

# Outcomes of Haematopoietic Stem Cell Transplantation in Beta Thalassemia Major with Fully Matched Parents as Donor

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## ABSTRACT

**Objective:** To determine the outcome of beta thalassemia major (BTM) patients undergoing haematopoietic stem cells (HSCT), with fully matched parents as donors vs. matched sibling donors (MSD).

**Study Design:** Observational Study.

**Place and Duration of the Study:** Department of Clinical Haematology and Bone Marrow Transplantation Centre, Rawalpindi, Pakistan, from January 2013 to July 2023.

**Methodology:** Group A consisted of BTM patients who underwent HSCT with fully matched siblings as donors, and Group B consisted of BTM patients who underwent HSCT with fully matched parents as donors. Study data included the age and gender of both recipients and donors, source and dose of stem cells infused, and stage and grades of acute and chronic graft versus host disease (GvHD). All patients received Myeloablative conditioning regimen (MAC). Data were collected to assess patients' demographics, response to HSCT, remission rate, disease free survival (DFS), relapse, and GvHD free survival (GRFS), and overall survival (OS).

**Results:** The mean age of the 54 patients was  $5.90 \pm 3.29$  years. The mean TNC and CD34 doses were  $4.99 \pm 1.13$  and  $5.42 \pm 3.70$ , respectively. Mean time for neutrophil engraftment in both groups was  $14.88 \pm 4.51$  days and platelets engraftment was  $23.0 \pm 5.35$  days. Most common cause of death was neutropenic sepsis followed by aGVHD. Seven patients had graft rejection. There was no significant association found between graft rejection with donor relation though graft rejection was higher in OS in this study was 70.4%. OS was equal in both groups. Disease free survival was superior in MSD (63%) than parent group (57.7%).

**Conclusion:** Allogeneic bone marrow transplantation with parents as donors in BTM patients yields outcomes comparable to those with matched sibling donors. This finding is especially relevant in regions like Pakistan, where donor registries and high-resolution HLA typing may be limited.

**Key Words:** Beta thalassemia major, Haematopoietic stem cell transplant, Post-transplant outcome.

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## INTRODUCTION

Beta-thalassemia major (BTM) is a hereditary condition in which beta-globin chain is reduced or absent.<sup>1</sup> Regular blood transfusions are cornerstone of medical care along with iron chelation therapy to prevent tissue damage brought on by transfusion related iron overload.<sup>2</sup> In developing countries, the mean life is 20 years due to unavailability of standard treatment options or due to non-affordability.<sup>2</sup>

Allogeneic haematopoietic stem cell transplantation (Allo-HSCT) from a human leukocyte antigen (HLA) matched family donor has revolutionised the prognosis of patients with homozygous beta-thalassemia.<sup>3</sup>

It is the sole curative therapeutic option because Allo-HSCT has reported 91% thalassemia-free survival at an early stage of the disease with a mortality risk of ~8%. Since 1982, when the successful HSCT for thalassemia major was carried out, more than 1500 transplants have been completed globally.<sup>4</sup> According to published data, overall survival (OS) is over ~80% and event-free survival (EFS) rates is close to 70%.<sup>5</sup>

Age, stem cell source, histocompatibility, and conditioning regimen are some of the variables that may have an impact on the results of HSCT in BTM.<sup>6</sup> HLA mismatch is thought to be the main risk factor for the development of graft versus host disease (GvHD). Other risk variables include the recipient's CMV viral seropositivity, recipient and donor age, recipient and donor gender mismatch, GvHD prophylaxis, graft type, and TNC and CD34 dose. The scarcity of appropriate donors is one of the biggest obstacles to bone marrow transplantation. Fully matched sibling donors (MSD) have superior transplant results.<sup>7</sup> Many countries like Pakistan lack the facility of donor registries and the high cost of searching for unrelated donors make it practically impossible. In Pakistan, patients who do have not MSD, fully matched parents are the only option for bone

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marrow transplantation.<sup>8</sup> The objective of this research was to report the outcome of BTM patients undergoing HSCT, with fully matched parents as donor vs. MSD along with the identification of risk factors for the poor outcomes.

