequence of this mechanism of action, chemotherapy also may damage normal host tissues that are proliferating rapidly. Cells of the gastrointestinal (GI) tract are among the most rapidly proliferating cells in the body.[1] Intestinal cells absorb large amounts of glutamine, but apparently no other amino acid from the arterial side. These cells also metabolize nearly all absorbed dietary glutamine in addition to extracting circulating glutamine derived from other tissues.[2] Oral glutamine, but not parenteral glutamine, has been shown to be effective in reducing the bacteremia and mucosal injury associated with methotrexate-induced enterocolitis.[3] The severity of radiation-induced mucosal injury to the intestine also was reduced when oral glutamine supple-

mentation was provided to rats.[4-6] Animals given parenteral glutaminase to deplete circulating glutamine develop emesis, diarrhea, mild villous atrophy, mucosal ulceration, and intestinal necrosis.[7] Thus, glutamine is important in the preservation of gut integrity and mucosal structure after chemotherapy and radiation. Lack of glutamine may contribute to mucosal damage.

Glutamine is easily the most abundant amino acid in plasma. Concentrations of glutamine in plasma, muscle, and mucosa are reduced significantly after injury, sepsis, and nutritional depletion in humans.[8,9] The gut can be considered as a nitrogen processing organ in the metabolic response to illness; the GI tract uses glutamine as a respiratory fuel.[9] Glutamine is obtained by the GI tract via both the diet and export of glutamine from skeletal muscle or liver. The role of glutamine in maintaining a healthy gut and supporting the metabolic response to injury and infection has been reviewed previously by Souba et al.[10] Because of glutamine's importance as a nitrogen carrier and respiratory fuel for enterocytes of the gut and other rapidly proliferating cells including lymphocytes and fibroblasts, glutamine can be considered as a conditionally essential amino acid.[11]

Patients receiving chemotherapy often have reduced oral intake because of nausea and emesis during chemotherapy and stomatitis as a delayed side effect of chemotherapy. We conducted a pilot study to determine whether oral glutamine could be useful in maintaining the dose intensity of cancer chemotherapy known to have previously caused oral mucositis.[12,13] In this nonrandomized, open label study glutamine use was associated with both a significant reduction in duration oral mucositis (approximately 7 days) and a reduction in the severity of mouth sores in nearly all patients. Because of these promising preliminary results, we sought to demonstrate activity of glutamine against the development of oral mucositis associated with chemotherapy in a randomized, double blind crossover clinical trial in cancer patients who previously had experienced at least one episode of mouth pain.

PATIENTS AND METHODS

Between May 1, 1993 and April 26, 1996 24 patients were identified who previously had experienced moderate to severe oral mucositis associated with at least 1 prior course of cancer chemotherapy. To be eligible for the study patients also needed to have at least two or more identical courses of chemotherapy scheduled in the future. There were no age or disease exclusions. Twenty-four patients were entered on the study after informed consent was obtained.

TABLE 1
Disease Characteristics of Patients

Diagnosis	Chemotherapy	No.
Sarcoma	CAD	3
Ewing's sarcoma	VAdrC	3
Osteosarcoma	IA, CDDPAdr MTX	5
Rhabdomyosarcoma	VAdrC	1
Neuroblastoma	VAdrC	1

CAD: cyclophosphamide, doxorubicin, and dacarbazine; VAdrC: vincristine, doxorubicin, and cyclophosphamide; IA: ifosfamide and doxorubicin; CDDPAdr: cisplatin and doxorubicin; MTX: high dose methotrexate.

Twenty-one of the 24 patients received doxorubicin-containing regimens including 1 patient who also received high dose methotrexate; 1 patient was treated with 5-fluorouracil (5-FU) and leucovorin, 1 patient was treated with carboplatin and etoposide, and 1 patient was treated with high dose methotrexate. Patients were provided with "mouth sore study suspension." In addition to the patients, the nurses and oncologists involved in the care of these patients also were blinded as to whether glutamine (active) or glycine placebo was provided.

The study was approved by the University of Minnesota Committee on the Use of Human Subjects in Research and the Mayo Clinic Institutional Review Board. Glutamine and placebo (glycine) as used in this study also were covered by an investigator initiated IND from the Food and Drug Administration (IND number 36,978). Table 1 details the disease characteristics of patients entered on the study. Figure 1 illustrates the calendar utilized by patients to record when mouth pain occurred after chemotherapy and how stomatitis affected enteral intake.

