A randomized, double blind comparative study of prophylactic parenteral nutritional support with or without glutamine in autologous stem cell transplantation for hematological malignancies – three years' follow-up*

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Forty-four adult autologous transplant patients with hematological malignancies were randomized to receive either prophylactic parenteral nutrition PN (P group), or PN given *ad hoc* (C group). In each group, they were further randomized to receive standard PN (B group), or PN with 0.5 g glutamine/kg as L-Ala-L-Gln (A group). The overall survival (OS), disease-free survival (DFS) and event-free survival (EFS) in groups C vs. P and A vs. B were compared during follow-up with median 38 months. The final outcome rates in C/P/A/B groups, respectively (OS 65/81/63/85%, EFS 45/53/33/65% and DFS 56/50/35/77%), were not significantly different, apart from A<B in DFS rate (p=0.03, Fisher's exact test). Also in survival analysis (logrank test), no significant difference between groups C and P was found but generally worse parameters were observed for A vs. B group: for DFS (p=0.04) and EFS (p=0.01) the difference was significant, and for OS (p=0.09) it was borderline. In the three years' follow-up, no clinically useful benefit of prophylactic PN in autologous transplant patients was proven. Also, glutamine supplementation was not helpful, and was even connected with apparently worse long-term outcome.

Key words: autologous stem cell transplantation, hematological malignancies, parenteral nutrition, glutamine, long-term outcome

The optimal method of nutritional support in bone marrow transplantation (BMT) has been a matter of controversy [8, 20]. Carefully designed study by WEISDORF et al in the late eighties [19] found a beneficial effect of parenteral nutrition (PN) given prophylactically, i.e. started with the cytoreductive regimen, even in well-nourished patients, and the positive effect was most pronounced in the long-term outcome (survival analysis). Furthermore, later studies, namely that by ZIEGLER et al [24, 25, 26], have shown an additional benefit of glutamine (Gln) supplementation. However, the benefit of Gln has remained controversial. While some of the subsequent studies by other groups documented positive effects on clinical and laboratory parameters [3, 10, 11, 16], other studies suggested no important benefit [14, 18]. Especially in autologous transplantation the newer techniques of supportive care that shorten the critical posttransplant period may render these particular aspects of nutritional support less important. Then, a standard PN provided *ad hoc*, when the patient cannot eat, would serve as well, at considerably less cost.

Most of the studies, however, were focused primarily on the hospitalization phase, and a possible benefit on the long-term outcome, similar to that proven by WEISDORF [19], was rarely analyzed. In one study by SCHLOERB [17] the short-term effect of Gln (oral and parenteral) was limited but there was a suggestion of improved long-term survival in the Gln group. In contrast, PYTLIK et al [14] found worse survival with Gln. Also, most of the studies were performed on a heterogeneous sample, with a wide spectrum of diagnoses, often including both hematological malignancies and solid tumors.

Therefore, we have conducted a controlled, double-blind

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study in a relatively homogeneous group of 44 hematooncological patients undergoing autologous stem cell transplantation (ASCT) in 2000–2003, with the aim to evaluate the role of prophylactic PN and/or Gln supplementation. We have previously documented no clinically useful benefit of either of them during the hospital stay. There was no important difference in the total length of hospital stay, length of hospital stay after transplantation, days with fever, antibiotics consumption, time to leucocyte engraftment, granulocyte stimulating factor (G-CSF) consumption, nutritional markers and need of hemosubstitution [12, 13].

Here, we present the long-term outcome data of this group after three years' follow-up with median 38 months in terms of overall survival (OS), disease-free survival (DFS) and event-free survival (EFS).

Patients and methods

Patients. Study participants (n=44, median age = 50 years) were recruited from among patients who received ASCT for hematological malignancies: 15 for non-Hodgkin's lymphoma (NHL), 14 for multiple myeloma (MM), 8 for Hodgkin's lymphoma (HL) and 7 for acute leukemia (AL) in our department from 2000 to 2003. All patients signed informed consent approved by the Local Ethical Committee. They were placed in laminar airflow rooms in our transplant unit and received standard conditioning regimens for their diagnoses (Tab. 1) and standard supportive care.

