Outcome of Haematopoietic Stem Cell Transplant in Beta-Thalassaemia Major: Single Centre Experience from a Low- and Middle-Income Country

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ABSTRACT

Objective: To determine the outcome of haematopoietic stem transplant (HSCT) in beta-thalassaemia major (BTM) patients.

Study Design: Descriptive Study.

Place and Duration of the Study: Department of Clinical Haematology, Armed Forces Bone Marrow Transplant Centre (AFBMTC), Rawalpindi, Pakistan, from April 2018 to December 2023.

Methodology: All cases of BTM undergoing HLA-matched allogeneic HSCT after myeloablative conditioning were included. Cases undergoing second HSCT and HSCT with treosulfan-based conditioning were excluded. Age, gender, complications, mortality, and associated factors were evaluated.

Results: This study analysed the data of 118 cases of BTM including 71 (60.2%) males undergoing HSCT after myeloablative conditioning during the study period. The mean age at the time of HSCT was 85.7 ± 33.6 months. Eighty-one (68.6%) cases were in Pesaro Class III. Neutropenic fever was the most common complication documented in 117 (99.2%) cases. Mortality at day-100 was 14 (11.9%). Overall treatment-related mortality (TRM) was 23 (19.4%). In univariate analysis, factors having a statistically significant association with TRM were graft failure ($p = 0.001$), Pesaro class ($p = 0.03$), severity of acute graft *versus* host disease (aGVHD) ($p = 0.02$), and veno-occlusive disease (VOD) ($p = 0.02$). The median follow-up time was 26.87 ± 16.60 months with overall survival (OS) and disease free survival (DFS) rates of 80.5% and 78.0%, respectively.

Conclusion: The OS of around 80% is promising which can be further improved with better transfusion services, regular iron chelation, and HSCT at a younger age.

Key Words: *Haematopoietic stem cell transplant, Beta-thalassaemia major, Pakistan*.

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INTRODUCTION

Among all the haemoglobinopathies, beta-thalassaemia major (BTM) is the most common variety with mutations in the beta-globin gene.[1] Worldwide, approximately 80 million people carry the thalassaemia gene mutation. Around 23,000 children are affected by BTM each year, of which, around 90% belong to nations with low to middle socio-economic status.[2]

In Pakistan, the prevalence of the carrier state of thalassaemia is 5-7%, resulting in a significant population of approximately 10 million carriers. Around the country, there are 50,000 thalassaemia patients registered in treatment facilities, which is one of the highest reported global prevalence rates for transfusion-dependent BTM.[3] In Pakistan, the average life expectancy of BTM patients is approximately 10 years, while life expectancy in developed countries is around 50 to 60 years.[3,4]

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This difference is due to poor quality of transfusion support, transfusion-transmitted infections (TTIs), inadequate iron chelation leading to hepatotoxicity, and cardiac failure.[2,3]

Haematopoietic stem cell transplantation (HSCT) is a globally accepted curative treatment and is preferred over transfusion and iron chelation, promising long life in these patients.[2,5]

The outcome of HSCT in BTM depends on various factors including the recipient's age, stem cell source, Pesaro risk class (hepatic fibrosis, hepatomegaly, and iron chelation), serum ferritin levels, HLA matching, and conditioning regimen.[6,7] In the developed countries, the overall survival (OS) and thalassaemia-free survival (TFS) are around 92% and 90%, respectively.[8]

In Pakistan, there are a few established bone marrow transplant centres performing HSCT for both benign and malignant haematological conditions. Although thalassaemia is the major indication for HSCT in these centres, there is relatively little published data related to transplant outcome. This study aimed to determine the outcome of HSCT in BTM, in the Pakistani population.