Glutamine and glycine were obtained as a crystalline amino acid powders form from Ajinomoto USA (Teaneck, NJ). Vehicle sweetener (Ora Sweet) and suspending agent (Ora Plus) were purchased from Paddock Laboratories (Minneapolis, MN). Amino acid (500 mg/mL) was mixed with Ora Sweet, Ora Plus, and water in a 2:1:1 ratio, respectively. Both the glutamine (active) and glycine (placebo) suspensions were quite sweet and had a gritty texture, similar to that experienced after brushing teeth with toothpaste. The dose and administration schedule of the study suspension was 2 g/M^2 twice daily (i.e., 4 mL/M^2 twice daily) beginning on the day of chemotherapy and continuing for at least 14 days after chemotherapy. Patients were instructed to swish and swallow the suspension in the morning
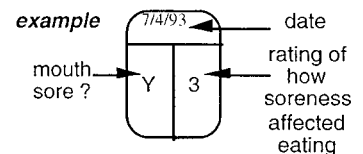
FIGURE 1. Questionnaire/calendar utilized by patients (or parents) to report onset, duration, and severity of mouth pain associated with chemotherapy. No mucositis results in a "NO" score; any pain is scored as a "Y"; severity sufficient to change eating patterns is graded as ≥ 2.

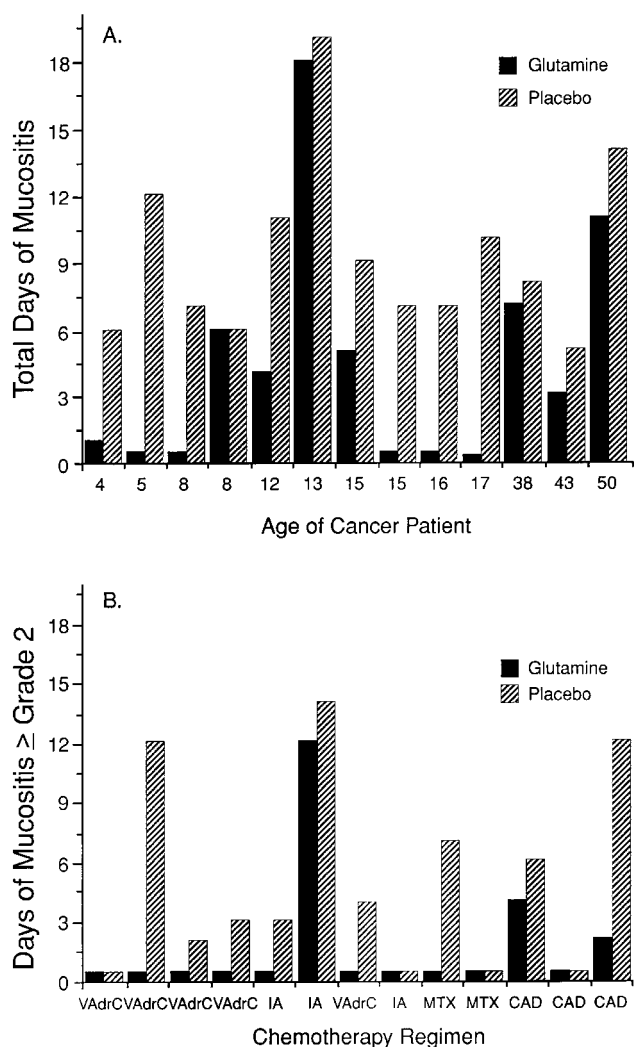## Statistical Methods

The study was designed as a randomized, placebo, double blind, crossover study with patients serving as their own controls over four courses of chemotherapy. Patients were assigned randomly to two courses of glutamine and two courses of glycine. Paired chemotherapy courses with glutamine and placebo utilized identical chemotherapy agents and doses. At the time of final analysis, much of the data regarding all four courses for each patient were missing. Therefore, the final analysis had to be tailored to meet these circumstances. Wilcoxon's rank sum test was used to compare the duration (number of days) and severity (number of days of mouth pain severity ≥ Grade 2; Modified Eastern Cooperative Oncology Group grad-

ing system) of mouth pain over the first course of chemotherapy between those patients randomized to receive glutamine and those patients randomized to receive placebo for the first course.

