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Original Research Article

HIGH RISK ALLELES AFFECTING OUTCOME IN HAPLO-IDENTICAL BONE MARROW TRANSPLANTATION FOR THALASSEMIA

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Abstract: ***Background:*** Human Leucocyte antigen (HLA) compatibility is the crucial requirement to perform an allogeneic hematopoetic stem cell transplantation (HSCT) and remains the most meaningful predictor of long term survival. ***AIM*** To identify functional HLA characteristics that could help guide donor selection to improve overall success of haploidentical transplantation. ***Methodology*** We analyzed 55 consecutive patients with thalassemia major transplanted from a related haploidentical donor after receiving myeloablative conditioning regimen in our centre. We assessed HLA incompatibility based on total number of HLA mismatches and their correlation with the transplant outcomes. ***Results*** Of the 55 cases of patients who underwent haploidentical transplantation, 42(76.4%) engrafted while 13 (23.6%) rejected. Overall survival was 85%.
There were 9 patients (16.36%) who underwent Haploidentical transplants with a 6/12 match and of these 7 (77.7%) rejected.
A class II match was associated with better outcome. Class II match in both DRB1 and DQB1 (23.6%) and either DRB1 alone (32.7%) or DQB1 alone (27.9%) had the best outcome. The best outcome was observed in cases where boys received a graft from the father with an engraftment status of 91.76%. Of the 55 transplants 15 patients (27.3%) had a common allele of 40:06:01G in class I HLA-B from their donor. Our analysis showed it to be associated with adverse outcomes. ***CONCLUSION*** The outcome of haploidentical transplantation using PTCy is improved when the donor is HLA-Class II matched with best outcome in HLA DRB1 match.

Keywords: Human Leucocyte antigen, Haploidentical transplant, Thalassemia major

INTRODUCTION

Hematopoietic stem cell transplantation between genetically different individuals became possible by identifying the human leucocyte antigen (HAL) system at the major histocompatibility complex (MHC). Located on chromosome 6 it encodes cell surface molecules which then present antigenic peptides to T-cell receptors. Divided into two major

classes, Class I MHC molecules are seen on the surface of all nucleated cells and platelets and are encoded as HLA-A, B, or C. Lymphocytes reactive to Class I molecules express CD8 molecules that have effector cytotoxic function. ClassII MHC molecules are present on antigen-presenting cells like B cells, macrophages, dendritic cells, Langerhans cells, thymic epithelium, and activated T cells. Both polypeptide chains are encoded by genes in HLA-DR, -DQ, -DP. Lymphocytes reactive to class II molecules express CD4 and are often helper T cells. Most patients suffering from Thalassemia major treated with allo-HSCT show a good response to treatment, and recent advancements in transplantation technology have improved the OS and TFS rates to around 90% and 80%, respectively (1,2). Most transplants use HLA fully-matched sibling donors, but limitations in the number of matched related donors have led to the use of mismatched related donors, matched unrelated donors, and mismatched unrelated donors (3). Although research has indicated that good results can be achieved with mismatched donors, the outcomes tend to be worse than those obtained with matched donors for both β-thalassemia (4-6) and other diseases (7,8). Hematopoietic stem cell transplantation (HSCT) from relatives sharing only 1 haplotype has revolutionized curative options by HSCT for patients suffering from benign blood disorders. Improvement in HLA-haploidentical transplantation with the use of cyclophosphamide post-transplant (PT-Cy) has substantially reduced severe acute and chronic graft versus host disease(GVHD). Haploidentical family members share 1 complete HLA haplotype with the patient and differ for a variable number of alleles on the nonshared haplotype. The immunogenicity of a given HLA mismatch may relate to specific amino acid epitopes recognized by T-cells and allogeneic HLA peptides presented by HLA. In the case of HLA DPB1[Tcell epitopes (TCE)], matching or permissive mismatching is associated with less acute GVHD and better survival but also higher relapse after unrelated transplantation.

We performed a retrospective analysis on all the patients who underwent haplo-identical transplantation from March 2016 to August 2023 to study the effect of individual and combined HLA locus mismatching after haploidentical transplantation using PTCy.

AIM

To identify functional HLA characteristics that could help guide donor selection to improve the overall success of haploidentical transplantation.

METHODS

We analyzed 55 consecutive patients with thalassemia major transplanted in our center. Informed consent and approval were obtained from all patients. Institutional Ethical Committee approval was obtained for conducting the study: MGMC&H/IEC/JPR/2023/1710 dated 02/11/2023.

