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Comparable Outcomes of Allogeneic Peripheral Blood versus Bone Marrow Hematopoietic Stem Cell Transplantation in Major Thalassemia: A Multivariate Long-Term Cohort Analysis

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Allogeneic hematopoietic stem cell transplantation (HSCT) currently is the only available curative option for transfusion-dependent thalassemia. Peripheral blood is a more convenient source for HSCT in comparison with bone marrow. Information about the relative success of transplantation with these 2 graft sources would help physicians and patients choose between them. The aim of this study was to evaluate the pros and cons of using peripheral blood instead of bone marrow as the graft source in thalassemia transplantation. We analyzed the transplant results of 567 transfusion-dependent thalassemia patients who received a transplant between 1998 and 2015 considering their stem cell source as a comparative variable. In multivariate Cox analysis the survival advantage for bone marrow compared with peripheral blood was not significant after adjusting for sex, age, and hepatic fibrosis presence. Rejection incidence was significantly lower in patients who used peripheral blood as their graft source. Acute and chronic graft-versus-host disease were more frequent in peripheral blood transplants, but the difference was not statistically significant. This study shows that peripheral blood could be an alternative stem cell source in patients undergoing allogeneic HSCT for thalassemia.

INTRODUCTION

Historically, the only available source for hematopoietic stem cell transplantation (HSCT) was bone marrow (BM) obtained from the donor's pelvis bone under general/regional anesthesia [1]. Throughout the last 2 decades a shift has occurred [2]. Today, peripheral blood stem cells (PBSCs) are increasingly replacing BM stem cells (BMSCs) as the major allograft source in HSCT [3-7]. Several randomized controlled trials have compared these 2 sources and reached incongruent results [8-17]. Considering the donor's benefit, published data specify that both BM and PBSC donations are safe and have a low incidence of serious adverse events (1.34% in BM donors versus .6% in PBSC donors) [18-21]. On the other hand, considering the recipient's point of view, neutrophil and platelet reconstitution is consistently reported to occur faster after allogeneic PBSC transplantation (PBSCT). The higher $CD34^+$ cell count contained in PBSC allografts may contribute to improved immune reconstitution [22,23]. However, some studies showed a significantly higher probability of chronic graft-versus-host disease (GVHD) after allogeneic PBSCT than after allogeneic BM transplantation [23,24].

Currently, allogeneic HSCT as the only curative option for thalassemia major (TM) has progressively grown in popularity worldwide. So far, in HSCT for thalassemia patients, most centers still prefer using BMSCs instead of PBSCs. In the report from the European Society for Blood and Marrow Transplantation, stem cells were sourced from PB only in 20.3% of the TM patients, and their only explanatory motive for this approach was a higher risk of developing severe acute GVHD in patients who had received PBSCs compared with BMSCs [25].

In Iran, as 1 of the pioneer countries in thalassemia transplantation and after decades of experience, because of our donors' preferences, we have used PBSCs as the main source of our allografts. We have analyzed the outcomes of thalassemia patients who have been transplanted in our center, regarding with the used graft source, to determine whether our findings would confirm or disprove the existing data and herein report the results.

METHODS

Since March 1991 to December 2015, 715 TM patients received allogeneic HSCT in the Hematology, Oncology and Stem Cell Transplant Research Center of Shariati Hospital, Tehran, Iran, consecutively. All patients were transfusion dependent, and deferoxamine was the mainly used iron chelator. The mean age at transplantation was 9.83 years (range, 2 to 30).

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Because we wanted to include patients over 17 years of age in our analysis, we could not classify all patients by Pesaro classification, which is defined only for patients aged less than 17 years. Thus, we defined another variable according to the result of liver biopsy conducted before HSCT in all patients, and we considered the presence of hepatic fibrosis as an indicator of organ iron deposition.