METHODOLOGY

This study was conducted retrospectively at the Armed Forces Bone Marrow Transplant Centre (AFBMTC), Pakistan, using data from April 2018 to December 2023. All cases of BTM who were

diagnosed as per standard criteria and undergoing HLA-matched allogeneic HSCT after myeloablative conditioning were included. Cases undergoing second HSCT and HSCT with treosulfan-based conditioning were excluded. The data of cases were extracted from hospital's patient records.

After obtaining approval from the Hospital's Institutional Review Board, written informed consent was taken from the parents of all patients according to the Declaration of Helsinki. Study variables included risk class, the total number of blood transfusions before going for HSCT, source of stem cells, donor characteristics days to neutrophils and platelet engraftment, causes of mortality, post-transplant acute and chronic complications, disease-free survival (DFS) and OS.

A liver biopsy was done in all cases for assessment of hepatic fibrosis and patients were classified as per Pesaro classification.[6] For statistical analysis, cases were also divided into two age groups consisting of the age less than and more than seven years.

A myeloablative conditioning regimen consisting of Cy/Flu/Bu/ATG was used for all cases. Fludarabine was given at 30 mg/m^2/day for four days, from day-16 till day-13. Anti-thymocyte globulin (ATG) was given at 10-15 mg/kg, or thymoglobulin (TG) at 5-7.5 mg/kg, divided into three doses from day-12 to day-10. Busulfan was administered from day-10 to day-7 at a dose of 2 mg/kg every 12 hours for four days. The Busulfan doses was adjusted according to the weight of the patient. (Patients weighing <9 kg; 2 mg/kg, weighing 9 to <16 kg; 2.4 mg/kg, weighing 16 to 23 kg; 2.2 mg/kg, weighing >23 to 34 kg; 1.9 mg/kg, and for patients weighing >34 kg; 1.6 mg/kg), cyclophosphamide; 40 mg/kg/day from day-5 to -2. The doses of ATG and TG were increased to 15 mg/kg and 7.5 mg/kg, respectively in cases undergoing HSCT with a female donor or peripheral blood stem cells (PBSC) as a stem cell source.

Cyclosporine (CSA) in a dose of 3 mg/kg by intravenous route was used twice daily from day-2 and methotrexate in a dose of 10 mg/m^2 IV bolus on day +1 and 8 mg/m^2 on days +3 and +6 was used for graft *versus* host disease (GVHD) prophylaxis. CSA was continued for six months and then tapered over the next three months post-transplant, with a trough level of plasma cyclosporine between 200 and 250 ng/ml.

Neutrophil engraftment was defined as the first of three consecutive days of achieving a sustained absolute neutrophil count (ANC) >0.5 × 10^9/L, while platelet engraftment was defined as independence from platelet transfusion for at least seven days with a platelet count >20 × 10^9/L.[9] Primary graft failure (PGF) was defined as the failure to achieve neutrophil engraftment by day +28 and secondary graft failure (SGF) was defined as persistent neutropenia (ANC <0.5 × 109/L) after initial engraftment.[9,10]

Oral mucositis was graded as per the WHO criteria.[11] Acute GVHD was diagnosed and staged according to the Glucksberg criteria[12] Veno-occlusive disease (VOD) / sinusoidal obstruction syndrome (SOS), was diagnosed according to new EBMT criteria for grading the severity of SOS/VOD in children.[13]

Statistical analysis was performed with SPSS version 25.0 software. Frequencies and percentages were calculated for categorical variables. Median and mean ± SD were calculated for continuous variables. In univariate analysis, Chi-square tests were used to compare the association of TRM with variables. DFS and OS were compared by Kaplan-Meier survival curves using the log-rank test. Multivariate analysis for the prognostic factors with 95% confidence intervals (95% CIs) was performed by the Cox-regression analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

