The Outcomes of Allogenic Bone Marrow Transplantation for B-Thalassemia Major Patients: Single-Centre Experience

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ABSTRACT

Objectives: The primary objective of this study is to assess the outcome of Allogenic Bone Marrow Transplantation for B-Thalassemia Major (B-TM) Patients at KFSHD, also to compare our local results with international outcomes, and to identify the complications of this modality of treatment in our cohort.

Design: This is a retrospective descriptive study. It includes all patients’ less16 year transfusion-dependent, b-TM patients who underwent matched-related donor (MRD) allogeneic stem cell transplantation at KFSHD, pediatric hematology/oncology department between January 2013 and December 2020. Total number of cohort is 21 patients.

Methods: After obtaining the IRB approval, all the data and information were retrieved from the patients’ hard and electronic medical records and then computerized using a Microsoft Excel sheet. Computerized data exported to (SPSS) program updated version 24 (IBM Corp., Armonk, NY, USA) which was used for analysis of the data.

Results: The results of the 21 patients with b-TM who underwent MRD allogenic BMT at KFSHD highlighted the role of MRD/BMT as curative therapy of b-TM with no increase in transplantation-related complications when compared with similar results. In our study, SOS rate was found to be 33.3%, GVHD was 23.8% but non-invasive infections were 76.2%, which is high but not influential. The overall survival (OS) was 90.5% and the disease-free survival (DFS) was 95.2%.

Conclusion: Because of the perfect, promising figures of survival for stem cell transplantation in b-thalassemia major (b-TM) patients during the last decades and the noticeable improvement in the quality of their life after that, and since our study showed similar good comparable outcome and survival rates with other international centers, we strongly recommend early transplantation for b-TM if a suitable donor is available in an experienced BMT center. The overall survival (OS) was 90.5% and the disease-free survival (DFS) was 95.2%, which are comparable outcomes with other international similar centers.

Introduction

Thalassemia is one of the most widely diffused hereditary hemoglobinopathies in the world, and it is related to the deficiency of the production of either the α- or β-globin chains [1]. β-Thalassemia involves a deficient or absent synthesis of the β-globin chains that constitute adult hemoglobin molecules. This genetic defect affects erythropoiesis through the entire process of maturation and proliferation, resulting in ineffective erythropoiesis.
and severe anemia, which could be fatal in the absence of life-long RBC transfusions [2].

A program consisting of sequential red blood cell transfusions along with iron chelation therapy was considered the mainstay of treatment for thalassemia major many decades ago, with the risk of death during the first or second decades if left untreated or partially treated. The available therapeutic approaches for thalassemia nowadays include regular RBC transfusion with iron chelation therapy, gene therapy or HSCT [3].

The first allogeneic hemopoietic stem cell transplantations (HSCT) were performed in patients with thalassemia almost more than 30 years ago [4]. Currently, it remains the only widely available curative therapy for this condition. The best outcome was seen when allogeneic HSCT is offered early before iron overload related or transfusion-transmitted infections complications occurred, with significant survival rates of over 90% being reported in these patients [5].

They found that the outcome of stem cell transplantation varies according to specific risk parameters, and currently, the Pesaro group identified risk groups in children under 16 years and stratified the outcomes using hepatomegaly, liver fibrosis, and inadequate iron chelation as the main risk factors for mortality [6]. The improvement in the understanding of the pathophysiology of iron and its role in organ toxicity, in addition to the environmental factors such as infections, supports the concept of continuous chelation of toxic iron before and after HSCT for best results [7].

In the current study, we evaluated the outcome HSCT as a curative modality of therapy for the B-thalassemia major and assessed the complications associated with these major procedures.

**Methodology**

**Design**

This is a retrospective descriptive study. It includes all BMT patients below sixteen years who were diagnosed as b-TM based on hemoglobin electrophoresis and treated previously with RBC transfusion and iron chelation therapy. These patient who underwent an organ well-being screening programs, received, at least one allogeneic stem cell transplantation from a fully matched related donor as a curative therapy. All patients who had missing clinical data from their soft or hard electronic medical records, with no matched donor were excluded from this study. It is a study of a single institute at King Fahd specialist hospital in Dammam, pediatric hematology/oncology, and SCT department between January 2013 and December 2020.

**Setting**

It is a single-center study at King Fahad Specialist Hospital in Dammam, which is 400 beds tertiary referral hospital with 27 beds in the pediatric oncology Ward, four beds for stem cell transplantation, and 18 beds in the daycare unit.

