ARTICLE

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Thalassemia-free and graft-versus-host-free survival: outcomes of hematopoietic stem cell transplantation for thalassemia major, Turkish experience

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We report the national data on the outcomes of hematopoietic stem cell transplantation (HSCT) for thalassemia major (TM) patients in Turkey on behalf of the Turkish Pediatric Stem Cell Transplantation Group. We retrospectively enrolled 1469 patients with TM who underwent their first HSCT between 1988 and 2020 in 25 pediatric centers in Turkey. The median follow-up duration and transplant ages were 62 months and 7 years, respectively; 113 patients had chronic graft versus host disease (cGVHD) and the cGVHD rate was 8.3% in surviving patients. Upon the last visit, 30 patients still had cGvHD (2.2%). The 5-year overall survival (OS), thalassemia-free survival (TFS) and thalassemia-GVHD-free survival (TGFS) rates were 92.3%, 82.1%, and 80.8%, respectively. cGVHD incidence was significantly lower in the mixed chimerism (MC) group compared to the complete chimerism (CC) group ($p < 0.001$). In survival analysis, OS, TFS, and TGFS rates were significantly higher for transplants after 2010. TFS and TGFS rates were better for patients under 7 years and at centers that had performed over 100 thalassemia transplants. Transplants from matched unrelated donors had significantly higher TFS rates. We recommend HSCT before 7 years old in thalassemia patients who have a matched donor for improved outcomes.

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INTRODUCTION

Hemoglobinopathies are the most common single-gene disorders. They are estimated to affect millions of people globally, and they constitute an important health problem for several countries. In addition to regular transfusion, developments in oral chelation and supportive treatments have improved the life expectancy and quality of life of patients, and differentiated from a fatal disease of childhood to a chronic disease that extends to adult life. However, the only curative treatment is hematopoietic stem cell transplantation (HSCT). Excessive iron overload as a result of regular blood

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transfusions in transfusion-dependent thalassemia patients can lead to various morbidities and mortality. The aim of allogenic HSCT in patients with thalassemia major (TM) is to prevent irreversible organ damage due to iron overload that may develop over the natural course of the disease.

There have been reports of good survival of patients who have undergone HSCT in several publications globally [1, 2]. We had already reported the outcomes of HLA-matched family hematopoietic stem cell transplantation in Turkish children with beta TM [3]. Since TM is a non-malignant disease, GVHD-free survival has become meaningful in recent years [4].

In this paper, we present the national data on HSCT outcomes in thalassemia patients in Turkey, where beta-thalassemia is more prevalent, on behalf of the Turkish Pediatric Stem Cell Transplantation Group.

PATIENTS AND METHODS

This study enrolled 1469 patients with TM who received their first HSCT between January 1988 and August 2020 in 25 pediatric centers in Turkey. All patients were transfusion-dependent. Clinical data were retrospectively collected from all centers that participated in this study using an SPSS data form. The study was approved by the ethics committee of each participating institution and conducted following the consent of the patients.

All related donors were HLA fully matched (6/6 or 10/10) with low- or high-resolution typing. Unrelated donors were searched for based on high-resolution HLA typing, and 9/10 and 10/10 matched volunteers were accepted as donors.

The stem cell sources included bone marrow (BM), peripheral blood stem cells (PBSC), and umbilical cord blood (UCB). If the sibling donor was too young, the combination of UCB and BM was preferred. No haploidentical donor was used.

All patients received a myeloablative conditioning pretransplant consisting of a combination of busulfan/treosulfan and cyclophosphamide/fludarabine and/or thiotepa depending on center preference. All centers used MTX (+1,+3,+6 days) and CsA/Tacrolimus for post-transplant GVHD prophylaxis. Also, all but 171 patients received ATG (Fresenius) for conditioning with total doses of 15–50 mg/kg depending on center preference. ATG was not given to 171 patients who received less than 10 transfusions.

Engraftment was defined as the first of three consecutive days on which the neutrophil count exceeded 500/μL and the platelet count exceeded 20.000/μL without transfusion support for 7 consecutive days. Complete donor chimerism was defined as having more than 95% donor cells after HSCT and stable mixed chimerism (MC) was having less than 95% donor cells without transfusion dependence. Primary graft failure was defined as a lack of evidence of engraftment or hematological recovery of donor cells within the first month after transplantation and transfusion dependence. In contrast, secondary graft rejection was defined as cytopenia after the initial engraftment with donor chimerism of less than 5% and a return to a thalassemic bone marrow or bone marrow hypoplasia requiring red cell transfusion. Poor graft was defined as insufficient graft function in a patient with complete donor chimerism.

