

Comparison of Peripheral Blood Stem Cell Transplant With Bone Marrow Transplant in Class 3 Thalassemic Patients

Masoud Iravani,¹ Emytis Tavakoli,² Molouk Hadji Babaie,³ Asiyeh Ashouri,⁴
Farnaz Khatami,⁵ Ardeshir Ghavamzadeh⁵

Abstract

Objectives: This study aimed to compare outcome of bone marrow transplant with peripheral blood stem cell transplant in class 3 thalassemic patients.

Materials and Methods: Respectively, 32 and 20 class 3 thalassemic patients received bone marrow transplant and peripheral blood stem cell transplant from human leukocyte antigen identical sibling donors. Conditioning regimen consisted of busulfan (16 mg/kg) and cyclophosphamide (160 mg/kg) followed by cyclosporine and methotrexate as graft-versus-host disease prophylaxes.

Results: Median time to absolute neutrophil count was significantly shorter in the peripheral blood stem cell transplant group (12 vs 23 days); however, there was no significant difference regarding platelet recovery between the 2 groups (20 vs 28 days). Acute graft-versus-host disease occurred in 47% of patients. Chronic graft-versus-host disease developed in 28% of patients which was significantly higher in the peripheral blood stem cell transplant group ($P = .06$). During 50 months' follow-up, thalassemia recurrence, overall survival, and thalassemia-free survival were 17%, 80%, and 65%, respectively, and there were no significant differences between the 2 groups.

Conclusions: These results showed that stem cell transplant is an effective treatment in class 3

thalassemic patients with the outcome relatively similar to bone marrow transplant. Although engraftment time is shorter in peripheral blood stem cell transplant method, it is associated with higher rate of chronic graft-versus-host disease.

Key words: β -Thalassemia class 3, Transplant, Graft-versus-host disease

Introduction

Thalassemia is the world's most-common congenital disease, which results from a single gene defect that leads to hemolytic anemia (1). Bone marrow transplant in thalassemic patients was first reported in 1982 (2), and currently, stem cell transplant is considered the only curative treatment for this disease (3, 4).

The prognosis of patients with β -thalassemia undergoing bone marrow transplant is determined by 3 risk factors: (1) hepatomegaly > 2 cm; (2) presence of portal fibrosis, and (3) inadequate chelation therapy. Patients with all 3 risk factors are categorized in class 3 (5).

Class 3 patients are more likely to experience transplant-related mortality or disease recurrence due to iron overload organ damage and donor minor histocompatibility antigen reaction due to preceding multiple blood transfusions (3, 6). Overall survival, thalassemia-free survival, transplant-related mortality, and rejection rate for the class 3 patients have been reported as 79%, 58%, 40%, and 16% (7).

Recently, peripheral blood stem cell transplant has emerged as an alternative option for bone marrow transplant in treating hematologic diseases (8). Peripheral blood stem cell transplant has the advantage of avoiding general anesthesia and harvesting a donor's bone marrow; moreover, it leads to faster engraftment and carries less treatment-

From the ¹Tehran University of Medical sciences, Department of Hematology, ²Tehran University of Medical Sciences, Center of Bone Marrow Transplantation, ³Tehran University of Medical Sciences, Department of Pharmacology, ⁴Tehran University of Medical sciences, Department of Statistics and Epidemiology, ⁵Center of Bone Marrow Transplantation, Shariati Hospital, Tehran University of Medical Sciences, Department of Hematology.

Acknowledgements: We would like to thank all the nurses and staff in the bone marrow transplant ward, Shariati Hospital, who cooperated with us.

Address reprint requests to: Emytis Tavakoli MD, Shariati Hospital, Center of Bone Marrow Transplantation, Third floor, BMT Research Department, Tehran, Iran

Phone: +98-21-849 02662 (in case of urgency):+98-912-321 8285 **Fax:** +98-21-880 04140

E-mail: tavakoli79@yahoo.com

Experimental and Clinical Transplantation (2010) 1: 66-73

related toxicity (9, 10). A high incidence of graft-versus-host disease associated with allogeneic peripheral blood stem cell transplant is one of its major disadvantages (11, 12). In our previous study, comparison of peripheral blood stem cell transplant with bone marrow transplant results in class 1 and 2 thalassemic patients revealed no difference between the 2 methods regarding overall survival and thalassemia-free survival. Though peripheral blood stem cell transplant was associated with nonsignificant, faster engraftment compared with bone marrow transplant, acute and chronic graft-versus-host disease occurred more frequently in the peripheral blood stem cell transplant group (13).