After obtaining the IRB approval, all the data and information were retrieved from the patients’ hard and electronic medical records and then computerized using a Microsoft Excel sheet. Computerized data exported to (SPSS) program updated version 24 (IBM Corp., Armonk, NY, USA). Frequency tables were drawn to explore the findings (frequencies, percentages, grade/stage… etc). Overall survival and disease-free survival were illustrated by the Kaplan-Meier curves.

**Results**

All the patients were referred from local secondary hospitals to our Centre, KFSHD, BMT service, between 2013 and 2020 as cases of B-thalassemia major and transfusion-dependent for stem cell transplantation. During the study period, 21 patients with b-thalassemia major transfusion dependent were eligible; the majority were female, 16 (76.2%), and 5 (23.8%) were males. The median age for transplants was 5.4 years range (1-11) years.

Fifteen patients (71.4%) were transplanted before the age of 7 years, and six patients (28.6%) were transplanted after the age of 7 years. Concerning iron burden before the transplantation period, patients' ferritin levels were routinely assessed. Nine of the patients (42.9%) had their ferritin levels below 1000 ng/ml, and 12 (57.1%) had the ferritin levels > 1000ng/ml. In all patients, the ferritin level ranged from 156 to 4462 ng/ml; only one patient had a level of 4462 ng/ml just shortly before the transplant.

MR imaging is a valuable and fast non-invasive diagnostic tool for evaluating iron overload in patients, but unfortunately, this diagnostic modality wasn’t done in any patient because of the unavailability of the necessary software. As in many other treatment centres, deferoxamine infusion was also used to treat chronic iron overload and high ferritin levels in 14 patients (66.7%) before BMT.

Pesaro's classification in 3 patients (14.3%) was found to be class 3 based on the data that indicated the presence of fibrosis grade 3-4 in liver biopsies done in those 3 patients; another three patients (14.3%) were found to fit with class 2 Pesaro's, while the rest 15 (71.4 %) were class 1. Viral screening before the HSCT, revealed only 3 (14.3%) patients with CMV positive, and no EBV positive cases in our cohort.

All the other associated morbidities were studied carefully during the evaluation for BMT. We found that only one patient (4.8%) was diagnosed with mild Congestive heart failure in the pre-transplant workup and was transplanted smoothly without complication and discharged from our clinic at the age of 18 years in good health status.

No Endocrinopathies issues were reported in the patients at pre-transplant assessment. Most of our patients were on chronic transfusion programs before HSCT; monthly transfusions were ranging from 3 to 132 months, starting from the time of diagnosis until the time of transplant. Alloimmunizations were reported in 2 (9.5%) of the patients; one of them started on azathioprine and the other one was refractory, so his challenging issue was resolved with splenectomy.
Studying the features of the stem cell donors for the patients, all of them were HLA fully matched donors (100%), hence, no haploidentical donors. The stem cell source was the bone marrow with no peripheral blood used in any of our patients. Four of the donors (19%) were thalassemia traits, and 13 (61.9%) of them were CMV+. Three of them (14.3%) were donors for CMV +ve recipients, CMV infection occurred in 1 recipient (4.8%) who was CMV –ve and received his graft from a CMV+ donor. The rest of the patient who got CMV reactivation were originally CMV + (14.3%).

Concerning the conditioning regimens, a myeloablative regimen (MAC) was used in all of them, with 4 (19%) patients received Bu/Cy/Flu, and 17 (81%) received ATG instead of fludarabine. The variations in the conditioning regimens were based on patient clinical condition. Most patients were infused with good doses of CD34 except one. The median of doses were 5.98×10^6 (1.5×10^6 -14×10^6). The median time to neutrophil engraftment was +18.3 days (12-28); however, the most prolonged engraftment period was reported in one patient, at day +28.

Graft failure (GF) happened in only one patient (4.8%) with transient engraftment for a few days only. Total chimerism of this patient on day + 30 was 100% recipient cells. We postulated the cause of GF in this patient to a relatively small dose of CD 34 (1.5×10^6/kg).

Chimerism was done by STR (days +30, +100, +180, +365). Day +30 chimerasms showed complete donor cells in 20 (95.3%) of patients. Only one (4.7%) showed 100% recipient cell, which indicated GF, this patient received the smallest dose among the cohort.

On day +100, chimerism testing were done for only 19, two were excluding because of GF in one and death, before day +100 in the other one. The results showed three patients (15.8%) had mixed chimerism and the rest (84.2%) had complete donor cells.