The diagnosis and grades of acute and chronic GVHD were based on consensus criteria [5, 6]. All grades of cGVHD were recorded. The patients who had never encountered any sign of cGVHD or had a history of completely resolved cGVHD were recorded as GVHD-free.

The primary end-points were overall survival (OS), thalassemia-free survival (TFS), and thalassemia-GVHD-free survival (TGFS). OS was defined as the time from the date of transplantation until death from any cause or the last follow-up while TFS was defined as survival without graft rejection. TGFS was defined as being alive without thalassemia and GVHD.

Statistical analysis

All statistical analyses were performed using SPSS for Windows (version 16.0.0; SPSS Inc., Chicago, IL). The descriptive statistics of the qualitative variables are expressed as frequencies and percentages. The endpoints of this study were OS, TFS, and TGFS, which were calculated using the Kaplan-Meier estimates. Univariate analyses for potential prognostic factors such as age, gender, donor type, source of stem cells, and the presence of GVHD were performed using the log-rank test. Variables with log-rank test p-values of < 0.200 were included in the multivariate analysis (stepwise Cox proportional hazard regression analysis). Associations were expressed as hazard ratios (HRs) and 95% confidence interval (CI). Statistical significance was set at $P < 0.05$.

RESULTS

The pre-transplant and transplant characteristics of the patients are presented in Table 1. The median follow-up duration of the patients was 62 months; the longest follow-up was 402 months, with a range of 15–402 months. During HSCT, the median age of the patients was 7 years, and the range was 1–29 years. Six of the centers participating in our study had transplanted more than 100 patients with thalassemia between 11 and 22 years duration.

The proportion of patients with primary graft failure was 2,7%. Besides that, 7.3% of the patients experienced secondary graft rejection and 1.3% had a poor graft. At the time of this study, the last chimerism results for 1249 patients had been recorded, and 84.4% of them were being followed up for full donor chimerism. Stable mixed chimerism was found in 15.5% of the patients alive without transfusion (Table 2).

After the transplant, 111 patients died. A total of 130 patients experienced cGVHD. Of those patients, 113 survived. The overall cGVHD rate was 8.3% among the surviving patients. During the follow-up, the cGVHD findings resolved in 83 patients, and at the last visit, 30 patients still had chronic GvHD (2.2%)(Fig. 1). The 5-year OS, TFS, and TGFS were 92.3%, 82.1%, and 80.8%, respectively (Fig. 2). Regarding the last chimerism status, the cGVHD rates were 11.4% (120/1055) and 3.6% (7/194) in the complete donor chimerism and MC groups, respectively ($p < 0.001$). No secondary malignancy was reported in any patient during the follow-up period.

Table 1. Patient and transplant characteristics.

n	1469
Male/Female	779/690
Median age	7 years (1–29 years)
Median follow-up	62 months (15–402 months)
Transplant period	
Before 2010	254
After 2010	1215
Center experience	
<100 Thalassemia transplant	578
>100 Thalassemia Transplant	891
Stem Cell Source	
Bone Marrow	953
Peripheral Blood	380
Bone Marrow+Cord Blood	118
Unknown	18
Donor type	
Matched Sibling	1020
Matched Related	194
Matched Unrelated	255
Unrelated Donor Matching	
9/10	44
10/10	211
cGVHD experience in alive patients	
Yes	113
No	1245

cGVHD chronic graft versus host disease.