## METHODOLOGY

All BTM patients who underwent fully matched HSCT at Bone Marrow Transplant Centre (AFBMT), Rawalpindi, Pakistan, from January 2013 to February 2023. Total 386 patients underwent bone marrow transplants. Fifty-four patients were included in the final analysis. These patients were divided into two groups. Group A consisted of BTM patients who underwent HSCT with fully matched siblings as donors, and Group B consisted of BTM patients who underwent HSCT with fully matched parents as donors. Ethical guidelines were followed by getting the participant's parents or guardians informed consent, and official approval was obtained from the institutional review board (IRB#008/AFBMT/Approval/2021). Using Hb electrophoresis and/or PCR diagnosis for BTM was made. Age, gender, source, and dosage of infused stem cells as well as stages and grades of acute and chronic GvHD were all included in the study data. All patients underwent the Myeloablative conditioning regimen (MAC) which included Fludarabine (Flu), Busulphan (BU), and Cyclophosphamide (Cy) with or without TG. A clinical evaluation of GvHD affecting the skin, gastrointestinal tract, and liver was done using Glucksberg-Seattle criteria. The records of patients with insufficient data and those who underwent a second transplant were excluded.

Information was gathered to evaluate patient characteristics, HSCT response, disease-free survival (DFS), relapse, GVHD-free survival (GRFS), and overall survival (OS). Statistical Package for Social Sciences (SPSS) 25 was used to analyse data. Study produced a variety of variables and among them, frequencies and percentages were determined for categorical and mean, median and standard deviation for continuous data. The link between GvHD and post-transplant complications with Donor-relationship was assessed at univariable analysis using the Pearson Chi-square test and OS was computed using Kaplan-Meier test with statistically significant p-value = 0.05 with 95% confidence interval.

## RESULTS

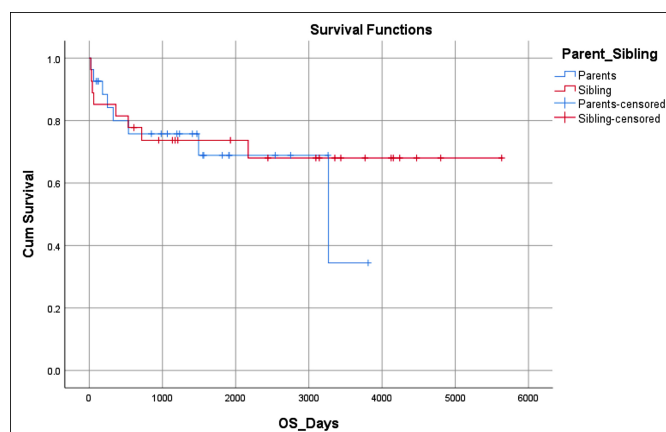
Out of 54 participants, 33 (61.1%) were males and 21 (38.9%) were females. The mean age of the at the time of transplant was  $5.90 \pm 3.29$  years. patients. Bone marrow was the main source used for the collection of stem cells from the donors. The mean TNC and CD34 doses infused into the patients was  $4.99 \pm 1.13$  and  $5.42 \pm 3.70$ , respectively. The mean time for granulocyte recovery in both groups was  $14.88 \pm 4.51$  days, whereas the mean time for a self-sustained platelet recovery was  $23.0 \pm 5.35$  days. Thirteen (24.1%) patients had major ABO mismatch, 8 (14.8%) had minor ABO, and 33 (61.1%) had no ABO mismatch. Twenty-nine (53.7%) patients were younger than 5 years, 17 (31.5%) were between 5-10 years and 8 (14.8%) were older than 10 years. Out of the 52 donors, 42 (77.8%) were Thalassemia trait. Patients and donor characteristics are given in Table I.