Using peripheral blood stem cell transplant in thalassemia is relatively new (13-15) and there are few small series have compared peripheral blood stem cell transplant with bone marrow transplant in thalassemic class 3 patients (14, 16). Thus, this study was designed to compare the results of peripheral blood stem cell transplant with bone marrow transplant in thalassemic class 3 patients.

Materials and Methods

Patients and donors

This study was conducted at the bone marrow transplant ward, Shariati Hospital, Tehran University of Medical Sciences, and covers the time from 1992 to 2007. The ethical committee of human research of Tehran University of Medical Sciences approved the protocol of study, and written, informed consent was obtained from patients' parents. The study was conducted according to the guidelines of the Declaration of Helsinki.

Inclusion criteria for patients were as follows:

1. Diagnosis of major thalassemia with hemoglobin chain electrophoresis.
2. Fulfilling the criteria of class 3 thalassemia as mentioned above.
3. Presence of a full-matched human leukocyte antigen-identical sibling donor.
4. No history of hypersensitivity reaction to drugs of conditioning regimen.
5. Appropriate cardiac function confirmed by left ventricular ejection fraction of greater than 55% in echocardiography.
6. Serum creatinine level $< 132.6 \mu\text{mol/L}$.
7. Liver function test results of less than 2 times the

upper limits of normal values, and normal viral hepatitis (B and C), and HIV serologic tests.

8. Receiving either bone marrow transplant or peripheral blood stem cell transplant from human leukocyte antigen-identical sibling donors.

Patients with liver biopsy compatible with cirrhosis or hypersensitivity reaction to drugs of conditioning regimen were excluded from the study.

Conditioning regimen, graft-versus-host disease prophylaxis, and stem cell collection

The conditioning regimen administered before transplant included busulfan 4 mg/kg for 4 consecutive days from day (-9) to day (-6) and cyclophosphamide 40 mg/kg for 4 consecutive days from day (-5) to day (-1). Graft-versus-host disease prophylactic regimen consisted of cyclosporine 3 mg/kg IV from day (-2) to day (+5) followed by cyclosporine 12.5 mg/kg orally combined with methotrexate 10 mg/m² on day (+1) and 6 mg/m² on days (+3) and (+6). Cyclosporine was tapered according to the patient's condition.

In the bone marrow transplant group, the donor's bone marrow was collected using the standard techniques on the day of infusion. The minimal number of acceptable mononucleated cells was 2×10^8 cells/kg. In the peripheral blood stem cell transplant group, donors received subcutaneous granulocyte-colony stimulating factor at a dosage of 10 $\mu\text{g/kg/d}$ for 5 consecutive days. Then, the donor's peripheral blood stem cells were collected using the apheresis procedure. Antibiotics were administered according to the usual policies for prevention and treatment of neutropenia complications and infectious diseases.

Definitions and evaluations

Hematopoietic recovery was defined as absolute neutrophil count (ANC) greater than 50×10^8 cells/L and platelet (Plt) count greater than 20×10^9 particles/L without receiving platelet infusion for 3 consecutive days. Diagnosis of acute graft-versus-host disease (aGVHD) and chronic graft-versus-host disease (cGVHD) was determined by clinical symptoms and graded according to International Bone Marrow Transplant Registry criteria. Transplant-related mortality was defined as death after engraftment due to transplant complications (nonrelapse mortality). Thalassemia-free survival

(TFS) was defined as survival in continuous thalassemia-free period without any events (rejection, recurrence of thalassemia, aplasia, or death). Overall survival was considered as survival with or without thalassemia recurrence. Recurrence was defined according to clinical presentations in patients who were transfusion-dependent and confirmed by laboratory testing for mixed chimerism, which showed less than 75% of the donor's stem cells in patient's body.