To spotlight the effect of graft source on our transplant outcomes, we excluded 9 patients whose source of transplant was cord blood and 67 patients whose donor was anyone other than full matched sibling. Furthermore, to overcome the time bias we excluded 72 patients who had been transplanted before 1998, the year on which our first PBSCT was conducted on thalassemia patients. Then, we categorized the patients into 2 groups: BMSCT and PBSCT.

BMSCs were harvested from iliac crests of the donor under general anesthesia and directly infused into the recipients without further manipulation. The PBSCs were first mobilized by granulocyte colony-stimulating factor, using 5 μg/kg on 4 consecutive days and 10 μg/kg on the fifth day and then collected.

The myeloablative conditioning regimen comprised busulfan and cyclophosphamide. In PBSCT antithymocyte globulin was also included. Regarding GVHD prophylaxis, cyclosporine (1.5 mg/kg daily, i.v., on day −2 and then 3 mg/kg on days +7 [PBSCT] or +11 [BMSCT]) combined with methotrexate (10 mg/m^2 on days +1 and 6 mg/m^2 on days +3, +6, and +11) was administered in all patients. Cyclosporine was continued orally for at least 6 months after HSCT and discontinued in the absence of GVHD.

Overall survival (OS) was calculated from date of stem cell transplantation to death from any cause. Thalassemia-free survival (TFS) was defined as being thalassemia free and alive. Neutrophil engraftment and platelet engraftment was defined to occur on the first of 3 consecutive days in which the absolute neutrophil count was $>.5 \times 10^9$/L and an unsupported platelet count was $>20 \times 10^9$/L, respectively. Primary graft failure was defined as graft rejection occurrence less than 1 month after transplantation. According to standard criteria, acute and chronic GVHD were diagnosed and recorded. Written informed consent had been sought from all patients or from their parents.

Statistical Analysis

Homogeneity between graft source pairs was evaluated using the chi-square test for qualitative variables and median test and Student's *t*-test for continuous variables. A 2-sided $P = .05$ or lower was considered to be statistically significant. Kaplan-Meier curves were derived to determine OS and TFS and were compared by means of the log-rank test. Median follow-up time was established with the reverse Kaplan-Meier method. The assumption of proportionality of hazards was checked using Schoenfeld residuals (results not shown). Cox proportional hazard regression model was used for univariate and multivariate analyses of survival. Cumulative incidences of graft rejection were calculated by Gray's method. Death without rejection was considered as a competing event for rejection. All variables with $P \leq .2$ in the univariate analysis were incorporated in the multivariate analysis. Analyses were conducted using STATA (statacorp, Texas, USA) version 11.2 and Packages "survival" and "cmprsk" in R software version 3.3.1.

RESULTS

By the end of December 2017 the median follow-up time after HSCT in our thalassemia patients was 6.5 ± .19 years, which was almost the same in the 2 source groups. Among the included 567 patients, 15-year OS and TFS were 74.57% (95% confidence interval, 70.41% to 78.24%) and 69.12% (95% confidence interval, 64.85% to 72.99%), respectively. Considering the graft source, 425 patients (74.96%) had received PBSCT and 142 patients (25.04%) BMSCT. The characteristics of the patients and donors in the 2 source groups are outlined in Table 1.

Survival

The 2-, 5-, and 15-year OS and TFS in the PB group are compared with the BM group in Table 2. No significant difference in survival was found between the 2 cohorts (Figures 1 and 2).

Variables significant in univariate analysis were entered in a multivariate model, and 4 variables proved to be suppressive survival predictors: older age, male gender, presence of hepatic fibrosis, and PB as a stem cell source. As demonstrated in Table 3, a multivariate Cox model with adjustment for age, sex, and having hepatic fibrosis was performed that also showed no significant difference for OS and TFS between the 2 source groups ($P = .09$ and $P = .92$, respectively).