Study protocol. Patients were randomized to receive either prophylactic PN starting with the cytoreductive regimen (prophylactic P group, n=21), or PN initiated next day after oral intake became inadequate (control C group, n=23). Oral intake was assessed daily by a qualified dietitian and it was considered inadequate if less than half of maintenance energy needs (estimated as resting energy expenditure from Harris-Benedict formula multiplied by 1.3) was covered. In both groups, PN was stopped after the leucocyte count grew over $1x10^9$/l and oral intake became adequate again. Patient characteristics in C and P group are shown in

Table 1. Conditioning regimens used in our patients

Regimen	Diagnosis	Composition
BEAM	HL, NHL	BCNU 300 mg/m^2 i.v. on day –6 (total dose 300 mg/m^2) Etoposide 200 mg/m^2 i.v. for 4 consecutive days (day –5 through –2, total dose 800 mg/m^2) Cytarabine 200 mg/m^2 twice daily i.v. for 4 consecutive days (day –5 through –2, total dose 1600 mg/m^2) Melphalan 140 mg/m^2 i.v. on day –1 (total dose 140 mg/m^2)
MEL 100	MM	Melphalan 100 mg/m^2 i.v. on day –1 (total dose 100mg/m^2)
MEL 200	MM	Melphalan 200 mg/m^2 i.v. on day –1 (total dose 200 mg/m^2)
BUCY 2	AML	Busulphan 4 mg/kg p.o. for 4 consecutive days (day –7 through -4, total dose 16 mg/kg) Cyclophosphamide 60 mg/kg i.v. for 2 consecutive days (day –3 through –2 (total dose 120 mg/kg)
TBI +C	ALL	Total body irradiation 1.5 Gy twice daily for 4 consecutive days (day –7 through –4, total 8 doses, 12 Gy) Cyclophosphamide 60 mg/kg i.v. for 2 consecutive days (day –3 through –2 (total dose 120 mg/kg)

Table 2. Patient characteristics in control (C) and prophylactic (P) group at study entry and immediate clinical response to ASCT

Variable	C group (n = 23)	P group (n = 21)	Significance
Sex (n, male/female)	13/10	8/13	NS
Age (median, range)	50 (25-69)	47 (18-69)	NS
Diagnosis (n)			
NHL 8	7	NS	
MM 7	7	NS	
HL	4	4	NS
AL	4	3	NS
Conditioning regimen (n)			
BEAM	12	11	NS
MEL 100(200)	7	7	NS
BUCY 2	3	2	NS
TBI + CP	1	1	NS
Indication for ASCT (n)			
1st line treatment	12	11	NS
relapse	6	7	NS
PR	4	3	NS
CRu	1	0	NS
Clinical state before ASCT (n)			
CR	8	5	NS
PR	14	14	NS
MR	1	2	NS
Number of PBPC infused (CFU-GM .10^5/kg) (median, range)	3.5 (1.1–10.5)	2.8 (0.7–17.0)	NS
Clinical response to ASCT (n)			
CR	16	12	NS
CRu	2	0	NS
PR	4	7	NS
SD	1	2	NS

ASCT – autologous stem cells transplantation, MM – multiple myeloma, NHL – non-Hodgkin's lymphoma, HL – Hodgkin's lymphoma, AL – acute leukemia, CR – complete remission, CRu – complete remission/unconfirmed, PR – partial remission, MR – minimal response, PBPC – peripheral blood progenitor cells, CFU-GM – colony forming units-granulocyte macrophage, SD – stable disease, NS – not significant.
Significance tested by Fisher's exact test, or Mann-Whitney test (for age and number of PBPC by CFU-GM).

Table 2. Randomization produced two comparable groups with no significant difference in baseline parameters.

