BLOOD RESEARCH
VOLUME 54 · NUMBER 1
March 2019
ORIGINAL ARTICLE

Efficacy of parenteral glutamine supplementation in adult hematopoietic stem cell transplantation patients

Yun Kyung Cho[1], So Yeon Hong[1], Su Jeoung Jeon[1], Hyung Wook Namgung[1], Eunsook Lee[1], Euni Lee[2], Soo-Mee Bang[3]

[1]Department of Pharmacy, Seoul National University Bundang Hospital, Seongnam, [2]College of Pharmacy, Seoul National University, Seoul, [3]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

p-ISSN 2287-979X / e-ISSN 2288-0011
https://doi.org/10.5045/br.2019.54.1.23
Blood Res 2019;54:23-30.

Received on June 17, 2018
Revised on August 21, 2018
Accepted on September 27, 2018

Correspondence to
Soo-Mee Bang, M.D., Ph.D.
Department of Internal Medicine, Seoul National University Bundang Hospital, Gumi-ro 173 Beon-gil 82, Bundang-gu, Seongnam 13620, Korea
E-mail: smbang7@snu.ac.kr

Background
Hematopoietic stem cell transplantation (HSCT) patients need parenteral nutrition because of nausea, vomiting, and mucositis caused by conditioning regimens. The demand for glutamine increases during the HSCT period. We evaluated the effects of glutamine-containing parenteral nutrition on the clinical outcomes of HSCT patients.

Methods
In this retrospective analysis, we reviewed HSCT patients from Seoul National University from August 2013 to July 2017. Depending on their glutamine supplementation status, 91 patients were divided into 2 groups: glutamine group (N=44) and non-glutamine group (N=47). We analyzed the rate of weight change, infection (clinically/microbiologically documented), complications (duration of mucositis and neutropenia, acute graft versus host disease), and 100-days mortality in each group.

Results
Regarding the clinical characteristics of the patients, there were no significant differences between the 2 groups except that there was a larger proportion of myeloablative conditioning regimen in the glutamine group (P=0.005). In the glutamine group, the average number of days of glutamine use, parenteral nutrition, and mucositis was 7.6±1.4, 14.6±9.9, and 13.3±9.5, respectively. Furthermore, multivariate analysis revealed odds ratios of 0.37 (95% CI, 0.14–0.96; P=0.042) and 0.08 (95% CI, 0.01–0.98; P=0.048) for clinically documented infection and 100-days mortality, respectively, in the glutamine group.

Conclusion
Results showed that the glutamine group had less clinically documented infection and 100-days mortality than the non-glutamine group, but the other outcomes did not show significant differences. The extended duration of glutamine supplementation according to the period of total parenteral nutrition and mucositis should be considered.

Key Words Glutamine, Hematopoietic stem cell transplantation, Parenteral nutrition

INTRODUCTION

The majority of hematopoietic stem cell transplantation (HSCT) patients undergo pre-HSCT conditioning, i.e., high-dose exposure to a variety of antineoplastic drugs, often combined with radiotherapy. They are at a higher risk for undernutrition compared to general chemotherapy patients because they experience difficulty with oral ingestion due to nausea, vomiting, mucositis, and gastrointestinal dysfunction. Poor nutrition and weight loss are common contributors to cancer mortality, and parenteral nutrition (PN) is recommended when oral intake is less than 60% of the required amount of intake [1-3].

Glutamine is classified as a non-essential amino acid; however, increased demand for and insufficient endogenous synthesis of glutamine in stress and catabolic conditions, such as HSCT, can lead to its progressive deficiency. As a protein

precursor and regulator of protein synthesis, glutamine is involved in various metabolic-biochemical processes and acts as an inter-organ nitrogen shuttle, playing an important role in rapid proliferation of immune and intestinal cells and providing various supportive functions. In particular, it is known to be involved in energy production, synthesis of amino acids, and regulation of cell cycle activity in intestinal mucosal cells [4-8].

The European Society for Clinical Nutrition and Metabolism (ESPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines state that nutrition support is recommended to HSCT patients who are at a risk of malnutrition and are unable to receive enteral nutrition and are anticipated to experience starvation for a period longer than 7 to 14 days. ESPEN and ASPEN propose that "HSCT patients may benefit from glutamine-supplemented PN" (grade B) and "pharmacologic doses of parenteral glutamine may benefit patients undergoing hematopoietic cell transplantation" (grade C), respectively [1, 3].