Table 2. Univariate analysis of prognostic factors after 1st HSCT in thalassemia major patients for 5 years survival analysis.

	n	OS	*p*	TFS	*p*	TGFS	*p*
All patients	1469	92.3% (95% CI 90.9–93.7)		82.1% (95% CI 80.1–84.1)		80.8% (95% CI 78.0–82.4)	
Donor chimerism							
Full chimeric	1055	94.7% (95% CI 93.3–96.1)	0.65	94.6% (95% CI 93.2–96.0)	0.88	92.9% (95% CI 91.3–94.5)	0.16
Mixed chimeric	194	95.3% (95% CI 92.3–98.4)		95.3% (95% CI 92.3–98.4)		95.3% (95% CI 92.3–98.4)	
Transplant age							
<7 years old	762	93.7% (95% CI 91.9–95.5)	0.06	84.3% (95% CI 81.5–87.1)	0.02	83.3% (95% CI 80.5–86.1)	0.01
>7 years old	707	90.7% (95% CI 88.5–92.9)		79.8% (95% CI 76.8–82.8)		78.0% (95% CI 74.8–81.2)	
Gender							
Male	779	91.8% (95% CI 89.8–93.8)	0.49	80.8% (95% CI 78.0–83.6)	0.16	79.8% (95% CI 76.8–82.8)	0.49
Female	690	92.8% (95% CI 90.8–94.8)		83.7% (95% CI 80.9–86.5)		81.9% (95% CI 78.9–84.9)	
Donor type							
MSD	1020	92.7% (95% CI 91.1–94.3)	0.04	82.1% (95% CI 79.7–84.5)	<0.01	81.7% (95% CI 79.3–84.1)	<0.01
MRD	194	88.0% (95% CI 83.2–92.8)		74.9% (95% CI 68.5–81.3)		72.9% (95% CI 66.3–79.5)	
MUD	255	94.1% (95% CI 91.1–97.1)		88.6% (95% CI 84.6–92.6)		82.6% (95% CI 77.2–88.0)	
MUD Donor							
9/10	44	88.4% (95% CI 79.0–98.6)	0.09	74.9% (95% CI 61.7–88.1)	<0.01	66.5% (95% CI 50.3–82.7)	<0.01
10/10	210	95.2% (95% CI 92.2–98.2)		91.4% (95% CI 87.6–95.2)		85.8% (95% CI 80.4–91.2)	
Transplant period							
<2010	254	87.1% (95% CI 82.9–91.3)	<0.01	71.3 % (95% CI 65.7–76.9)	<0.01	71.3% (95% CI 65.7–76.9)	<0.01
>2010	1215	93.4% (95% CI 92.0–94.8)		84.5 % (95% CI 82.3–86.7)		82.8% (95% CI 80.6–85.0)	
Center experience							
<100 TM transplant	578	91.1% (95% CI 88.5–93.7)	0.22	78.4% (95% CI 74.8–82.0)	<0.01	77.4% (95% CI 73.8–81.0)	<0.01
>100 TM transplant	891	93.0% (95% CI 91.2–94.8)		84.5% (95% CI 82.1–86.9)		82.9% (95% CI 80.3–85.5)	
cGVHD							
No	1339	92.9% (95% CI 91.5–94.3)	0.02	81.8% (95% CI 79.6–84.0)	0.14		
Yes	130	86.8% (95% CI 80.2–93.0)		84.8% (95% CI 78.0–91.6)			
Stem Cell Source Sibling Donor							
BM	717	93.9% (95% CI 92.1–95.7)	<0.01	82.8% (95% CI 80.0–85.6)	0.02	82.4% (95% CI 79.4–85.4)	0.02
PB	169	85.6% (95% CI 80.2–91.0)		73.3% (95% CI 66.5–80.1)		72.6% (95% CI 65.8–79.4)	
MUD Donor							
BM	124	91.9% (95% CI 86.9–96.9)	0.17	83.7% (95% CI 77.1–90.3)	0.02	81.5% (95% CI 74.3–88.7)	0.33
PB	131	96.1% (95% CI 92.7–99.5)		93.1% (95% CI 88.7–97.5)		82.5% (95% CI 74.1–90.9)	
All Patients							
BM	953	93.1% (95% CI 91.5–94.7)	0.02	81.7% (95% CI 78.9–84.3)	0.12	80.9% (95% CI 78.3–83.5)	0.03
BM + CB	118	95.8% (95% CI 92.0–99.6)		89.0% (95% CI 84.2–94.8)		89.0% (95% CI 83.2–94.8)	
PB	380	89.1% (95% CI 85.9–92.2)		80.5% (95% CI 76.3–84.7)		77.1% (95% CI 72.5–81.7)	

OS overall survival, *TFS* thalassemia-free survival, *TGFS* thalassemia-GVHD free survival, *MSD* matched sibling donor, *MRD* matched related donor, *MUD* matched unrelated donor, *TM* thalassemia major, *BM* bone marrow, *CB* cord blood, *PB* peripheral blood.