During the study period, 144 cases underwent HSCT at the AFBMTC. Twenty-six cases undergoing second HSCT and treosulfan-based conditioning were excluded. The data of 118 cases including 71 (60.2%) males and 47 (39.8%) females were analysed. The mean age at the time of HSCT was 85.7 ± 33.6 months (range, 32.5-162). Thirty-seven (31.4%) cases were in Pesaro Class II while 81 (68.6%) were in Class III. There was no case in Pesaro Class I. The mean number of blood transfusions was 66.5 ± 32.3, ranging from 10-150. Only 7 (5.9%) cases had regular iron chelation and only 15 (12.7%) cases had less than 1000 ng/ml serum ferritin levels. Most of the stem cell donors were matched siblings, including 57 (48.3%) sisters and 46 (39%) brothers. Eighty-eight (74.6%) donors were thalassaemia traits. Bone marrow was used as the main source of stem cells used in 112 (94.9%) transplant cases. The mean TNC dose was 4.98 × 10^8/kg ± 1.33 and the CD 34+ stem cell dose was 6.35 × 10^8/kg ± 3.67. Neutrophil engraftment and platelet engraftment occurred at a mean of 14 ± 1.53 days and 28 + 13.35 days, respectively (Table I).

Neutropenic fever was the most common complication documented in 117 (99.2%) cases followed by cyclosporine-induced hypertension in 110 (93.2%) cases. Grade 3 and 4 mucositis was recorded in 29 (24.6%) and 4 (3.4%) cases, respectively. Thirteen (11%) had haemorrhagic cystitis. VOD was documented in 34 (28.8%) cases, including 18/34 (52.9%) mild and 16/34 (47.1%) severe VOD cases. Acute GVHD was documented in 41 (34.7%) cases. Most of them 29/41 (70.7%) had grade I (stage-1 Skin) GVHD, 5 cases had grade II, 6 had grade III, and one case had grade IV GVHD. Chronic GVHD was documented in 9/109 (8.2%) cases. Among cGVHD cases, 7/9 (77.7%) cases had limited skin GVHD, and 2/9 (22.2%) cases had extensive gut GVHD. CMV reactivation was occurred in 61 (51.7%) cases, and 47/61 (70%) were treated with oral valganciclovir (Table II). Mortality at day-100 was 14/118 (11.9%) and overall treatment-related mortality (TRM) was 23 (19.4%). Infection was the most common cause of death documented in 16/23 (69.6%) cases. Four (17.4%) cases died of VOD. GVHD and intracranial bleeding lead to mortality in two and one case, respectively. In univariate analysis, factors having a statistically significant association with TRM were graft failure (p = 0.001), pesaro class (p = 0.035), severity of aGVHD (p = 0.02), and VOD (p = 0.025).

The median follow-up time was 26.87 ± 16.60 months with OS and DFS rates of 80.5% and 78.0%, respectively. Pesaro risk

class, VOD, and severity of aGVHD had a statistically significant influence on OS and DFS. The OS was 91.9% in the Pesaro Class II and decreased to 75.3% in the Pesaro Class III group (p = 0.046, Figure 1).

Table I: Clinical and laboratory characteristics of BTM cases (n = 118).

Parameters		n	%
Age	Mean ± SD	85.73±33.59	
	<3 years	5	4.2
	3 to 7 years	54	45.8
	7 to 10 years	39	33.1
	>10 years	20	16.9
Gender	Male	71	60.2
	Female	47	39.8
RCT	<50	50	42.4
	50- to 100	54	45.8
	>100	14	11.9
Iron chelation	Regular	7	5.9
	Irregular	111	94.1
Hepatomegaly	<2cm	40	33.9
	2 to 5cm	72	61
	>5cm	6	5.1
Hepatic fibrosis	Stage 0	26	22
	Stage 1	27	22.9
	Stage 2	32	27.1
	Stage 3	32	27.1
Splenomegaly	0 cm	68	57.6
	<2cm	40	33.9
	2 to 5cm	6	5.1
	>5cm	2	1.7
	Splenectomy	2	1.7
Pesaro class	Class I	0	0
	Class II	37	31.4
	Class III	81	68.6
Serum ferritin	<1000 ng/ml	15	12.7
	1000-2000 ng/ml	50	42.4
	>2000 to 5000 ng/ml	53	44.9
ABO mismatch	No mismatch	77	65.3
	Major mismatch	15	12.7
	Minor mismatch	21	17.8
	Bidirectional mismatch	5	4.2
Donor relation	Brother	46	39
	Sister	57	48.3
	Father	5	4.2
	Mother	10	8.5
Stem cell source	BM	112	94.9
	PBSC	4	3.4
	BM + PBSC	2	1.7

RCT = Red cell transfusion before HSCT.