Our study was conducted to evaluate the effects of glutamine-enriched PN on weight change, infection, and complication and mortality among HSCT patients.

MATERIALS AND METHODS

Study participants and period

Our study included patients aged ≥19 years, who received HSCT at the Seoul National University Bundang Hospital from August 1, 2013 to July 31, 2017. The exclusion criteria were as follows: 1) non-referral to the Nutrition Support Team (NST), 2) oral intake more than 60% of the daily caloric requirement, 3) no administration of total PN (TPN) or its discontinuation due to hepatic and/or renal failure, 4) inability to accurately assess the clinical outcome due to early death or other causes, and 5) inability to determine the response to conditioning regimens. Prior to the study, the study protocol was approved by the IRB of the Seoul National University Bundang Hospital (IRB no. B-1709-420-108). A waiver of participant consent was obtained due to the retrospective nature of our study.

Data collection and study design

In a retrospective review of the patients' electronic medical records, we collected various sets of data, including basic patient information [age, gender, height, weight, body mass index (BMI), and duration of hospital stay], HSCT-related information (diagnosis, source of stem cells, HLA match in allogeneic transplantation, pre-HSCT therapeutic exposure, and pre-HSCT comorbidity), amount of oral intake, duration of TPN administration, and duration of glutamine supplementation. To obtain the clinical outcomes of the patients, we collected data regarding the onset and duration of mucositis, absolute neutrophil count (ANC), microbial culture and other infection-related test results, date of graft-versus-host disease (GVHD) diagnosis, and date of death.

Patients were divided into 2 groups: the glutaminesupplemented TPN group (referred to as the "glutamine group") and the non-glutamine-supplemented TPN group ("non-glutamine group"). The minimum calorie and protein requirements specified in the ASPEN guidelines were considered as reference values for evaluating patients' nutritional status (Supplementary Table 1).

Conditioning was divided into myeloablative conditioning (MA) or non-MA conditioning depending on the intensity of the pre-HSCT conditioning regimens. Non-MA conditioning included both reduced intensity conditioning (RIC) and non-myeloablative conditioning (NMA). Although a conditioning regimen involving fludarabine/busulfan/ATG (FluBuATG) is not typically classified as MA, if the busulfan dose was ≥12.8 mg/kg then the conditioning regimen was classified as MA according to the working group definition [9]. Moreover, busulfan/cyclophosphamide and total body irradiation/cyclophosphamide/ATG regimen were also classified as MA.

The clinical course was evaluated using the following variables: weight change rate (days 8 and 15 of TPN), infections (clinically documented/microbiologically documented), complications (duration of mucositis, duration of neutropenia, occurrence of acute GVHD), and 100-day mortality. The weight change rate was checked on days 8 and 15 of TPN, considering the maximum health insurance coverage period of 8 days for glutamine TPN supplementation. Infection was classified into either clinically documented or microbiologically documented infection. Clinically documented infections were defined as fever associated with local inflammation, such as pneumonia, skin-infection, or cellulitis, whose microbiological pathogenesis could not be ascertained. Infectious organisms detected in cultures, even without localized inflammation ware mandatory in microbiologically documented infections [10]. Neutropenia was defined as an ANC under 500/μL.

Statistical analysis

Analysis was performed using the statistical software package IBW SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA). Comparisons between groups were made using an independent 2-sample *t*-test and Mann-Whitney U test for continuous variables and the chi-square test and Fisher's exact test for categorical variables. Additionally, logistic regression analysis (95% confidence interval) and multiple regression analysis were performed in order to adjust for the influence of glutamine administration on the occurrence of infections and complications and the 100-day mortality. Results were considered statistically significant when the *P*-value was less than 0.05.

RESULTS

Characteristics of patient groups

A total of 286 patients aged ≥19 years underwent HSCT

at the Seoul National University Bundang Hospital from August 1, 2013 to July 31, 2017. A total of 91 patients were included in our study after excluding 167 patients who were not referred to the NST, 7 patients whose oral intake exceeded 60% of the daily caloric requirements, 10 patients who were not subjected to TPN or whose TPN administration was discontinued due to hepatic and/or renal failure, 7 patients whose clinical outcomes were not clearly documented, and 4 patients whose responses to conditioning regimens could not be identified. Table 1 outlines the characteristics of the patient groups.