Day +180 chimerism studies were done for only 18 patients (after excluding the graft failure and the 2 patients who passed away). A total of 4 (22.2%) patients showed mixed chimerism and continued to have stable mixed chimerism after 2 years of follow up. All mixed chimerism patients continued to be transfusion-independent, and chimerism studies were performed more frequent for them.

Day +365 showed the same result as day +180. Patients whoever had mixed chimerism, continued to be mixed chimerism with good hemoglobin levels.

As part of the supportive care, our Centre adopted GVHD prophylaxis regimens using cyclosporine (CSA) & 4 doses of methotrexate (MTX) after SCT infusion (+1, +3, +6, +11). Day + 11 MTX doses were omitted in most of the patients because of severe mucositis. CSA level was monitored closely, aiming at 200-300 ng/dl serum levels. The median time to stop immunosuppressive therapy was about 12 months post-stem cell infusion in all patients who did not develop GVHD. All patients received antimicrobial prophylaxis for Pneumocystis Jiroveci and Herpes simplex. As part of SOS prophylaxis and considering of availability of defibrotide (defi), defi was only started for two patients (9.5%) as prophylaxis, one with class 3 Pesaro. One patient had continued to receive defi. until SOS, which developed later had resolved; the other patient who have a high ferritin level (4462 ng/ml) and that had received defi. as prophylaxis, 6.25/k/dose q 6 hr from day -9 till +20 after engraftment; the later did have SOS. GCSF was started for all patients at times ranging from day +1 till +14, the majority were started after day +6.

Regarding the post-transplant complications, SOS was developed in 7 (33.3%) patients diagnosed based on modified Seattle criteria, 4 (19%) had mild disease and treated conservatively with fluid restriction and diuretics. One was moderate (4.8%) SOS, and 2 (9.5 %) were classified as severe diseases, one was treated with defibrotide and the other one didn’t because of unavailability of the drug. In the absence of defibrotide patients were treated with supportive measures plus steroids.

Table 1: Respondents’ frequencies and percentages of GVHD

<table>
<thead>
<tr>
<th>Site</th>
<th>Grade</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver-GVHD</td>
<td>None</td>
<td>21</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Grade I</td>
<td>2</td>
<td>9.5%</td>
</tr>
<tr>
<td>Skin-GVHD</td>
<td>Grade II</td>
<td>1</td>
<td>4.8%</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>18</td>
<td>85.7%</td>
</tr>
<tr>
<td>GIT-GVHD</td>
<td>Grade II</td>
<td>2</td>
<td>9.5%</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>19</td>
<td>90.5%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>21</td>
<td>100%</td>
</tr>
</tbody>
</table>

GVHD is a known complication post-HSCT. In our study, (23.8%) patients developed GVHD (19% aGVHD, 4.7% cGVHD). Two (9.5%) of aGVHD had grade 1-2 (skin and gut) one who developed posterior reversible encephalopathy syndrome (PRES) was shifted from CSA to tacrolimus and systemic steroids. Three (14.3%) of patients who had stage 1-2 skin aGVHD, were treated with local hydrocortisone for stage 1 and local tacrolimus and systemic methyl-prednisone for stage 2. Chronic skin GVHD in one patient was controlled well with systemic prednisone and oral CSA. No liver GVHD occurred in our study, (Table 1).

On the other side, the infection rate was high in our study population, occurring in a total of 16 (76.2%). Seven (33.3%) of them developed a viral infection. Four (19%) had CMV viremia based on PCR testing done post transplantation. Two (9.5%) of the patient had EBV viremia although they had negative EBV status before transplant and their donors were also negative based on serology testing. One patient (4.7%) developed symptomatic HSV gingivostomatitis although he was on acyclovir prophylaxis.

Bacterial infection was less common than viral; six patients were infected (28.6%) with different bacterial species. Three (14.3%) patients had gram-positive, 2 (9.4%) had gram-negative and one (4.8%) had both gram-positive and negative bacteremia.
One patient (4.7%) had non-invasive fungal infection, and two patients (9.5%) had a protozoal disease (cryptosporidium) which was confirmed by GI biopsy (Table 2).

All of the infected patients were treated appropriately in a multidisciplinary fashion. All patients were cured except one patient who died from extensive cryptosporidium infection shortly after stem cell infusion. Although this patient was treated with nitazoxanide like the other patient, she got many other systemic complications such as lung involvement and pulmonary hemorrhage.