Paired data analysis

A major strength of the study design was the use of paired data analysis using patients as their own controls. The Wilcoxon signed rank test was used to compare the duration and severity of mouth pain using the first complete outcome data pair of comparable chemotherapy courses in which the subject received glutamine or glycine. If more than one set of data were available, only the first set of paired data was utilized in the final analysis. The paired data set was ranked according to age and is depicted graphically in Figure 2A; the same age ranking is present in Figure 2B but the abscissa contains the type of chemotherapy associated with the development of prior mucositis.

and evening. If the mouth sores made swallowing difficult, swishing and spitting the suspension out was permitted.

FIGURE 2. (A) Total duration of mouth pain (stomatitis) associated with chemotherapy after glutamine supplementation (solid bar) and glycine placebo supplementation (hatched bar). The graph depicts paired data comparisons of courses of glutamine versus glycine placebo suspension for individual patients from the youngest (age 4 years) to the oldest (age 50 years). Glutamine was associated with significantly fewer days of mouth pain ($P = 0.0005$). (B) The severity of mouth pain (stomatitis $\geq$ Grade 2) associated with chemotherapy after glutamine supplementation (solid bar) and glycine placebo supplementation (hatched bar) is shown. The graph depicts the same patients from the youngest to oldest but also denotes chemotherapy agents previously associated with stomatitis and for which paired data comparisons of glutamine versus glycine placebo are depicted. Glutamine was associated with significantly less severe mouth pain ($P = 0.002$). VAdrC: vincristine, doxorubicin, and cyclophosphamide; IA: ifosfamide and doxorubicin; MTX: methotrexate; CAD: cyclophosphamide, doxorubicin, and dacarbazine.

RESULTS
Study Compliance and Data Acquisition
Thirteen patients were able to complete at least 2 courses of identical chemotherapy (i.e., the same agents and doses with the same granulocyte-colony stimulating factor schedule), take prescribed doses, and complete a calendar describing the severity of mouth pain during and after chemotherapy. Six patients experienced progressive disease within 1 month after study entry and had chemotherapy changed or discontinued. Because this group received only a single chemotherapy course, no paired comparisons between glutamine and glycine placebo were possible. Because of a pharmacy error, one patient received glutamine but no placebo for two courses and therefore no evaluable paired courses of glutamine versus placebo-supplemented chemotherapy were available for evaluation. Four patients had incomplete questionnaires or removed themselves from the study (i.e., noncompliant with study suspension, data capture, and/or refused a second course), resulting in incomplete paired data.

The randomization sequence, chemotherapy prescribed, and mouth pain and enteral intake data collected during glutamine versus glycine administration are detailed in Table 2. Virtually all patients were able to swish and swallow the amino acid suspension without difficulty. Only one patient swished and spit out the amino acid suspension, a 13-year-old boy who also had herpes virus reactivation associated with chemotherapy during both placebo and glutamine administration. This individual also had the least improvement in stomatitis associated with glutamine administration.

Outcome Data for the First Course of Chemotherapy
Outcome data were available for 19 patients (79%). Twelve patients were randomized to receive glutamine first and 7 patients were randomized to receive placebo first. A Wilcoxon rank sum test was used to compare the duration of mucositis between these two groups. The results of this test were inconclusive ($P = 0.42$). With such small sample sizes and known heterogeneity in the duration and severity of mucositis associated with differing chemotherapy courses, there was not appropriate power to detect a clinically significant difference between groups. Similar results were found for the severity of mouth pain.