Statistical Analysis

The baseline characteristics of patients and donors were compared using a chi square analysis or Mann-Whitney *U* test between peripheral blood stem cell transplant and bone marrow transplant groups. Probabilities of neutrophil and platelet recovery, incidence of acute and chronic graft-versus-host disease, overall survival, and thalassemia-free survival were estimated by the Kaplan-Meier method and compared between the 2 groups of peripheral blood stem cell transplant and bone marrow transplant using the log rank test in univariate analysis. We used the Cox proportional hazard regression model for adjusting differences in baseline characteristics and assessing potential, independent, predictors of the outcomes in the multivariate analyses. A value for *P* less than .05 was considered statistically significant in all analyses.

Results

Patients and Donors

Fifty-two, class 3, major thalassemic patients were transplanted from a human leukocyte antigen-matched sibling donor (32 patients in the bone marrow transplant group, 20 patients in the peripheral blood stem cell transplant group). Table 1 demonstrates baseline characteristics of donors and recipients in bone marrow transplant and peripheral blood stem cell transplant groups. There were no significant differences between the 2 groups regarding baseline characteristics, except in donor age, which was higher in peripheral blood stem cell transplant group (*P* = .005).

Engraftment, transfusion, and hospitalization period Table 2 shows number of total neutrophil count (TNC), median neutrophil count (MNC), CD34+ and CD3+ cells in both groups. The overall median time to absolute neutrophil count

Table 1. Patients and donors characteristics.

	Total	Group BMT (%)	PBSCT (%)
Number of patients	52	32 (61)	20 (39)
Median recipient age in years (range)	9 (3-18)	9 (3-17)	8.5 (4-18)
Median donor age in years (range)	11 (2-29)	8 (2-29)	14 (8-23)
Recipient sex			
Male	27 (52)	20 (63)	7 (35)
Female	25 (48)	12 (37)	13 (65)
Donor sex			
Male	24 (46)	16 (50)	8 (40)
Female	28 (54)	16 (50)	12 (60)
Sex mismatch	23	12 (38)	11 (55)
Female donor to male recipient	13	8 (25)	5 (25)
Median time to diagnosis in years (range)	7 (<1-18)	6 (<1-17)	7 (3-18)
Karnofsky/Lansky score			
70-80	5	3	2
90-100	42	27	15
Unknown	5	2	3
Transplant year			
1992-1999	28	20	8
2000-2007	24	12	12
CMV serology antibody†			
R+/D+	31	14	17
R+/D-	5	4	1
R-/D+	6	6	0
R-/D-	6	5	1
Median follow-up for survival in patients in months (range)	50 (2-116)	48 (2-116)	50 (5-106)

†CMV serology in recipient or donor was not available for 4 patients (one PBSCT and 3 BMT patients).

Abbreviations: BMT, bone marrow transplant; PBSCT, peripheral blood stem cell transplant; R, recipient; D, donor.

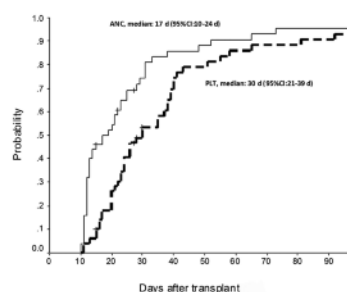


Figure 1. Homeostasis model of beta-cell function.

> 0.5×10^9 cells/L was 17 days (range, 10-37 days) (Figure 1). Patients who received peripheral blood stem cell (PBSC) graft had significantly faster absolute neutrophil count recovery than those who received bone marrow graft (12 days vs 23 days, respectively) (*P* = .005). Figure 2 shows the details.

The overall median time to $\text{Plt} > 20 \times 10^9$ /L was 30 days (range, 11-92 days) (Figure 1). Median time to platelet recovery in peripheral blood stem cell transplant and bone marrow transplant groups was 20 days (range, 13-65 days) and 28 days (range, 11-92 days). This difference was not significant (Table 2). The median amount of posttransplant Plt

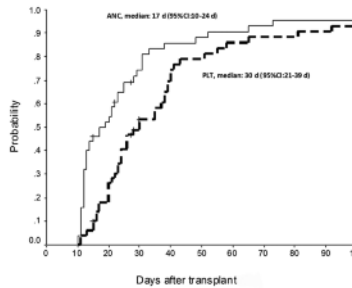


Figure 2. Probability of absolute neutrophil count recovery for graft types.

