Glutamine-Enriched Nutrition Does Not Reduce Mucosal Morbidity or Complications After Stem-Cell Transplantation for Childhood Malignancies: A Prospective Randomized Study

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Background. Intravenous glutamine-enriched solution seems to be effective in posttransplant period in decreasing the severity and duration of mucositis. The aim of this randomized study was to determine the benefit of glutamine supplementation both on mucosal morbidity and in posttransplant associated complications.

Methods. Children undergoing allogeneic hematopoietic stem-cell transplantation (HSCT) for malignant hematological diseases were randomly assigned to standard total parenteral nutrition (S-TPN) or glutamine-enriched (GE)-TPN solution consisting of 0.4 g/kg/day of L-alanine-glutamine dipeptide. This treatment started on the day of HSCT and ended when the patients could orally cover more than 50% of their daily energy requirements. The severity and the rate of post-HSCT mucositis were based on World Health Organization criteria. All the analyses were conducted on intention-to-treat principle.

Results. One hundred twenty consecutive patients (83 men; median age, 8.1 years) were enrolled. The mean duration of treatment was 23.5 and 23 days in the two treatment arms. The mean calorie intake was 1538 kcal/d in the S-TPN group and 1512 kcal/d in GE-TPN group. All patients were well nourished before and after HSCT. Mucositis occurred in 91.4% and 91.7% of patients in S-TPN and GE-TPN arm, respectively ($P=0.98$). Odds ratio adjusted by type of HSCT was 0.98 (95% confidence interval, 0.26–2.63). Type and duration of analgesic treatment, clinical outcome (engraftment, graft versus host disease, early morbidity, and mortality, relapse rate up to 180 days post-HSCT) were not significantly different in the two treatment arms.

Conclusion. GE-TPN solution does not affect mucositis and outcome in well-nourished HSCT allogeneic patients.

Keywords: Glutamine, Mucosal complications, Childhood malignancies, Transplantation.

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In the past, major surgery, intensive care and gastroenterology patients constituted the main candidates for oral or intravenous glutamine supplementation (*1–3*). High dose chemo-radiotherapy followed by hematopoietic stem-cell transplantation (HSCT) has been claimed to be one of the main causes of severe mucositis and related complications, resulting in severe catabolism, disruption of the gastrointestinal (GI) mucosa, and marked immunosuppression. Some reports underlined that GI tract cells are among the most

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rapidly proliferating in the body and metabolize nearly all absorbed dietary glutamine in addition to extracting circulating glutamine derived from other tissues (*4*). Glutamine, an essential amino acid for enterocytes, seems therefore to be depleted during damage toward enteric mucosa (*5*).

Intravenous glutamine-enriched solution has been advocated as one of the support treatments that is able to improve post-HSCT-marked body protein wasting and oxidative stress. Although a variety of studies have shown that supplementation with glutamine, in a free or dipeptide form, seems to be effective in the posttransplant period, few reports have been really informative on the efficacy of this amino acid in decreasing the severity and duration of mucositis associated with pretransplant conditioning regimens (*6–8*).

We did a prospective double-blind, controlled trial in HSCT recipients to determine the benefit of intravenous glutamine supplementation both in mucosal morbidity and in post-HSCT-associated complications.

RESULTS

One hundred twenty consecutive patients (83 men, median age at SCT, 8.1 years) who received allogeneic HSCT were randomized to receive standard total parenteral nutrition (S-TPN) (58/120) or glutamine-enriched (GE)-TPN (62/120). Two male patients were excluded from the analysis because they lacked data on outcome and did not receive any parenteral treatment, one because of hyperbilirubinemia and cerebral vasculitis before HSCT, and the other for an unknown reason.

The two study groups were comparable in age, gender, diagnosis, type of transplant, and conditioning regimen (Table 1). The mean duration of treatment was 23.5 days in the S-TPN versus 23 days in the GE-TPN arm. None patient underwent plasma levels of free glutamine before and after starting the study. The mean calorie intake was 1538 kcal/d in the S-TPN group and 1512 kcal/d in GE-TPN group.