**Table I: Demographics of the patients and donors.**

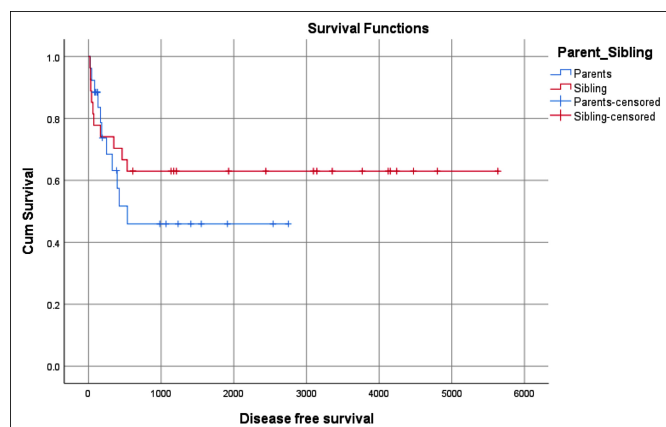
	Patient		Donor	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Age (Mean + S.D)	$5.90 \pm 3.29$ years		$9.130 \pm 8.13$ years	
RCC Transfusion				
Less than 50	34	63		
50-100	13	24.1		
More than 100	7	13		
Iron Chelation				
Regular	8	14.8		
Irregular	46	85.2		
Ferritin				
<2000 ng/ml	28	52		
>2000 ng/ml	26	48		
Organomegaly				
Liver				
Less than 2 cm	19	35		
2-5 cm	33	61		
More than 5 cm	2	4		
Spleen				
Non-palpable	35	65		
Palpable	19	35		
Pesaro Class				
Class I	8	13		
Class II	15	27.8		
Class III	31	57.4		
Donor Relation with Patient				
Brother			8	14.8
Sister			19	35.2
Father			11	20.6
Mother			16	29.6

**Table II: Relationship of donor status with GvHD.**

	aGVHD		p-value	cGVHD		p-value
	Yes	No		Yes	No	
	n (%)	n (%)		n (%)	n (%)	
Relation of Donor						
Parents	13 (24.0)	14 (26)	0.009	2 (7)	25 (93)	0.5
Sibling	22 (40.7)	5 (9.4)		1 (4)	26 (96)	
Relation of Donor						
Sister	6 (75)	2 (25)	0.035	0 (0)	19 (100)	0.54
Brother	16 (94)	1 (6)		1 (12.5)	17 (87.5)	
Father	5 (45.5)	6 (54.5)		1 (9)	10 (91)	
Mother	8 (61.5)	5 (38.5)		1 (6)	15 (94)	
Donor Gender Mismatched						
Female to Male	16 (64)	9 (36)	0.9	0 (0)	25 (100)	0.09
No Mismatch	19 (65.5)	10 (34.5)		3 (10)	26 (90)	



**Figure 1: Overall survival (70.4%).**



**Figure 2: Disease free survival (60.4%).**

Patients were analysed for immediate posttransplant complication out of which neutropenic infections were the most commonly encountered complication i.e. 94.4% (n=51) patients. Neutropenic infections were treated aggressively following the guidelines of neutropenic sepsis. The second most immediate posttransplant complication was cyclosporine-induced hypertension for which patients require introduction of anti-hypertensive. Mucositis was more common in the parent group (n=16, 52%) than the sibling group (n=15, 48%) and this was not statistically significant (p=0.7). Venocclusive disease was more common in the parent group (n=6, 75%) than the sibling group (n=2, 25%) with p-value

of 0.12. CMV reactivation was observed more in parent group (n=12, 75%) than sibling group (n=4, 25%) and this was statistically significant (p=0.01).

Acute GVHD (aGVHD) was more common in the sibling group and showed statistically significant (p=0.009). aGVHD also showed statistically significant correlation with the relation of donor (p=0.035). Gender mismatch showed no statistically significant relation with aGVHD. However, aGVHD was more common in females than males gender. Details of aGVHD and cGVHD are given in Table II. CMV reactivation was more common in the parent group (85.1%) than in the sibling group (77.7%).

Out of 54 patients, 16 (29.6%) patients died, eight in each group. Most common cause of death was neutropenic sepsis followed by aGVHD. Seven (12.9%) patients had graft rejection. There was no significant association found between graft rejection with donor relation though graft rejection was higher in parents (7.4%) than in siblings (3.7%) (p=0.38).

OS in this study was 70.4% (Figure 1). OS was equal in both groups. DFS in these patients was 60.4% (Figure 2). DFS was superior in MSD (63.0%) than the parent group (57.7%). The impact of the donor's relation with the patient on the outcomes of HSCT was analysed. Different outcomes had statistical significant impact with the relation of the donor to the patient. The outcome which was analysed included achieving successful engraftment of both neutrophils and platelets, development of mucositis, haemorrhagic cystitis, infections, CMV reactivation, aGVHD, cGVHD, day 100 mortality and long-term OS and DFS. Also, the impact of the donor relation on the fate of graft was analysed. None of the parameters was statistically affected by the donor's relation except the development of aGVHD and CMV reactivation.

