Clinical Research

Allogeneic Hematopoietic Stem Cell Transplantation in Adult Patients with Thalassemia: A Single-Center Experience and Literature Review

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ABSTRACT

Objective: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only curative treatment modality in thalassemia. Its use has been limited by age, transplant-related mortality (TRM), graft rejection, and graft versus host disease (GvHD), especially in adult patients. We aimed to present our allo-HSCT experience in adult patients with thalassemia major.

Material and Method: Patients' demographic and clinical features, donor types, resource of stem cells, conditioning regimens, GvHD prophylaxis, time to neutrophil and platelet engraftments, acute and chronic GvHD, thalassemia -free survival (TFS) and overall survival were examined.

Results: The study included six patients. The median age was 21.5 (20-26) years. The median ferritin levels were 1498.4 (347.4-6992.3) pg/ml. The matched sibling donor (MSD) was used in 4 patients while matched unrelated donor (MUD) was used in 2 patients. The median time to neutrophil and platelet engraftments were 17 (15-35) and 18 (15-40) days, respectively. Acute and chronic GvHD were detected in 2 and 1 patients, respectively. The TRM was detected in 2 patients (33.3%), due to infection and acute GVHD. At a median follow-up of 28 months after transplantation, 4 (66.6%) patients were alive and TFS was achieved in 2 (33.3%) patients. Graft failure was detected in 3 (50%) patients.

Conclusion: Graft rejection, TRM and GvHD limited the use of allo-HSCT, especially in adult patients. These complications were reduced by reduced-intensity conditioning regimens and allo-HSCT should be done primarily in patients under the age of 20 years and without organ damage due to iron overload.

Keywords: *Allogeneic Hematopoietic Stem Cell Transplantation, Conditioning Regimen, Graft versus Host Disease, Thalassemia, Thalassemia Free Survival.*

ÖZ

Erişkin Talasemi Hastalarında Allojenik Hematopoetik Kök Hücre Nakli: Tek Merkez Deneyimi ve Literatür Derlemesi

Amaç: Allojenik hematopoietik kök hücre nakli (allo-HKHN), talasemide hala tek küratif tedavi yöntemidir. Ancak yaş, transplant ilişkili mortalite, greft reddi ve greft versus host hastalığı (GvHH) nedeniyle özellikle erişkin hastalarda kullanımı sınırlıdır. Biz de erişkin talasemi majörlü hastada allo-HKHN deneyimimizi sunmayı amaçladık.

Gereç ve Yöntem: Hastaların demografik ve klinik özellikleri, donör tipleri, kök hücre kaynakları, hazırlama rejimleri, GvHH profilaksisi, nötrofil ve trombosit engraftman süresi, akut ve kronik GvHH, talasemisiz sağ kalım ve toplam sağ kalım incelendi.

Bulgular: Bu çalışmaya altı hasta dahil edildi. Ortanca yaş 21,5 (20-26) yıldı. Ortanca ferritin seviyeleri 1498.4 (347.4-6992.3) pg/ml idi. 4 hastada tam uyumlu kardeş donör, 2 hastada tam uyumlu akraba dışı donör kullanıldı. Nötrofil ve trombosit engraftman medyan süresi sırasıyla 17 (15-35) ve 18 (15-40) gündü. İki hastada akut ve 1 hastada kronik GvHH saptandı. Enfeksiyon ve akut GvHH nedenli olmak üzere 2 hastada (%33,3) transplant ilişkili mortalite saptandı. Nakil sonrası ortalama 28 aylık takipte 4 (%66,6) hasta hala hayatta ve 2 (%33,3) hastada talasemisiz sağ kalım sağlandı. Üç (%50) hastada greft yetmezliği saptandı.

Sonuç: Greft reddi, transplant ilişkili mortalite ve GvHH, özellikle erişkin hastalarda allo-HSCT kullanımını sınırlamaktadır. Bu komplikasyonlar azaltılmış yoğunluklu hazırlama rejimleri ile azaltılmış olsa da allo-HKHN, öncelikle 20 yaşın altında ve aşırı demir yüklenmesi nedeniyle organ hasarı olmadan yapılmalıdır.

Anahtar Sözcükler: *Allojenik Hematopoetik Kök Hücre Nakli, Hazırlama Rejimi, Greft versus Host Hastalığı, Talasemi, Talasemisiz Sağ Kalım.*

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Thalassemia is a common inherited hemoglobin disorder characterized by a reduced synthesis of one or more of the globin (α, β, γ, etc.) chains. It is most common in the Mediterranean, Middle Eastern and Southern Asian countries all over the world (1, 2).