Mucositis in the first 3 to 4 weeks from SCT occurred in 94.8% and 96.7% of patients in the S-TPN and GE-TPN arm, respectively ($P=0.68$) (Table 2). No significant difference in appearance of mucositis in mouth and gut alone was found in the two arms of the study, when patients were evaluated for 24 hr/d. Mucositis grade 1, 2, and 3 was present in the 25.9%, 58.6%, and 10.3% of S-TPN patients, and in the 21.7%, 68.3%, and 6.7% of GE-TPN patients without any statistical significant difference both in univariate and in multivariate analysis.

Odds ratio adjusted by type of HSCT was 1.73 (95% confidence interval, 0.27–11.27). Neither type of analgesic treatment nor duration of opioid or opiate treatment (13.5 and 14 days median for S-TPN and GE-TPN patients, respectively) was significantly different ($P=0.80$ and 0.78, respectively). Engraftment, length of hospital stay, transplant-related mortality at 6 months, acute or chronic graft versus host disease (GVHD) pattern, incidence of severe infectious diseases, and relapse rate of malignancies were similar in the two groups (Table 3). Changes in nutritional status (before HSCT, 10 days after and at the end of parenteral nutrition), as measured by weight, cholinesterase, prealbumin, or albumin values were not significantly different by treatment arm (Table 4). Because of the difficulty in recording data, lymphocyte subsets have only been measured for 20 patients in the S-TPN group and 23 patients in the GE-TPN group. Data concerning the immunological recovery at 1, 3, and 6 months after HSCT for these patients found no difference in either arm (data not shown).

TABLE 1. Clinical profile of the patients

Items	S-TPN (n=58) n (%)	GE-TPN (n=60) n (%)
Male gender	39 (67.2)	42 (70)
Age (yr); median (range)	8.4 (0.4–18.6)	8.0 (0.9–18.6)
Diagnosis		
ALL	31 (53.5)	30 (50)
AML	13 (22.4)	15 (25)
CML	1 (1.7)	8 (13.3)
NHL	4 (6.9)	2 (3.3)
HGD	2 (3.5)	1 (1.7)
MDS	3 (5.2)	3 (5)
MLH	1 (1.7)	0 (0)
Secondary AML	0 (0)	1 (1.7)
Rhabdomyosarcoma	1 (1.7)	0 (0)
JMML	2 (3.5)	0 (0)
Type of transplant		
Related	18 (31)	17 (28.3)
Unrelated	35 (60.3)	30 (50)
Cord blood	4 (6.9)	7 (11.7)
Haplo	1 (1.7)	6 (10.0)
Chemotherapy+TBI	34 (58.6)	31 (51.7)
TPN median duration in days (range)	23.5 (11–66)	23.0 (10–101)

S-TPN, standard total parenteral nutrition; GE-TPN, glutamine-enriched total parenteral nutrition; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myelogeneous leukemia; NHL, non-Hodgkin lymphoma; HGD, Hodgkin disease; MDS, myelodysplastic syndrome; MLH, malignant lymphohistiocytosis; JMML, juvenile myelomonocytic leukaemia; TBI, total body irradiation.

DISCUSSION

Cochrane methodology meta-analyses have so far shown at least 17 randomized studies without providing a reliable consensus on the benefit of glutamine administration in HSCT patients (*9*). Many of those studies are based on small series and are not easily comparable because they differ in patient demographics, type of disease, stem cell source, and type of transplant.

The current prospective double-blind randomized study is one of the few designed to evaluate the effect of GE-TPN on decreasing mucosal complications in the setting of children undergoing allogeneic HSCT for malignancies. Our study shows that GE-TPN was not sufficient to decrease incidence and severity of oral or GI mucosa after HSCT and consequently did not offer an advantage on clinical outcome, as claimed by other retrospective or randomized studies (*10–13*), none of which focused exclusively on children.