Table II: Complications in BTM patients (n = 118).

Parameters	n	%
Neutropenic fever	117	99.2
Hypertension	110	93.2
Mucositis	*89*	*75.4*
Grade-1	15	12.7
Grade-2	41	34.7
Grade-3	29	24.6
Grade-4	4	3.4
CMV reactivation	61	51.7
Veno-occlusive disease (VOD)	34	28.8
Mild VOD	18	15.3
Severe VOD	16	13.6
Acute GVHD (aGVHD)	41	34.7
Grade-1	29	24.6
Grade-2	9	7.6
Grade-3	2	1.7
Grade-4	1	0.8
No GVHD	77	65.3
Haemorrhagic cystitis	13	11.0
Grade-1	4	3.4
Grade-2	6	5.1
Grade-3	2	1.7
Grade-4	1	0.8

OS was also adversely affected by the severity of VOD. OS decreased from 85.7% in cases having no VOD to 67.6% in cases with VOD (p = 0.01, Figure 2). The OS was 83.3% in mild VOD and 50% in severe VOD, respectively (p = 0.032). OS was 91.2% in mild aGVHD and decreased to 57.1% in severe aGVHD (p = 0.011, Figure 3). Age at the time of HSCT also influenced the OS. OS was 100% in cases undergoing HSCT before three years of age and reduced to 75% in cases more than 10 years of age, though this difference was not statistically significant. Gender, hepatomegaly, serum ferritin levels, and degree of hepatic fibrosis had no statistically significant affection for OS and DFS (Table III).

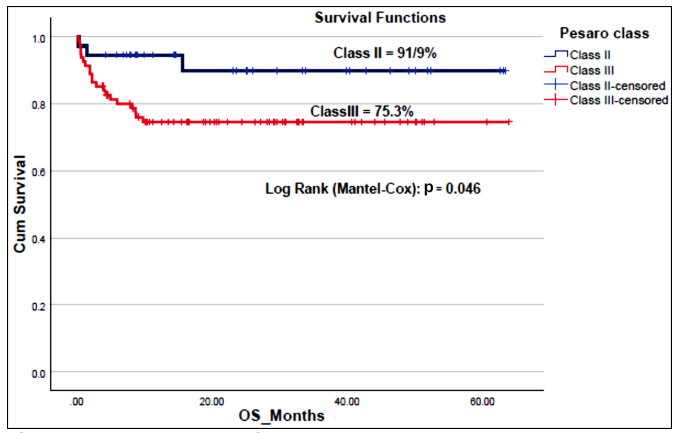

Figure 1: OS as per pesaro class.

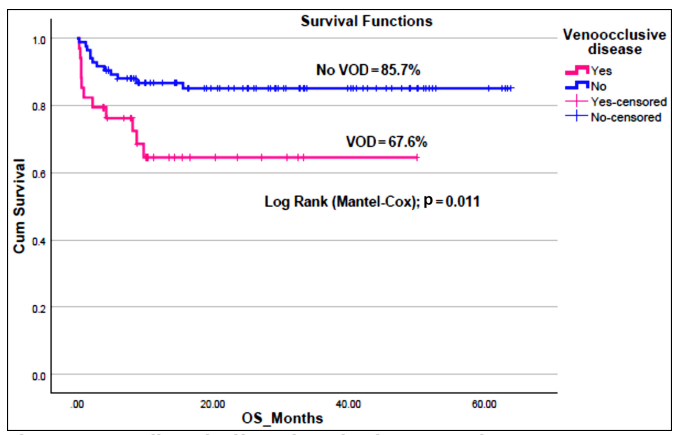

Figure 2: Overall survival in patients having VOD and No VOD.