Regarding the post-BMT endocrinopathies, one patient (4.8%) developed premature ovarian failure and hypothyroidism diagnosed at the long-term follow-up clinic.

Another patient (4.8%) developed hemorrhagic cystitis within ten days from stem cell infusion time and was treated with hydration and aggressive blood products supportive transfusion till it resolved ultimately after three months. TA-MHA was diagnosed in one case (4.8%) who shifted to tacrolimus and did need plasma exchange. She fully recovered later without any long term squally.

The median follow-up duration was 48 months, and the disease-free survival (DFS) was 95.2%. Twenty (95.2%) patients were free from primary disease after the transplant. Only 1 (4.8%) patient developed graft failure and had undergone a second BMT after conditioning with a small dose of fludarabine and ATG on day 47 post-first infusion using the same donor as the source of stem cell. Unfortunately, this attempt had failed too, and the patient was referred to another center for 3rd transplant, (KM1).

The overall survival (OS) was 90.5%. We had 9.5% treatment-related mortality (TRM) as two patients had died during the BMT course, the first died due to severe cryptosporidium infection that is unresponsive to treatment followed by severe gastrointestinal and pulmonary hemorrhage on day +52, and the second patient died after 4 months post-transplant due to pulmonary hypertension following a long course of fungal infection and prolonged intubation, (KM 2).

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Item</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral-Infection</td>
<td>None</td>
<td>14</td>
<td>66.7%</td>
</tr>
<tr>
<td></td>
<td>CMV</td>
<td>4</td>
<td>19.0%</td>
</tr>
<tr>
<td></td>
<td>EBV</td>
<td>2</td>
<td>9.5%</td>
</tr>
<tr>
<td></td>
<td>Herpes</td>
<td>1</td>
<td>4.8%</td>
</tr>
<tr>
<td>Bacterial-Infection</td>
<td>Gram +ve</td>
<td>15</td>
<td>71.4%</td>
</tr>
<tr>
<td></td>
<td>Gram -ve</td>
<td>3</td>
<td>14.3%</td>
</tr>
<tr>
<td></td>
<td>Bothe (Gram +ve &amp; Gram -ve)</td>
<td>2</td>
<td>9.5%</td>
</tr>
<tr>
<td>Fungal-Infection</td>
<td>None</td>
<td>20</td>
<td>95.2%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
<td>4.8%</td>
</tr>
<tr>
<td>Protozoal-Infection</td>
<td>None</td>
<td>19</td>
<td>90.5%</td>
</tr>
<tr>
<td></td>
<td>Cryptosporidium</td>
<td>2</td>
<td>9.5%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>21</td>
<td>100%</td>
</tr>
</tbody>
</table>

Figure 1: Kaplan-Meier 1, Disease-free survival.

Figure 2: Kaplan-Meier 2, Overall survival.

Discussion

Allogeneic SCT is the only treatment modality that offers a potential cure for patients with B-thalassemia major. Age is known to have an essential role in the outcomes. Statistically significant differences were reported in OS and EFS in different age groups; the threshold age for optimal transplant outcomes was around 14 years, with an outstanding OS of ≥ 90% (range 90–96%) and EFS of ≥ 83% (range 83–93%) in all age groups under this threshold. In addition, they continued to have good outcomes [8]. However, in the current study, we did not find any impact of the age factor on the outcome as all the patients were below 14 years of age.

More recently, clinical status, rather than age, is the most crucial predictor of transplant outcome [9]. A few decades back, the criteria for risk stratification were not very well defined for patients of B-thalassemia major until 1998, when G Lucarelli et al. identified the Pesaro classification that works as a sensitive and effective tool in adjusting the risk stratification parameters, helps in tailoring the therapy, and predicts the clinical outcomes.

Pesaro classification classifies the patients into three risk groups (Pesaro Class I, II, and III) based on the liver size (>2 cm), the presence of liver fibrosis, and inadequate iron chelation [10,11]. Patients with none of the above risk factors are classified as Class I, those with one or two of these are Class II and those with all three adverse risk factors are classified as Class III.
In a study by Emanuele et al., for survival outcomes for the different Pesaro groups, the overall survival and thalassemia-free survivals were 94% and 87%, 84% and 81%, and 50% and 47% in Class 1, 2, and 3, respectively.