Univariate analysis showed that the rates of OS, TFS, and TGFS were significantly higher in patients who received a transplant after 2010. The TFS and TGFS rates were better for the patients with a transplant age of <7 years and those who received their transplant at a center with more than 100 thalassemia transplants. Considering the donor type, all three survival rates were low for transplantations from non-sibling relative donors (MRD). There was statistically no difference for all survival parameters between maternal and paternal grafts. When sibling (MSD) and unrelated (MUD) donors were compared, the OS and TGFS were not different, but TFS was significantly higher for transplants from MUD donors. The TFS and TGFS were significantly lower for transplants from 9/10 matched donors than for 10/10 unrelated donors. As a stem cell source, the bone marrow in sibling donors had a positive effect on all life outcomes; however, TFS was higher for peripheral blood transplantation in the MUD group. When all transplants were evaluated, it was observed that the stem cell source affected OS and TGFS, but not TFS. OS was lower in the presence of cGVHD; however, TFS was not affected (Table 2).

Multivariate analyses showed that OS, TFS, and TGFS were significantly better for transplants received after 2010 and patients younger than 7 years. Having experience with more than 100 transplants positively affected the TFS and TGFS rates, but it did not affect OS. Similarly, MRD did not affect OS; however, it negatively affected TFS and TGFS. The use of peripheral blood did not affect all three parameters. There was no statistical effect of the presence of cGVHD on OS and TFS (Table 3).

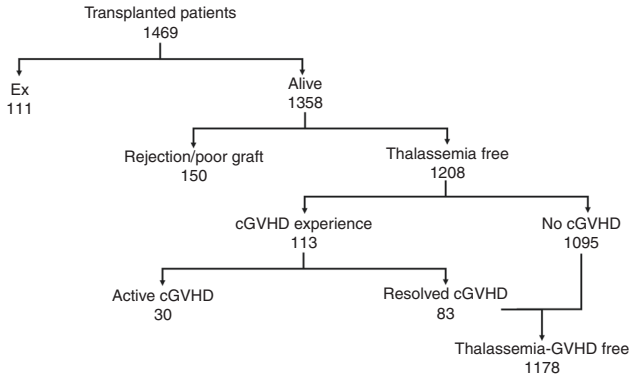

Fig. 1 Study flow diagram.

DISCUSSION

Forty years have elapsed since the first HSCT was successfully performed for a patient with TM; allogeneic HSCT from a matched donor is accepted as standard clinical practice in thalassemia patients, and it is increasingly applied globally. Using the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry data, Baronciani and colleagues [1] retrospectively analyzed the outcomes of 1493 consecutive patients with β-thalassemia major who underwent HSCT between 2000 and 2010 at 127 centers globally (14% of them were from Turkey). They reported 2-year OS and TFS of 88 ± 1% and 81 ± 1%, respectively, after a median observation duration of 2 years [1]. In

