ISSN 2515-8260 Volume 9, Issue 9, 2022

INFECTIOUS COMPLICATIONS AND OUTCOME AFTER ALLOGENEIC HEMATOPOETIC STEM CELL TRANSPLANTATION FOR THALASSEMIA

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ABSTRACT

Background: Hematopoetic stem cell transplantation (HSCT) is one of the most aggressive treatments for a variety of hematologic malignancies, blood disorders and rare genetic disorders. Infections in HSCT are amongst the major causes of morbidity and mortality in the post-transplant period.

Objectives: To study the characteristics of infectious complications and outcomes in patients after Allogeneic HSCT for thalassemia in a tertiary care centre.

Materials &Methods: This is an ambispective study and all children who underwent HSCT for thalassemia and had infection from 1st January 2017 to 31st July 2022 were included in the study.

Results: Majority of the patients were males (n=65, 68.4%). Of the total 95 recipients, 40 recipients (42.10%) had documented infections after the transplant.19 recipients had bacterial infection, so the bacterial infections account for 47.5% of total infections. Of them gram-negative bacilli infection was present in 10 (52.63%), gram positive cocci infection was encountered in 9patients (47.37%). Total 18 recipients had viral infection; viral infections account for 45% of total infections. majority of them had Cytomegalovirus (CMV) infection (n=12, 66.67%), 4 had

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BK virus infection (22.22%), 1 recipient (5.56%) each had Varicella zoster virus (VZV) and Parvo-virus B19 infection. Three patients (7.5%) were infected by fungal infection.
Of the 40 patients with infection 14 patients died.
Conclusion: Judicious clinical work up, strict asepsis measures and early diagnosis and intervention remain the key to good clinical outcome.
Keywords: Ambispective, Allogeneic, Stem Cell Transplantation, Thalassemia

INTRODUCTION

Thalassemias are the most common human monogenic disorders related to the deficiency of the production of either the α- or β-globin chains [1]. In β-thalassemia, absent or reduced synthesis of the β-globin chain results in ineffective erythropoiesis and peripheral hemolysis. Anemia of the most severe form of the disease, known as β-thalassemia major (β-TM) or transfusion-dependent thalassemia, is treated with lifelong red blood cell transfusions associated with chelation therapy in order to limit chronic complications and premature deaths related to iron overload. β-thalassemia is a larger clinical problem because its homozygous form, thalassemia major, leads to severe morbidity and mortality due to very low endogenous hemoglobin levels which are incompatible with life [2]. Even though educating the society at large, mass screening, cohort counselling and prenatal diagnosis can be applied to very effectively reduce the incidence of β-thalassemia major (β-TM), this has only been achieved in some countries [3]. More than 50,000 children with this disease are born worldwide each year, adding to the disease burden of this condition [4]. Hypertransfusion and iron chelation have been the mainstay of therapy for thalassemia major for nearly 50 years [5]. However, these therapies are often ineffective due to complications related to repeated transfusions and inadequate iron chelation. The need for curative therapy for thalassemia major was addressed with the success of allogeneic hematopoietic stem cell transplantation (alloHSCT),

AlloHSCT remains the only widely available curative therapy for this condition at present. The best results are seen when alloHSCT is offered early, before complications related to iron overload or transfusion-transmitted infections set in, with survival rates of over 90% being reported in these patients [6]. Hematopoietic stem cell transplantation has been successfully performed over the last 30 years [7] with current thalassemia-free survival rates of 80-90% in children transplanted with HLA-matched sibling donor (MSD) before the onset of complications related to their disease or to the supportive treatment [8,9]. However, there are many challenges in offering alloHSCT as a therapy for these patients all over the world [10].

Hematopoietic stem cell transplantation potentially results in a better long-term quality of life than that observed in patients treated with regular transfusion and chelation therapy [11,12].

Despite all the advances in the field of alloHSCT, it does remain to be a procedure with several potential complications, infectious being one of the major ones. The type of transplant influences the risk of infection and graft versus host disease (GVHD) in stem cell recipients. Immediately after transplantation, irrespective of implementation of myeloablative regimen, there is a period of pancytopenia and thus patients are most prone to febrile neutropenia in this phase. This is the

ISSN 2515-8260 Volume 9, Issue 9, 2022

pre-engraftment phase which usually spans from few days to three to four weeks depending on the type of transplant [13].

So, the present study was undertaken to evaluate the characteristics of infectious complications in patients undergoing Allogenic Hematopoietic stem cell transplantation for treatment of thalassemia.

AIM AND OBJECTIVE

1. To study the characteristics of infectious complications in patients after Allogenic HSCT for thalassemia in a tertiary care centre.
2. To analyse and assess the outcome of infectious complications in allogenic HSCT for Thalassemia.

