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Effects of Glutamine Supplements and Radiochemotherapy on Systemic Immune and Gut Barrier Function in Patients With Advanced Esophageal Cancer

[Review Article]

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Abstract

Objective: The objective of this study was to determine whether oral glutamine supplements can protect lymphocyte and gut barrier function in patients with advanced esophageal cancer undergoing radiochemotherapy.

Summary Background Data: Glutamine supplements improved protein metabolism in tumor bearing rats who underwent chemotherapy and reduced the toxicity of chemotherapy through an enhancement of glutathione production in rats.

Methods: Thirteen patients with esophageal cancer were randomly placed in either a control or a glutamine group. Glutamine was administered orally (30 g/day) at the start of radiochemotherapy and for the subsequent 28 days. All patients underwent mediastinal irradiation and chemotherapy consisting of 5-fluorouracil and cisplatin. The lymphocyte count was determined, and blast formation was assessed after stimulation with phytohemagglutinin and concanavalin A. Gut barrier function was assessed by measuring the total amount of phenolsulfonphthalein excreted in the urine after the oral administration of phenolsulfonphthalein.

Results: Glutamine supplements prevented a reduction in the lymphocyte count (control: $567 \pm 96/mm^3$ *vs.* glutamine: 1007 ± 151, $p < 0.05$), and blast formation of lymphocyte (phytohemagglutinin, control: 19478 ± 2121 dpm *vs.* glutamine: 33860 ± 1433, $p < 0.01$, concanavalin A, control: 19177 ± 1897 dpm *vs.* glutamine: 29473 ± 2302, $p < 0.01$), and amount of phenolsulfonphthalein excretion in the urine was greater with control than with glutamine group (control: $15.4 \pm 2.4\%$ *vs.* glutamine: 7.4 ± 1.2, $p < 0.05$) 7 days after the initiation of radiochemotherapy.

Conclusions: Oral glutamine supplementation protects lymphocytes and attenuates gut permeability in patients with esophageal cancer during radiochemotherapy.

Although the surgical resection of a tumor and the regional lymph nodes is the primary form of treatment for patients with esophageal cancer,[1] the recurrence rate is 100% with surgery alone if the tumor has invaded adjacent organs such as the aorta, heart, or bronchus.[2] One attempt to reduce the recurrence rate is to administer neoadjuvant radiochemotherapy. Although the complete and partial response rate of neoadjuvant radiochemotherapy in patients with advanced esophageal cancer is 70%, the toxicity of this therapy often precludes further therapy such as resection of the primary tumor.[2] The major side effects of combined radiochemotherapy are decreases in the lymphocyte count, an impairment of lymphocyte function secondary to radiation exposure,[3] and the toxicity of anticancer drugs.[4]

Glutamine is a preferred energy source for both enterocytes [5] and lymphocytes,[6] and it regulates muscle protein turnover.[7] Glutamine supplementation accelerates healing of the small intestine after whole abdominal radiation [8] and enhances immune function in septic rodents.[9] Our previous article showed that glutamine supplementation enhanced muscle protein synthesis and reduces whole body protein breakdown rates in tumor-bearing rats that underwent chemotherapy.[10] Furthermore, Rouse et al.[11] demonstrated that glutamine supplements reduced the toxicity of chemotherapy because of enhanced glutathione synthesis in tumor bearing rats. In a clinical study, Zeigler et al.[12] reported that glutamine supplementation reduced the number of infectious complications and shortened hospital

stays after bone marrow transplantation. The objective of this randomized control study was to determine whether glutamine supplementation would maintain or enhance systemic lymphocyte function and protect gut barrier function in patients with esophageal cancer who received neoadjuvant radiochemotherapy.

PATIENTS AND METHODS

Patients

The experimental protocol was reviewed and approved by the Kurume University and the St. Mary's Hospital ethics committees. The risks were explained to each patient, and written informed consent was obtained before the randomization.