Paired Outcome Data
The effect of glutamine versus placebo as paired data after chemotherapy was available for 13 patients and is illustrated in Figure 2. Based on this data, there is convincing evidence to suggest that glutamine supplementation during and after chemotherapy significantly reduced both the duration and the severity of oral mucositis (Wilcoxon signed rank test, $P = 0.0005$ and 0.002, respectively). The overall duration of oral

TABLE 2
Patients Entered on Mucositis Study

Age (yrs)	Disease	Accrual sequence[a]	Clinical comments
4	RMS	gln(1,0)-gln(0,0)-gly(7,5)-gly(0,0)	VAdrC, IA, repeat
5	NBL	gln(0,0)-gly (12,12)-gln-gly	Progressive disease after Course 2
8	EWS	gly(7,2)-gln (0,0)-gly-gln	VAdrC
8	EWS	gln(5,0)-gln(2,0)-gly(5,0)-gly(1,0)	VAdrC 1,3; IE 2,4
12	OGS	gly(11,3)-gln(4,0)-gln(4,0)-gly(11,4)	IA, IE, IA, IE
13	OGS	gly(19,14)-gln(18,12)-gln(11,4)-gly(7,4)	IA, IA, MTX, MTX
15	OGS	gln(0,0)-gly(7,0)-gln-gly	IA, IA
15	EWS	gly(10,5)-gly-gln(6,0)-gln	VAdrC Course 1 and 3
16	OGS	gly(7,7)-gln-gly (7,0)-gln(0,0)	MTX 1,3,4 I/E, 2
17	OGS	gln(0,0)-gln(8,0)-gly(10,5)-gly	CDDPAdr 1,3, MTX 2,4
38	Sarcoma	gln(7,5)-gly (8,6)-gly-gln	CAD
43	Sarcoma	gly(5,0)-gln(3,0)-gly(10,0)-gln(7,0)	CAD
40	Sarcoma	gly-gln-gly(14,12)-gln(11,2)	CAD

RMS: rhabdomyosarcoma; gln: glutamine; gly: glycine; VAdrC: vincristine, doxorubicin, and cyclophosphamide; IA: ifosfamide and doxorubicin; NBL: neuroblastoma; EWS: Ewing's sarcoma; I/E: ifosfamide and etoposide; OGS: osteosarcoma; MTX: high dose methotrexate; CDDPAdr: cisplatin and doxorubicin; CAD: cyclophosphamide, doxorubicin, and dacarbazine.

[a] Numbers in parentheses indicate days of mouth pain; days mouth pain severity was ≥ Grade 2. If no numbers are present, data collection was incomplete or the chemotherapy course not identical.

mucositis was 4.5 days less when glutamine was provided compared with placebo. The duration of severe painful mucositis (i.e., days of oral mucositis ≥ Grade 2 requiring that the patient's diet be modified to soft food) was 4 days less when chemotherapy courses were supplemented with glutamine versus the placebo suspension.

DISCUSSION

Glutamine is a nutrient and a major product of metabolism in skeletal muscle. Because of its solubility and stability (4 g/100 mL; some conversion to glutamate), glutamine is absent from standard total parenteral nutrition (TPN) formulas. It has been shown that glutamine supplementation of TPN improves gut immune function,[14] maintains intramuscular glutamine concentrations after major surgery,[15] and improves nitrogen balance after surgery.[16] Both oral and intravenous glutamine supplementation have been well tolerated in normal volunteers and in catabolic patients.[17,18]

The provision of glutamine in TPN prevented deterioration of gut permeability and preserved mucosal structure.[19,20] However, high dose parenteral glutamine (0.285g/kg once daily × 4 weeks) was associated with the transient elevation of hepatic transaminases.[21] Other studies failed to demonstrate hepatic toxicity at doses of 0.285 g/kg and 0.57 g/kg, respectively.[22–24] Although these studies demonstrated a reduction in the rate of infections and the length of hospital stay in bone marrow transplantation patients

receiving glutamine-supplemented TPN, no effect on mucositis was observed.

The normal dietary intake of glutamine is approximately 1 g/day. Patients with malignant tumors including those of the breast, GI tract, and head and neck have reductions in plasma glutamine.[25] It is not known whether this is related to a reduction in muscle mass and subsequent conversion of glutamate to glutamine by muscle, tumor uptake of glutamine, or decreased oral glutamine intake.