## DISCUSSION

Many countries like Pakistan lack the facility of donor registries as high cost of searching for unrelated donors make it practically impossible. In Pakistan, patients who not have MSD, fully matched parents are the alternate donor option for bone marrow transplantation.

Mean age of patients in this study was  $5.90 \pm 3.29$  years. Aydinok *et al.* from Turkey reported mean age at the time of HSCT in patients with BTM was reported as 6.6 years.<sup>9</sup> Mean stem cells dose (CD34 and TNC) in study was  $4.99 \pm 1.13$  and  $5.42 \pm 3.70$ , respectively. Gaziev *et al.* reported a similar dose of stem cells in BTM patients 4.3 and 6.3, respectively.<sup>10</sup> Mean time for neutrophil and platelets engraftment was  $14.88 \pm 4.51$  days, and  $23.0 \pm 5.35$ , respectively. However, Anurathapan *et al.* from Thailand reported mean of neutrophils and platelets engraftment was 14 and 20 days respectively.<sup>11</sup> Infection (94.40%) was the most common immediate post-transplant complication followed by CSA-induced hypertension (85.20%). CMV Reactivation was more common in the parent group and this was statistically significant ( $p=0.01$ ). In contrast, a recent study from Thailand reported mucositis as the most common immediate posttransplant complication followed by VOD. This study did not correlate immediate complications with relation of donor.<sup>12</sup>

Acute GVHD in this study was more common in the sibling group with statistical significance ( $p=0.009$ ). Acute GvHD was more common in the group of female donors to male recipients but this was statistically not significant ( $p=0.1$ ). Chronic GvHD was reported in three cases (5.5%), two were from sibling and one was from the parent group with no statistically significant correlation with donor gender ( $p=0.5$ ). The authors did not find any national or international data that directly compared the outcomes of allogeneic bone marrow transplantation utilising fully matched parents as donors versus matched sibling donors. However, Swaminathan *et al.* from India reported that aGVHD was more common in match unrelated donors (MUD) (60%) than MSD (20%).<sup>13</sup> This was statistically significant ( $p=0.001$ ). Swaminathan *et al.* reported higher incidence of cGVHD in the MUD group than MSD and showed statistically significant relationship ( $p=0.003$ ).<sup>13</sup>

OS was equal in both groups (70.4%). This was not statistically significant ( $p=0.11$ ). DFS in these patients was 60.4%. DFS was superior in MSD (63.0%) than the parent group (57.7%). Caocci *et al.* from Italy reported superior OS (78%) in MSD than unrelated donors (57.6%). DFS was also superior (76.7%) in the MSD group. This was not statistically significant ( $p=0.014$ ).<sup>14</sup> Graft rejection in this study was reported in six patients (11.8%). Graft rejection was higher in the parent group (7.4%) than in the sibling group (3.7%). This was not statistically significant ( $p=0.38$ ). Korula *et al.* reported a high incidence of graft rejection in match related donors (20.8%) than MSD (5.2%) and was statistically significant ( $p=0.027$ ).<sup>15</sup> In this study, total 14 (25.9%) patients died, 8 in the sibling group and 6 in the parent group. Most common cause of death was neutropenic sepsis followed by aGVHD. However, Korula *et al.* reported higher incidence of death in match related donors (20.8%) than MSD (15.8%).<sup>15</sup> The main limitation of the study was small number of patients.

## CONCLUSION

In summary, this research demonstrates that allogeneic bone marrow transplantation with parents as donors in BTM patients yields outcomes comparable to those with matched sibling donors. This finding is especially relevant in regions like Pakistan, where donor registries and high-resolution HLA typing may be limited. In other countries or regions with more advanced transplant infrastructure, the findings may not necessarily apply, and other donor options could be considered.

## ETHICAL APPROVAL:

Ethical approval was obtained from the institutional review board of Armed Forces Bone Marrow Transplantation Centre. (IRB#008/AFBMT/Approval/2021).

## PATIENTS' CONSENT:

Informed consent was obtained from patients to publish the data.

## COMPETING INTEREST:

The authors declared no conflict or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

## AUTHORS' CONTRIBUTION:

AAK: Acquisition, drafting the work, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

NS: Conception and design of the work.

TKA, MF: Revising it critically for important intellectual content.

TG: Analysis and interpretation of data for the work.

H: Final approval of the version to be published.

All authors approved the final version of the manuscript to be published.

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