The extent of the tumors in the 128 patients with esophageal cancer was evaluated by computed tomography, fiberscopic ultrasound, and magnetic resolution imaging from April 1994 through September 1996. Eleven of the 128 patients entered the study and were diagnosed with having stage IV disease caused by tumor invasion into the adjacent organs (T4). Two patients without any adjacent organ invasion (T3) were included, because they selected neoadjuvant radiochemotherapy rather than only surgical resection of the esophagus and regional lymph nodes. These 13 patients subsequently were randomized into 2 groups: control (n = 6) and glutamine (n = 7). There were no differences between the two groups in body weight, height, and total plasma protein and albumin levels at the time of hospital admission, which suggests that the nutritional status of the patients in the two groups was equivalent (Table 1 and Table 2).

	Control	Glutamine Supplement
n	6	7
Gender (male:female)	5:1	6:1
Age	60.7 ± 2.6	61.6 ± 5.3
Body weight (kg)	49.8 ± 5.5	53.4 ± 2.6
Height (cm)	163.1 ± 6.3	162.4 ± 3.3
Total plasma protein (g/dL)	7.1 ± 0.4	6.5 ± 0.1
Plasma albumin (g/dL)	3.7 ± 0.3	3.5 ± 0.2
Total radiation dose (Gy)	36.0 ± 0.0	36.2 ± 0.9
CDDP (mg)	154 ± 7	150 ± 10
5-Fu (mg/body)	5750 ± 519	5214 ± 145
Mean calorie intake (kcal/day)	1829 ± 56	1562 ± 249
Mean nitrogen intake (gN/day)	10.1 ± 3.7	13.2 ± 2.4

Body weight, height, total protein, and albumin levels in the plasma were measured on admission to the hospital. These parameters were equivalent between the two groups. Radiation therapy was carried out by hyperfractionation (1.2 Gy × 2/day) and all chemotherapy was given intravenously. Mean intake of calorie and nitrogen was calculated from the record of food consumption and iv infusion during the study.

CDDP: cisplatin; 5-Fu: 5-fluorouracil.

Table 1. PATIENT'S CHARACTERISTICS

	No.	TNM Classification	The Site of T4 Organs	Response
(Control)	1	T4N3M0	Thoracic duct	PR
	2	T4N1M1(LYM)	Aorta	PD
	3	T4N1M0	Aorta	NC
	4	T4N1M0	Rt. lung	PR
	5	T3N1M0	None	MR
	6	T4N1M1(LYM)	Pericardia	PR
(Gln.)	1	T4N0M0	Lt. bronchus	PR
	2	T4N1M1(LYM)	Lt. bronchus	PD
	3	T4N1M1(LYM)	Aorta	PD
	4	T4N1M1(LYM)	Aorta	PR
	5	T4N1M1(LYM)	Aorta	PR
	6	T4N4M0	Lt. bronchus	PR
	7	T3N0M0	None	PR

TNM classification was evaluated by CT scan, MRI, and fiberscopic ultrasound. LYM: cervical lymph node metastasis; PD: progressive disease, defined as the appearance of one or more new lesions; NC: no change, defined as a less than 50% decrease of tumor size; MR: minor response defined as a 50% decrease in tumor size for less than 4 weeks; PR: partial response, defined as at least a 50% decrease in tumor size for over 4 weeks. None of the patients had organ metastases, but 6 patients had cervical lymph node metastases.

Table 2. TUMOR EXTENSION AND RESPONSE TO THERAPY

Study Design

Radiochemotherapy

The patients underwent hyperfractionated irradiation (1.2 Gy twice a day) from days 1 to 5, days 8 through 12, and days 15 through 20. The total dose administration was 36.0 ± 0 and 36.2 ± 0.9 Gy in the control and the glutamine groups, respectively (Table 1).

Chemotherapy consisted of cisplatin (CDDP; Nihon Chemical, Tokyo, Japan) and 5-fluorouracil (5-Fu, Kyowa Hakkoh, Tokyo, Japan). These drugs were administered by intravenous infusion from days 1 through 5 and days 8 through 12. The total dose administration of each drug was the same (5-Fu: control; 5750 ± 519 mg *vs.* glutamine, 5214 ± 145 mg, (NS), CDDP: control, 154 ± 7 mg *vs.* glutamine, 150 ± 10 mg, (NS), Table 1).