Animal models have provided some insights regarding glutamine action relative to control of cancer. Oral glutamine supplementation enhanced the effectiveness of chemotherapy against rhabdomyosarcoma and reduced chemotherapy-associated toxicity in a rat methotrexate model.[26,27] The significance of glutamine in tumor growth in malignant cell lines and animal models has been reviewed extensively by Souba.[28] Thus, it would appear that the augmentation of tumor growth by glutamine is counterbalanced by support of host glutamine stores, glutathione production, and increased immune function, particularly natural killer cell (NK) activity.[29,30] Rats with mammary tumor implants had no augmentation of tumor growth kinetics when diet was enriched with enteral glutamine.[31] This finding possibly is related to suppression of PGE2 synthesis and improved NK function.[32] Thus, the therapeutic benefits of glutamine against cancer in animals appears to be related to improved host defenses and the ability to tolerate chemotherapy.[33]

The oral route of glutamine administration is an inexpensive and convenient means to provide this nutrient to cancer patients receiving chemotherapy. The normal dietary intake of glutamine is approximately 1 g/day; the remainder is synthesized by muscle via the glutaminase reaction. In a pilot study of oral glutamine in cancer patients a low dose of glutamine (approximately 0.13 g/kg/day) was used to simulate an enteral diet highly enriched with glutamine.[12,13] When used as a concentrated suspension (500 mg/mL) in an open label trial,[12,13] glutamine was demonstrated to have beneficial effects against the development of stomatitis. Therefore, to eliminate bias we conducted a randomized, double blind, crossover study of oral glutamine using the same 2 g/M^2 dose given twice daily. Because a low dose of oral glutamine (1 g) has been shown to result in a detectable increase in plasma glutamine, an increase in plasma bicarbonate, and increased growth hormone,[34] the dose of 2 g/M^2 twice daily also would be expected to result in these anabolic effects. One means to differentiate between the local and systemic effects of glutamine in the amelioration of stomatitis would be to compare swish and swallow regimens with swish and spit regimens.

Our study was conducted mostly in children and adolescents. Therefore, in addition to a suspending agent to keep the glutamine from settling out immediately after shaking the suspension, a sucrose vehicle was used. The sweet suspension proved to be very palatable to young children, but adolescents and adults sometimes found this formulation "too sweet." The palatability of glutamine is excellent because glutamine nearly is without taste. We would recommend use of a thick suspension and suspending agent and 2 weeks of supplementation because the duration of supplementation and local contact with the mouth possibly may be important variables for determining the effectiveness of glutamine against stomatitis. A study of 16 g of glutamine diluted in 150 mL water and divided into four times daily doses for a total of 8 days had no effect on 5-FU/folinic acid-induced mucositis.[35]

Furthermore, in tumor-bearing dogs receiving oral glutamine for the amelioration of radiation-associated oral mucositis, it has been necessary to continue treatment for at least 1 week after the last dose of radiation to avoid development of mucositis (unpublished data). Thus we would recommend that for the amelioration of mucositis associated with chemotherapy (or radiation) glutamine be provided not only during treatment but for at least 2 weeks after the completion of treatment (i.e., well into the recovery period).

Despite chemotherapy-induced oral mucositis being a common side effect of chemotherapy, relatively few treatments have been shown to be of benefit in reducing the severity or duration of mouth pain. Oral cryotherapy has been shown to be a useful adjunct to agents given by bolus such as 5-FU.[36,37] Granulocyte-macrophage-colony stimulating factor had a beneficial effect on oral mucositis in patients with head and neck carcinoma after chemotherapy with cisplatin, 5-FU, and leucovorin.[38] There was no suggestion to indicate that sucralfate could reduce the duration of mouth pain when it occurred after 5-FU chemotherapy.[39] The optimal use of low dose oral glutamine in the context of other preventive or comfort interventions remains to be determined.

In our study and subsequent clinical experience with patients with leukemia, Burkitt's lymphoma, and sarcomas, glutamine particularly was effective with chemotherapy regimens in which the use of doxorubicin or methotrexate was associated with prior stomatitis. Methotrexate particularly is interesting in view of its known decreased clearance when associated with glutamine administration.[40] Our results and additional clinical experience since this study was conducted indicate that for cancer patients receiving chemotherapy with a high risk of inducing oral mucositis (e.g., autologous bone marrow transplantation[41] or prior mucositis after anthracycline chemotherapy), oral glutamine supplementation is a simple and modestly effective means to decrease the duration and severity of oral mucositis. Because of the small numbers in this report of a randomized, double blind, crossover study of low dose oral L-glutamine, additional studies to determine the most effective schedule, dose, and form of administration of glutamine (e.g., thick suspension, Popsicle, or food additive) are needed.

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