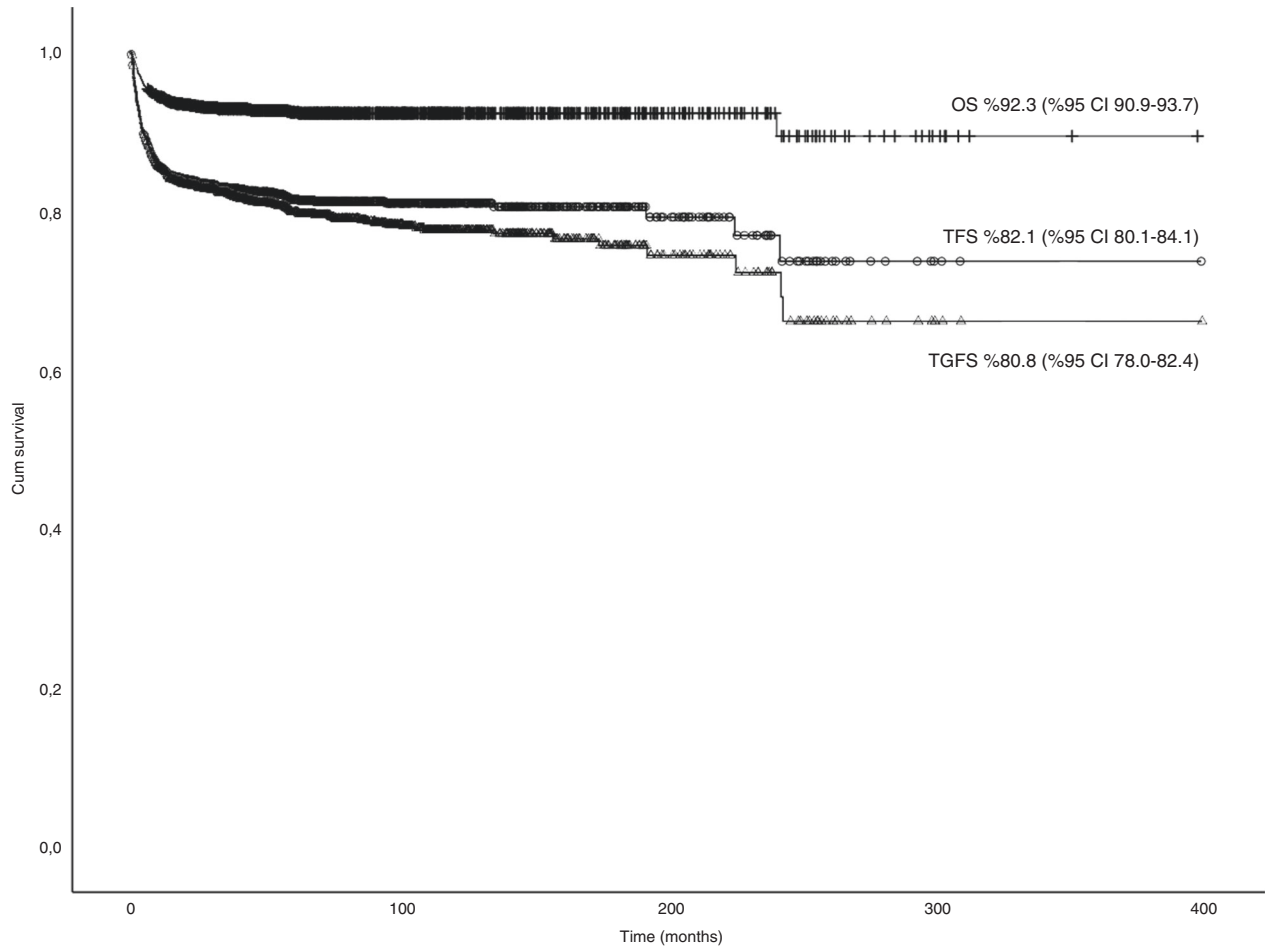

Fig. 2 The 5-year probabilities of overall, thalassemia-free and thalassemia-GVHD-free survival for thalassemia major patients.

Table 3. Multivariate analysis of the prognostic factors.

	OS	TFS			TGFS	
	HR (%95 CI)	*p*	HR (%95 CI)	*p*	HR (%95 CI)	*p*
Transplant age						
<7 years old	1		1		1	
>7 years old	1.5 (1.0–2.2)	0.03	1.4 (1.1–1.7)	<0.01	1.4 (1.1–1.8)	<0.01
cGVHD						
No	1		1		1	
Yes	1.6 (0.9–2.7)	0.10	0.6 (0.4–1.0)	0.07	-	
Donor type						
MSD	1		1		1	
MRD	1.5 (0.9–2.6)	0.07	1.6 (1.1–2.2)	<0.01	1.6 (1.2–2.2)	<0.01
MUD	0.9 (0.5–1.7)	0.79	0.8 (0.5–1.3)	0.38	1.0 (0.7–1.5)	0.96
Stem Cell Source						
BM	1		1		1	
BM + CB	0.6 (0.2–1.5)	0.30	0.5 (0.3–0.9)	0.04	0.5 (0.3–0.9)	0.03
PB	1.3 (0.8–2.0)	0.28	0.9 (0.7–1.2)	0.53	0.9 (0.7–1.2)	0.62
Transplant period						
Before 2010	1		1		1	
After 2010	0.5 (0.3–0.8)	<0.01	0.5 (0.4–0.7)	<0.01	0.6 (0.4–0.8)	<0.01
Center experience						
<100 TM transplant	1		1		1	
>100 TM transplant	0.7 (0.5–1.0)	0.10	0.7 (0.5–0.9)	<0.01	0.7 (0.6–0.9)	<0.01