Nutritional Support and Glutamine Supplements

Calorie counts were recorded daily. When anorexia resulted from chemoradiotherapy, intravenous infusions of glucose and amino acids were administered to the patients. The mean calorie intake per patient per day including both oral consumption and intravenous infusions during the study was equivalent between the two groups (mean calorie intake from days 1 to 28, control group: 1829 ± 56 kcal/patient per day *vs.* glutamine group: 1562 ± 249 kcal/patient/day).

Oral glutamine (30 g/day; Glumine, Kyowa Hakkoh, Tokyo, Japan) was administered from days 1 through 28 to the Gln group. A standard amino acid solution (30 g/day; Amiparen, Otsuka Pharmaceutical, Tokushima, Japan) was administered intravenously to the control patients to make control isonitrogenous with the Gln group (mean nitrogen intake from days 1 through 28, control:10.1 ± 3.7 gN/patient/day *vs.* glutamine: 13.2 ± 2.4 gN/patient per day, [NS]).

Measurement Items and Analytic Procedures

Blood and saliva were collected on days 0 (before treatment), 7, 14, 21, and 28. The blood was centrifuged at 2500 rpm to collect the plasma. The plasma and saliva were stored at -70°C until analysis for glutamine and immunoglobulin A (IgA) concentrations.

Glutamine and Glutamate Levels in the Plasma

The plasma (0.5 mL) was mixed with 4% sulfosalicylic acid and centrifuged at 10,000 rpm for 15 minutes to precipitate plasma protein. The supernatant (100 μL) was injected into an automatic amino acid analyzer (Hitachi, Tokyo, Japan) to measure levels of glutamine and glutamate.

Immunoglobulin A Levels in the Plasma and Saliva

Secretory IgA levels in the plasma and saliva were measured by a double sandwich enzyme-linked immunosorbent assay using a standard technique (Special Reference Laboratories, Tokyo, Japan).

Lymphocyte Count

The blood lymphocytes were stained with Wright's methylene green solution (Omron, Tokyo, Japan) and the percentages of lymphocytes counted by light microscopy. The total white blood cells were counted by an automatic blood analyzer (Towa, Tokyo, Japan), and the number of lymphocytes was calculated. The number of T and B cells was counted using flow cytometric analysis (Special Reference Laboratories, Tokyo, Japan).

Mitogenic Activity of Lymphocytes

Phosphate-buffered saline (PBS, Nissui Chemical, Tokyo, Japan) was added to 5 mL blood, and the samples were centrifuged at 3000 rpm for 20 minutes to separate the lymphocyte from the rest of the blood. The lymphocytes were washed with phosphate-buffered saline and centrifuged again at the same speed. The mitogenic responses of the blood lymphocytes were tested using phytohemagglutinin and concanavalin A. The baseline mitogenic activity of lymphocytes was measured in the absence of these mitogens and used as standard. The lymphocytes were incubated in RPMI 1640 medium (Nissui Chemical, Tokyo, Japan) with 10% fetal calf serum for 72 hours in 5% CO_2 at 37°C. At that time, 0.25 μCi ^{3}H-thymidine was added to the culture. After an 18-hour incubation period with ^{3}H-thymidine, the cells were harvested, washed in phosphate-buffered saline, and counted in a [beta]-counter. Each assay was performed in duplicate, and the mean value was expressed as disintegrations per minute (dpm).

Gut Barrier Function Test

After the patients voided, they were administered oral doses of 30 mg phenolsulfonphthalein (PSP; Daiichi Pharmaceutical, Tokyo, Japan) with 100 mL water at 10 PM, and their urine was collected for the subsequent 8 hours. During this 8-hour period, the patients were not permitted any oral intake of food or water. The urine volume was measured, and the concentration of phenolsulfonphthalein in the urine was determined according to the method of Sasaki et al.[13] Briefly, 10 mL urine was diluted with de-ionized water to 1000 mL and the absorbance of this solution was measured at a wavelength of 560 nm (Special Reference Laboratories, Tokyo, Japan). Because phenolsulfonphthalein excretion in the urine is affected by renal function, the blood urea nitrogen and the creatinine levels in the plasma were determined in the clinical laboratory at St. Mary's Hospital by urease-glutamine dehydrogenase and picric acid, respectively.

