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Allogeneic Stem Cell Transplantation in the Treatment for Transfusion-Dependent Thalassemia: Centre Experience

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Abstract

BACKGROUND: Allogeneic stem cell transplantation (allo SCT) is still the only curative option for transfusion depended on β-thalassemia major (TDT). In patients with good risk features it is reasonable to anticipate a greater than 90% chance of a successful transplant outcome. With better risk stratification and supportive care, the results of allo-SCT have been improved even in high risk patients who have significant iron overload related organ dysfunction. Choosing the optimal conditioning regimen before allo SCT, stem cell source and focusing on transfusion free survival, as well as graft versus host disease (GVHD) free survival is a challenge in providing the quality of life in the post-transplant period for this indication. The aim of this article is to present first experience in the treatment of TDT with allo SCT from matched related donor (MRD).

CASE PRESENTATION: We present a case of male patient diagnosed as thalassemia major (TM) at the age of 15 years referred at University Clinic for pediatric disease in Skopje, Republic of North Macedonia for treatment with allogeneic stem cell transplantation (allo SCT) from matched related family donor (MRD). Patients experienced two allo SCT due to early graft rejection after the first transplantation. The conditioning was done with MAC regimens, busulfan based for the first transplant and treosulfan based for the second transplant.

CONCLUSION: Disease severity and the age of the patient has a crucial impact on transplant related mortality (TRM), event free survival (EFS) and the incidence of veno-oclusive liver disease as one of the main complications during SCT. More data is required on the etiology of frequent graft rejection in TDT studying the aspects of the graft and subsequent immune reconstitution that can improve the outcome of allo HSCT for thalassemia major.

Introduction

Allogeneic stem cell transplantation (allo SCT) from matched related family donors (MRD) is currently considered the only curative standard therapeutic approach for transfusion-dependent thalassemia (TDT), despite recent advantages with the approval of gene therapy for the treatment of this disease [1].

Unrelated donor transplants, cord blood and haplo-identical transplants provide new horizons in increasing the donor pool for this indication, since TDT patients are considered to have rare unique genotypes. Choosing the optimal conditioning regimen before allo SCT, stem cell source and focusing on transfusion free survival, as well as graft versus host disease (GVHD) free survival is a challenge in providing the quality of life in the post-transplant period for this indication [2].

Survival outcomes in pediatric patients with an HLA MSD decrease with age. Survival rates for children <14 years old (2-year overall survival (OS) of 90%–96% and thalassemia free survival -TFS of 83%–93%) were higher than those for adolescents (2-year OS of 82% and TFS of 74%) and adults (2-year OS of 80% and TFS of 76%) [3].

There is limited experience of allo-HSCT in adult patients, as very few centers perform allo-HSCT in patients over the age of 18 years, and transplant-related mortality (TRM) has persistently remained around 25% [4].

The aim of this article is to present first experience in the treatment of TDT with allo SCT from matched related donor (MRD).

Clinical history

We present a case of male patient diagnosed as thalassemia major (TM) at the age of 15 years at University Clinic for pediatric disease in Skopje, Republic of North Macedonia. The patient showed signs and symptoms within the first two years of life and since then was treated with frequent blood transfusions, every 3-4 weeks and chelation therapy with deferoxaamine and later with deferasirox that was irregularly provided. Due to splenomegaly and increased need for transfusions, the patient was referred to splenectomy at the age of 8 years. Blood transfusions were provided with leucoreduced packed red blood cells with a minimum hemoglobin content of 40g and mainly indicated with the level of Hb < 7g/dl according to the recommendations of the Council of Europe [5]. The genetic analysis revealed both his parent's carriers (heterozygotes) for β-beta thalassemia, and his sister 19 years of age was HLA DNA identical donor 10/10.

Patient referred at BMT unit at University Clinic for hematology, Skopje during December 2019 for treatment with allogeneic SCT from HLA DNA identical sibling.

Pretransplant analysis of the donor are presented on Table 1.