Patients in Class I and II are low risk and have an excellent long-term outcome following an allogeneic SCT [10,11]. Similar results were obtained from our class 1 Pesaro, which was 15 patients with 100% OS; however, for our class II Pesaro cases, we got one mortality out of the three patients belonging to this class, the death was due to pulmonary hypertension on day +126. Class III patients, on the other hand, are considered high risk and have inferior outcomes following an SCT. In the current data, our class 3 patients had 33% mortality with OS of 67%, but the thalassemia-free survivals were 66.7%, which is better than the above-mentioned figures in the Emanuele study [12].

Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections are widely distributed throughout the world. With prevalence range from 60% to 100% of the global population. These viruses can remain latent in the host cells and be reactivated when the host immune system is compromised. CMV and EBV infections are also common causes of complications in patients with hematological malignancies and one of the major limiting factors in the successful treatment of patients [13].

Hence, most of the stem cell transplantation protocols adopted the policy for pre-BMT screening for these two viruses by monitoring their activities and reactivations during the transplantation process by performing routine diagnostic polymerase chain reaction (PCR) assays of serum or plasma samples. Preemptive therapy with ganciclovir or Foscarnet (depending on ANC counts and engraftment status) was initiated when CMV reactivation was detected. Patients with a viral load >1000 copies/mL were preemptively treated as described above [14].

Fortunately, for all 4 cases who had high CMV titer during the transplant course and received directed therapy as per hospital policy guidelines, all of them recovered completely without any further systemic complications or impact on the engraftment processes. On the other hand, we had two patients who were originally EBV -ve at pre-BMT screening workup, and their donors were also negative; they acquired EBV viremia during their course of transplant, necessitating starting them on rituximab with a good outcome.

Cidofovir was used when adenovirus or BK virus was detected in blood with clinical symptoms of hemorrhagic cystitis (HC). Fortunately, none of our patients developed HC (Secondary to adenovirus or BK virus infection). Primary graft failure is defined as a lack of neutrophil engraftment (ANC<0.5x10^9/L) measured for three consecutive days by 28 days post-transplant with cytopenia and a hypocellular marrow (aplasia) or count recovery with transfusion dependence (autologous recovery). Secondary graft rejection was defined when initial engraftment was followed by the subsequent development of ANC<0.5x10^9/L for three consecutive measurements and pancytopenia with a hypocellular marrow or recurrence of transfusion dependence [15].

In our study, we had 4.8% primary graft failure probably explained by a small-infused stem cell dose since the child donor donated for two siblings with thalassemia major, and the collection was only done once at the beginning for both patients. Unfortunately, this patient had 2nd transplant that also failed with primary graft failure despite sufficient cell dose infused from the same donor in the 2nd transplant. Subsequently, we referred this patient to another national institution to consider 3rd attempt for transplant with no further data on the progress of her condition.

The Pesaro experience has shown that a significant group of patients (11% of the entire Pesaro experience) develop long-term, stable-mixed chimerism after transplantation [15]. This has been confirmed by other groups [16]. Mixed chimeric patients, despite a limited (even 20%) engraftment, achieve a functioning graft status characterized by average hemoglobin level, no red blood cell transfusion requirement, and no iron increment [17]. Thus, in mixed chimeric patients, the genetic disease is under substantially complete clinical control without achieving complete eradication of the thalassemic hemopoietic clones [19]. In another study, up to 30% of patients who had early mixed chimerism (within 60 days of transplantation) will go on to reject the graft [20].

In this study, four patients had stable mixed chimerism and continued to be transfusion-independent. The lowest chimeric study in our population was 16% total donor cells. Sinusoidal obstruction syndrome (SOS) (previously known as a veno-occlusive disease) incidence ranges from 5% to 40% in HSCT setting. The cause of hepatic SOS is not entirely clear, but several risk factors have been reported in the literature [21], including thalassemia major, a history of previous liver disease, hepatitis C virus (HCV) infection, conditioning regimen with Busulfan (Bu), and cyclophosphamide (Cy) and the use of methotrexate (MTX) and cyclosporine (CSA) as graft-versus-host disease (GvHD) prophylaxis [22].

Cappelli et al. mentioned that oral defibrotide prophylaxis could safely reduce the SOS incidence in pediatric thalassemia HSCT recipients [22]. Among the 58 patients that had been included in his study, none of them developed SOS.

In a similar national study from RIYADH by M Essa et al. addressing the SOS among B-thalassemia majors who underwent BMT, the risk of SOS was almost double when compared between the two groups of patients who had been given prophylactic defibrotide vs not, which was about 1/8 12.5% in the group with prophylaxis therapy vs. 28.5% (2/7) in the group who did not receive prophylactic defibrotide [23].