In each group, patients were further randomized to receive either standard PN (B group, n=20), or isocaloric, isonitrogenous PN containing 0.5 g Gln/kg body weight per day (A group, n=24). Randomization was performed and PN prepared in the nutritional centre of our hospital and distributed to the transplant unit as all-in-one bag. Except for the responsible member of the nutritional centre, all other personnel involved in the study were blinded, as were the patients. In this manner, the clinical outcome in both C vs. P group and A vs. B group could be compared, and the latter comparison was double-blind. Patient characteristics in A and B group are shown in Table 3. Again, randomization produced two comparable groups with no significant difference in baseline parameters.

PN characteristics and composition. PN was provided as all-in-one system from our nutritional centre and infused continuously (24 hours/day) into the central venous catheter. Standard PN (group B) had total energy content calculated as resting energy expenditure from Harris-Benedict formula multiplied by 1.3, based on glucose (ca 60%), lipid emulsion (up to 30%) and standard amino acid (AA) mixture (1.8 g/kg body weight). Water and electrolytes were added as necessary to keep a stable profile. Vitamins and trace elements were given in recommended daily doses. PN enriched with Gln (group A) was isocaloric and isonitrogenous, with an equivalent water, electrolyte, vitamin and trace element profile. The only systematic difference from the standard PN was the content of Gln (0.5 g/kg body weight per day) provided as commercially available alanyl-glutamine dipeptide (Dipeptiven, Fresenius-Kabi). The mixture was then complemented to 1.8 g AA/kg body weight by an AA mixture enriched with essential AA (Amino Mel Nephro, Fresenius-Kabi), in order to equilibrate both groups also in the essential AA content.

Response criteria and follow-up. Standard criteria [2, 5, 21] for complete remission (CR), complete remission/unconfirmed (CRu), partial response (PR), minimal response (MR), stable disease (SD), progressive disease (P), relapse of disease (R), overall survival (OS), event-free survival (EFS), and disease-free survival (DFS) were used. Patients were checked regularly in the outpatients post-transplant clinic and the results of this follow-up with median 38 months are presented below.

Statistical analysis. Categorical data (e.g. clinical outcome) were analyzed using Fisher's exact test. Survival analysis was performed according to the Kaplan-Meier methods, and survival differences were analyzed using logrank test. For calculations, NCSS software was utilized. P values <0.05 were considered significant.

Results

After three years of follow-up (median 38 months), 32 of 44 patients (73%) were still alive. Of the 12 non-survivors, 1 patient died during the transplant hospital stay of early septic complication, 5 patients died later of disease progression and related complications, in 4 patients CR was followed by relapse resistant to treatment and eventually fatal, and 2 other patients with CR died of sepsis without a relapse.

Ad hoc (C) vs. prophylactic (P) parenteral nutrition. The clinical outcome rates at the end of follow-up were not significantly different (Fisher's exact test) in control vs. prophylactic group (Tab. 4), and in fact were very similar, with no clear-cut preference of either group. Also, in survival analysis no significant difference was found (logrank test), with p values 0.34, 0.47, and 0.56 for OS, EFS, and DFS respectively.

Glutamine-enriched (A) vs. standard (B) parenteral nutrition. In contrast, comparison of Gln-supplemented and standard PN seemed to favor the standard one. In all the parameters of clinical outcome at the end of follow-up (Tab. 5) group B scored better than group A, and in disease-free survival rate (77% vs. 35%) this tendency reached statistical significance (Fisher's exact test, p=0.03). Even more impressive results came from survival analysis (logrank test), with p values 0.09, 0.01, and 0.04 for OS, EFS, and DFS respectively. The Kaplan-Meier curves of EFS and DFS are shown in Figures 1 and 2, respectively.