The glutamine and non-glutamine groups mostly showed similar characteristics; however, significant differences were observed in the conditioning regimen, especially in its intensity. The intensity of pre-HSCT conditioning depends on the type of chemotherapy. In particular, a high-intensity conditioning regimen involves high-dose alkylating agents or a combination of alkylating agents and radiotherapy to the extent that recovery is impossible without the injection of hematopoietic stem cells, resulting in a longer duration of neutropenia as compared with a reduced-intensity pre-HSCT conditioning regimen. Both groups showed no significant difference in disease status at the time of transplant. The number of patients who had complete remission (CR) or partial remission (PR) was 42 (95.5%) in the glutamine group and 42 (89.3%) in the non-glutamine group.

However, significant differences were observed in the conditioning regimen, especially in its intensity. The glutamine group showed a significantly higher rate of high-intensity conditioning regimen compared with the non-glutamine group. One patient was classified into the MA arm because of fludarabine/busulfan (12.8 mg)/ATG conditioning.

Nutritional supply by group

Table 2 outlines the nutritional supply results expressed as the percentage of the supplied calorie and protein relative to the required amount. Calorie supplies of the glutamine and non-glutamine groups were 99.6±19.1% and 104.5±21.1% (P=0.249), respectively, and protein supplies were 89.2±17.3% and 85.0±16.9% (P=0.263), respectively. The duration of TPN for the glutamine and non-glutamine groups was 14.6±9.9 and 16.2±9.1 days, respectively. During TPN administration in the glutamine group, the duration of glutamine supplementation was 7.6±1.4 days. During this period, the glutamine group received the full daily dosage of Dipeptiven;

Table 1. Characteristics of the patients.

	Glutamine group (N=44)	Non-glutamine group (N=47)	P
Male/female (%)	26/18 (59.1/40.9)	32/15 (68.1/31.9)	0.372
Body weight (kg)	65.0±13.4	66.1±13.2	0.541
BMI (kg/m^2)	23.4±3.5	23.9±3.5	0.357
Height (cm)	165.8±8.9	165.9±8.6	0.781
Length of stay (days)	22.2±10.8	23.0±12.7	0.670
Age (yr)	47.1±12.3	44.5±11.3	0.201
Diseases			0.437
Acute myeloid leukemia	13 (29.5)	13 (27.7)	
Acute lymphoblastic leukemia	7 (15.9)	4 (8.5)	
Myelodysplastic syndrome	3 (6.8)	5 (10.6)	
Multiple myeloma	5 (11.4)	10 (21.3)	
Non-Hodgkin lymphoma	12 (27.3)	10 (21.3)	
Hodgkin lymphoma	3 (6.8)	1 (2.1)	
Others[a]	1 (2.3)	4 (8.5)	
Hematopoietic stem cell transplantation type			
Allogeneic (%)	29 (65.9)	25 (53.2)	0.217
Transplantation sources in allogeneic HSCT	Peripheral blood	Peripheral blood	0.988
Full matched sibling	8 (29.6)	8 (32.0)	
Full matched unrelated donor	11 (37.9)	9 (36.0)	
1–2 loci mismatched sibling or unrelated donor	5 (17.2)	4 (16.0)	
Haplo-matched family donor	5 (17.2)	4 (16.0)	
Conditioning regimen			0.005[c]
MA[b]	18 (40.9)	7 (14.9)	
Non-MA	26 (59.1)	40 (85.1)	
Disease status at transplant			0.436
Relapsed/refractory	2 (4.5)	5 (10.7)	
Complete remission/partial response	42 (95.5)	42 (89.3)	

Data are presented as mean±SD or N (%).
[a]Each 1 case of HLH (hemophagocytic lymphohistiocytosis), MPAL (mixed phenotype acute leukemia of T and myeloid lineages). [b]Busulfan/cyclophosphamide, fludarabine/busulfan (12.8 mg/kg)/ATG, total body irradiation/cyclophosphamide/ATG. [c]$P<0.05$.
Abbreviation: MA, myeloablative conditioning.

Table 2. Status of the nutritional support.

	Glutamine group (N=44)	Non-glutamine group (N=47)	*P*
Calorie (kcal/kg)	28.2±6.0	29.3±6.3	0.397
Total delivered/required caloric ratio (%)	99.6±19.1	104.5±21.1	0.249
Protein (g/kg)	1.2±0.3	1.2±0.3	0.170
Total delivered/required protein ratio (%)	89.2±17.3	85.0±16.9	0.263
Duration of TPN (days)	14.6±9.9	16.2±9.1	0.450
Duration of glutamine (days)	7.6±1.4	-	-

Data are presented as mean±SD.
Abbreviation: TPN, total parenteral nutrition.