Table 2. Engraftment, transplant, and graft-versus-host disease.

	Total	Group BMT	PBSCT	P value
Number of patients	52	32 (61%)	20 (39%)	
TNCs infused $\times 10^8$ /kg	6.85 (2.18-18.87)	4.83 (2.18-11.61)	9.84 (4-18.87)	< .001
MNCs infused $\times 10^8$ /kg [†]	4.22 (1.13-14.52)	2.24 (1.13-5.47)	8.46 (3.68-14.52)	< .001
CD34+ cells infused	1.75 (0.3-17)	2.10 (0.3-4)	1.60 (0.3-17)	—
CD3+ cells infused	25 (6.8-81)	19 (11-46.5)	38.30 (6.8-81)	—
Median days to				
ANC > 0.5×10^9 /L	17(10-73)	23(12-73)	12(10-17)	.005
PLT > 20×10^9 /L	30(11-92)	28 (11-92)	20 (13-65)	NS
PLT unit transfusion, median (range)	13 (1-44)	13 (1-36)	8 (1-44)	NS
Days of hospitalization after transplant, median (range)	41 (17-200)	41 (17-83)	38 (18-200)	NS
Acute GVHD [‡] *	51	31	20	
None	27 (53%)	19 (61%)	8 (40%)	NS
Grade 1-2	16	9	7	
Grade 3-4	8	3	5	
Chronic GVHD*	47	28	19	
None	34 (72%)	23 (82%)	11 (58%)	0.062
Overall grade				NS
Limited	6	4	2	
Extensive	7	1	6	

*In alive patients more than 23 days.

†In alive patients more than 85 days.

‡MNC was unknown in 13 patients.

Abbreviations: Abbreviations: TNC, total nucleated cell; MNC, mononucleated cell; ANC, absolute neutrophil count; PLT, platelet; RBC, red blood cell; NS, not significant. BMT, bone marrow transplant; PBSCT, peripheral blood stem cell transplant; GVHD, graft-versus-host disease.

infusion was 13 units (range, 1-44 units), with no significant difference between peripheral blood stem cell transplant and bone marrow transplant groups. Median hospitalization was 41 days (range, 17-200 days), and there was no significant difference between the 2 groups (Table 2).

On univariate analysis, TNCs had a significant association with faster absolute neutrophil count and PLT recovery. As the Table 3 demonstrates, TNCs of greater than 6.85×10^8 cells/kg were associated with the shorter engraftment time ($P = .001$). Multivariate analysis showed the same finding (Table 4).

Table 3. Univariate analysis.

Outcome	Relative risk (95% confidence interval)	P
ANC more than 0.5×10^9 /L		
Graft		
BM	1	.005
PB	2.467 (1.308-4.653)	
Patient CMV		
Positive	1	.031
Negative	0.439 (0.208-0.926)	
TNCs infused $\times 10^8$ /kg [†]		
less than 6.85	1	< .001
more than 6.85	3.496 (1.786-6.841)	
PLT more than 20×10^9 /L		
TNCs infused $\times 10^8$ /kg [†]		
less than 6.85	1.00	.008
more than 6.85	2.279 (1.240-4.189)	
Chronic GVHD		
Graft		
BM	1.00	.074
PB	2.775 (.904-8.515)	
Treatment failure (recurrence and/or death)		
Donor sex		
Female	0.422 (0.156-1.143)	.090
Male	1	
Patient CMV		
Positive	1	.070
Negative	2.520 (0.927-6.848)	
Time to death		
Patient CMV		
Positive	1	.019
Negative	4.477 (1.283-15.627)	
Acute GVHD (grades 2-4)		
Yes	3.064 (0.884-10.624)	.078
No	1	

[†]TNC was categorized based on its median.

Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; PB, peripheral blood; PLT, platelet; GVHD, graft-versus-host disease.

Table 4. Multivariate analysis.