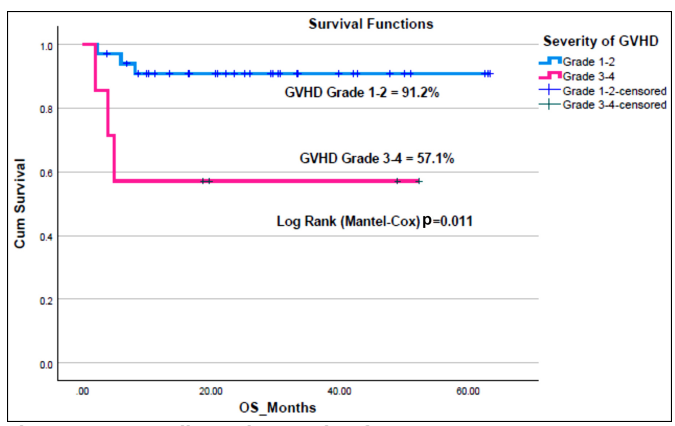

Figure 3: OS according to the severity of GVHD.

Table III: Results of statistical tests of association between OS and DFS study variables in BTM (n = 118).

Variables	OS				DFS			
	Value (%)	95% CI	Log-rank	p-value	Value (%)	95% CI	Log rank	p-value
Age								
<7 years (59)	86.4	48.65-59.90			84.7	46.89-58.64		
>7 years (59)	74.6	41.08-54.95	2.869	0.090	71.2	38.18-52.55	3.215	0.073
Gender								
Male (71)	84.5	48.92-59.46	1.762	0.184	81.7	46.31-57.50	1.338	0.247
Female (47)	74.5	39.77-55.26			72.3	37.86-53.68		
Pesaro risk class								
Class II (37)	91	51.61-63.91	3.971	0.046	89.2	49.02-62.39	3.685	0.055
Class III (81)	75.3	42.78-54.41			72.8	40.48-52.47		
Serum ferritin								
<1000(15)	100		3.684	0.158	100		4.369	0.113
Between 1000-2000(50)	78				76			
>2000 to 5000 (53)	77.4				73.6			
Liver size below the costal margin								
<2 cm (40)	85.0	47.02-60.91	0.869	0.351	82.5	44.83-59.36	4.913	0.086
>2 cm (78)	78.2	44.37-55.91			77.8	43.40-55.40		
Hepatic fibrosis								
Stage <2 (53)	86.8	48.88-60.77	2.164	0.141	84.9	48.88-60.77		
Stage ≥2 (64)	75.0	41.33-54.23			71.9	41.33-54.23	2.164	0.141
VOD								
Yes (34)	67.6%	25.75-41.53			61.8%	22.22-38.40		
No (84)	85.7%	50.46-59.70	6.519	0.011	84.5%	48.98-58.52	8.884	0.003
Severity of VOD								
Mild (18)	83.3%	22.53-33.53	4.60	0.032	83.3%	22.11-33.05	7.59	0.006
Severe (16)	50.0%	13.02-37.13			37.5%	7.69-30.51		
aGVHD								
Yes (41)	85.4%	48.10-61.10			85.4%	47.86-60.61		
No (77)	77.9%	43.63-55.62	1.250	0.264	74.0%	40.41-52.95	2.377	0.123
Severity of aGVHD								
Grade 1-2 (34)	91.2%	52.44-63.82	6.452	0.011	91.2%	51.95-63.32	6.50	0.011
Grade 3-4 (7)	57.1%	13.63-49.39			57.1%	13.08-48.88		

VOD: Venoocclusive disease, aGVHD: Acute graft versus host disease.