To our knowledge, only one past study, which was designed like ours but used oral glutamine from the beginning of conditioning regimen has drawn a favorable conclusion in the setting of shorter morphine treatment for mucositis and a reduction of median number of days of TPN (*14*). However, those authors underlined a bias due to the fact that a higher

TABLE 2. Severity, grade of mucositis and analgesic treatment

Items	S-TPN (n=58) n (%)	GE-TPN (n=60) n (%)	Univariate analysis OR[b] (95% CI)	*P*	Multivariate analysis[a] OR[b] (95% CI)	*P*
Mucositis	55 (94.8)	58 (96.7)	1.58 (0.25–9.83)	0.68	1.73 (0.27–11.27)	0.57
Mouth	39 (67.2)	43 (71.7)	1.23 (0.56–2.7)	0.69	1.42 (0.62–3.22)	0.40
Gut	2 (3.4)	2 (3.3)	0.97 (0.13–7.09)	1.00	—	
Mouth and gut	14 (24.1)	13 (21.7)	0.87 (0.37–2.05)	0.83	0.76 (0.31–1.88)	0.56
Grade 1	15 (25.9)	13 (21.7)	0.79 (0.34–1.86)	0.67	0.71 (0.29–1.71)	0.44
Grade 2	34 (58.6)	41 (68.3)	1.52 (0.72–3.24)	0.34	1.65 (0.76–3.58)	0.21
Grade 3	6 (10.3)	4 (6.7)	0.62 (0.17–2.32)	0.53	0.66 (0.17–2.54)	0.54
Major treatment	42 (72.4)	45 (75)	1.14 (0.50–2.60)	0.84	1.43 (0.6–3.43)	0.42
Morphine	27 (46.6)	29 (48.3)	1.07 (0.52–2.21)	0.86		
Codeine	1 (1.7)	0 (0)	—	0.49		
Tramadole or other	8 (13.8)	6 (10)	0.69 (0.23–2.14)	0.58		
Codeine+morphine	1 (1.7)	2 (3.3)	1.97 (0.17–22.28)	1.00		
Tramadole or other+morphine	5 (8.6)	8 (13.3)	1.63 (0.5–5.31)	0.56		
Major treatment (d) median (range)	13.5 (5–37)	14.0 (1–27)		0.78		
Minor treatment	9 (15.5)	8 (13.3)	0.53 (0.3–2.34)	0.80	0.75 (0.26–2.17)	0.60
Paracetamol	1 (1.7)	0	—	0.49		
Novalgina	1 (1.7)	0	—	0.49		
Novalgina+paracetamol	2 (3.4)	3 (5)	0.93 (0.24–9.16)	1.00		
Other	5 (8.6)	5 (8.3)	0.66 (0.26–3.52)	1.00		

[a] OR estimated by a logistic model adjusting by type of SCT.
[b] OR, odds ratio GE-TPN vs S-TPN.
S-TPN, standard total parenteral nutrition; GE-TPN, glutamine-enriched parenteral nutrition.

TABLE 3. Secondary end-points

Items	S-TPN (n=58) Total number (%)	GE-TPN (n=60) Total number (%)	Univariate analysis OR[a] (95% CI)	*P*
TRM	5 (8.6)	7 (11.7)	1.40 (0.42–4.69)	0.76
Relapse	10 (17.2)	5 (8.3)	0.44 (0.14–1.37)	0.17
Hospital stay (d); median (range)	44 (23–141)	45 (22–183)		0.20
Infection	32 (55.2)	33 (55)	0.99 (0.48–2.05)	1.00
Resolved	26 (44.8)	27 (45.0)		
Partially resolved	3 (5.2)	4 (6.7)		
Failure	3 (5.2)	2 (3.3)		
GVHD	39 (67.2)	41 (68.3)	1.05 (0.49–2.28)	1.00
Grades 1–2	35 (60.3)	30 (50)	0.66 (0.32–1.36)	0.27
Grades 3–4	4 (6.9)	11 (18.3)	3.03 (0.91–10.14)	0.10
Skin	24 (41.4)	24 (40.0)	0.94 (0.45–0.97)	1.00
Liver	2 (3.5)	0 (0)	—	0.24
Gut	2 (3.5)	4 (6.7)	2.00 (0.35–11.36)	0.68
Skin+liver	3 (5.2)	2 (3.3)	0.63 (0.10–3.93)	0.68
Skin+gut	6 (10.3)	9 (15.0)	1.53 (0.51–4.61)	0.59
Skin+liver+gut	2 (3.5)	2 (3.3)	0.97 (0.13–7.09)	1.00
Post–BMT engraftment	57 (98.3)	59 (98.3)	1.04 (0.06–16.95)	1.00
Polymorpho nuclear cells, median (range)	18 (10–58)	19 (6–45)		0.62
Platelets, median (range)	19 (1–598)	20 (1–136)		0.44