OS overall survival, *TFS* thalassemia-free survival, *TGFS* thalassemia-GVHD free survival, *MSD* matched sibling donor, *MRD* matched related donor, *MUD* matched unrelated donor, *BM* bone marrow, *CB* cord blood, *PB* peripheral blood, *TM* thalassemia major.

that study, the best outcomes were for those with HLA MSD donors; they also reported that the threshold age for optimal transplant outcomes was ~14 years, with an OS of 90–96% and an EFS of 83–93% when transplants were performed before the age of 14 years. In this study, only 133 patients aged 18 years or more received transplants after 2000. It shows that the recommendation by the Pesaro group for transplantation for thalassemia patients as soon as possible has been accepted by most EBMT centers [7]. In our study, OS and TFS were 92.3% and 82,1%, respectively, after 5 years of follow-up, which was consistent with the report by Baronciani. Since the median transplantation age in our study was 7 years, HSCT results were significantly better for patients under 7 years old than for older patients (Table 2). Similarly, Sabloff et al. [8] reported that proceeding with HSCT in children younger than 7 years before the development of end-organ damage, particularly in the liver, should improve results for thalassemia major.

After successful outcomes for HSCT for the treatment of thalassemia in several countries, a long follow-up for monitoring transplant complications and quality of life has gained importance [4, 9–11]. Chronic GVHD is one of the most important factors for determining the quality of life after HSCT. Therefore, we believe TGFS should be specified along with OS and TFS. In an EBMT multicenter study, the 2-year risks of developing limited chronic or extended chronic GvHD in 1140 patients who survived with a functioning graft for >100 days were 15 ± 1% and 6 ± 1%, respectively. Ramprakash et al. [12] reported 4.2% cGVHD and 74.6% GVHD/Rejection-free survival for 71 thalassemia patients who underwent HSCT with an MSD donor. Li et al. [13] also reported 5.7% cGVHD and 89.5% TGFS rates for patients with TM who received G-CSF-mobilized blood and BM grafts as the source of stem cells for HLA-identical sibling transplantation. In another Chinese study, a TGFS rate of 86.9% was reported for 521 thalassemia patients [14]. In our study group, 8,3% of the patients alive had experienced cGVHD. At the last visit, 2,2% of the patients had mild/limited chronic GvHD in our study, which was similar to the 3% reported by a French study [10]. We found that a TGFS rate of 80.8% was indicative of being alive without thalassemia and GVHD. It is noteworthy that, most patients received serotherapy as part of the conditioning regimen, which may have reduced cGVHD rates. However, given the retrospective nature of the study, it was not possible to analyze the effects of ATG and ATG dosing in this cohort. Patients with a stable MC are expected to have a lower risk of cGVHD, possibly because of the induction of donor/recipient immune tolerance. Van Beisen et al. [15] reported that MC was predictive of a lower risk of acute and, particularly, chronic GVHD. In our study, the rate of cGVHD was significantly lower in the MC than in the complete donor chimerism group ($p < 0.001$). However, TGFS was slightly higher, and the difference was not statistically significant (Table 2). This is an interesting result, however, this finding and interpretation would be more meaningful if we could present split chimerism results on erythroid engraftment for the mixed chimerism group.

It is well-known that the developments in HSCT applications in recent years and the experience of the transplant center directly affect the success of HSCT. Univariate analysis showed significantly better TF and TGFS for patients who received their transplant in an experienced center (with experience with more than 100 thalassemia transplants). The associations between TF and TGF survival rates and the experience of the transplant center are realistic. As described by several authors, the HSCT outcomes improved significantly with time [1, 2, 16]. In our study, the OS, TFS, and TGFS were significantly better for patients who received their transplant after 2010; they significantly improved over time (Table 2). We believe that careful patient selection, a full matched donor selection with high-resolution HLA typing, planning of an optimum conditioning regimen, and effective GVHD prophylaxis protocols improves both parameters.