Engraftment

Among patients who received PBSCs as compared with those received BMSCs, the median time for neutrophil and platelet engraftment was 3 days and 11 days shorter, respectively ($P < .001$). Figure 3 demonstrates this significant difference. At the time of this report, 50 patients (8.82%) had experienced graft failure.

The proportion of patients recorded as primary graft failure in BMSCT versus PBSCT was 15.38% and 4.17% ($P = .18$), respectively. Rejection incidence was significantly lower in the PBSCT group. Multivariate analysis also confirmed this advantage in the mentioned group (Table 3).

Graft-versus-Host Disease

Acute GVHD grades I to IV developed in 33.33% versus 50.83% of patients receiving BM or PB grafts ($P < .001$). Chronic GVHD developed in 26.06% versus 51.44% BM versus PB grafts ($P < .001$). First, we compared the prevalence of acute and chronic GVHD in our 2 groups of patients, which was significantly increased in the PBSCT group compared with the BMSCT group. Next, in univariate analysis the only significant predictor of acute GVHD occurrence other than graft source was hepatic fibrosis. Multivariate Cox models with adjustment for hepatic fibrosis showed no significant difference between the 2 graft sources. Chronic GVHD occurrence, however, was increased significantly in male and older aged patients but was not influenced by the presence of hepatic fibrosis. Multivariate Cox models with adjustment for patient sex and age was also used for comparing the chronic GVHD incidence between the 2 source groups and showed no significant difference (Table 4).

Table 1
Patients and Donors Characteristics Compared in the 2 Graft Source Groups

	PBSCT	BMSCT	*P*
Patients, n (%)	425 (74.96)	142 (25.04)	
Gender F/M, %	41.8/57.2	43.6/56.4	.71
Age at transplantation, %			<.0001
2-5 yr	24.7	19.7	
5-10 yr	30.5	40.8	
10-15 yr	18.7	34.5	
15-17 yr	6.4	3.5	
>17 yr	19.7	1.4	
Mean serum ferritin, ng/dL	1875.97	2647.32	.0004
Donor gender F/M, %	48.1/51.9	61.1/38.89	.008
Mean donor age, yr	15.6	14.2	.88
CD34, $\times 10^6$/kg	4.56	3.04	<.0001
CD3, $\times 10^6$/kg	292.25	77.92	<.0001
Time to myeloid engraftment (mean ± SD), days	15.2 ± 6.06	18.1 ± 6.00	.0002
Time to platelet engraftment (mean ± SD), days	20.8 ± 8.67	31.0 ± 9.64	<.0001

Table 2
Fifteen-Year OS, TFS, and Rejection Incidence for 2 categories of patients

	Patient Category	2-Year	5-Year	15-Year	*P*
OS	PBSCT	78.52 (74.27-82.16)	74.87 (70.34-78.81)	72.97 (67.96-77.34)	.19
	BMSCT	83.10 (75.67-88.43)	79.38 (71.29-85.41)	79.38 (71.29-85.41)	
TFS	PBSCT	74.91 (70.47-78.79)	71.31 (66.65-75.45)	69.78 (64.68-74.29)	.25
	BMSCT	68.66 (60.29-75.63)	66.85 (58.31-74.04)	6685 (58.31-74.04)	
Rejection incidence	PBSCT	5.48 (3.78-8.26)	5.74 (3.78-8.26)	5.74 (3.78-8.26)	<.0001
	BMSCT	18.46 (12.53-25.33)	18.46 (12.53-25.33)	18.46 (12.53-25.33)	

Values in parentheses are 95% confidence intervals.