DISCUSSION

The major challenges faced in HSCT in thalassaemia are high graft failure and TRM rates. Over the last four decades, attempts have been made to modify conditioning protocols to reduce these complications. Reduction in the dose of cyclophosphamide from 200 mg/kg to 160 to 120 mg/kg reduced TRM but increased the rejection rate up to 30%.[6,14] Reduced toxicity conditioning regimens consisting of treosulfan, fludarabine, and thiotepa (TT) also produced mixed results.[15-17] Incorporation of TT in the conditioning regimen is associated with an increased risk of permanent infertility. In the standard BuCy conditioning protocol, substituting TT with ATG has been reported as safe and effective with expected higher fertility rates.[18]

The AFBMTC is the largest transplant unit in Pakistan performing transplants since 2001 and has performed more than 1,500 transplants. Currently, around 150 HSCTs are performed annually. Over the last two decades, the conditioning protocol for BTM also underwent modifications to arrive at the present protocol. The present cohort of 118 cases presents the largest number of BTM patients treated with HSCT in the country.

In this study, the mean age of HSCT was more than seven years. Older age at HSCT was associated with poor OS. Similar results have been reported by Mathews *et al*. from India and Yesilipek *et al*. from Turkiye.[17,19]

A higher Pesaro risk class is also associated with poor OS and DFS.[6,7,20] The same finding was also documented in the current study. Pesaro Class III was associated with higher TRM, resulting in poor OS. This was mainly due to inadequate blood transfusion, and irregular iron chelation secondary to affordability and availability of parenteral iron chelator.

Thalassaemia is a very high-risk disease for hepatic VOD due to pre-existing hepatic damage caused by iron deposition. In the present study, VOD was documented in more than a quarter of cases and incidence was inversely proportional to Pesaro risk class. VOD was also associated with higher TRM and decreased OS. Lai *et al*. reported a 6.1 to 33% incidence of VOD in thalassaemia patients undergoing BMT and reported no association with OS.[21] Sabloff *et al*. reported an overall incidence of 32% VOD in their study; one-third of patients with risk Class II and 50% of patients with risk Class III developed VOD.[20] In the present study, the high frequency of VOD and VOD-associated TRM was because of pre-existing liver damage caused by iron overload, myeloablative conditioning regimen using Busulfan, and non-availability of defibrotide.

The aGVHD is a common and potentially life-threatening complication following HSCT and has been reported as high as 40%.[22] In the present study, around one-third of cases had aGvHD. However, only 6% of cases had severe GVHD and had no statistically significant impact on OS.

The present study had several limitations. The sample size is not very large, and it is not a randomised study. The authors recommend a larger cohort of patients with longer follow-ups. Most of the cases included in the study had inadequate blood transfusions, irregular iron chelation, higher age group, and Pesaro class associated with higher graft failure and TRM.

CONCLUSION

BTM poses a significant healthcare challenge in developing countries such as Pakistan due to the high costs associated with blood transfusion and iron chelation therapy. HSCT is a promising treatment option for BTM patients, offering the potential for cure and improving long-term outcomes. The promising survival of around 80% can be further improved with better transfusion services, regular iron chelation, and HSCT at a younger age.

ETHICAL APPROVAL:
Ethical approval of the study was obtained from the hospital Institutional Review Board of the Armed Bone Marrow Transplant Centre, Rawalpindi, Pakistan (Reference No: IRB-013/AFBMTC/Approval/2022).

PATIENTS' CONSENT:
Informed consent was obtained from the parents of the patients to be included in the study.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
HK: Conceptualisation and writing of the original draft.
TG: Supervision.
HK, TG: Formal analysis.
HK, TG, NS, TAK, UR, MNA: Data curation.
HK, TG, NS, TAK: Writing, reviewing, and editing.
All authors approved the final version of the manuscript to be published.

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