Table 3. Infections.

	Clinically documented infection		Microbiologically documented infection	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.00 (0.95–1.05)	0.945	1.03 (0.97–1.08)	0.349
Gender		0.432		0.696
Male	1		1	
Female	0.69 (0.27–1.76)		1.25 (0.41–3.84)	
Glutamine		0.042[a]		0.237
No	1		1	
Yes	0.37 (0.14–0.96)		0.50 (0.16–1.6)	
MA		0.058		0.877
No	1		1	
Yes	3.48 (0.96–12.63)		1.11 (0.295–4.18)	
BMT type		0.850		0.004[a]
Autologous	1		1	
Allogeneic	1.13 (0.33–3.82)		10.69 (2.14–53.36)	
Response		0.466		0.156
Relapsed/refractory	1		1	
PR/CR	0.52 (0.09–3.04)		5.55 (0.52–59.04)	

Data are presented as odds ratio (95% CI). [a]$P < 0.05$.
Abbreviations: BMT, bone marrow transplantation; CR, complete remission; MA, myeloablative conditioning regimen; PR, partial response.

1 bottle (100 mL) is intended for a single use and contains 20 g of L-alanyl-L-glutamine (13.46 g of L-glutamine).

Clinical outcomes

Weight change rate: The day-8 weight change rates of the glutamine and non-glutamine groups were 0.74±1.5%, and 1.0±1.9%, respectively, showing no statistically significant difference (*P*=0.620). There was no significant difference between the 2 groups in the day-15 weight change rate (0.55±2.2% vs. 0.78±4.1%; *P*=0.765).

Infection: The frequency of infection was examined in 2 types of infections: clinically documented and microbiologically documented. Clinically documented infections occurred in 36.4% of patients in the glutamine group and 51.1% of patients in the non-glutamine group. Microbiologically documented infections occurred in 20.5% of patients in the glutamine group and 25.5% of patients in the non-glutamine group. The most frequent clinically documented infection was sepsis followed by pneumonia. The most frequent isolates in microbiologically documented infection were Gram-negative bacteria such as, *Escherichia coli*. There were 3 patients with fungal infection (Supplementary Table 2).

Multivariate analysis and logistic regression analysis were performed adjusting for different factors associated with infection. The effect of glutamine supplementation on infection was analyzed after adjusting for age, gender, high intensity conditioning, HSCT type, and response to pre-HSCT chemotherapy (recurrent or refractory, partial or complete remission), which were considered influential factors. Our results revealed that the glutamine group had 0.37 times lower the odds of having a clinically documented infection compared to the non-glutamine group (95% CI, 0.14–0.96; *P*=0.042). However, for microbiologically documented infections, no statistically significant difference between the 2 groups was observed (OR=0.50; 95% CI, 0.16–1.6; *P*=0.237). Odds ratio analysis of microbiologically documented infections categorized by the type of HSCT revealed that the odds of having a microbiologically documented infection was 10.69 times higher in allogeneic HSCT patients compared to that in autologous HSCT patients (95% CI, 2.14–53.36; *P*=0.004) (Table 3).

Mucositis, neutropenia, and acute GVHD: The duration of

mucositis in the glutamine group was 13.3±9.5 days and 10.8±7.6 days in the non-glutamine group. According to multivariate analysis, which considered age, gender, high-intensity conditioning, HSCT type, and response to pre-HSCT chemotherapy as risk factors, glutamine administration was not associated with the duration of mucositis (B=0.03, *P*=0.751). In contrast, high-intensity conditioning and allogeneic HSCT were associated with a significantly longer duration of mucositis (Supplementary Table 3). The duration of neutropenia was 11.9±6.1 days in the glutamine group and 9.4±4.6 days in the non-glutamine group; no statistically significant difference between the 2 groups was observed even after adjustment for gender, high-intensity conditioning, HSCT type, and response to pre-HSCT chemotherapy (*P*=0.098). Post-HSCT development of acute GVHD occurred in 31.0% of patients in the glutamine group and 28.0% of patients in the non-glutamine group within the first 100 days of HSCT. Multivariate analysis was performed to adjust for risk factors, including age, gender, high-intensity conditioning, match or mismatch of the donor's and recipient's histocompatibility antigens, and response to pre-HSCT chemotherapy. The odds of developing GVHD was 1.38 times higher in the glutamine group compared to that in the non-glutamine group, albeit without statistical significance (95% CI, 0.36–3.74; *P*=0.649).