Among thalassemia subtypes, beta thalassemia major

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has the most severe clinical outcome. In beta thalassemia major, severe ineffective erythropoiesis and massive erythroid hyperplasia occur in the bone marrow and extra medullary regions with the absence of the beta chain or decreased production and abnormal accumulation of the alpha chain. As a result of ineffective erythropoiesis and chronic hemolytic anemia, the patient becomes transfusion dependent. Due to chronic transfusion, there is a serious iron load in organs such as the heart, liver, and endocrine, leading to organ dysfunction and increased mortality/morbidity (1, 3, 4). In recent years, especially with the use of oral iron chelations, iron-related complications have been reduced and life expectancy has been increased in thalassemia patients. Despite advances in chelation therapies and supportive therapies such as regular transfusion, allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only curative treatment modality in thalassemia (5).

The goal in allo-HSCT is to destroy genetically abnormal hematopoietic stem cells and subsequently to restore normal erythropoiesis in the bone marrow and excellent results are achieved, especially in the pediatric patient group. However, some factors as age, transplant related mortality, graft rejection, and graft versus host disease (GvHD) limit its use, especially in adult patients. At present, these complications have been reduced with reduced-intensity conditioning regimens, chelation treatments before transplantation, and supportive treatments such as hydroxyurea (6, 7).

In this study, we aimed to present our experience with allo-HSCT in adult patients with thalassemia major.

MATERIAL AND METHOD

This retrospective and single center study was approved by the Ethics Committee of Inonu University under approval number of 2021/2693 and was carried out in accordance with the principles of the Helsinki Declaration. All data were collected from the hospital registries and patients' clinical notes. The study included 6 patients between January 2016 and December 2020.

Patients' demographic features, ferritin levels, spleen, and liver sizes at the time of transplantation, donor types, resource of stem cells, conditioning regimens, GvHD prophylaxis, time to neutrophil and platelet engraftments, acute and chronic GvHD status, post-transplant transfusion-free survival and overall survival (OS) were examined. No pre-transplant risk classification was made because of lack of liver biopsy in all patients.

A reduced-intensity regimen (RIC), PESARO protocol, was used as the conditioning regimen for all patients. According to this regimen, the patients received hydroxyurea at a dose of 25-30 mg/kg per oral and azathioprine at a dose of 3 mg/kg/day per oral were administered from day-42 to day-11. Fludarabine at a dose of 20 mg/m^2/day intravenous (IV) from day-17 through day-13, busulfan 3.2 mg/kg daily divided into 4 doses IV for 4 days (day-9 to day-6), cyclophosphamide 22,5 mg/kg daily IV for 4 days (day-5 to day-2) and anti-lymphocyte globulin 4-10 mg/kg daily IV for 4 days (day-4 to day-1).

Peripheral blood was the stem cell source for all patients. All patients received cyclosporine A (CSA) and methotrexate for GvHD prophylaxis. CSA 3 mg/kg IV daily (divided into 2 doses) from day-1 until day of oral administration. Oral CSA at dose of 12.5 mg/kg daily (divided into 2 doses) was used at least 6 months if tolerated. Methotrexate 7,5 mg/m^2 IV daily once was used on days +1, +3 and +6.

Granulocyte colony stimulating factor (GCSF) was administered from +1 day until neutrophil engraftment. Time to neutrophil engraftment was defined as the time from the day of stem cell infusion to the first of three consecutive days with absolute neutrophil counts $\geq 0.5\times10^9$/L. Time to platelet engraftment was defined as the time from the day of stem cell infusion to the first of three consecutive days with platelet counts more than 20×10^9/L without transfusion. Febrile neutropenia was defined as the combination of granulocyte counts below 500 cell/µl and a body temperature over 38 ºC.

Acute GvHD was evaluated according to the revised Glucksberg scale, where Grade 1-2 were defined as mild acute GvHD, grade 3-4 were defined as severe acute GvHD (8). Chronic GvHD was defined as either limited or extended.

Transplant-related mortality (TRM) was defined as death within the first 100 days after ASCT without any evidence of disease relapse or progression. OS was defined from date of first day of allo-HSCT to death from any cause.