Patients were transplanted from March 2016 to August 2023 from a related haploidentical donor after receiving a myeloablative conditioning regimen and PTCy GVHD prophylaxis.
All the patients were genetically proven transfusion-dependent beta-thalassemia.
The best-related donor was selected according to the following algorithm: donor health, donor age, cytomegalovirus status, and ABO compatibility, and a different number of mismatches and DSA. There was no matched-related donor available for the patients in all 55 cases. Haploidentical transplantation was offered in our center and the option of the unrelated donor was discussed with each patient and given an option of transplantation at other centers using MUD.
In all 55 cases, either of the parents was the donor. All the donors were thalassemia carriers with baseline hemoglobin ranging from 8.9 gms/dl to 14.3 gms /dl.

Each donor underwent pretransplant work up which included infectious profile, renal function tests, liver function tests, and Donor specific antibodies. All the selected donors were negative for infectious panel and donor specific antibodies. Each patient underwent strict pre transplantation work up and only those patients were selected who had a ferritin level less than 1000ng/ml with no hepatosplenomegaly and liver enzymes less than twice normal.
All the patients received two cycles of five days each of Fludarabine and Dexamethasone from Day -68 to -64 and then -40 to -36.

All the patients received ATG, Busulphan, Fludarabine, and Thiotepa as conditioning regime along with post-transplant cyclophosphamide at a dose of 200 mg per kilogram of body weight. Unmanipulated bone marrow was used as stem cell support at day 0. The white blood cell count was used to calculate the final WBC count to be infused with an aim of at least 10 x108 cells and not more than 20 x10 8 cells per kg. Donors underwent bone marrow harvest under general anesthesia. Anti-infectious prophylaxis was started and consisted of Trimethoprim + sulfamethoxazole until day +120, acyclovir until day +90, and Fluconazole until day +32. Graft versus Host Disease prophylaxis was done with Mycophenolate Mofetil10 mg/kg/dose PO TID from day +5 to +60 and Cyclosporine A 3 mg/kg/day IV starting at days +5 adjusted to serum levels and tapered from day +120 to +300
Weekly cytomegalovirus monitoring by PCR until day +100 was done. In case of viral reactivation patients were put on oral or intravenous Ganciclovir for CMV reactivation and treatment was given for

three consecutive weekly negative RT-PCR. Patients received PRBC and platelets transfusion as per our center's treatment protocol.
The diagnosis of acute and chronic GVHD was clinical based on standard criteria. First and second-line therapy for GVHD was according to our center's protocol. The patients were monitored with weekly cyclosporine levels which were maintained between 100 to 200 ng/ml.
Graft failure was defined as <5% donor DNA chimerism by day + 30 of transplant. Peripheral blood chimerism was done at +30, +60, +120, +180, and one year post-transplant.
We assessed HLA incompatibility based on a total number of HLA mismatches and their correlation with the transplant outcomes. We analyzed the different HLA classes and correlated them with the outcomes and also tried to correlate HLA with gender mismatch.

RESULTS

Of the 55 transplants, 17 were girls while 38 were boys. The ages ranged from 4.7 years to 11 years with a median age range of 5.5 years at the time of transplantation. Based on liver size and ferritin and aminotransferase levels all children belonged to the low-risk group for bone marrow transplantation. Major ABO incompatibility was seen in two patients while minor ABO incompatibility was seen in 6 patients. ABO incompatibilty was not associated with any adverse effects and all these 8 patients engrafted.
The median time to neutrophilic recovery was 17 days while the median time to platelet engraftment was 22 days.
Of the 55 cases of patients who underwent haploidentical transplantation, 42(76.4%) engrafted while 13 (23.6%) rejected.
There were 9 patients (16.36%) who underwent Haploidentical transplants with a 6/12 match and of these 7 (77.7%) rejected.
We further analyzed the 13 patients who had rejected and of these 7(53.8%) were 6/12 match, 5 patients (38.46%) were identified as Haplo in Class II while only 1 patient(7.69%) who had a rejection was haplo in class I.
Overall survival (OS) was 85% while thalassemia-free survival (TFS) was 71%.
CMV reactivation was seen in 7 patients (12.7%) and all of them responded to Ganciclovir.
BK virus in urine was documented in three patients (5.5%) and of these one patient died one year later of renal failure.
The incidence of graft versus host disease (GVHD) was 18% (10).

TABLE 1 Recipient Characteristics

Characteristics (n= 55)	Number	Percentage %
Girls	17	30.9
Boys	38	69.1
Overall survival (OS)	47	85
Thalassemia Free Survival (TFS)	39	71
Engrafted	42	76.4
Rejected	13	23.6
Major ABO incompatibility	2	3.6
Minor ABO incompatibilty	6	10.9
CMV Reactivation	7	12.7
BK Virus infection	3	5.45
Acute Graft versus Host Disease (aGVHD)	10	18

Seven of these had skin GVHD grade 2 and all responded to oral steroids. Three of the patients had gut GVHD and all were grade 4. Of these two patients died.
Overall the total mortality rate was 15%. Infection- gram-negative sepsis was the cause of death in five of these patients while grade 4 gut GVHD resulted in two deaths. One patient died of acute renal failure post-BK virus infection.
Cytokine Release Storm (CRS) was encountered in two patients and both responded to steroids but later on one of them developed severe sepsis and expired.
A class II match was associated with a better outcome. Class II match in both DRB1 and DQB1 13 (23.6%) and

either DRB1 alone 18 (32.7%) or DQB1 alone15 (27.9%) had the best outcome.