Table 1: Patient, graft and donor characteristics during MRD transplant for TDT

Parameter	Value
Disease status before transplant	***TDT***
Patient Body weight (kg)	68
HPC Apheresis (ml)	312
Number of apheresis procedures	1
CD34+cells/kg	5,1x10^6/kg
Bone Marrow	1
MNCx10^8/kg	800
Engraftment (day)	4,4
WBC>1.0×10^9/L	
Plt>20×10^9/L	+12
Transfusion policy	+13
Er transfusions -units (filtered and irradiated)	
Plt concentrates	
Donor characteristics	8
Matched related	53 doses
CMV IgG	
CMV IgM	10/10
Blood Type	positive
Donor	negative
Patient	
Conditioning	B Rh (+)
MAC conditioning	B Rh (+)
Immunosupression	Thiotepa/treo/flu/rATG Cyclosporine/MMF

TDT-transfusion dependent thalassemia, MMF-mycofenolate mofetil, CMV-cytomegalovirus, WBC-white blood cells, Plt-platlets, MNC-mononuclear cells, HPC-hematopoietic cells.

A liver biopsy was done before transplant to evaluate the level of hemosiderosis in the liver. Histology confirmed parenchymal liver degeneration with low grade hemosiderosis. Magnetic resonance (MR) with T2 sequence of hearth and liver showed 0.598 mg/g iron in the myocardium and 2,404 mg/g iron in the liver which was evaluated as mild iron overload. Heart ultrasonography showed ejection fraction rate (EFR) 56% with mild mitral regurgitation (MR). The patient was classified as Pesaro class II/III before MRD transplant. Virology analysis before transplant revealed: HIV ½ negative, HbsAg negative, anti HbsAb positive, antiHBcAb negative, anti HCV Ab negative, CMV IgM negative, CMV IgG positive, EBV IgM negative, EBV IgG positive, Toxoplasmosis IgM negative, Toxoplasmosis IgG positive. Laboratory analysis revealed Hb 136 g/dL, WBC 10x10^9/L, Plt 507x10^9/L, iron 73umol/L, ferritin 1370 ng/ml, total bilirubin 95 μmol/L, indirect bilirubin 70 μmol/L, direct bilirubin 25 μmol/L, CRP 0,2 mg/L, AST 20 U/L, ALT 15 U/L, AP 283 U/L, LDH 430 U/L.

Patient received conditioning according to Pessaro class II for TM shown on Table 2.

A bone marrow was used as stem cell source harvested from his HLA DNA identical sister in the amount of 800ml WBC 40x10^9/L and MNC 4.4x10^8/kg. Immunosuppression was provided with cyclosporine and MTX (days +1, +3,+6 and +11). Engraftment was detected on day + 15 with Hgb 100g/dL, WBC 3.3 x10^9/L, Plt 300. On day +40 post-transplant chimerism analysis were performed and the patient had 14% donor DNA in bone marrow. Immunosuppression was discontinued 60 days posttransplant. We registered complete graft rejection at +4 months after MRD transplant. Patient became transfusion dependent.

A second MRD transplant with the same donor of SC was planned 12 months after previous conditioning during May 2022. Autologous stem cell rescue with cryopreserved PBSC previously primed with G-CSF were provided before conditioning for the second transplant. (3x10^6/kg CD34+cells).

The second sibling transplant was conditioned with fludarabine 30 mg/m^2 days -6 to -2, treosulfan 14 g/m^2 days -5 to -3, thiotepa 5 mg/kg days -6 and ATG (Thymoglobulin) 7.5 mg/kg days -3 to-1. Donor was primed with granulocyte colony stimulating factor (G-CSF) and peripheral blood stem cells (PBSC) were collected in Apheresis Cobe Spectra system in one procedure in the total amount of 312 ml with 5,1x106/kg CD34+ cells. GvHD prophylaxis was provided with ciclosporin and MMF (Fig. 1).

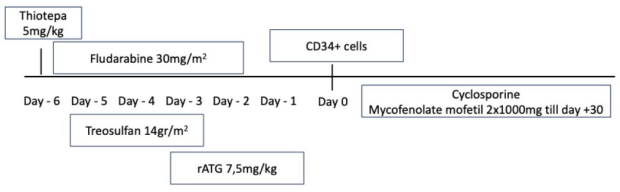

Figure 1: Conditioning for the second MRD transplant

Patient engrafted on day + 13 with Hgb 97g/dL, WBC 3,9 x10^9/L, Plt 59x10^9/L (Fig 2). Patient was on immunosuppression with cyclosporine until +11 months posttransplant. His chimerism analysis showed complete chimerism of 95% donor DNA in bone

marrow at +1, +3, +6, +12 months post second MRD transplant. At +12 months post-second transplant he continued immunization for transplant recipients.