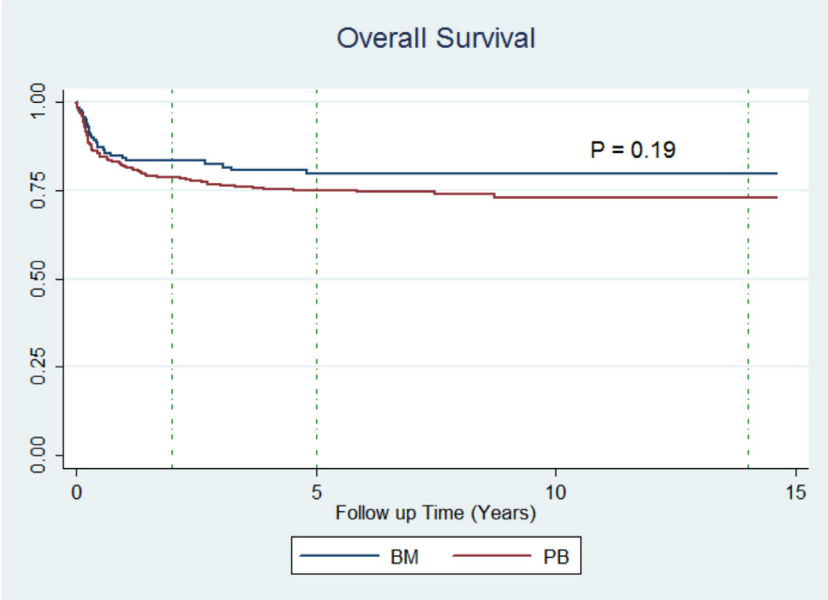

Figure 1. Fifteen-year OS in the 2 categories of patients.

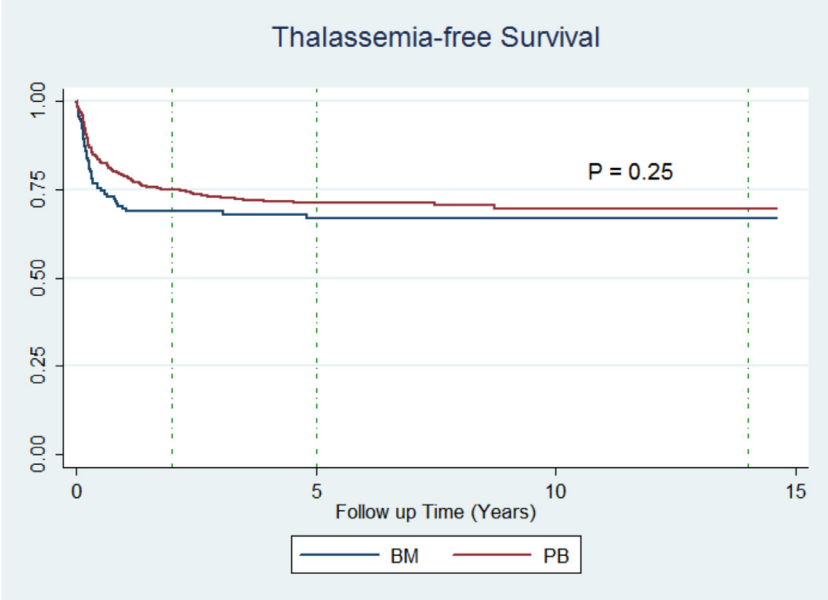

Figure 2. Fifteen-year TFS in the 2 categories of patients.

DISCUSSION

More than 3 decades have passed since the first HSCT was performed in TM patients, and a large clinical experience has been gained with more than 2000 HCSTs in different centers around the world [26]. In the eastern Mediterranean area, Iran is 1 of the main countries with high prevalence of β-thalassemia. It is estimated that there are more than 20,000 TM patients in Iran [27]. Since 1991

Table 3
Univariate and Multivariate Cox Regression Models for OS, TFS, and Rejection Incidence