TABLE 2 Donor characteristics

DONOR CHARACTERISTIC	ENGRAFTED	REJECTED
Mother (n=37)	27(72.9%)	10(27.1%)
Father (n=18)	15(83.3%)	3(16.7%)
Father to son (n=12)	11(91.76%)	1(8.34%)
Mother to daughter(n=11)	8(72.7%)	3 (27.3%)
Mother to son (n=26)	19(73%)	7(27%)
Father to daughter (n=6)	4(66.7%)	2(33.3%)

The mother was the donor in 37 (67.3%) transplants and the father in 18(32.7%) of the transplants. 83.3% (15) of the patients who received a graft from the father engrafted while 72.9% (27) of the patients who received a graft from the mother engrafted. In sex mismatch, 73.07% of boys who received a graft from the mother engrafted while 66.6% of the girls who received a graft from the father engrafted. The best outcome was observed in cases where boys received a graft from the father with an engraftment status of 91.76%.

TABLE 3 Association of Allele and Outcome

Common allele: 40:06:01G	Engrafted	Rejected	Acute GVHD
15 (27.3%)	8(53.3%)	7(46.7%)	6(40%)

Of the 55 transplants 15 patients (27.3%) had a common allele of 40:06:01G in class I HLA-B from their donor. Our analysis showed it to be associated with adverse outcomes because 7 (46.7%) of these rejected while 6 patients (40%) developed acute graft versus host disease. We had a total incidence of 18% (10)of acute graft versus host disease and of these 60% of patients had this common allele.

DISCUSSION

Although a matched sibling donor is ideal for allo-HSCT, the availability is limited. Other sources of cells for transplantation include matched unrelated donors, mismatched related donors, mismatched unrelated donors, and cord blood (9).

Human leukocyte antigen (HLA) mismatch causes an immune reaction between recipient and donor cells after hematopoietic stem cell transplantation (HSCT). Extensive studies have demonstrated that HLA mismatch is associated with a higher risk of graft-versus-host disease (GVHD) and takes a longer time to engraft, leading to poor outcomes of HLA-mismatched recipient-donor pairs in transplantation from related or unrelated donors. Early studies focused on the number of mismatched HLA antigens or alleles, and the quantification of HLA antigens and alleles is the basic priority in donor selection (10,11). HLA locus matching and the direction of mismatch are also potent prognostic factors and are considered in clinical settings (12-15). HLA mismatching patterns have also been studied for prognosis based on HLA supertypes and haplotypes (16-18). However, we still need to learn a lot about the relation between the heterogeneous effect of HLA mismatching on HSCT outcomes.

Haploidentical donor transplantation poses many challenges but also brings hope to patients. A study in Thailand described the successful transplantation of peripheral blood stem cells from a haploidentical donor when a novel preconditioning regimen was used (19). In their study, continuous engraftment was achieved, with low incidence rates of severe complications and GVHD (19). A haploidentical transplantation study in China also reported good outcomes: 3-year OS and TFS reached 100%, the incidence of grade III-IV aGVHD was low, and only 1 patient developed cGVHD (20). In another retrospective study by Chuwen Huang 22 patients received two or more HLA allele-mismatched grafts and of these four of them died at the last follow-up. A total of 15 patients received a graft from a parent, and three of them died at the last follow-up, indicating that parent donor-based transplantation is a choice for allogeneic HSCT for Thalassemia (21). In our retrospective study, the outcomes were comparable to the above-mentioned studies with an overall survival of 85%. Class II matches showed better outcomes. The incidence of acute graft versus host disease in our study was 18% and 60% of these patients had a common allele on HLA-B locus. Further studies and analysis may help to identify the exact reason for outcomes.

CONCLUSION

In conclusion, the outcome of haploidentical transplantation using PTCy is improved when the donor is HLA-Class II matched with the best outcome

in the HLA DRB1 match. 6/12 haploidentical matches have a poor outcome while the allele 40:06:01 G in class I HLA-B from the donor has the worst outcome in terms of rejection and graft versus host disease.

HLA factors influence the success of haploidentical transplantation and their consideration may help to optimize the selection of haploidentical-related donor.

Declarations and Statements:
Competing Interests: None
Conflict of Interest: None
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