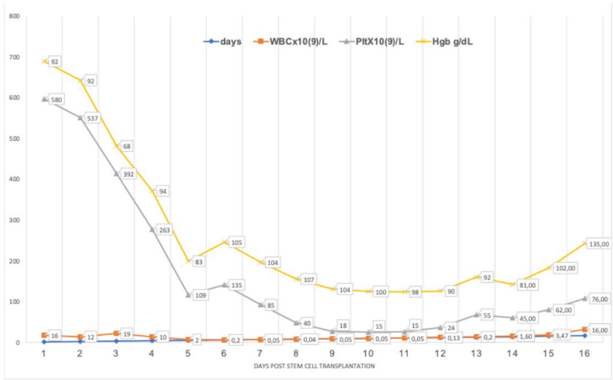

Figure 2: Engraftment after second MRD transplant

His last checkup was made during September 2024, +27 months after second transplant, with laboratory analysis Hb 149g/dL, WBC 9,3x10^9/L, Plt 335x10^9/L, ferritin 17 ng/ml free of drugs and immunosuppression with good quality of life.

Table 2: Conditioning regimen for matched related donor (MRD) transplant for TDT

Drug	dose	Days of conditioning regimen																														
		-45	...	-16	-15	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12
Hydroxyurea	27-30 mg/kg/day	+	+	+	+	+	+	+	+																							
Azathioprine	2,7-3 mg/kg/day	+	+	+	+	+	+	+	+																							
Fludarabine	30 mg/m^2/day				+	+	+	+	+																							
Busulfan IV	3,2 mg/kg/day									+	+	+	+																			
Thiotepa	10 mg/kg/ day													+																		
ATG (rabbit)	8-9 mg/kg/ day															+	+	+	+													
Cyclophosphamide	40 mg/kg/ day														+	+	+	+														
Mesna	400 mg/m^2/ day														+	+	+	+														
Cyclosporin	3 mg/kg/ day																		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Methotrexate	8 mg/m^2/ day																				+		+			+						
Ca leukovorin	15 mg/m^2																					+		+			+					
G-CSF	5-10 μgr/kg/ day																								+	+	+	+	+	+	+	+
Sulfamethoxazole, trimethoprim	150 mg TMP/m^2	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+														
Fluconazole	3-5 mg/kg/ day								+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ciprofloxacin	20-30 mg/kg/ day													+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acyklovir	1500 mg/m^2/ day																		+	+	+	+	+	+	+	+	+	+	+	+	+	+
IVIG	0,3 gr/kg/ day																				+							+				
DFO	50 mg/kg/ day	+	+	+	+	+	+	+	+	+	+	+	+																			

DFO- Deferoxamine , IVIG -intravenous immunoglobulin, G-CSF- granulocyte colony stimulating factor.

Discussion

The transplantation frequency for hemoglobinopathies in Europe has been increasing in the last decade. [6] According to the EBMT data (Fig 3) in the last decades more than 120 patients annually with hemoglobinopathies have been treated with allo SCT. An international survey including 1000 HLA identical transplants, performed between 1986 and 2013 and reported to EBMT, Eurocord, and the CIBMTR, showed a 5-year EFS and OS of 91.4% and 92.9%, respectively. Graft failure was observed in 23 patients [7]. Age at transplantation is an important predictor of survival. Patients younger than 5 years have an excellent OS and EFS. The incidence of chronic graft versus host disease (cGVHD) in matched sibling donors can rise beyond 20%.