Outcome	Relative risk (95% confidence interval)	P
ANC more than 0.5×10^9 /L		
TNCs infused 10^8 /kg [†]		
less than 6.85	1.00	< .001
more than 6.85	3.496 (1.786-6.841)	
PLT more than 20×10^9 /L		
TNCs infused 10^8 /kg [†]		
less than 6.85	1.00	.008
more than 6.85	2.279 (1.240-4.189)	
Chronic GVHD		
Graft		
BM	1.00	.074
PB	2.775 (.904-8.515)	

[†]TNC was categorized based on its median.

Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; GVHD, graft-versus-host disease; PB, peripheral blood; PLT, platelet.

Graft-versus-host disease, recurrence, cause of death, and survival

One patient in the bone marrow transplant group died at the hospital due to cardiac toxicity before day 23. The remaining 51 patients were evaluated for the incidence of acute graft-versus-host disease, which occurred in 24 patients. Sixteen patients developed acute graft-versus-host disease grades 1 and 2, and 8 patients developed acute graft-versus-host disease grades 3 and 4. Acute graft-versus-host disease

occurred in 40% of bone marrow transplant patients, and 61% of peripheral blood stem cell transplant patients; however, this difference was not significant (Table 2).

From day 23 to 85, two peripheral blood stem cell transplant patients died due to poor engraftment and hemorrhage at the hospital, and 2 bone marrow transplant patients died due to cardiac toxicity. Among 47 patients who survived after the day 85, thirteen (23%) developed chronic graft-versus-host disease (Table 2). Overall incidence of chronic graft-versus-host disease was greater in the peripheral blood stem cell transplant group compared to the bone marrow transplant group (42% vs 18%) ($P = .048$) (Table 2 and Figure 3). There was no risk factor for chronic graft-versus-host disease on univariate or on multivariate analyses (Tables 3 and 4).

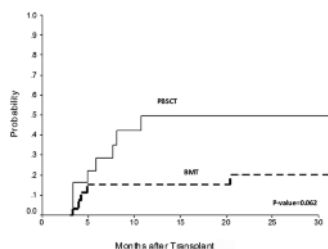


Figure 3. Probability of absolute neutrophil count recovery for graft types.

Thalassemia recurred in 9 patients (17%). Although it was not statically significant, recurrence was more frequent in the bone marrow transplant group (22% vs 15%). Seven patients benefited from diluted lymphocyte infusion after recurrence.

The median follow-up was 50 months. During this time, 7 patients died because of transplant complications (Table 5). Mortality rate and transplant-related mortality were 19% ($n=6$) and 13.5% ($n=4$) in bone marrow transplant and peripheral blood stem cell transplant groups. There was no significant difference between the bone

Table 5. Causes of death.

	Group BMT	PBSCT
ARDS	–	1
GVHD	–	1
Infection	1 (Meningitis)	1 (pseudomonas)
VOD	1	–
Graft rejection or failure	2	1
Cardiac toxicity	2	–
Total	6	4

Abbreviations: BMT, Bone marrow transplant; PBSCT, peripheral blood stem cell transplant; GVHD, graft-versus-host disease; ARDS, acute respiratory distress syndrome; VOD, veno-occlusive disease.

marrow transplant and peripheral blood stem cell transplant groups regarding mortality rate.

Treatment failure (recurrence and/or death) was affected by 2 factors on univariate analysis; first, the donor's age, and second, the patient's serology results for cytomegalovirus antibody (Table 3). Incidence of treatment failure was less in patients who received grafts from female donors (RR, 0.42; 95% CI: 0.15,1.14) ($P = .09$). Patients with negative serology for cytomegalovirus failed the treatment in greater amounts (RR, 2.52; 95% CI: 0.92, 6.54) ($P = .07$).

On univariate analysis for prediction of patient's time to death, incidence of acute graft-versus-host disease grades 2-4 (RR, 3.06; 95% CI: 0.88, 10.62) ($P = .078$) and negative serology for cytomegalovirus (RR, 4.74, 95% CI: 1.28,15.63) ($P = .09$) had significant association (Table 4), while on multivariate analysis, no factor was found as independent predictor of patient's time to death.