The univariant analysis also showed that all three life parameters were significantly worse for cases with non-sibling-

Table 4. Some recent publications which report the outcomes after HSCT in patients with thalassemia.

Author	Country	Publishing Year	Transplant interval	*n*	Donor type	Follow-up Median	OS %	TFS %	TGFS %	Comment
Alonso [33]	Spain	2019	1989–2014	43	MSD, MRD, MUD	3 years	92	81	NA	In 6 centers in Spain
Choudhary [32]	India	2019	2008–2017	203	MSD, MRD, MUD, Haplo	29 months	88.5	82	NA	12.9% cGVHD
Li [21]	China,India, USA	2019	2000–2016	1110	MSD, MRD, MUD, Haplo	5 years	≤6 years old 90 7–15 years old 84 16–25 years old 63	86 80 63	NA	An International study, 90% of patients in the last decade
Galambrun [16]	France	2013	1985–2007	108	MSD, MRD, MUD	12 years	86.8	69.4	NA	96 siblings, 12 cGVHD
Caocci [34]	Italy	2017	1987–2016	258	MSD, MUD	11 years	82.6	77.8	NA	Adult OS 70,TFS 67.3, cGVHD 12.9%
Ramprakash [12]	India, Pakistan, Sri Lanka	2017	2013–2016	71	MSD	17.5 months	93	83	74.6	BU oral,CY, ATG, cGVHD 4%
Li [13]	China	2019	2007–2018	184	MSD	3 years	97.8	97.3	89.5	G-CSF-Mobilized Blood and BM Grafts
Lai [14]	China	2021	2007–2019	521	MSD, MUD, Haplo	3 years	94.3	92.5	86.9	VOD 10.4%
Current study	Turkey	2021	1988–2020	1469	MSD, MRD, MUD	62 months	92.3	82.1	80.8	Only first transplantation results, whole country results from 25 pediatric centers

OS overall survival, *TFS* thalassemia-free survival, *TGFS* thalassemia-GVHD free survival, *MSD* matched sibling donor, *MRD* matched related donor, *MUD* matched unrelated donor, *BM* bone marrow, *PB* peripheral blood, *cGVHD* chronic Graft Versus Host Disease, *BU* busulphan, *CY* cyclophosphamide, *VOD* veno-occlusive disease.

related donors. This may be attributed to the low-resolution HLA typing, especially for some transplants before 2000, which may have caused mismatched transplantation using an incompatible donor. Another explanation may be related to immunology, such as maternal or paternal causes. Korula et al. [17] reported that event-free survival and OS were significantly lower for the non-sibling family donor cohort than for the MSD group, which had a total of 99 thalassemia patients, because of the higher rates of complications such as viral infections, GVHD, and rejection. In contrast, no significant difference was found during the survival analysis between the donor types in a few studies [1, 18, 19]. In our study, our MUD and MSD transplant outcomes were comparable; the outcomes for the MUD were slightly better. We believe that, careful patient and donor selection influenced these outcomes, in addition to the fact that all unrelated transplants were performed after 2010. In 2005, La Nasa et al. [20] reported that 30 thalassemic patients in risk classes 1 and 2 had OS and DFS of 96.7% and 80.0%, respectively, whereas 38 patients in risk class 3 had OS of 65.2% and DFS of 54.5%. Recently, the authors of a multicenter study reported comparable event-free and overall survival after HLA-matched related and unrelated donor transplantation in patients with TM [21]. They also recommended initiating a simultaneous search for HLA-matched related and unrelated donors early in the course of the disease and performing the transplantation using an HLA-matched unrelated donor if an HLA-matched sibling is not available. In that study, delaying transplantation beyond 15 years resulted in a 20–25% absolute decrement in event-free and overall survival [21]. An international panel also reported that if a well-matched donor (related or unrelated) is available, allogeneic HSCT, as soon as possible, is a suitable option for a child with life-long control of iron overload and the absence of iron-related tissue complications before the development of iron overload [2].

It is well-known that the success of transplantation decreases and complications increase in HSCT as the mismatch in the HLA loci increases. TFS and TGFS were significantly lower for transplants from 9/10 compatible donors than those from 10/10 donors among unrelated donors in this study, as expected based on this knowledge. In recent years, promising results for haploidentical donor transplants in patients with thalassemia major have been published [22, 23]. However, we believe enough experience has not been gathered, and it is too early for routine applications. No haploidentical transplantation was observed in our registry.