Comparatively, our current study showed a higher incidence of SOS reaching 33.3%. A possible explanation for our high incidence is that defibrotide was not started as prophylaxis in majority of cases due to non-availability issues in our transplant center. In addition to the pre-existing liver damage caused by iron
overload, 28.6% of our cases were classified as Pesaro 2-3 groups.

Acute GVHD (aGVHD) remains a major challenge in allogeneic stem cell transplantation and is associated with significant morbidity. In a study from India by Biju George et al. [24] out of 321 patients who underwent allogeneic HSCT for thalassemia, acute GVHD (Grade I – IV) occurred in 125 patients (38.9%), grade II-IV in 28%, and grade IV in 5.3% and they concluded that acute GVHD is seen in 39% of patients undergoing SCT for thalassemia major but it does not have a significant impact on overall survival.

In another study, they reported that the incidence of grade II-IV acute and chronic graft versus host disease (GvHD) was 23.6% and 12.9% respectively [24]. Our data showed a very similar incidence of acute GVHD, at a rate of 23.8%. All had stage I- II skin and II gut none had liver aGVHD. All of these GVHD events had resolved completely with a standard approach. Children undergoing stem cell transplantation are at risk of developing infectious complications, which peri-engraftment and extends to several months after SCT.

One study addressing that issue found a high rate of definite infections after engraftment to be about 1.7-fold higher in marrow recipients (P = .001).

While the rate of severe infections required to be treated in the inpatient section was 2.4-fold higher in that group (P = .002), the most significant infection rate was for fungal infections, intermediate for bacterial infections, and the lowest for viral infections. Some mortalities were reported to be associated with severe fungal or bacterial infections and could happen between day 30 and day 365 after transplantation [14].

Mentioning that previous study, our data in comparison showed that the highest risk for infection was viral, followed by bacterial infections, and the lowest was for fungal infection, with an overall incidence of infection rate was about three-quarters of our study population. Many centers adopted different strategies to minimize the risk of infection. Using preemptive and prophylactic antimicrobial therapies plus administration of GCSF and immunoglobulin infusions during severe neutropenia was very effective in reducing the infection rate. We thought that the management approach might have a tremendous positive impact on infection prevention. This is probably behind our patients' relatively low bacterial and fungal infections.

In a Turkish experience reported by M. Akif Yesilipek et al., the 5-year overall survival (OS) and the thalassemia-free survival (TFS) rates were 92.3% and 82.1%, respectively [25]. Similar comparable data was reported by the European group as the outcome for threshold age for optimal transplant outcomes was around 14 years, with an OS of 90-96% and an EFS of 83-93% when transplants were performed before this age [26]. Interestingly, our study showed exactly a similar survival rate with the overall survival (OS) being 90.5% and DFS 95.2%. Early transplant-related mortality (TRM) was typically reported to range from 5% to 20% [27]. Again, our data showed about 9.5 % TRM which is going along with what is reported in the literature.

The improvement in the outcome of BM transplantation in patients with beta-thalassemia major during the last decades was due to many factors, including better disease knowledge, the provision of optimum supportive care, and adjustment of conditioning regimens to obtain the best outcome with fewer side effects.

Our study had a few limitations. Firstly, this study has a small sample size and was conducted at a single center in Saudi Arabia. Secondly, the retrospective nature of the study. And lastly, the short duration of follow-up.

**Conclusion**

To date, hematopoietic stem cell transplantation remains the only available curative treatment for hemoglobinopathies. The allogeneic HSCT provides the definitive solution to the serious, long-term complications of severe B-Thalassemia major.

The increased prevalence of thalassemia syndrome in the Arabian Gulf area necessitates more regional research work through multi-centered prospective studies, if possible, to estimate the magnitude of this health problem and its impact on the community.

Great efforts of the health care providers should be directed to improve the screening measures, diagnostic tools, and early planning for the management of β-thalassemia by enrolling the patients in a Thalassemia Center of Excellence to ensure maximum service and to prevent disease complications. Because of the perfect, promising figures of survival for stem cell transplantation in thalassemia major (TM) patients during the last decades and the noticeable improvement in the quality of their life after that, and since our study showed smaller good comparable outcome and survival rate to other international centers so we strongly recommend early transplantation for TM if a suitable donor is available in an experienced BMT center.

Nowadays, trials in gene therapy have shown significant success and could provide an alternative to a cure. Yet, it needs to demonstrate at least equivalent results in terms of safety and cost/benefit ratio with HSCT before being adopted globally as a treatment modality for B-thalassemia major.

**References**

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