At present, 42 patients are alive at a median posttransplant follow-up of 50 months (range, 2-116 months). Successively, 26 (81%) and 16 patients (80%) belong to bone marrow transplant and peripheral blood stem cell transplant groups. In this study, the 5-year overall survival- and thalassemia-free survival for transplant in thalassemia major class 3 patients was 80% and 65% (Figure 4). Type of graft did not have a significant association with overall survival and thalassemia-free survival.

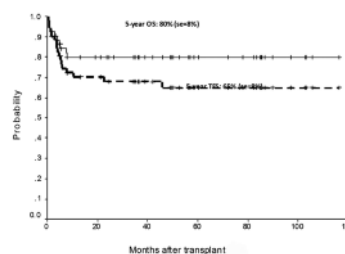


Figure 4. Overall survival and thalassemia-free survival.

Discussion

The present study revealed that median time of ANC recovery was significantly shorter in peripheral blood stem cell transplant patients ($P = .005$). Chronic graft-versus-host disease occurred in 28% of patients, which was significantly higher in the peripheral blood stem cell transplant group ($P = .06$). During

follow-up, thalassemia recurrence, overall survival, and thalassemia-free survival were 17%, 80%, and 65%, respectively, and did not have significant association with the type of graft.

The greatest bone marrow transplant experience in class 3 thalassemic patients has been reported by Lucarelli and colleagues in 1996 in 214 patients (6). Their findings showed overall survival of 62%, thalassemia-free survival of 51%, and recurrence of 22% (Table 6). Compared to the results of our experience (overall survival, 80%; thalassemia-free survival, 65%), an improvement in transplant results in these patients is observed. As the conditioning regimen was similar in both trials, the difference might be due to better supportive care and prophylactic regimens that are available today.

With regard to development of graft-versus-host disease, most of the studies suggested similar incidence of graft-versus-host disease after either peripheral blood stem cell transplant or bone marrow transplant (12, 16). Flowers and associates compared chronic graft-versus-host disease in bone marrow transplant and peripheral blood stem cell transplant (12). Their results did not show a significant difference with regard to the development of graft-versus-host disease between the 2 groups; however, they suggested that chronic graft-versus-host disease after peripheral blood stem cell transplant may be more extensive and refractory to treatment compared with chronic graft-versus-host disease after bone marrow transplant (12). Irfan and associates compared the bone marrow transplant and peripheral

blood stem cell transplant in 56 thalassemic patients including 16 thalassemic class 3 patients (16). Their results did not show significant difference between the 2 groups regarding development of chronic graft-versus-host disease; however, graft-versus-host disease was more prevalent in the peripheral blood stem cell transplant group (24% vs 30%). In the present study, we found higher rate of chronic graft-versus-host disease in peripheral blood stem cell transplant group; however, the rate of acute and chronic graft-versus-host disease in the peripheral blood stem cell transplant group of our study was higher than previous report by Yesilipek and associates (14). They reported results of 15 PBSC transplants from human leukocyte antigen identical donors in all classes of thalassemia, 5 of them were in class 3. Their results showed a 26% and a 20% incidence for acute and chronic graft-versus-host disease. Lower numbers of thalassemic class 3 patients in their study may explain this difference.

Faster engraftment is expected using peripheral blood stem cell transplant method compared with the bone marrow transplant (16-18). In the 2 studies conducted by Irfan and associates (16) and Ghvamzadeh and associates (13), faster ANC and platelet recovery was reported using peripheral blood stem cell transplant compared with bone marrow transplant. In the present study, we found ANC and platelet recovery in the peripheral blood stem cell transplant group; however, the difference between the bone marrow transplant and peripheral blood stem cell transplant, with regard to platelet

Table 6. Comparison of transplant results in thalassemic patients of this study and 3 previous studies.

