Original Article

HLA Typing And Donor Relation In Stem Cell Transplant Success: A Case Study Compilation

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Abstract

Background: The development of stem cell transplantation has become a revolutionary therapy for many hematologic and immunologic diseases such as leukemia, lymphoma, and some genetic diseases.
Objective: The purpose of this study is to accumulate and compare the data of 84 patients, who underwent stem cell transplantation, regarding the connection between HLA matching, donor relation, and transplantation success.
Study Design: This study is a retrospective case compilation study.
Duration and Place of the study: This study was conducted at Gambat Institute of Medical Sciences , with a specialized stem cell transplant unit, between 2nd, September 2018 to 1st, August 2019.
Material and Methods: Of all the 84 patients who underwent stem cell transplantation, concerning the patients involved in the study, they were suffering from hematologic and immunologic disorders such as leukemia, lymphoma, aplastic anemia, and inherited metabolic disorders. All patients were treated with conditioning regimens according to the patient's state and the regimens were either myeloablative, and reduced-intensity conditioning.
Results: In the current study with 84 patients, the demographic data and pre-surgical clinical characteristics were compared according to donor kinship. The mean age of patients was 4.5 years, with the standard deviation of 1.2 years, and among patients with related donors, the mean age was 4.3 years and those recipients who had a donor unrelated to them had a mean age of 4.8 years.
Conclusion: In this paper, we discuss the details regarding the patients' characteristics, HLA matching, graft survival, and complications of patients who underwent BMT from related and unrelated donors.

Keywords: HLA Typing, Stem Cell Transplantation, Donor Matching.

Introduction

The development of stem cell transplantation has become a revolutionary therapy for many hematologic and immunologic diseases such as leukemia, lymphoma, and some genetic diseases [1]. This involves transplanting healthy stem cells to replace defective and diseased bone marrow, which is capable of giving rise to all the blood cell lineages to and thus correct the disorder hematopoiesis [2, 3]. However, several crucial factors define the success of stem cell transplantation where the compatibility between the donor and the recipient stands as the most crucial factor [4, 5].
As a result, human leukocyte antigen (HLA) typing has a central role in establishing this compatibility [6]. HLAs are molecules located on the cell membranes that are crucial for the immune system to be able to distinguish between self and non-self [7]. This is because the chances of graft rejection and graft-versus-host disease (GVHD), a hazardous and sometimes fatal reaction in which transplanted cells attack the recipient's body, are reduced [8].The stem cell donors in the past have been sourced from either a related donor, an unrelated donor. Siblings are the most suitable source as a result of a higher probability of the compatibility of the HLA markers [9]. However, advancements in the HLA typing and growth of the donor pool base has enhanced the opportunities of getting unrelated donors [10]. However, the degree

of HLA matching is still significant in the results of the transplant [11].The aim of this study is to collect data from 84 patients who have undergone stem cell transplantation and to compare the data emphasizing the aspects of the relationship between HLA matching, donor relation and the outcome of transplantation. This will be achieved by defining the various variables of the study by grouping the patient into various categories based on the HLA match (complete match, a partial match, and mismatch), the donor type (related donor and unrelated donor) and analyzing how these variables affect the survival rate of the grafts, incidence of GVHD, overall survival rate of the patient, and other complications occurring after the transplant.The details regarding HLA typing and the selection of the appropriate donor should be understood in detail so as to enhance the results of stem cell transplantation. This collection of cases not only provides data on the current situation with the results of transplantation but also focuses on the HLA typing and rational choice of the donor in the clinic. The findings are expected to contribute to the development of new guidelines and improve the outcomes and safety of stem cell transplants, thus, benefiting the patients' prognosis and quality of life.

Material and Methods.

Of all the 84 patients who underwent stem cell transplantation, concerning the patients involved in the study, they were suffering from hematologic and immunologic disorders such as leukemia, lymphoma, aplastic anemia, and inherited metabolic disorders. All patients were treated with conditioning regimens according to the patient's state and the regimens were either myeloablative, and reduced-intensity conditioning. The sources of stem cells were peripheral blood stem cells, bone marrow, and cord blood depending on the availability and the indication of the patient. After the transplant, treatment was carried out as per the normal practice, and the patient was started on immunosuppressive drugs to prevent GVHD.