Statistical Analysis

Data are expressed as the mean ± SEM. Statistical analyses was done by analysis of variance (ANOVA), and Fisher's protected least significant difference test was used to differentiate significant differences between the means, using a Macintosh Perfoma 588 (Apple Computer, Cupertino, CA: Statview 412 supplied by Abacus Concepts, Berkeley, CA). The mean differences were considered statistically significant at $p < 0.05$.

RESULTS

Glutamine levels in the plasma were decreased in the control patients 7 days after the initiation of radiochemotherapy, but glutamine supplements prevented this reduction (Table 3). The glutamine levels in the controls recovered to the levels in glutamine group on day 14 and remained the same in both groups on days 21 and 28. Glutamate levels in the plasma did not vary with glutamine supplements. During the study, there were no differences in plasma glutamate levels between the two groups.

	Group	Pretreatment	Day 7	Day 14	Day 28
Glutamine	control	440.6 ± 42.4	399.5 ± 19.4	483.3 ± 30.4	470.3 ± 48.1
(μmole/mL)	glutamine	496.5 ± 22.9	494.2 ± 30.6*	494.2 ± 30.6	466.4 ± 49.5
Glutamate	control	71.2 ± 10.5	74.3 ± 16.5	71.1 ± 14.4	63.6 ± 12.3
(μmole/mL)	glutamine	69.7 ± 10.4	82.4 ± 14.6	72.9 ± 16.9	67.4 ± 6.6
sIgA (μg/mL)	control	13.5 ± 2.9	14.6 ± 3.9	14.3 ± 2.3	13.3 ± 3.4
Plasma	glutamine	17.5 ± 3.9	16.3 ± 2.6	16.3 ± 3.5	16.0 ± 2.8
sIgA (μg/mL)	control	419.8 ± 83.9	777.0 ± 187.9	485.4 ± 100.1	770.2 ± 289.0
Saliva	glutamine	539.3 ± 141.2	952.9 ± 277.3	1250.5 ± 225.1*	677.0 ± 182.2

Glutamine, glutamate, and s-IgA levels in the plasma, and s-IgA levels in the saliva.
The blood and saliva were collected 0 (pretreatment), 7, 14, and 28 days after the initiation of radio-chemotherapy
* $p<0.05$ *vs* control.

Table 3. GLUTAMINE, GLUTAMATE, AND S-IgA LEVELS IN THE PLASMA, AND S-IgA LEVELS IN SALIVA

Although there were no differences in the plasma s-IgA levels, the s-IgA levels in the saliva were significantly greater on day 14 in those who received glutamine than in those who did not (Table 3).

Radiochemotherapy reduced the lymphocyte count in proportion to the total dose of radiation and chemotherapy. Glutamine supplements, however, prevented this reduction compared with the control group on day 7 (567 ± 96 mm^3 [control] *vs* 1007 ± 151 mm^3 [glutamine], $p < 0.05$; Table 4). There were no differences in the lymphocyte counts on days 14 and 28 between the 2 groups. Similar to the lymphocyte count, the T- and B-cell counts were greater with glutamine supplement than without it on day 7.

	Group	Pretreatment	Day 7	Day 14	Day 28
WBC	control	6112 ± 874	6798 ± 1541	4143 ± 441	2696 ± 485
(/mm³)	glutamine	6974 ± 582	5270 ± 537	4162 ± 446	2852 ± 278
Lymphocyte	control	1383 ± 69	567 ± 96	387 ± 64	420 ± 81
(/mm³)	glutamine	1740 ± 169	1007 ± 151*	633 ± 150	551 ± 121
T-cell	control	1117 ± 139	467 ± 80	330 ± 52	393 ± 112
(/mm³)	glutamine	1474 ± 172	854 ± 106*	556 ± 127	489 ± 106
B-cell	control	133 ± 32	45 ± 14	28 ± 7	16 ± 6
(/mm³)	glutamine	165 ± 43	86 ± 13*	34 ± 12	19 ± 3
PHA (dpm)	control	37424 ± 3305	19478 ± 2121	19284 ± 3848	26836 ± 6959
	glutamine	39012 ± 5638	33860 ± 1433†	30399 ± 2455*	31751 ± 1415
ConA (dpm)	control	31797 ± 3677	19177 ± 1897	16515 ± 2904	25324 ± 4304
	glutamine	35595 ± 3893	29473 ± 2302†	31372 ± 2523†	25810 ± 2167
Standard	control	161 ± 13	187 ± 30	221 ± 64	146 ± 69
(dpm)	glutamine	186 ± 38	165 ± 44	184 ± 31	126 ± 21