Discussion

Control (C) vs. prophylactic (P) group. Our data do not support the use of prophylactic PN in patients with ASCT for hematological malignancies. The idea of nutritional prophylaxis was based mainly on the results of well documented randomized trial by WEISDORF et al [19]. In their group of 137 transplant patients with normal nutritional status, prophylactic PN (71 patients given 150% their basal energy expenditure during cytoreductive therapy, later decreased to 130% and finally to 110%) did not improve the course of hospital stay (duration of hospitalisation, engraftment, infectious and other complications), when compared to PN provided *ad hoc*, when nutritional depletion developed (i.e. 40 of 66 control patients). In contrast, in the median follow-up of 2 years there was remarkably better long-term outcome (overall survival, time to relapse and disease-free survival) in the prophylactic group, making this approach more popular in the next years [20]. In our study, a similar prophylactic regimen similarly did not affect the hospitalization phase [12, 13]. However, in our setting the long-term outcome in the prophylactic group (median follow-up 38 months) was not improved, either.

There are important differences between our group of patients and that of WEISDORF et al [19], probably accounting for the different long-term effect. Their group was more heterogeneous, including patients with both autologous and allogeneic transplantation, with a wide range of diagnoses (mostly leukemias but also solid tumors, and even non-ma-

Table 3. Patient characteristics in glutamine (A) and standard (B) group at study entry and immediate clinical response to ASCT

Variable	A group (n = 24)	B group (n = 20)	Significance
Sex (n, male/female)	13/11	8/12	NS
Age (median, range)	49 (18-69)	51 (19-69)	NS
Diagnosis (n)			
NHL 8	7	NS	
MM 6	8	NS	
HL	4	4	NS
AL	6	1	NS
Conditioning regimen (n)			
BEAM	12	11	NS
MEL 100(200)	6	8	NS
BUCY 2	4	1	NS
TBI + CP	2	0	NS
Indication for ASCT (n)			
1st line treatment	12	11	NS
relaps	7	6	NS
PR	5	2	NS
CRu	0	1	NS
Clinical state before ASCT (n)			
CR	7	6	NS
PR	15	13	NS
MR	2	1	NS
Number of PBPC infused (CFU-GM .10^5/kg) (median, range)	3.4 (0.8-17.0)	3.0 (0.7-13.8)	NS
Clinical response to ASCT (n)			
CR	16	12	NS
CRu	1	1	NS
PR	4	7	NS
SD	3	0	NS

ASCT – autologous stem cells transplantation, MM – multiple myeloma, NHL – non-Hodgkin's lymphoma, HL – Hodgkin's lymphoma, AL – acute leukemia, CR – complete remission, CRu – complete remission/unconfirmed, PR – partial remission, MR – minimal response, PBPC – peripheral blood progenitor cells, CFU-GM – colony forming units-granulocyte macrophage, SD – stable disease, NS – not significant.
Significance tested by Fisher's exact test, or Mann-Whitney test (for age and number of PBPC by CFU-GM).

Table 4. Clinical outcome at the end of three years' follow-up (median 38 months), control (C) vs. prophylactic (P) group

Outcome rates	C group	P group	P value
Overall survival rate[a]	15/23 (65%)	17/21 (81%)	0.32
Event-free survival rate[b]	10/22 (45%)	10/19 (53%)	0.76
Disease-free survival rate[c]	10/18 (56%)	6/12 (50%)	1

[a]proportion of all patients, [b]of patients with CR, CRu and PR, [c]of patients with CR and CRu (response categories defined in Ref. 17). P values aply to Fisher's exact test.

Table 5. Clinical outcome at the end of three years' follow-up (median 38 months), glutamine (A) vs. standard (B) group

Outcome rates	A group	B group	P value
Overall survival rate[a]	15/24 (63%)	17/20 (85%)	0.17
Event-free survival rate[b]	7/21 (33%)	13/20 (65%)	0.06
Disease-free survival rate[c]	6/17 (35%)	10/13 (77%)	0.03

[a]proportion of all patients, [b]of patients with CR, CRu and PR, [c]of patients with CR and CRu (response categories defined in Ref. 17). P values aply to Fisher's exact test.