The preferred source of stem cells in patients with thalassemia major is the bone marrow. However, there are several reports of successful results with peripheral blood stem cells and umbilical cord blood [24–27]. In our previous report on the use of PBSCs as the graft source in 55.9% of thalassemia patients, no statistical differences in the mortality rate and prevalence of acute GVHD were demonstrated between PBSCs and BMSCs [3]. Despite the good results related to engraftment, the use of PBSCs from an MSD or MFD is not the first choice as a stem cell source in patients with TM, due to the possible increase in the risks of both acute and chronic GvHD [28]. It is well-known that the GVHD risk was lower; however, there have been reports that a higher risk of graft failure risk is associated with UCB in thalassemia patients [27–30]. In our study, bone marrow was used for 65%, peripheral blood was used for 26%, and cord blood of the same sibling with bone marrow was used in 8% of the cases. We found that the use of bone marrow from sibling donors had a positive effect on life outcomes. Good results have been reported after co-transplantation of a UCB unit and BM cells harvested from the same sibling donor [29, 31]. Combined infusion is aimed at increasing the number of transplanted cells and improving hematopoietic recovery while maintaining the cord blood-related protective effect on the occurrence of GVHD [29]. In our study, all three survival parameters were better after the combination of UCB and BM. Interestingly, TFS was significantly higher when peripheral blood was used as a stem cell source for transplants from unrelated donors. When all transplants were compared for outcome parameters, the stem cell source affected OS and TGFS, but it did not affect TFS. This finding shows that the choice of the stem cell source affects complication-free survival.

The multivariate analyses showed that all survival parameters were significantly better for transplants performed after 2010 and patients younger than 7 years old. The TFS and TGFS rates were improved at centers with experience with more than 100 transplants for TM patients; OS was not affected. Regarding the donor type, MRD did not affect OS; however, it negatively affected the TFS and TGFS rates. For the stem cell source, peripheral blood use did not affect all three survival parameters. The univariate analysis showed a negative effect on OS; however, no effects of cGVHD on OS and TFS were observed in the multivariate analysis (Table 3).

Regional, ethnic, and genotypic features may lead to differences in the course of thalassemia patients. Table 4 shows some recent publications [12–14, 16, 21, 32, 33] from different parts of the world, which report the outcomes after HSCT for patients with thalassemia. Compared with these studies, we believe that our study makes significant contributions to the literature with its high number of patients and sufficient follow-up duration.

In conclusion, this study confirmed that allo-HSCT is an effective approach for patients with TM, and its outcomes have been improving significantly over time. We can recommend that if a thalassemia major patient has an HLA-matched donor, HSCT should be performed under 7 years of age before the development of organ damage due to iron overload for better post-transplant quality of life. Our study also showed that TFS and TGFS rates were better at experienced centers that conducted over 100 transplants for TM patients. There was no difference between OS and TGFS rates in MSD and MUD, but TFS was significantly higher for transplants from MUD donors. TFS and TGFS rates were significantly lower for transplants from 9/10 matched donors than for 10/10 unrelated donors. The cGVHD rate was significantly lower in the MC group than in the complete donor chimerism group. This study is important because it reports the transplant results for thalassemia patients for an entire country with high case participation. Today, the criteria of thalassemia-free survival used for the evaluation of HSCT results are not sufficient, but it is important to consider survival without cGVHD, which determines the quality of life and the factors affecting it. We believe that our study results will shed light on this issue and contribute significantly to improving the quality of life of patients with thalassemia major after HSCT.

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AUTHOR CONTRIBUTIONS

AY was responsible for designing the study, analyzing data and writing the report. AY and VU extracted the data, interpreted the results, and do the statistical analysis. AK, GK, GO, ME, IS, HD, EG, VH, TF, GS, SK, BK, BA, NO, EUI, SO, FTK, KY, SA, CB, MK, SK, DA, HO, SA, FVO, CA, FDY, IOB, TI, OG, BSK, GTK, SC, ME, BAA, EY, AT, STA, ZOS, GO, DU, IK, DA, AA, OAB, HFC, EK, BM, SA, HAD, SCK, AMG, EZ, SO, and ABA collected the data and contributed to improve the text.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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