		OS				TFS				Rejection Incidence			
		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Sex	Female	Ref	.01	Ref	.05	Ref.	.00	Ref	.01	Ref	.07	Ref	.11
	Male	1.52 (1.06- 2.18)		1.43 (.99-2.05)		1.59 (1.15-2.20)				1.45 (.96-2.20)		1.38 (.92-2.08)	
Hepatic fibrosis	No	Ref	.00	Ref	.00	Ref	.00	Ref	.00	Ref	.00	Ref	.00
	Yes	1.93 (1.37-2.72)		1.83 (1.17-2.87)		2.06 (1.51-2.79)				3.33 (2.18-5.07)		3.02 (1.60-5.71)	
Age, yr	2-5	Ref	.00	Ref		Ref	.03	Ref		Ref	.01	Ref	
	5-10	1.41 (.82-2.42)		1.26 (.35-.84)	.40	1.36 (.85-2.17)			.61	1.42 (.77-2.06)		.92 (.50-1.69)	.80
	10-15	1.66 (.95-2.92)		1.30 (.40-.87)	.38	1.71 (1.05-2.77)			.42	2.27 (1.24-4.13)		1.06 (.58-1.96)	.83
	15-17	2.43 (1.16- 5.08)		1.44 (.60-.88)	.38	2.00 (1.01-3.96)			.70	2.08 (.89- 4.89)		.99 (.40-2.46)	.99
	>17	2.54 (1.45- 4.47)		1.42 (.49-1.02)	.30	2.09 (1.26-3.46)			.53	.92 (.42- 2.01)		.49 (.19-1.24)	.13
Graft source	BMSCs	Ref	.18	Ref	.09	Ref	.25	Ref	.92	Ref	.00	Ref.	.00
	PBSCs	1.32 (.86-2.01)		1.51 (.36-1.70)		.81 (.58-1.15)				.28 (.19-.41)		.44 (.24-.81)	

we have initiated transplantation in our TM patients, and by the time of this report the 20-year OS and TFS in our patients has been 74.83 and 68.63%, respectively.

Several transplant groups have focused on different aspects of thalassemia transplant to improve their survival rates. In a long-term cohort study we have spotlighted the impact of stem cell source on our transplant results.

In recent years PBSCs have increasingly replaced BM as the chosen source of stem cells because of their simplicity of collection, more rapid engraftment, and cost-effectiveness [28-30]. Graft rejection as a major cause of transplant failure in thalassemia could be potentially fatal. A 15-year probability of 23.4% was reported by a French study group for graft failure/thalassemia recurrence after the first transplantation [31]. The 15-year probability of graft rejection in our study was 8.9%. This probability was significantly lower in our PBSCT group compared with the BMSCT (5.7% versus 18.4%). Although the addition of antithymocyte globulin to the pretransplant myeloablative conditioning regimen in the PBSCT group could partially rationalize this significant difference, the impact of the graft source is undeniable.

GVHD is developed by the existing donor T cells in the stem cell graft. Considering that a noticeably larger dose of mature T cells would be transferred from PBSC grafts compared with BMSC grafts, concerns about an increase in the rate of GVHD development exists and so has led to the guarded adoption of using PBSCs in TM patients. Although there is no persuasive evidence on the increased incidence of acute GVHD after PBSCT when compared with BMSCT, there is a possibility of the raised incidence of chronic GVHD in the literature [8,9,16,32-34]. Despite these unconvincing results, BM is still being used as a stem cell source in patients with thalassemia in most countries [35]. This is difficult to understand, particularly because of the significant greater risk of graft rejection in BM grafts, which may have short- and long-term consequences on morbidity and mortality, without the necessity of potential graft-versus-leukemia effect in thalassemia. As another perspective, several trials have examined the relative economic benefits associated with PBSCT and have demonstrated decreased hospital stay and lower costs in comparison with BMSCT [9,15,24].

Donor preference may also affect the choice of stem cell source. Donors who donated BM reported more discomfort early after the donation. Several experiences have been published describing PBSC donor outcomes and have confirmed the safety of this method for donors [19,20,36-38].