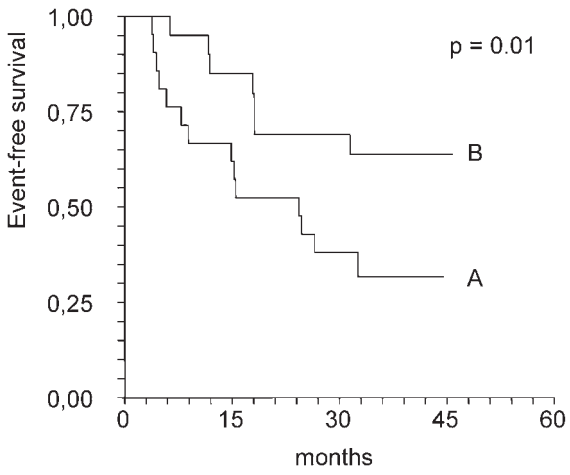

Figure 1. Event-free survival in groups A (glutamine) vs. B (standard).

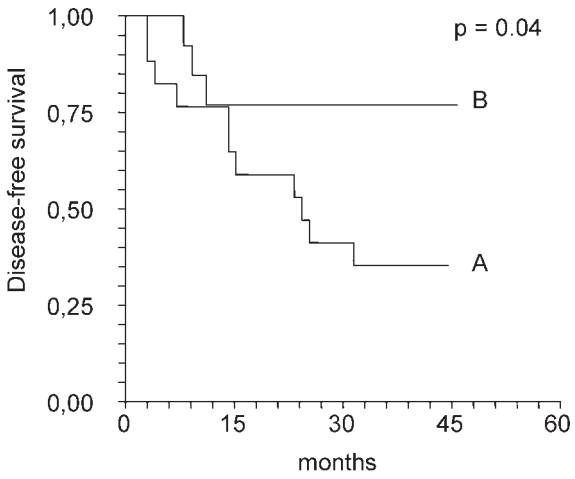

Figure 2. Disease-free survival in groups A (glutamine) vs. B (standard).

lignant diseases) and age (important proportion of children). Also, since their study other important improvements of general supportive care (e.g. growth factors, new antiemetics, antibiotics etc.) have shortened time to engraftment and hospital stay, decreased the rate of acute complications, and improved the long-term outcome. With this general progress, nutritional support, while still important part of supportive care, may by itself be less affecting the clinical outcome. Our data suggest that at least in patients with ASCT for hematological malignancies prophylactic PN does not bring additional benefit (while it makes the care more costly, data not shown). Actually, also in the study by WEISDORF et al [19], the subgroup analysis of autologous patients (16 in each group) found a non-significant difference in median survival (11 months in prophylactic vs. 7 months in control group).

Group with glutamine (A) vs. without glutamine (B). Our results also do not favor glutamine-supplementation against

standard parenteral nutrition. Actually, in some parameters the long-term outcome was worse in the Gln-enriched group.

The wide interest in Gln-supplemented PN after BMT came from the pioneering randomized study by ZIEGLER et al [24]. Their 24 Gln-supplemented adults receiving allogeneic BMT for hematological malignancies had shorter hospital stay, better nitrogen balance and less infectious complications than 21 similar patients in the control group. There was, however, no significant difference in the incidence of fever, antibiotic requirements, or time to neutrophil engraftment. The authors further analyzed this group in later papers and found less hospital cost [9], improvement in mood [23], and enhanced recovery of circulating T lymphocytes [25] (total, CD4+ and CD8+) in patients receiving Gln, compared with controls. In their earlier paper on a subset of 20 patients, prevention of ECF expansion by Gln was demonstrated, too [15] (Tab. 6, upper panel). Unfortunately, there is no information about the long-term outcome of this group. These studies have opened general discussion about the utility of Gln as adjunctive therapy in BMT [22, 26].

Apart from the above-mentioned studies by the Boston group, 6 other randomized, placebo-controlled studies with Gln-enriched PN have been published (Tab. 6, lower panel), some of them with positive, and other with negative results. As they used various types of patients, allogeneic as well as autologous transplantation, various doses of Gln, and various markers of efficacy, they are not easily comparable. Interestingly, only the study by PYTLIK et al [14] included also the long-term follow-up as an important marker. Of the two last published studies that by PYTLIK et al [14] found no important benefit, whereas PICCIRILLO et al [10] report a beneficial effect on immune reconstitution and mucositis.