[a] OR, odds ratio GE-TPN vs. S-TPN.
S-TPN, standard total parenteral nutrition; GE-TPN, glutamine-enriched total parenteral nutrition; TRM, transplant-related mortality; GVHD, graft versus host disease; BMT, bone marrow transplantation.

TABLE 4. Nutritional conditions

Items	S-TPN (n=58)	GE-TPN (n=60)	*P*
Weight	(n=58)	(n=60)	
Pre–TPN (mean)	35.6	31.6	
End TPN (mean)	34.6	30.8	0.703
Cholinesterase	(n=46)	(n=48)	
Pre–TPN (mean)	5405.5	5212.1	
10 d (mean)	5850.0	5481.1	
End TPN (mean)	6237.0	6321.1	0.6338
Prealbumin	(n=23)	(n=32)	
Pre–TPN (mean)	47.2	36.5	
10 d (mean)	49.3	29.2	
End TPN (mean)	49.6	46.6	0.5132
Albumin	(n=55)	(n=54)	
Pre–TPN (mean)	15.4	17.1	
10 d (mean)	13.9	16.2	
End TPN (mean)	14.8	16.9	0.5517

S-TPN, standard total parenteral nutrition; GE-TPN, glutamine-enriched nutrition.

number of children in the placebo group were seropositive for herpes simplex virus before HSCT and therefore more at risk for severe post-HSCT mucositis. Other studies regarding the use of oral glutamine given alone or as a part of enteral-enriched formulas have shown variable results (*15–17*).

A partial explanation of the lack of benefit in using GE-TPN for our transplanted children seems to be the type of nutritional status at the beginning of the conditioning regimen: it was rather good as one can see by the pretransplant body weight and nutritional parameters including prealbumin, which is a marker of rapid protein synthesis. A favorable trend of nutritional status was maintained throughout the most critical period post-HSCT in both groups, as we have already demonstrated (*18*), using an elevated caloric intake in both groups according to current recommendations (*19*, *20*). This nutritional regimen applied in non-malnourished patients could explain the reason of the lack of impact of GE-TPN on the mucositis and tissue damage. In addition, our experience is in line with other authors who claimed that the well-nourished patients have a shorter time to engraftment and less probability of developing severe posttransplant complications (*21*, *22*). It is of interest that similar considerations have recently emerged by a large randomized study in which intravenous glutamine did not show an advantage in the outcome of well-nourished patients with cancer undergoing major surgery (*23*) in contrast with previous observations (*24*). The same authors had the possibility to measure the plasma level of glutamine in patients undergoing standard TPN with or without glutamine-enriched solution, but they did not find a significant variation of this amino acid throughout the study (*23*).

In regard to the past statement on favorable glutamine supplementation both on gut damage and on reduction of infection (*2*, *7*, *11*, *25*), the majority of the studies performed are small and have poor methodological reporting. In the current study, neither severe infectious diseases potentially derived from mucositis nor acute GVHD combined or not with other organ complications had a severe impact in the short-term outcome of S-TPN versus GE-TPN group.

Our patients given GE-TPN supplementation did not have a different transplant-related mortality or relapse rate compared with the S-TPN group, confirming the nontoxicity of glutamine in high-risk patients and, most of all, the non-increased relapse rate due to glutamine which, as hypothesized by some authors (*26–28*), could be a nutrient capable of inducing abnormal growth of tumor cells.

Some doubts might be raised as to whether glutamine enhances immunological recovery after HSCT. It goes without saying that immunosuppressive drugs differently used in the pre- and post-HSCT period according to institutional schedules could influence lymphocyte immunomodulation per se (*7*, *29*). In our experience, we did not record enough information about the immunological recovery because of difficulty in collecting serial data in this setting.