White blood cell, lymphocyte, T-cell, B-cell count, and lymphocyte blast formation.
Standard was defined as the baseline formation of lymphocyte blasts without stimulation of the lymphocytes.
* p<0.05 vs control.
† p<0.01 vs control.
WBC: white blood cell; PHA: phytohemagglutinin; Con A: concanavalin A; dpm: disintegrations per minute.

Table 4. WHITE BLOOD CELL, LYMPHOCYTE, T-CELL, B-CELL COUNTS, AND LYMPHOCYTE BLAST INFORMATION

The baseline lymphocyte blast formation was the same in the two groups. Although the lymphocyte count decreased with radiochemotherapy on day 28 in both groups, lymphocyte blast formation stimulated by phytohemagglutinin was maintained in the glutamine group, it was reduced to 19478 ± 2121 and 19284 ± 3848 in the control group on days 7 and 14, respectively ($p < 0.05$) *versus* the glutamine group (Table 4). Similarly, blast formation by concanavalin A was greater in the glutamine group than in the control group on days 7 and 14.

A transient increase in urinary phenolsulfonphthalein excretion was found in the control patients on day 7. Glutamine supplementation reduced phenolsulfonphthalein excretion to 7.4 ± 1.2% ($p < 0.05$ *vs* control, Table 5). No differences were noted in urinary phenolsulfonphthalein excretion in the urine between the two groups on days 14 and 28.

	Group	Pretreatment	Day 7	Day 14	Day 28
PSP(%)	control	11.4 ± 0.8	15.4 ± 2.4	6.8 ± 2.1	13.8 ± 4.6
	glutamine	9.5 ± 1.4	7.4 ± 1.2*	7.5 ± 1.3	10.1 ± 3.2
BUN(mg/dL)	control	13.6 ± 3.9	19.7 ± 3.7	18.6 ± 4.2	13.8 ± 3.2
	glutamine	13.3 ± 2.8	19.1 ± 2.5	18.7 ± 3.9	18.7 ± 2.2
Crea(mg/dL)	control	0.63 ± 0.06	0.66 ± 0.07	0.71 ± 0.09	0.69 ± 0.10
	glutamine	0.71 ± 0.08	0.76 ± 0.06	0.79 ± 0.06	0.75 ± 0.06

Cumulative 8-hour PSP excretion in the urine, blood urea nitrogen, and plasma creatinine levels.
PSP: phenolsulfonphthalein; BUN: blood urea nitrogen; Crea: creatine.
* p<0.05 vs control.

Table 5. PSP EXCRETION IN THE URINE, BLOOD UREA NITROGEN, AND PLASMA CREATININE LEVELS

DISCUSSION

Glutamine is a nonessential amino acid and is the most abundant amino acid in free amino acid pool.[14] Glutamine levels in the plasma were decreased in tumor-bearing rats even though there was an increase in glutamine production in tumor-bearing rats.[15] This is because glutamine use is increased in enterocytes,[16] immune cells such as lymphocytes and macrophages, and tumor cells.[17-19] In this study, the glutamine levels before radiochemotherapy (day 0) were in the normal range in patients with advanced esophageal cancer. This is probably because the patients maintained on a normal diet that may contain 6 to 7 grams of glutamine.[20] Seven days after the initiation of

radiochemotherapy, the glutamine levels decreased and were significantly less in the control group than in the glutamine-supplemented group. This is probably caused by an increase in glutamine utilization for intestinal mucosal repair because of the mucosal damage induced by a systemic chemotherapy.[10,21] The reduction of glutamine levels in the plasma was transient and there were no differences in glutamine levels between the control and glutamine groups on days 14 and 28. This recovery may have resulted because patients became adapted to radiochemotherapy, which resulted in an enhancement of glutamine production either from an increase in proteolysis or glutamine synthesis in skeletal muscle. Indeed, we have already demonstrated that whole body protein breakdown rate was increased during chemotherapy in rats.[10]