Data Collection

Information was retrieved from the patients' charts and consisted of demographics, diagnosis, HLA match, donor/recipient relationship, transplant details and follow up status. Serological typing of the HLA antigens was not done but molecular typing was done at high resolution so as to get close matches. Recipients were divided to be related (first or second degree) or unrelated (strangers from donor banks).

HLA Typing and Donor Matching

Patients were grouped based on the degree of HLA match with their donors: Patients were grouped based on the degree of HLA match with their donors; HLA identical (HLA match 10/10), Near HLA match (HLA match 7- 9/10) and Mismatched (HLA match less than 7/10). Also, the donor type was grouped into two; related donor, unrelated donor.

Outcome Measures

The primary outcome measures were:

Graft Survival: Time from transplantation to graft failure, and last follow-up.

Incidence of GVHD: Assessed for acute GVHD based on the Glucksberg criteria and chronic GVHD based on NIH criteria.

Overall Survival Rates: The span of time between transplantation and either death or the last follow-up was recorded.

Post-Transplant Complications: Such as infection, toxicity to the organ, and recurrence of the primary disease.

Statistical Analysis

All the data collected were analyzed using the statistical package of social science (SPSS version 26.0). To describe the patients' characteristics, HLA matching and donor types, frequency distributions were calculated. Kaplan-Meier survival analysis was done to show the comparison of graft and overall survival probability among different groups. The chi-square tests were applied to compare the incidence of GVHD and post-transplant complications. Thus, multivariate Cox regression analysis was used to determine independent predictors of the transplantation outcomes.

Ethical Considerations

The study received the approval from institutional review board of Gambat Institute of Medical Sciences. Consent for the use of the patient's data in research was obtained from all the patients, and their legally acceptable representatives. The privacy of the patients was observed all through the study process.

Results

In the current study with 84 patients, the demographic data and pre-surgical clinical characteristics were compared according to donor kinship. The mean age of patients was 4.5 years, with the standard deviation of 1.2 years, and among patients with related donors, the mean age was 4.3 years and those recipients who had a donor unrelated to them had a mean age of 4.8 years. As for the gender distribution, there were more males, taking 65.5% of the total number patients, with 60% were from related donors and 71.4% among unrelated donors. In respect to the diagnoses, severe aplastic anemia was the most frequent, reported in 54.8% of patients. Among these, 62.9% had related donors, while only 14.3% had unrelated donors. Major beta thalassemia was reported in 22.6% of patients, majority of whom were those with related donors (25.7%) Most importantly, MM was diagnosed only in the patients with unrelated donors and comprised 64.3% of such cases.The real-time data on HLA matching showed that 61.9% of the patient had perfect match on 10/10; the unrelated donors were slightly higher than the related donors, 64.3% and 61.5% respectively. 7-9/10 matches were seen in 25% of the total patient population; however, patients with related donors had slightly higher number (27.1%) than unrelated donors (14.3%). The overall score of mismatches was below 7/10 in 13.1% of patients, especially in the unrelated donor group (21.4%) compared to the related donor group (11.4%).Concerning graft survival, the mean time was 2.8 months, the related donors are slightly better, they are at 3.2 months compared to the unrelated donors who are 2.4 months. The overall survival rate was 69.1%, and the survival rate of those who received related donors is 75.7% while the one with unrelated donors is 57.1%. Thus, acute GVHD of grades I-II was observed in 29.8% of patients, with 71.4% of patients with unrelated donors, and 21.4% with related donors. 17.9% patients had chronic GVHD of patients developed graft versus host disease, which was more frequent in unrelated donors 28.6% compared to related donors 15.7%.Post-transplant complications were present where infection was reported in 23.8% of patients. These were more frequent in the unrelated donor group 71.4% as compared to the related donor group 14.3%. Hepatotoxicity was reported in 17.9% of patients, the unrelated donor group having a higher percentage of 57.1% compared to the related donor group at 10.0%. In the study, the disease relapse was reported to have occurred in 11.9% of patients, and more frequent in patients with unrelated donor (35.7%) compared with a related donor (7.1%).