100-day mortality: The mortality rates at 100 days post-HSCT in the glutamine and non-glutamine groups were 2.1% (N=1) and 10.4% (N=5), respectively. The causes of death included septic shock (N=4), progressive disease (N=1), and stress-induced cardiomyopathy (N=1). Our multivariate analysis showed that the 100-day mortality was significantly lower in the glutamine group than that in the non-glutamine group (OR=0.078; 95% CI, 0.01–0.98; *P*=0.048) (Table 4).

DISCUSSION

Our study aimed to investigate the effect of glutamine-enriched TPN on HSCT patients' body weight, infections, complications, and mortality. Our results showed that glutamine-supplemented TPN was associated with decreased rates of clinically documented infection and 100-day mortality.

Glutamine is abundantly present in the blood. Our body's requirement for glutamine increases under stress conditions. Glutamine is involved in nitrogen transfer and ammoniagenesis, and is a primary fuel source for enterocytes, hepatocytes, lymphocytes, and macrophages [5]. Enterocytes are especially sensitive to glutamine deficiency, which leads to inflammatory cytokine production and increased permeability. In a systematic review, it was reported that glutamine administration decreases mortality in critically ill patients; although animal studies have shown that glutamine supplementation reduces the degree of mucositis and bacterial translocation in the intestinal tract after chemotherapy; it remains controversial in human trials [4, 7, 11, 12].

Our results demonstrated that there was no significant difference in the calorie and protein supply between the glutamine and non-glutamine groups during the post-HSCT convalescence period. In this context, it should be noted that glutamine was not administered to the glutamine group for the entire duration of TPN (only for 7.6 out of 14.6 days). This is due to the fact that glutamine was replaced by a different protein solution to continue TPN, because health insurance coverage for the glutamine TPN solution is limited to 8 days. In non-Korean publications that study glutamine-supplemented PN regimens, the duration of gluta-

Table 4. Day 100 mortality.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	0.93 (0.86–1.00)	0.059	0.96 (0.07–14.10)	0.424
Gender		0.323		0.170
Male	1		1	
Female	3.02 (0.34–27.01)		6.07 (0.46–79.67)	
Glutamine		0.144		0.048[a]
No	1		1	
Yes	0.20 (0.02–1.74)		0.08 (0.01–0.98)	
MA		0.218		0.413
No	1		1	
Yes	2.86 (0.54–15.25)		2.63 (0.26–26.49)	
BMT type		0.998		0.998
Autologous	1		1	
Allogeneic	-		-	
Response		0.410		0.981
Relapsed/refractory	1		1	
PR/CR	0.38 (0.04–3.80)		0.97 (0.07–14.10)	

Data are presented as odds ratio (95% CI). [a]$P < 0.05$.
Abbreviations: BMT, bone marrow transplantation; CR, complete remission; MA, myeloablative conditioning regimen; PR, partial response.

mine TPN ranged between 7 and 28 days, and the amount administered also varied widely from 0.2 to 0.97 g/kg [12]. ESPEN guidelines recommended ~0.6 g/kg as an optimal level for a glutamine-supplemented PN regimen [3]. The patients in the glutamine group of our study received 13.46 g/d glutamine for a maximum of 8 days, and it is likely that the duration of glutamine administration or the supply amount was not long or large enough to adequately evaluate the effect of glutamine.

To evaluate the frequency of infection, several risk factors, such as age, gender, high-intensity pre-HSCT conditioning, HSCT type, and response to pre-HSCT chemotherapy (recurrent or refractory, partial or complete remission) were considered. Our results showed that the glutamine group developed infections less frequently than the non-glutamine group in general, while a statistically significant decrease was observed in the frequency of clinically documented infections. Due to the difficulty in considering various long-term infection risk factors, only short-term infection frequency could be determined (during the period between HSCT and discharge). Furthermore, the glutamine group tended to have neutropenia for a longer time, presumably because of the significantly higher rate of high-intensity conditioning in this group. Our multiple regression analysis revealed that there was no significant difference between groups.