In our previous report about the effect of stem cell source on HSCT outcomes in thalassemia patients 10 years ago, no survival advantage for BM over PB was observed [39]. A study reported from a Turkish group who used PBSCs as the graft source in 55.9% of their thalassemia patients demonstrated no statistical difference in terms of mortality and acute GVHD between PBSCs and BMSCs [34]. We did not find any other study in the literature thta encompasses large numbers of TM patients undergone PBSCT.

As a retrospective analysis, there are perceptible limitations in this study. The gradings of GVHD and the details of transplant-related events were not precisely documented.

In conclusion, this large, single-center study did not show a significant difference in the rates of survival and acute and chronic GVHD while using PBSCs as the graft source compared with BMSCs. Faster donor cell engraftment and lower rejection rate by PBSCs were also confirmed. Ultimately, although the choice of the most appropriate stem cell graft in thalassemia still remains to

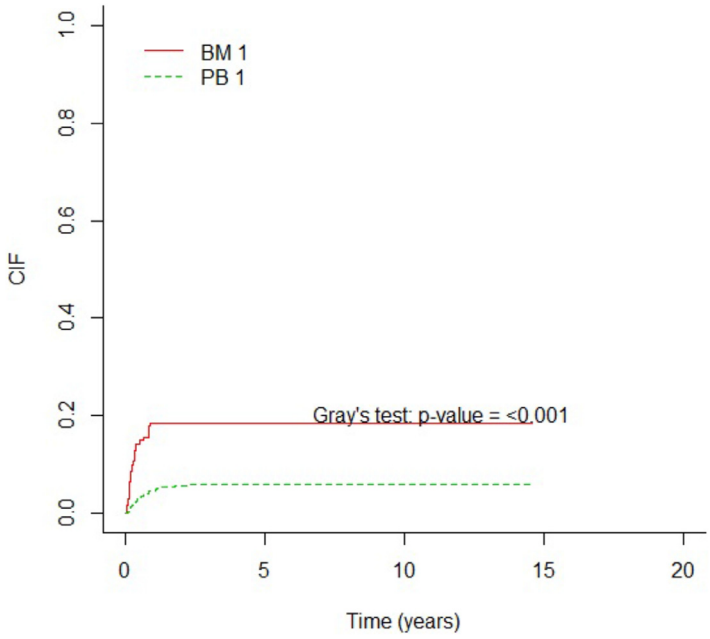

Figure 3. Fifteen-year rejection incidence in the 2 categories of patients.

Table 4
Univariate and Multivariate Cox Regression Model for Acute And Chronic GVHD

		Acute GVHD				Chronic GVHD			
		Univariate		Multivariate		Univariate		Multivariate	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex	Female	Ref	.83			Ref	.19	Ref	.36
	Male	1.02 (.78-1.34)				1.28 (.88-1.87)		1.19 (.81-1.74)	
Hepatic fibrosis	No	Ref	.04	Ref	.20	Ref	.88		
	Yes	.75 (.57-.99)		.83 (.62-1.10)		1.02 (.71-1.47)			
Age, yr	2-5	Ref	.94			Ref	.00	Ref	
	5-10	.92 (.60-1.41)				1.53 (.75-3.15)		1.66 (.80-3.43)	.17
	10-15	.85 (.54-1.33)				1.58 (.75-3.29)		1.70 (.80-3.60)	.16
	15-17	1.03 (.59- 1.79)				2.73 (1.23-6.02)		2.54 (1.14-5.65)	.02
	>17	.97 (.62- 1.49)				2.80 (1.41-5.56)		2.60 (1.30-5.21)	.00
Graft source	BMSCs	Ref	.02	Ref	.08	Ref	.02	Ref	.26
	PBSCs	1.52 (1.06-2.20)		1.41 (.95-2.07)		1.64 (1.06-2.56)		1.33 (.80-2.21)	

be seen, implementation of improved GVHD prophylaxis and T cell depletion of PBSC grafts could facilitate the road toward adopting this more convenient graft source.

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