	Lucarelli 3 experience BMT	Iravani experience (class 1 & 2) PBSC	BMT	This study (class 3) PBSC	BMT	Yesilipek experience PBSC
Overall survival	62%	83%-89%		80%		86%
Thalassemia-free survival	51%		76%	65%		86%
Recurrence	22%	9%-18%		15%-22%		0%
ANC recovery	...	11 d	19 d	12 d	23 d	12 d
PLT recovery	...	18 d	26 d	30 d		16 d
Acute GVHD	16%					26.6%
Grades 2-4		74%	57%			
				36%-61%		
Grades 3-4	...	36%	22%			
Chronic GVHD	...	48%	19%	42%	18%	20%
Extensive Chronic GVHD	...	18%	4%	14.9%		0%
transplant-related mortality	32%	9%-14%		20%		13%

1. Lucarelli et al, BMT in 214 class 3 patients (1996).

2. Iravanni et al, PBSC (87 patients versus BMT (96 patients) in class 1 and 2 (2007).

3. Yesilipek et al, PBSC in 15 patients of all classes.

Five of class 3 (2001), and this study, PBSC (20 patients) versus BMT (31 patients) in class 3.

Abbreviations: ANC, absolute neutrophil count; BMT, bone marrow transplant; GVHD, graft-versus-host disease; PBSC, peripheral blood stem cell transplant; PLT, platelet.

recovery time, was not significant. With regard to platelet recovery, our results are also different from a recent study by Gaziev and colleagues, which showed, using peripheral blood stem cells, that transplant is associated with faster absolute neutrophil count and platelet recovery in patients with recurrence of thalassemia following rejection of the first graft (19). The only independent predictor of faster absolute neutrophil count and PLT recovery was $TNCs > 6.85 \times 10^8$ cells/L in our study. This finding is inconsistent with a previous report by Bittencourt and associates (20), which suggested that infusion of $CD 34+ > 3.7 \times 10^6$ cells/kg and $MNC > 2.4 \times 10^8$ cells/kg would not only decrease the risk of postoperative fungal infection and transplant-related mortality, but also would increase the 5-year overall survival.

Champlin and associates, in a multivariate analysis, compared results of 288 peripheral blood stem cell transplants with 536 bone marrow transplants in leukemic patients and reported that transplant-related mortality was lower, and the DFS was higher in the peripheral blood stem cell transplant group (65% vs 53%) (8). Their study also revealed shorter posttransplant hospitalization period in peripheral blood stem cell transplant patients compared to the bone marrow transplant group (23 vs 28 days). In contrast, our study did not show any difference in overall survival, thalassemia-free survival, transplant-related mortality, and recurrence rate between peripheral blood stem cell transplant and bone marrow transplant methods, and did not reveal a decline in hospitalization using peripheral blood stem cell transplant.

Comparing the results of the present study with our previous report in class 1 and 2 thalassemic patients (13), better transplant prognosis was seen in patients with lower thalassemic classes than those with class 3 using the peripheral blood stem cell transplant method. This finding is in agreement with Lucarelli's results in bone marrow transplant setting (6) (Table 6).

To the best of our knowledge, the present study is the largest series comparing the results of bone marrow transplant and peripheral blood stem cell transplant in class 3 thalassemic patients ever reported. Our results show that stem cell transplant is an effective method for treatment of class 3 thalassemic patients, with an overall survival and thalassemia-free survival of 80% and 65%. The main

disadvantage of this method is development of graft-versus-host disease, which was observed more frequently in the peripheral blood stem cell transplant group than in the bone marrow transplant group. Although engraftment time was shorter in peripheral blood stem cell transplant, the hospitalization period was the same in both methods. Moreover, transplant parameters, including OS, DFS, and transplant-related mortality were not influenced by the graft type. Using a more-effective, graft-versus-host disease, prophylactic regimen, using a strategy to overcome the high rate of graft rejection among the class 3 recipients, and safe induction of sufficient immunologic suppression of the host immune system to facilitate donor engraftment, is recommended.