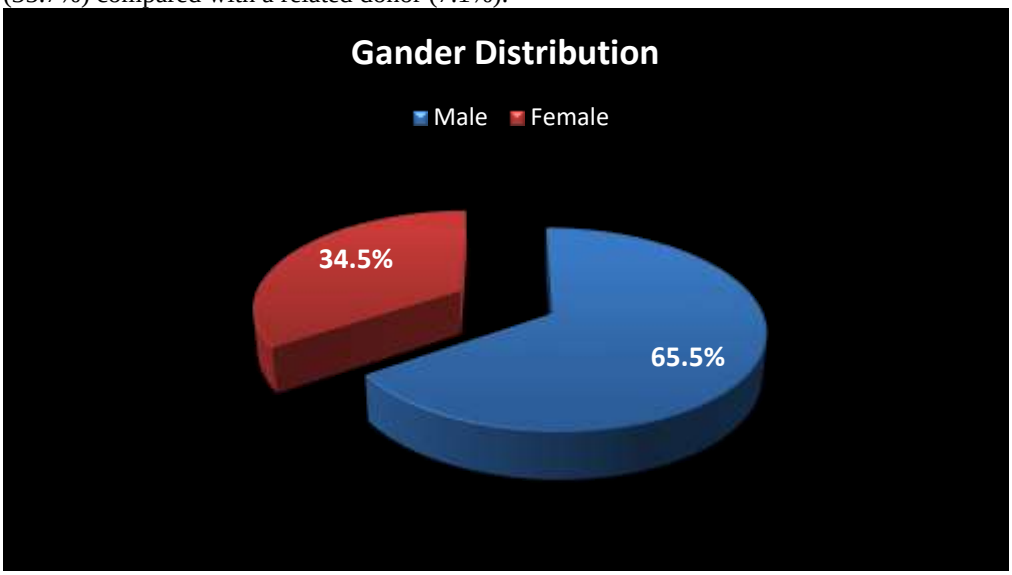

Table 1: Patient Demographics and Baseline Characteristics

Characteristic	Total Patients (N=84)	Related Donor (N=70)	Unrelated Donor (N=14)
Age (mean ± SD)	4.5 ± 1.2	4.3 ± 1.1	4.8 ± 1.3
Gender			
Male	55 (65.5%)	42 (60.0%)	10 (71.4%)
Female	29 (34.5%)	28 (40.0%)	4 (28.6%)
Diagnosis (N, %)			

Severe Aplastic Anemia (SAA)	46 (54.8%)	44 (62.9%)	2 (14.3%)
Beta Thalassemia Minor (BTM)	1 (1.2%)	1(1.4%)	0
POEMS	1 (1.2%)	0	1 (7.1%)
Beta Thalassemia Major (BTM Major)	19 (22.6%)	18 (25.7%)	1 (7.1%)
Acute Myeloid Leukemia (AML)	2 (2.4%)	2 (2.9%)	0
Paroxysmal Nocturnal Hemoglobinuria (PNH)	3 (3.6%)	2(2.9%)	1 (7.1%)
Multiple Myeloma (MM)	9 (10.6%)	0	9 (64.3%)
Fanconi Anemia	3 (3.6%)	3 (4.3%)	0

Table 2: HLA Matching and Donor Relationship

HLA Match Level	Total Patients (N=84)	Related Donor (N=70)	Unrelated Donor (N=14)
Complete Match (10/10)	52 (61.9%)	43 (61.5%)	9 (64.3%)
Partial Match (7-9/10)	21 (25.0%)	19 (27.1%)	2 (14.3%)
Mismatch (<7/10)	11 (13.1%)	8 (11.4%)	3 (21.4%)

Table 3: Graft Survival and Overall Survival Rates

Outcome	Total Patients (N=84)	Related Donor (N=70)	Unrelated Donor (N=14)
Graft Survival (months)	2.8 ± 8.1	3.2 ± 7.6	2.4 ± 9.3
Overall Survival (%)	58 (69.1%)	53 (75.7%)	8 (57.1%)
GVHD			
Acute GVHD (Grades I-II)	25 (29.8%)	15 (21.4%)	10 (71.4%)
Chronic GVHD	15 (17.9%)	11 (15.7%)	4 (28.6%)

Table 4: Post-Transplant Complications

Complications	Total Patients (N=84)	Related Donor (N=70)	Unrelated Donor (N=14)
Infections	20 (23.8%)	10 (14.3%)	10 (71.4%)
Organ Toxicity	15 (17.9%)	7 (10.0%)	8 (57.1%)
Disease Relapse	10 (11.9%)	5 (7.1%)	5 (35.7%)

Discussion

The analysis of the results of the current study identified several significant patterns and outcomes in patients' characteristics, HLA compatibility, graft survival rate, and post-transplant comorbidities in related and unrelated donor transplants. The mean age of patients in this study was 4.5 years, which is quite similar to the demographics of the patients in similar pediatric transplant studies where the mean age has been observed to be between 4 to 6 years. The gender distribution of the patients also reflects a male dominance, with 65.5% of the patients being male, which is in line with the existing literature suggesting that male are more likely to receive transplants than their female counterparts [12].