MATERIAL AND METHODS

The current study was an ambispective observational study conducted in a tertiary level care-based hospital, at Mahatma Gandhi Medical College and Hospital Jaipur, in Paediatric Bone Marrow Transplantation Unit. All the children who had infection after allogenic hematopoietic stem cell transplantation were included in the study. The baseline demographic profile (including age, sex) and relevant clinical profile of all included patients was recorded on a pre designed proforma. Pre-transplant serological screening was done for both donors and recipients which included HIV, CMV, HSV-1, HSV-2, hepatitis B virus, hepatitis C virus, by ELISA method.

Biochemical parameters like CBC, CRP, PCT and cultures as blood culture by BD-BACTEC, urine culture and stool culture and radiological findings (CXR, CT chest) were assessed as markers suggestive of infection.

At development of fever at least three blood cultures were taken, one from peripheral vein others from indwelling central venous catheters.

Bacterial infections were confirmed by blood cultures by BD-BACTEC. CMV infections were confirmed in recipients post allogenic HSCT, when there is detectable CMV DNA by PCR. BKV infections were considered clinically significant if BK viruria is noted. Fungal infections were confirmed on the basis of clinical signs and symptoms and radiological (CT Chest) or histopathological signs.

All patients were provided a bacteria-reduced diet. Leuko-depleted and irradiated blood products were used during the posttransplant period.

All clinical and demographic data of recipients were reviewed and recorded for up to >100 days post-transplant.

STATISTICAL ANALYSIS: The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. Descriptive statistics including computation of percentages, median was used.

RESULTS

The present ambispective observational study was conducted in the Department of Paediatrics and Bone Marrow Transplant Unit, Mahatma Gandhi Medical College and Hospital, Jaipur, after approval of the research review board, including 95 patients who underwent Allo-HSCT from 1

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January 2017 to 31st July 2022. and had infection, after considering the inclusion and exclusion criteria. The study protocol for all procedures was approved by the Institutional Review Board for Ethical Clearance of Mahatma Gandhi Medical College and Hospital, Jaipur. All subject's attendants were explained about the study and were asked to sign a written consent prior to commencement of the study. The information regarding each patient was kept confidential and was not revealed at any point of time. Detailed history taking was done from the study group. The clinical profile of all included patients was recorded on a pre designed pro-forma. Biochemical parameters like CBC, CRP, PCT and cultures were assessed as markers suggestive of infection. Majority of the patients were males (n=65, 68.4%). (Table 1) Of the total 95 recipients, 40 recipients (42.10%) had documented infections after the transplant. (Table 2)19 recipients had bacterial infection, so the bacterial infections account for 47.5% of total infections. of them gram-negative bacilli infection was present in 10 (52.63%), gram positive cocci infection was encountered in 9patients (47.37%).

Total 18 recipients had viral infection; viral infections account for 45% of total infections. majority of them had Cytomegalovirus (CMV) infection (n=12, 66.67%), 4 had BK virus infection (22.22%), 1 recipient (5.56%) each had Varicella zoster virus (VZV) and Parvo-virus B19 infection.

Three patients (7.5%) were infected by fungal infection.

Of the total 10 patients with GNB infection, 40% died and 60% achieved sustained donor cell engraftment. 9patients who were infected with GPC of them 55.55% died, 33.33.% achieved sustained donor cell engraftment and one patient had graft rejection (11.11%). Of 4 patients infected with BK infection, 50% died, 25% patients each had achieved sustained donor cell engraftment and Graft rejection. 12 patients who were infected with CMV, of them only 16.67% died and 83.33% achieved sustained donor cell engraftment. One patient each infected with VZV and Parvo-virus B19 had graft rejection. Of three patients infected with fungal infection, 33.33% died and 66.67% patients achieved sustained donor cell engraftment. (Table3).

Table 1: Sex - wise distribution among the recipients

Sex	No.	Percentage (%)
Male	65	68.4
Female	30	31.6
Total	**95**	**100**

Table 2: Infections among recipients after Allo-HSCT

Total patients	Documented infections	%
95	40	42.10

Table 3: Outcome of infectious complications in recipients, after allo-HSCT, according to type of infections

Infection (N=40)	Died		Engrafted		Rejected	
	N=14	%	N=22	%	N=4	%

Bacterial(N=19) 47.5%						
GNB (N=10)	4	40	6	60	0	0
Gram Positive cocci (N=9)	5	55.55	3	33.33	1	11.11
Virus (N=18) 45%						
BKV (N=4)	2	50	1	25	1	25
CMV (N=12)	2	16.67	10	83.33	0	0
VZV (N=1)	0	0	0	0	1	100
Paro-virus B19 (N=1)	0	0	0	0	1	100
Fungal (N=3) 7.5%	1	33.33	2	66.67	0	0

DISCUSSION

During the pre-engraftment phase, bacterial pathogens constituted major causative organisms. The outcome of transplantation is dependent on multiple clinical factors and development of CMV infection and engraftment are few of those important factors responsible for success.[14] The following observations were made in relation to these specific conditions and complications in present study.

Outcome after Allo-HSCT among the study group

Of the 95 patients included in present study, majority of recipients i.e., 62 (65.26%) achieved sustained donor cell engraftment, 20 (21.05%) patients died and Graft failure/rejection occurred in13 (13.68%) patients.