Statistical analysis

Patient characteristics were summarized using descriptive statistics, such as median, minimum, and maximum for qualitative data, and the number with percentage was used for categorical data. A p value of <0.05 was considered significant. All analyses were performed using the IBM SPSS Statistics v22 software.

RESULTS

Six patients with thalassemia were included in the study. Four of them were female, and 2 were male. The median age at the transplantation time was 21.5 (range, 20-26) years. Before the transplantation, 5 patients had received iron chelation therapy (deferasirox), but only 2 of them received iron chelation therapy regularly. The median ferritin levels at the time of transplantation were 1498.4 (347.4-6992.3) pg/ml. Splenectomy was performed in five patients before transplantation. Hepatomegaly was observed in 3 patients at the time of transplantation. Liver biopsy was performed in only one patient with a normal liver size, and grade 1 fibrosis was detected. Although liver biopsy was not available for all patients, 5 of them had at least 2 poor risk

factors, including irregular chelation therapy and hepatomegaly.

Transplantation and transplantation outcomes are shown in table 1.

Table 1. *Transplantation features and outcome of transplantation.*

Case	Gender	Age	Ferritin (pg/ml)	Donor type	Infused stem cell ($x10^6$/kg)	Neutrophil engraftmen (day)	Platelet engraftment (day)	aGvHD	aGvHD location	cGvHD	cGvHD location	The duration of transfusion independent (months)	The last status
1	26	F	1498,4	MSD	9,6	-	-	No	-	No	-	0	Alive
2	25	F	347,4	MUD	7,5	15	15	No	-	No	-	12	Alive
3	21	M	-	MSD	8,9	17	18	Yes	GİS/Skin	No	-	1	Exitus
4	22	F	1911,1	MUD	7,3	18	18	No	-	No	-	0	Exitus
5	20	F	6992,3	MSD	6,9	35	40	No	-	Yes	Liver	21	Alive
6	21	M	1099,1	MSD	8,8	15	18	Yes	Skin	No		0	Alive

aGvHD: acute graft versus host disease, cGvHD: chronic graft versus host disease, F: female, M: Male, MSD: matched sibling donor, MUD: matched unrelated donor.

The HLA-matched sibling donor (MSD) was used in 4 patients while HLA-matched unrelated donor (MUD) was used in 2patients. The median counts of infused stem cells were $8.1x10^6$/kg (range, $6.9\text{-}9.6x10^6$/kg). The median time to neutrophil engraftment and platelet engraftment were 17 (15-35) and 18 (15-40) days, respectively. The platelet and neutrophil engraftments were not observed in one patient who underwent allo-HSCT from matched related family donor. Febrile neutropenia was detected in patients. Acute GvHD was detected in 2 patients, including 1 mild cutaneous, 1 severe cutaneous, and 1 severe gastrointestinal acute GvHD. Chronic GvHD was detected in 1 patient as limited liver GvHD.

The transplant-related mortality (TRM) was observed in 2 patients (33.3%) due to infection and acute GvHD. At a median follow-up of 28 months after transplantation, 4 (66.6%) patients were alive and transfusion-independent and thalassemia-free survival was achieved in 2 (33.3%) patients. Graft failure was detected in 3 (50%) patients.

DISCUSSION

Currently the only curative treatment remains the allo-HCST for thalassemia major, and thalassemia-free survival (TFS) is higher in post-transplant outcomes (9). However, age at the transplant time, risk status of the disease, donor type, source of stem cells, and conditioning regimen are associated with the outcome in allo-HCST. Furthermore, high iron load increases the risk of post-transplant complications and affects the results of transplantation (10, 11).

The age plays an important role in transplantation outcome. Better outcomes are achieved in younger patients compared to adult/elderly patients. In the European Society for Blood and Bone Marrow Transplantation (EBMT) registry study which included a large number of patients, patients were categorized by age groups, and both OS and TFS were significantly better in patients younger than 14 years. OS was $\geqslant$ 90% and EFS was $\geqslant$ 83% in patients younger than 14 years, and thus the threshold age for optimal transplantation is considered 14 years (12). Pesaro group reported the results of allo-HSCT with RIC regimen in patients with a median age of 21 years (range, 17-31) and found that TFS and TRM were 67% and 27%, respectively (13). In our study group, all patients were older than 18 years and OS, TFS, and TRM were 66.6%, 33.3%, and 33.3%, respectively.