References

1. Rund D, Rachmilewitz E. New trends in the treatment of beta-thalassemia. *Crit Rev Oncol Hematol*. 2000;33(2):105-118.
2. Thomas ED, Buckner CD, Sanders JE, et al. Marrow transplantation for thalassemia. *Lancet*. 1982;2(8292):227-229.
3. Sodani P, Gaziev D, Polchi P, et al. New approach for bone marrow transplantation in patients with class 3 thalassemia aged younger than 17 years. *Blood*. 2004;104(4):1201-1203.
4. Lucarelli G, Polchi P, Galimberti M, et al. Marrow transplantation for thalassemia following busulphan and cyclophosphamide. *Lancet*. 1985;1(8442):1355-1357.
5. Lucarelli G, Giardini C, Baronciani D. Bone marrow transplantation in thalassemia. *Semin Hematol*. 1995;32(4):297-303.
6. Lucarelli G, Clift RA, Galimberti M, et al. Marrow transplantation for patients with thalassemia: results in class 3 patients. *Blood*. 1996;87(5):2082-2088.
7. Lucarelli G, Galimberti M, Polchi P, et al. Bone marrow transplantation in patients with thalassemia. *N Engl J Med*. 1990;322(7):417-421.
8. Champlin RE, Schmitz N, Horowitz MM, et al. Blood stem cells compared with bone marrow as a source of hematopoietic cells for allogeneic transplantation. IBMTR Histocompatibility and Stem Cell Sources Working Committee and the European Group for Blood and Marrow Transplantation (EBMT). *Blood*. 2000;95(12):3702-3709.
9. Levine JE, Wiley J, Kletzel M, et al. Cytokine-mobilized allogeneic peripheral blood stem cell transplants in children result in rapid engraftment and a high incidence of chronic GVHD. *Bone Marrow Transplant*. 2000;25(1):13-18.
10. Li CK, Yuen PM, Chik KW, et al. Allogeneic peripheral blood stem cell transplant in children. *Med Pediatr Oncol*. 1998;30(3):147-151.
11. Przepiorka D, Anderlini P, Saliba R, et al. Chronic graft-versus-host disease after allogeneic blood stem cell transplantation. *Blood*. 2001;98(6):1695-1700.
12. Flowers ME, Parker PM, Johnston LJ, et al. Comparison of chronic graft-versus-host disease after transplantation of peripheral blood stem cells versus bone marrow in allogeneic recipients: long-term follow-up of a randomized trial. *Blood*. 2002;100(2):415-419.
13. Ghavamzadeh A, Iravani M, Ashouri A, et al. Peripheral blood versus bone marrow as a source of hematopoietic stem cells for allogeneic transplantation in children with class I and II beta thalassemia major. *Biol Blood Marrow Transplant*. 2008;14(3):301-308.
14. Yesilipek MA, Hazar V, Kupesiz A, Kizilers A, Uguz A, Yegin O. Peripheral blood stem cell transplantation in children with beta-thalassemia. *Bone Marrow Transplant*. 2001;28(11):1037-1040.

15. Pakakasama S, Hongeng S, Chaisiripoomkere W, Chuansumrit A, Sirachainun N, Jootar S. Allogeneic peripheral blood stem cell transplantation in children with homozygous beta-thalassemia and severe beta-thalassemia/hemoglobin E disease. *J Pediatr Hematol Oncol.* 2004;26(4):248-252.
16. Irfan M, Hashmi K, Adil S, et al. Beta-thalassemia major: bone marrow versus peripheral blood stem cell transplantation. *J Pak Med Assoc.* 2008;58(3):107-110.
17. Diaz MA, Kanold J, Vicent MG, Halle P, Madero L, Demeocq F. Using peripheral blood progenitor cells (PBPC) for transplantation in pediatric patients: a state-of-the-art review. *Bone Marrow Transplant.* 2000;26(12):1291-1298.
18. Iravani M, Mousavi A, Gholibeikian S, et al. Cyclosporin A and mini short-term methotrexate vs cyclosporin A as graft-versus-host disease prophylaxis in patients with beta thalassemia major undergoing allogeneic blood and marrow transplantation. *Bone Marrow Transplant.* 2005;35(11):1095-1099.
19. Gaziev J, Sodani P, Lucarelli G, et al. Second hematopoietic SCT in patients with thalassemia recurrence following rejection of the first graft. *Bone Marrow Transplant.* 2008;42(6):397-404.
20. Bittencourt H, Rocha V, Chevret S, et al. Association of CD34 cell dose with hematopoietic recovery, infections, and other outcomes after human leukocyte antigen-identical sibling bone marrow transplantation. *Blood.* 2002;99(8):2726-2733.