While the duration of mucositis was not significantly influenced by glutamine supplementation, patients who were exposed to high-intensity conditioning and those who received allogeneic HSCT (vs. autologous HSCT) were more likely to develop mucositis. Even when we performed subgroup analysis for allogeneic HSCT and autologous HSCT, we found no significant difference in mucositis development by supplying glutamine. Piccirillo *et al.* [13] reported that glutamine-enriched PN decreases the severity of mucositis in autologous HSCT patients. This group conducted 2 studies, with various amounts of glutamine supplementation. In the first study, the mucositis-related pain score decreased significantly with 20 g glutamine, whereas in the second study, a decrease was observed with 13.46 g glutamine, but it was not statistically significant. However, Kuskonmaz *et al.* [14] showed that mucositis rate tended to decrease, but this result was not statistically significant.

Gama Torres *et al.* [15] reported that glutamine PN has a positive effect on short-term mortality rate in allogeneic HSCT patients and hypothesized that glutamine might act as an immunomodulator in intestinal immune cells. A previous animal model study revealed that animals that received PN with glutamine showed higher values of intestinal IgA, anti-inflammatory cytokine interleukin (IL-4), and IL-10 compared to those that did not receive PN with glutamine. Ziegler *et al.* [16] reported that glutamine supplementation is associated with improved nitrogen balance, decreased rate of clinical infections, and reduced length of hospital stay in allogeneic HSCT patients. In contrast, according to the results of Pytlik *et al.* [17] in 40 patients, the number of days of hospital stay and the rate of positive blood cultures were shown to be increased in the glutamine-supplemented group, but without statistical significance. More recently, a Cochrane systematic review reported that glutamine supplementation is not associated with a decrease in the number of days of hospital stay, mucositis, GVHD, and ANC recovery period, but decreases the rate of positive blood cultures [2, 18].

Although glutamine supplementation decreased the frequency of clinically documented infections and 100-day mortality in HSCT patients, no statistically significant results were obtained regarding body weight change and duration of mucositis. The post-HSCT duration of mucositis and the duration of TPN in the glutamine group were 13 and 15 days on an average, respectively, which is much longer than the insurance coverage period for glutamine TPN solutions (8 days) and the actual duration of glutamine supplementation in our study (7.6 days on average). Because this limited period is insufficient to adequately evaluate the effect of glutamine supplementation in clinical practice, a follow-up study is necessary to evaluate clinical merit by extending the duration of glutamine administration.

Our retrospective study may have contained confounding factors that influenced the clinical outcomes. However, to reduce confounding, we considered age, gender, high-intensity pre-HSCT conditioning, HSCT type, and disease status during transplant in our analysis. Because the number of patients included in the study was relatively small, we could not perform analysis according to the type of transplant (allogeneic and autologous transplant). Nevertheless, we demonstrated that glutamine PN had a significant positive influence on post-HSCT clinically documented infections and 100-day mortality. Our study is important because it is the first study in South Korea that investigates the effect of glutamine-supplemented PN on adult HSCT patients.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. August DA, Huhmann MB; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. JPEN J Parenter Enteral Nutr 2009;33:472-500.
2. Bozzetti F. Nutritional support of the oncology patient. Crit Rev Oncol Hematol 2013;87:172-200.
3. Bozzetti F, Arends J, Lundholm K, et al. ESPEN guidelines on parenteral nutrition: non-surgical oncology. Clin Nutr 2009; 28:445-54.
4. Newsholme P, Procopio J, Lima MM, Pithon-Curi TC, Curi R. Glutamine and glutamate-their central role in cell metabolism and function. Cell Biochem Funct 2003;21:1-9.