The disease risk score is also important for the outcomes with allo-HSCT. The poor risk factors include liver fibrosis, hepatomegaly (> 2 cm below the costal margin) and irregular chelation therapy. Based on these risk factors, patients are typically classified into 3 risk groups: class 1 with no risk factors; class 2 with 1 or 2 risk factors; and class 3 with all risk factors. Pesaro experience showed that the estimated TFS was 85% -90%, 80%, and 65% -70% in class 1, 2, and 3, respectively and TRM significantly increased from Pesaro class 1 to class 3 (14, 15). In our study, our patients had least 2 poor risk factors, including irregular chelation therapy and hepatomegaly and the rate of TRM was high.

Myeloablative conditioning regimen as combination of busulfan and cyclophosphamide is commonly used for allo-HSCT with HLA-matched related donor in patients with thalassemia. Busulfan is used to eradicate hyperplastic bone marrow, while cyclophosphamide is preferred for its immunosuppressive effect. This combination regimen is suitable for young and low-risk (class1-2) patients, however the liver toxicity of busulfan and the cardiac side effects of cyclophosphamide are not suitable for adult patients and high-risk (class 3) patients (16). Sinusoidal obstruction syndrome (SOS) is more common in class 3 patients associated with high iron load and busulfan increases the risk of SOS in this group. RIC regimen is usually preferred for adult patients and patients with high risk (class 3) (6, 11). The addition of fludarabine and anti-thymocyte globulin (ATG) to busulfan and cyclophosphamide is a RIC regimen that is preferred in class 3 young patients. The OS is improved by RIC regimen, while the graft rejection risk is increased (17). Pesaro group added fludarabine, ATG, hydroxyurea and azathioprine to the combination of cyclophosphamide and busulfan for both increasing the immunosuppression effect and eradicating the thalassemic bone marrow. Thus, it was aimed to reduce the risk of graft rejection and toxicity. This regimen was administered to 33 patients with

class 3 thalassemia younger than 17 years of age and they reported that OS rate was 93%, and the incidence of recurrent thalassemia decreased from 30% to 8% (18). Hussein et al. (19) presented a risk adopted allo-HSCT from matched related family donor in children. In this study, RIC with busulfan, fludarabine, total lymphoid irradiation and ATG was administered to patients with a Class 3 risk. They found that the 5-year OS and thalassemia-free-survival were 100% and 77%, respectively.

Allo-HSCT from MSD has favorable outcomes in younger patients with a lower risk of GVHD and it provides >90% OS, and >80% TFS. The survival outcomes (OS; ~70%, TFS; ~60-65%) of allo-HSCT from MSD are lower in adult patients compared to younger patients. The reason for this is that adults have more class 3 disease and iron-related organ damage is more common in adult patients (11, 12). In our study, allo-HSCT from MSD was administered in 4 patients and TFS was 25% in this group.

The alternative donors such as unrelated donors are used in thalassemia when MSD is not available. GITMO group reported outcomes in 27 adult patients, who received HSCT from a MUD, and both OS and TFS were 70%. They reported that the incidence of grade II–IV aGvHD and cGvHD was 37% and 27%, respectively (20). In our study, allo-HSCT was obtained from MUD in 2 patients, and TFS was achieved in 1 patient, and neither GVHD nor TRM were observed in any patient.

The peripheral blood as stem cell source for allo-HSCT in thalassemia is not preferred because of increasing risk of acute and chronic GVHH. The transplantation with cord blood or bone marrow as stem cell source has excellent outcomes in thalassemia (11, 21). Ghavamzadeh et al. (22) compared the peripheral blood and bone marrow as stem cell in class I-II thalassemic children who underwent HLA-matched sibling donor. They reported that the incidence of chronic GVHD was more frequent in the peripheral blood group versus bone marrow group (48% versus 19%; $P < .001$) and there was no difference in the 2-year OS after transplantation with stem cell from peripheral blood and from bone marrow (83% and 89%, respectively). In our study we used the peripheral blood as stem cell source in all patients. Acute GvHD was detected in 2 patients who underwent allo-HSCT from MSD, including 1 mild cutaneous, 1 severe cutaneous, and 1 severe gastrointestinal acute GvHD. Chronic GvHD was detected in 1 patient as limited liver GvHD.

The limitation in our study was that we had a small number of patients, so no comparison can be made, especially between the donor types.