According to study of **Goussetis E et al., (2015)** [15], With a median follow-up period of 10 years, 101 of 105 patients were alive while 96 of 105 were alive without evidence of primary disease. The overall survival and disease-free survival were 95% and90%, respectively. A total of 99 achieved sustained donor cell engraftment, while the median time to neutrophil recovery was 18 days (range 12–40 days), and the median time to platelet recovery was 34 days (range 10–60 days). Graft failure/rejection occurred in5 patients (n = 2 with primary graft failure, n = 3 with secondary graft failure). Four deaths were recorded; 2 of them were attributed to infections.

Bacterial infections among recipients after allogenic HSCT

Out of 95 study cases, total 19 recipients had bacterial infection in present research work, and bacterial infections account for 47.5% of total infections, of them gram negative bacilli infection was present in 10(52.63%) patients, gram positive cocci infection was encountered in 9 patients (47.37%)

In a study done by **Fayard A et al., (2019)** [16] similar observations were seen as around 41% of infections were of bacterial origin and gram-negative bacilli were the most prevalent micro-organism (59.3%).

Viral infections among recipients after allogenic HSCT

In present study, total 18 recipients (18.95%), out of total 95 patients, had viral infection, viral infections account for 45% of total infections. 12 of them (66.67%) had Cytomegalovirus (CMV) infection, 4 (22.22%) had BK virus infection, 1 patient (5.56%) each had Varicella zoster virus

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(VZV) and Parvo-virus B19 infection. In study done by **Goussetis E et al., (2015)** [15], The cumulative incidence of cytomegalovirus (CMV)viremia was 45.7% (95% confidence interval [CI] 33–55%), developing at a median of 48 (range 12–142) days without evidence of over CMV disease. Herpes zoster developed in 8 patients at a median of12 months post-transplant, while 10 patients presented with late onset haemorrhagic cystitis at a median of 35 days post-transplant.

Other infection

Three recipients (7.5%) were infected by fungal infection in present trial.

In a study done by **Slade M et al., (2017)** [17] 6% patients experienced fungal infections.

According to findings of **Goussetis E et al., (2015)** [15], No patient developed probable or definite invasive fungal infection.

Outcome of the Recipients after allogenic HSCT, to type of infections

When the outcome of the patient in present research was assessed according to infection, of 62 recipients who achieved sustained donor cell engraftment, of them 6 (9.68%) patients had GNB infection, 3 (4.84%) patients had GPC infection, 1 (1.61%) patient had BK virus infection, 10 (16.13%) had CMV infection and 2 (3.22%) patients had fungal infection. Of the total 20 patients died, 4 (20%) had GNB infection, 5 (25%) had GPC infection, 2 patients (10%) each had BK virus and CMV infection and 1patient (5%) had fungal infection. And of 13 patients in whom Graft failure/rejection occurred, one patient (7.69%) each had GPC infection, BK virus infection, VZV infection and Paro-virus B19.In present study, of the total 10 recipients with GNB infection, 4 (40%) died and 6 (60%) achieved sustained donor cell engraftment. 9recipients who were infected with GPC of them 5 (55.55%) died, 3 (33.33%) achieve (11.11%) had Graft rejection. Of 4 recipients infected with BK infection, 2 (50%) died, one recipient (25%) each had achieved sustained donor cell engraftment and Graft rejection. 12 recipients who were infected with CMV of them only 2 (16.67%) died and 10 (83.33%) achieved sustained donor cell engraftment. One recipient each infected with VZV and Parvo-virus B19 had graft rejection. Of three recipients infected with fungal infection, 1 (33.33%) died and 2 (66.67%) patients achieved sustained donor cell engraftment. According to study done by **Ullah K et al., (2007)** [18], in 40 patients treated for Thalassemia, Acute GvHD was in 16 subjects, Chronic GvHD in extensive in 2 patients and limited in 3 subjects, VOD in 3 subjects, rejection of graft was encountered in 5 patients, bacterial infection by gram negative bacteria was seen in 10 patients and by gram positive in 8 subjects, 9 subjects had fungal infection, one subject had tuberculosis and CMV in 3 subjects. Total 8 subjects died who were treated for thalassemia, of them one each had Acute GvHD and VOD, 2 had Septicaemia, 3 had CMV and one subject had tuberculosis.

CONCLUSION

ß-Thalassemia major is an inherited hemoglobinopathy associated with defective synthesis of ß-globin subunits, leading to ineffective erythropoiesis and massive haemolysis. In the last 4 decades, the prognosis for affected individuals has improved due to advances both in red cell transfusion management and in the prevention and treatment of complications due to iron overload. HSCT provides the best option for the treatment of β-thalassemia considering the excellent results and high success rate. From present study it can be concluded that 70% (14/20) of the pa-

ISSN 2515-8260 Volume 9, Issue 9, 2022

tient who died after transplant was due to some type of infection, so future work should focus on interventions to reduce infection and improve outcomes in children undergoing transplants in low- and middle-income countries.

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