When administered orally, phenolsulfonphthalein is poorly absorbed from the gastrointestinal tract in healthy subjects. When 24-mg oral phenolsulfonphthalein was administered to healthy subjects, approximately 2.4 mg phenolsulfonphthalein (10%) was excreted in the urine within 5 hours.[13] Similarly, approximately 10% of the phenolsulfonphthalein dose was excreted in the urine within 8 hours in the patients with advanced esophageal cancer, suggesting that gut permeability was not increased because of advanced esophageal cancer alone. This study showed that in association with a decrease in the plasma glutamine levels, phenolsulfonphthalein excretion was increased in the controls 7 days after the initiation of radiochemotherapy, whereas no change was found in the glutamine supplemented group. Because renal function as evaluated by blood urea nitrogen (BUN), and creatinine levels in the plasma were within normal range (BUN, < 20 mg/dL; creatinine, < 1.2 mg/dL) and were the same between the two groups, the phenolsulfonphthalein excretion data indicated that a transient increase in gut permeability induced by radiochemotherapy was inhibited by glutamine supplementation.

Results of many animal experiments have shown that glutamine supplementation protects the morphology of intestine,[22] improves immune function system in the gut,[23] and enhances gut mucosal protein synthesis.[24] Fox et al.[25] reported that gut morphology was improved with glutamine in methotrexate treated rats and that survival rate from methotrexate toxicity was attenuated because of a reduction of gut failure associated with sepsis. Furthermore, Tremel et al.[26] demonstrated that supplemented glutamine facilitates xylitol absorption in intensive care unit patients. Contrary to the xylitol test, this study showed that glutamine inhibited phenolsulfonphthalein absorption on day 7 compared with the controls. The absorption of phenolsulfonphthalein is increased in indomethacin treated rats [27] and patients with gastritis,[28] when gastrointestinal mucosal integrity was impaired. Hence, glutamine supplements prevented an impairment of gut integrity during radiochemotherapy.

In agreement with earlier studies,[3,4] the lymphocyte counts were decreased in the control patients who underwent combined radiochemotherapy. Glutamine supplementation, however, transiently preserved the lymphocyte count and maintained lymphocyte blastogenation during the radiochemotherapy. The toxicity of radiation and chemotherapy is mediated partially by oxidant injury, and this is associated with host glutathione depletion.[29] Glutamine is rate limiting for glutathione synthesis,[30] and the administration of glutamine caused an increase in glutathione levels in jejunum in tumor bearing rats.[31,32] Furthermore, glutathione levels were enhanced and methotrexate toxicity was reduced in methotrexate-treated rats administered glutamine.[11] Because glutamine was included in the media when the lymphocytes were stimulated with phytohemagglutinin or concanavalin A *in vitro,* the protection of lymphocyte function probably resulted from increased glutathione synthesis from the supplemental glutamine rather than the utilization of glutamine as an energy fuel or for DNA synthesis for lymphocyte replication.

Although there were no significant differences in the plasma s-IgA levels between the two groups, a significant increase in s-IgA levels in the saliva was found in the patients administered glutamine supplementation. This result was consistent with Alverdy's study [23] showing that the concentration of s-IgA in bile was increased in rats administered glutamine supplemented TPN. S-IgA is produced by

s-IgA-producing B cells supported by cytokines derived from T-helper cells, and the s-IgA is released into secretions, such as saliva, tears, bile, and intestinal succus.33 Because T cells are more radiosensitive than B cells 34 and glutamine supplementation preserved lymphocyte blast formation stimulated by phytohemagglutinin and concanavalin A, probably reflecting glutamine preservation of T-cell function during radiochemotherapy 35,36; preservation of T-helper cell function may enhance s-IgA secretion in saliva.

Previous studies 37-39 have reported that combined radiochemotherapy resulted in approximately a 90% complete response rate in patients with esophageal cancer. However, the 3-year survival rate with radiochemotherapy was only 18% if a tumor invaded adjacent organs.2 The administration of increased doses of radiation and chemotherapy may, therefore, be critical for reducing tumor progression and improving survival in such patients. This study indicated that glutamine supplements were a promising protection agent for both gut integrity and T-cell function during radiochemotherapy in patients with advanced esophageal cancer.

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