Conclusion

Transplant-related mortality, graft rejection, and GvHD limit the use of allo-HSCT, especially in adult patients. These complications have been reduced with reduced-intensity preparation regimens, the chelation treatments before the transplantation, and supportive treatments such as hydroxyurea. In our study, especially the transplant-related mortality rate was consistent with the literature. The high iron load before the transplantation and the patients older than 20 years of age contribute to mortality, so we suggest that allo-HSCT should be done primarily in patients under the age of 20 years and without organ damage due to iron overload.

REFERENCES

1. Sharma A, Jagannath VA, Puri L. Hematopoietic stem cell transplantation for people with β-thalassaemia. Cochrane Database Syst Rev 2021; 4: Cd008708.
2. Weatherall DJ, Williams TN, Allen SJ et al. The population genetics and dynamics of the thalassemias. Hematol Oncol Clin North Am 2010; 24: 1021-31.
3. Rachmilewitz EA and Giardina PJ. How I treat thalassemia. Blood 2011; 118: 3479-88.
4. Modell B, Khan M, Darlison M et al. A national register for surveillance of inherited disorders: beta thalassaemia in the United Kingdom. Bull World Health Organ 2001; 79: 1006-13.
5. Lucarelli G, Gaziev J. Advances in the allogeneic transplantation for thalassemia. Blood Rev 2008; 22: 53-63.
6. Strocchio L, Locatelli F. Hematopoietic Stem Cell Transplantation in Thalassemia. Hematol Oncol Clin North Am 2018; 32: 317-28.
7. Mathews V, Savani BN. Conditioning regimens in allo-SCT for thalassemia major. Bone Marrow Transplant 2014; 49: 607-10.
8. MacMillan ML, DeFor TE, Weisdorf DJ. What predicts high risk acute graft-versus-host disease (GVHD) at onset?: identification of those at highest risk by a novel acute GVHD risk score. Br J Haematol 2012; 157: 732-41.
9. Sabloff M, Chandy M, Wang Z et al. HLA-matched sibling bone marrow transplantation for β-thalassemia major. Blood 2011; 117: 1745-50.
10. Angelucci E, Matthes-Martin S, Baronciani D et al. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. Haematologica 2014; 99: 811-20.
11. Issaragrisil S, Kunacheewa C. Matched sibling donor hematopoietic stem cell transplantation for thalassemia. Current opinion in hematology 2016; 23: 508-14.
12. Baronciani D, Angelucci E, Potschger U et al. Hemopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000-2010. Bone Marrow Transplant 2016; 51: 536-41.
13. Gaziev J, Sodani P, Polchi P et al. Bone marrow transplantation in adults with thalassemia: Treatment and long-term follow-up. Ann N Y Acad Sci 2005; 1054: 196-205.
14. Giardini C, Lucarelli G Bone marrow transplantation for beta-thalassemia. Hematol Oncol Clin North Am 1999; 13: 1059-64.
15. Lucarelli G, Galimberti M, Giardini C et al. Bone marrow transplantation in thalassemia. The experience of Pesaro. Ann N Y Acad Sci 1998; 850: 270-5.
16. Lucarelli G, Andreani M, Angelucci E. The cure of thalassemia by bone marrow transplantation. Blood Rev 2002; 16: 81-5.
17. Bernardo ME, Piras E, Vacca A et al. Allogeneic hematopoietic stem cell transplantation in thalassemia major: results of a reduced-toxicity conditioning regimen based on the use of treosulfan. Blood 2012; 120: 473-6.
18. Sodani P, Gaziev D, Polchi P et al. New approach for bone marrow transplantation in patients with class 3 thalassemia aged younger than 17 years. Blood 2004; 104: 1201-3.
19. Hussein AA, Al-Zaben A, Ghatasheh L et al. Risk adopted allogeneic hematopoietic stem cell transplantation using a reduced intensity regimen for children with thalassemia major. Pediatr Blood Cancer 2013; 60: 1345-9.
20. Locatelli F, Merli P, Strocchio L Transplantation for thalassemia major: alternative donors. Current opinion in hematology 2016; 23: 515-23.
21. Locatelli F, Kabbara N, Ruggeri A et al. Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling. Blood 2013; 122: 1072-8.
22. Ghavamzadeh A, Iravani M, Ashouri A et al. Peripheral blood versus bone marrow as a source of hematopoietic stem cells for allogeneic transplantation in children with class I and II beta thalassemia major. Biol Blood Marrow Transplant 2008; 14: 301-8.