In those few analyzed patients, however, the overtime lymphocyte increase did not show a particular difference between the two groups in contrast to a previous study (*15*) in which posttransplant lymphocyte resumption was probably justified by the different type of transplant and less severe immunosuppression than ours.

Recent studies concerning alternative immunomodulatory formulas, that is, eicosapentaenoic acid, in the suppression of inflammatory cytokines, as tumor necrosis factor and interleukin-1 and interleukin-2, showed a prevention of some posttransplant complications including mucositis (*30*, *31*). However, a possible disadvantage of eicosapentaenoic acid could be the stimulation of the immune system in patients at risk for GVHD and therefore larger and randomized studies with this nutrient, with or without glutamine, need to be set up in the future.

In conclusion, although we were not able to demonstrate a reliable advantage in using GE-TPN after HSCT and therefore we are not in favor of routine use of glutamine, we think worthwhile to continue to explore what kind of different nutritional support could have a favorable impact on posttransplant mucositis- and organ-associated complications.

MATERIALS AND METHODS

The children eligible for this double-blind study had malignant hematological diseases and underwent allogeneic HSCT from June 2005 to June 2008 after high dose chemotherapy and total body irradiation. They were randomly assigned to S-TPN or glutamine-enriched nutrition (GE-TPN) consisting of 0.4 g/kg/day of L-alanine-glutamine dipeptide (equal to 0.25 g of free glutamine).The first dose of L-alanine-glutamine dipeptide was started on the day of HSCT after the randomization until the end of TPN when the patients could orally cover more than 50% of their daily energy requirements for at least 3 days.

This prospective study was carried out in four Italian pediatric HSCT (Associazione Italiana di Ematologia ed Oncologia Pediatrica) centers. Randomization was centrally performed by a computer-generated sequence, stratified by center. Each center investigator was responsible for requesting the random assignment by phone 2 days before starting the support treatment. The physician involved in transplant procedures received the corresponding parenteral formula from the pharmacy without knowing the type. All patients underwent analgesic, antibiotic, antiviral, and immunosuppressive treatment according to international guidelines for post-HSCT procedures, which take into consideration the management of the majority of posttransplant complications (*32*). In particular, the mucositis analgesic therapy was administered intravenously whenever the patients were not able to assume the drugs orally. The principal endpoint of the study was to assess

the presence, the rate, and the severity of mucositis (grades according to World Health Organization criteria). Each finding of GI mucosa injury was clinically evaluated at the best of doctors and nurses skills. The evaluation of the clinical outcome (type of mouth pain and analgesic treatment, associated infectious diseases, GVHD, and hospitalization time), hematological pattern (polymorphonuclear cells and platelets engraftment, lymphocytes and lymphocytes subset total number during the first 6 months after HSCT), and laboratory nutritional parameters were the secondary endpoints. Liver, renal function tests, and other biochemical investigations were performed routinely every other day or when required. A signed informed consent was obtained by patients, relatives, or tutors before any study procedure. A local ethical committee approved the study which was registered as study no. 39537-23-0 in the "Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali" (Roma, http://oss-sper-clin.agenziafarmaco.it/).

Statistical Analysis

The study was designed to accrue a total of 124 patients (62 per group) to demonstrate a 20% difference in terms of mucositis rate (baseline 90%) with an 80% power (α=0.05; one-sided tests). All analyses were conducted according to the intention-to-treat principle (*33*).

The difference in primary and secondary end-points between the two treatment groups has been evaluated by Fisher's exact and Wilcoxon tests, respectively, for categorical and continuous variables. A logistic regression model was also applied to evaluate the treatment effect on the occurrence of mucositis after adjusting by type of SCT. A paired *t* test was applied to evaluate the difference between the two groups in terms of nutritional status (and immunological pattern) before and after treatment.

The recruitment period was planned to last no more than 3 years and each participating center was invited to enroll at least 15 patients and follow them up to 6 months after randomization. Data were collected using standard case report forms.

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