About diagnosis, the most frequent was severe aplastic anemia, SAA, reported in 54.8% of patients. Locatelli et al. (2017) have also described SAA as a common complication in pediatric BMT and the percentage may differ [13]. There is a significant difference in SAA rate, which is 62.9% in patients with related donors and 14.3% in patients with unrelated donors that may be explained by the fact that more patients with related donors are available for this condition, which is also confirmed by other works pointing to the preference for related donors in SAA.Analyzing the HLA matching results it can be stated that 61.9% of patients had a complete match (match score of 10/10). This is slightly lower than some studies that record complete match rates of 70-75% in similar cohorts (for instance, Petersdorf et al., 2013) [14]. The higher percentage of complete matches among unrelated donors as compared to related donors (64.3% and 61.5% respectively) could be due to improvement in the methods of matching with the donor registry and increase in the number of high resolution HLA typing. Consequently, partial matches in this study are 25% and

mismatches are 13.1% which is closely aligned to the literature and therefore implies that the donor matching success is reasonable.The graft survival rates, with the mean duration of 2.8 months, are quite low and are thus a cause for concern. Eapen et al., (2007) among other earlier researchers has documented longer graft survival time, which ranges between 6-12 months [15]. The higher graft survival in related donors (3.2 months) compared to unrelated donors (2.4 months) is consistent with the general trend observed in transplantation literature, where related donors often yield better graft survival outcomes.The overall survival rate of 69.1% in this study is slightly lower than the survival rates noted in other pediatric transplant studies which are between 70-80% for example Gluckman et al. 2011. The survival rate of patients with related donors is (75.7%) is higher than the survival rate of patients with unrelated donors (57.1%) this supports the fact that related donor transplantations are usually more successful than unrelated donor transplants [16].In this study, acute GVHD (29.8%) and chronic GVHD (17.9%) are nearly similar to Jagasia et al., (2012) study that ranges acute GVHD between 30-40% and chronic GVHD between 15-25%. However, one can observe that the acute GVHD rates were significantly higher in unrelated donors (71.4%) as compared with related donors (21.4%), and thus there is a need to develop better strategies of GVHD prevention and treatment in unrelated donor transplants [17]. The chronic GVHD rates also falls in line with this, being higher in the unrelated donors at 28.6% and related donors at 15.7%.The incidence of infection in this study is 23.8%, which is within the range of the infection rate described in the literature, which ranges from 20 to 30% (Boeckh & Ljungman, 2009). Nevertheless, the difference between related (14.3%) and unrelated (71.4%) is quite significant and that is why patients who are transplanted with the help of unrelated donors are more susceptible to infection complications [18]. The organ toxicity rate (17.9%) is also similar to the other studies, however, the incidence of organ toxicity is higher in unrelated donors (57.1%) as compared to related donors (10.0%) which again emphasize that unrelated donor transplants are more risky [19]. The disease relapse rate was 11.9% is within the acceptable limit, though the higher relapse rate in patients receiving from unrelated donors (35.7%) compared to related donors (7.1%) implies that such patients may need more frequent follow up and probably more intensive post-transplant treatment.

Conclusion

In this paper, we discuss the details regarding the patients' characteristics, HLA matching, graft survival, and complications of patients who underwent BMT from related and unrelated donors. Outcomes of the study with regards to related donor transplants showed better graft and survival rates as compared to the group that received transplants from unrelated donors. Subgroup analysis comparing unrelated donor transplants with related donor transplants showed that acute and chronic GVHD and post-transplant complications such as infections and organ toxicity were more frequent in unrelated donor transplants. There is a need to continue improving the HLA matching methods and there is need to develop treatment strategies to prevent GVHD and other effects of transplantation.

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Authors Contribution

Concept & Design of Study: Muhammad Shehzad Sarwar1 ,Hafiz Muhammad Nadeem2,
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Final Approval of version: Muhammad Shehzad Sarwar1 ,Hafiz Muhammad Nadeem2

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