Our data are in good accord with those of PYTLIK et al [14]. We have also found no clinically important benefit of Gln in the hospital phase of treatment, and in the long-term follow-up (1 year longer than in their sample) the survival analysis has shown worse clinical outcome in the Gln group. Our sample was of similar size, more homogeneous, and the dose of Gln was approximately twice as high as theirs (and similar to that in ZIEGLER's group with positive results). We would therefore expect to find a major beneficial effect, if there were one.

Unlike PICCIRILLO et al [10], we have not particularly analyzed T lymphocytes recovery or mucositis severity. It is therefore possible that we have missed minor changes in these parameters. However, the effect on mucositis remains controversial as PYTLIK et al [14] in a similar design reported more severe mucositis in the Gln group. In other clinical parameters, e.g. hospital stay, infectious complications, time to neutrophil- and platelet recovery, use of antibiotics or transfusions, no difference was found in PICCIRILLO's as well as in PYTLIK's and our studies. No long-term outcome data of PICCIRILLO's sample are available.

The evidence of increased Gln requirements in catabolic states, together with preclinical and early clinical studies reporting a beneficial effect make it's administration in BMT intuitively tempting [26]. Our long-term outcome data, in accord with those of PYTLIK et al [14], rather surprisingly suggest a deleterious effect. Such an effect is difficult to explain on the basis of known physiological effects of Gln as conditionally essential amino acid in stress [26]. Rather, we agree with PYTLIK et al [14] that, though statistically significant, it may reflect a random variation in the samples and there may be no real difference between Gln and control "populations". Both studies, however, certainly do not support a beneficial long-term effect of Gln.

Compared with ZIEGLER's study with positive results, our sample was different in two important aspects: our patients received autologous transplant and our study was performed ten years later, with newer techniques of supportive care available. Both these aspects would make our sample less injurable, and therefore less sensitive to a possible protective effect of Gln. This can be demonstrated by the mean length of hospital stay after transplant in the control groups: 36 days in ZIEGLER's and 22 days in our study.

Table 6. Trials of parenteral glutamine vs. placebo in patients receiving BMT (SCT)

1st author, year	Transplant	Gln dose per day	No. patients	Gln better?	Why?
Scheltinga, 1991	allo	0.57 g/kg	20	yes	less ECF expansion
Ziegler, 1992	allo	0.57 g/kg	45	yes	less hospital stay
					less infection
					less negative N balance
Young, 1993	allo	0.57 g/kg	23	yes	improved mood
MacBurney, 1994	allo	0.57 g/kg	43	yes	less cost
Ziegler, 1998	allo	0.57 g/kg	20	yes	better T lymphocytes recovery
Schloerb, 1993	allo+auto	0.57 g/kg	29	yes	less hospital stay
					less bacteremia
					less ECF expansion
[a] van Zaanen, 1994	auto	26 g	15	no	
[b] Poynton, 1995	allo+auto?	33 g	50	yes	less mucositis
					less febrile days
Brown, 1998	allo+auto	33 g	34	yes	higher protein C and albumin
Pytlík, 2002	auto	20 g	40	no	
Piccirillo, 2003	auto	20 g	27	yes	better lymphocytes recovery
					less mucositis
		13.5 g	21	yes	better lymphocytes recovery

[a]Only some patients received ASCT. [b]Published only in abstract form.

Also, in our study only parenteral route was used for Gln supplementation. Several groups have utilized oral [1, 4, 6, 7] or combined oral/parenteral [17] Gln administration with conflicting results.

In conclusion, our data certainly do not suggest a favorable long-term effect of parenteral Gln supplementation in patients with hematological malignancies receiving ASCT. This does not exclude a possible beneficial effect of orally administered Gln or it's benefit in allogeneic transplant patients. Well-designed, probably multicentre studies would be necessary to answer these questions.

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