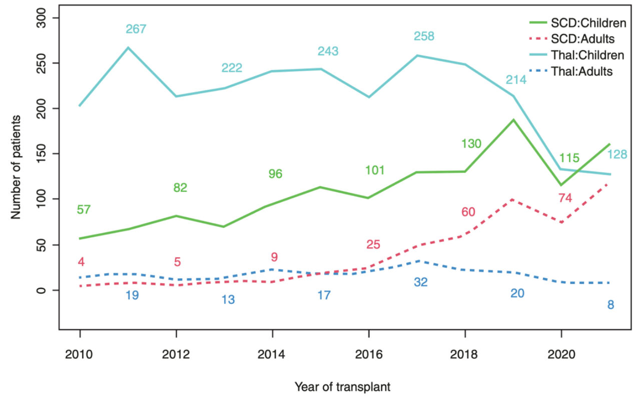

Figure 3: Transplant activities in the EBMT registries for hemoglobinopathies

Finding a suitable donor for allo SCT in TM patients is a challenge due to its unique genome and lack of unrelated SCT donors. Increasing the pool of unrelated donors or implementing haploidentical donor platforms for this indication is an ongoing process in various clinical studies [8]. The development of both vivo and ex vivo T-cell depletion strategies has facilitated the emergence of haploidentical donor HCT as a solution with universal availability of donors. For the second transplant in the presented case the unrelated donor search revealed lack of unrelated donors for the patient in the World marrow donor association (WMDA) database, and his parents were heterozygotes for thalassemia. That was the reason that it was decided to use the same donor for the second allo SCT.

Treosulfan (dihydroxy-busulfan), in the recent past, has attracted a lot of attention as an agent to replace busulfan in view of its favorable toxicity profile[8]. Hepatic sinusoidal obstruction syndrome (SOS) which is a common problem with conventional busulfan based myeloablative regimens with an incidence ranging from 5 to 40% occurs only infrequently with treosulfan.

The cumulative incidence of SOS in the very high-risk subset of patients (Class III VHR) has been reported to be as high as 78% and in 24% of such cases it led to multi-organ failure and death Use of a busulfan based conditioning regimens was associated with an increased incidence of SOS on a multivariate analysis in a prospective study. For the second transplant in our institution, we decided to use treosulfan to avoid hepatic SOS occurrence and other treatment related toxicity[9]. A SOS prophylaxis with defibrotide was not administered in our patient.

Bone marrow (BM) has been the preferred choice of stem cell source in non-malignant hematological disorders to reduce the risk of GVHD, though the incidence of both acute and chronic GVHD in pediatric population is low [10]. PBSC grafts when

used have been reported to be associated with faster engraftment and lower requirement of blood product support in the peri-transplant period and have also been associated with a low incidence of graft rejection. However, the risk of chronic GVHD is increased. Larger prospective studies are required to confirm the benefit of PBSC over BM in thalassemia major in Class III patients receiving treosulfan based conditioning. The current consensus, however, is that a BM graft should be used as far as possible for non-malignant conditions to reduce the risk of GVHD. The presented case had BM as source of stem cells for the first transplant and busulfan based myeloablative conditioning. Due to early graft rejection for the second transplant the dilemma was whether to incorporate treosulfan in the conditioning and PBSC as source of stem cells. The patient engrafted at day +13 and achieved full donor chimerism on the first month after transplantation.

Disease-related outcomes and late effects of allo-HSCT include monitoring and management of mixed chimerism, iron overload, cGvHD, immune reconstitution and susceptibility to infections and screening for malignancies following exposure to transplant conditioning regimens and immunosuppression. In the presented case graft rejection was predicted since day+40 after alloSCT, patient received posttransplant chelators during 10 months after the second transplant.

The use of donor cells in allo-HSCT introduces the risk of potentially life-threatening and graft rejection. Autologous PBSC were cryopreserved for later stem cell rescue if needed in the presented case.

TDT is a significant public health problem in the country since it is still an endemic disease. There is great need for effective transplant programs, so far pediatric patients were referred to foreign transplant centres. Absence of suitable donors, cost of treatment and lack of enough centers capable of offering this therapy are major challenges preventing wider use of this therapy. Carefully designed studies are still needed to confirm the efficacy, toxicity and long-term durability of all these approaches.

Conclusion

Allo SCT is the only curative option for β-thalassemia major. In patients with good risk features it is reasonable to anticipate a greater than 90% chance of a successful transplant outcome. With better risk stratification and supportive care, the results of allo-SCT are now very good even in high risk patients who have significant iron overload related organ dysfunction. The disease severity and the age of the patient has a crucial impact on transplant related mortality and the incidence of veno-occlusive liver disease as one of the main complications during SCT. More data is required on the etiology of frequent graft rejection in TDT studying the aspects of the graft and subsequent immune reconstitution that can improve the outcome of allo HSCT for thalassemia major. The case presentation was the BMT unit's first experience in SCT for this indication. Allo-SCTs should be done at younger age, between 2 and 5 years, well before any end organ damage occurs in these patients so that there are no sequelae of the disease after a successful allo-SCT and these children can then grow up to live normally.

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