5. Kuhn KS, Muscaritoli M, Wischmeyer P, Stehle P. Glutamine as indispensable nutrient in oncology: experimental and clinical evidence. Eur J Nutr 2010;49:197-210.
6. Wang X, Pierre JF, Heneghan AF, Busch RA, Kudsk KA. Glutamine improves innate immunity and prevents bacterial enteroinvasion during parenteral nutrition. JPEN J Parenter Enteral Nutr 2015;39:688-97.
7. Castell LM, Bevan SJ, Calder P, Newsholme EA. The role of glutamine in the immune system and in intestinal function in catabolic states. Amino Acids 1994;7:231-43.
8. Park HJ. Role of parenteral glutamine in nutrition support for critically Ill patients. J Clin Nutr 2015;7:42-8.
9. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant 2009;15:1628-33.
10. Cordonnier C, Engelhard D, Ljungman P, et al. Definitions of infectious diseases and complications after stem cell transplant: A proposal from the Infectious Diseases Working Party of the EBMT. Leiden, The Netherlands: EBMT, 2011. (Accessed July 26, 2018, at http://portal.ebmt.org/Contents/About-EBMT/Who-We-Are/ScientificCouncil/Documents/IDWPdefinitions.pdf).
11. Vanek VW, Matarese LE, Robinson M, et al. A.S.P.E.N. position paper: parenteral nutrition glutamine supplementation. Nutr Clin Pract 2011;26:479-94.
12. Crowther M, Avenell A, Culligan DJ. Systematic review and meta-analyses of studies of glutamine supplementation in haematopoietic stem cell transplantation. Bone Marrow Transplant 2009;44:413-25.
13. Piccirillo N, De Matteis S, Laurenti L, et al. Glutamine-enriched parenteral nutrition after autologous peripheral blood stem cell transplantation: effects on immune reconstitution and mucositis. Haematologica 2003;88:192-200.
14. Kuskonmaz B, Yalcin S, Kucukbayrak O, et al. The effect of glutamine supplementation on hematopoietic stem cell transplant outcome in children: a case-control study. Pediatr Transplant 2008;12:47-51.
15. da Gama Torres HO, Vilela EG, da Cunha AS, et al. Efficacy of glutamine-supplemented parenteral nutrition on short-term survival following allo-SCT: a randomized study. Bone Marrow Transplant 2008;41:1021-7.
16. Ziegler TR, Young LS, Benfell K, et al. Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone marrow transplantation. A randomized, double-blind, controlled study. Ann Intern Med 1992;116:821-8.
17. Pytlik R, Benes P, Patorkova M, et al. Standardized parenteral alanyl-glutamine dipeptide supplementation is not beneficial in autologous transplant patients: a randomized, double-blind, placebo controlled study. Bone Marrow Transplant 2002;30:953-61.
18. Murray SM, Pindoria S. Nutrition support for bone marrow transplant patients. Cochrane Database Syst Rev 2009:CD002920.

Supplementary Table 1. Nutrient requirements.

① Energy (kcal): 30 kcal/kg
② Protein (g): 1.5 g/kg
③ Bodyweight was based on calculated body weight (CBW).
- if ABW > IBW, then CBW = IBW + (ABW−IBW) × 0.25
- if ABW ≤ IBW, then CBW = ABW
  - ✓ IBW (Ideal body weight), ABW (Actual body weight)

Abbreviations: ABW, actual body weight; CBW, calculated body weight; IBW, ideal body weight.

Supplementary Table 2. The list of microorganisms identified.

Microorganisms identified	Glutamine group	Non-glutamine group
Gram-positive bacterium		
Coagulase-negative *Staphylococci*	1	1
Streptococcus agalactiae	-	1
Vancomycin-resistant *Enterococcus*	1	-
Enterococcus faecalis	1	1
Enterococcus faecium	-	1
Clostridium difficile	-	1
Gram-negative bacterium		
Escherichia coli (ESBL[a] negative)	3	1
Escherichia coli (ESBL positive)	2	-
Enterobacter cloacae	2	-
Klebsiella pneumonia	1	1
Others[b]	2	2
Fungus		
Aspergillus species	1	1
Candida albicans	-	1

[a]Extended-spectrum beta-lactamases. [b]Others includes Bacillus spp., Capnocytophaga spp., and 2 Gram-negative rods.

Supplementary Table 3. Duration of mucositis.

	Univariate analysis		Multivariate analysis	
	B	*P*	B	*P*
Age	-0.025	0.017[a]	0.102	0.402
Gender		0.331		0.696
Male	0		0	
Female	-0.10		0.06	
Glutamine		0.170		0.751
No	0		0	
Yes	0.15		0.031	
MA		< 0.001[a]		0.039[a]
No	0		0	
Yes	0.41		1.11 (0.295–4.18)	
BMT type		< 0.001[a]		0.004[a]
Autologous	0		0	
Allogeneic	0.47		0.38	
Response		0.416		0.783
Relapsed/refractory	0		0	
PR/CR	-0.09		-0.03	

Data are presented as regression coefficient (B). [a]$P < 0.05$
Abbreviations: BMT, bone marrow transplantation; CR, complete remission; MA, myeloablative conditioning regimen; PR, partial response.