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Outcome of Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Hematological Malignancies

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ABSTRACT

Introduction: Allogeneic hematopoietic stem cell transplantation is a potentially curative treatment modality for hematological malignancies. We evaluated the outcome of patients suffering from hematological malignancies, including acute leukemias, chronic myeloid leukemia and myelodysplastic syndrome after allogeneic transplantation.

Methods: All patients having hematological malignancies with HLA identical sibling donors who underwent allogeneic transplantation were included. Pre-transplant workup consisted of complete blood counts, evaluation of liver, kidneys, lungs, infectious profile, chest x-ray, paranasal sinus roentgenograms and dental review. Donors were given G-CSF at a dose of 5-10 µg/kg/twice daily for five days prior to harvest. The conditioning regimens included cyclophosphamide, busulfan and total body irradiation.

Results: A total of 41 allogeneic transplants were performed for hematological malignancies from April 2004 to December 2012. There were 31 males and 10 females. Median age ± SD was 28 ± 11.7 years (range 8 – 54 years). A mean of 7.7x108±1.5 mononuclear cells/kg were infused (range:6.2-9.2x108/kg). The median time to white cell recovery was 19±4 days (range:15-23 days). Transplant related mortality was 19.5%. The median overall survival was 53.6 months. Overall survival at a median follow up of 37 months was 67%.

Conclusion: Allogeneic stem cell transplantation is an effective treatment option in patients with hematological malignancies. Our outcomes are comparable with results from neighboring countries as well as the western world.

KEYWORDS: Allogeneic transplantation, Hematopoietic stem cell transplantation, Hematological malignancies, Treatment Outcome

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective treatment modality constituting the management of a variety of benign and malignant hematological disorders, especially hematological malignancies like leukemias, lymphomas and myelodysplastic syndromes.[1, 2] However, hematopoietic stem cell transplantation (HSCT) is an extremely high risk procedure and its benefits are often offset by the severe post-transplant complications that follow. Some of these complications include, but are not limited to, profound compromise of the immune system, sepsis and a variety of potentially fatal infections, failure of multiple organ systems, bleeding and graft-versus-host disease (GvHD). These complications can take place acutely in the

post-transplant period and/or chronically after discharge from the hospital.[2-4]

Some studies previously conducted in Pakistan reported transplant related mortality (TRM) of 18% to 22.7% in patients with hematological malignancies undergoing allo-HSCT, whereas the overall long-term survival of these patients ranges from 40% to 77%.[5-7] A review of the first decade of HSCT procedures performed in Pakistan stated an overall TRM of 18% in patients undergoing allo-HSCT for hematological malignancies, whereas the overall long-term survival in these patients was up to 54%.[8]

These findings are comparable with outcomes in neighboring countries from our region. For example, a study in China reported TRM of 15.66% with an overall survival (OS) of 73.49%.[9] The overall mortality in patients undergoing allo-HSCT for hematological malignancies in Iran was 28.5%, with an OS of 71%.[10] Data from India also exhibits similar results, with mortality of approximately 52% and OS of 48.2%.[11]

More or less similar outcomes have been reported from other countries, particularly the Western world. A multicenter study done by the EBMT showed a TRM of 14.7% with OS of 58%.[12]

We present the outcome of patients undergoing allo-HSCT for hematological malignancies at our center.

MATERIALS AND METHODS

Patients with malignant hematological disorders having an HLA matched sibling donor were evaluated. Hematological malignancies included were acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), acute biphenotypic leukemia (ABPL), chronic myeloid leukemia (CML) and myelodysplastic syndrome (MDS). These patients were stratified into standard and high risk groups, based on age, sex, disease stage, time interval between diagnosis and transplant, response to therapy and donor's gender according to the European Group for Blood and Bone Marrow Transplantation risk stratification.[13] All patients with AML, ALL and ABPL were in either first or second complete remission. All patients with CML were in chronic phase of the disease. Out of the patients with MDS, one patient had hypoplastic MDS, 2 patients had MDS with refractory cytopenia with multi-lineage dysplasia (RCMD) and 4 had MDS with refractory anemia with excess blasts-1 (RAEB-1).

Pre-transplant workup and characteristics

Pre-transplant work up for all patients and donors consisted of standard blood work, including complete blood counts (CBC), liver function tests, blood grouping and coagulation profile. Serological tests for hepatitis B surface antigen, hepatitis C antibody, human immunodeficiency virus antibody, Cytomegalovirus IgG and IgM antibodies, mantoux test and chest x-ray were also performed for patients and donors. Additionally, echocardiography, pulmonary function tests and dental evaluation were performed in patients as part of pre-transplant work up.

All patient-donor pairs were positive for Cytomegalovirus IgG. All patients received complete HLA-matched allografts from siblings except three AML patients, who each had one mismatched HLA allele in the allograft from sibling donors.

Transplant environment

All patients undergoing allo-HSCT were kept in protective isolation equipped with High-efficiency particulate air (HEPA) filters, positive pressure and laminar air flow ventilation. Food for the patients was cooked and packaged using terminal pressure and neutropenic precautions.Double lumen Hickman or peripherally inserted catheters were used and dressed once every week by trained nursing staff till the day of discharge. Patients from outside the city were advised to stay near the hospital for the first 100 days after discharge for ease of access to health care and surveillance.

Antimicrobial prophylaxis

Standard prophylaxis with ciprofloxacin (500mg twice daily or 20-30mg/kg/two divided doses), fluconazole (200mg once daily or 6mg/kg/day) and valacyclovir (500mg twice daily or 10mg/kg twice daily) were started for antibacterial, antifungal and antiviral prophylaxis, respectively, in all patients on day -5.

Stem cell source

In all patients filgrastim (recombinant G-CSF) mobilized peripheral blood progenitor cells were used as the only source of stem cells. All donors received filgrastim at a dose of 5µg/kg twice daily for five days prior to stem cell harvest.

Conditioning regimens

Patients with, Philadelphia negative ALL, ABPL, CML and MDS received busulfan (4mg/kg/day for 4 days from day -7 to day -4; total dose: 16mg/kg) and cyclophosphamide (60mg/kg/day for 2 days from day -3 to day -2; total dose: 120mg/kg). Patients with Philadelphia positive ALL, AML and one antigen mismatch donors received cyclophosphamide (60mg/kg/day for 2 days from day -6 to day -5; total dose: 120mg/kg) and total body irradiation (1.5cGY twice daily for 4 days from day -3 to day 0).

Graft versus host disease prophylaxis

Patients were started on intravenous cyclosporine on day – 1. Drug levels were maintained at 200-250ng/dl and 150-200ng/dl for adult and pediatric patients, respectively. Doses were adjusted accordingly. Methotrexate administered at a dose of 15mg/m^2 on day +1 was followed by a dose of 10mg/m^2 on days +3 and +6. Irradiated and leukocyte reduced blood products were used for supportive treatment during hospital admission and post-transplant period. Grading was done according to the Glucksberg classification.

Statistical analysis

All the data was entered SPSS version 19 (SPSS Inc., Chicago, IL, USA) for computing means, standard deviations and range of all descriptive variables.

RESULTS

A total of n=114 allogeneic transplants were performed at the Aga Khan University Hospital from April 2004 to December 2012. Out of these, n=41 were done for hematological malignancies and were included in this study. There were 31 males and 10 females. The remaining n=73 transplants were for other indications and were not included in the study.

The indications for allo-HSCT were AML (n=14), ALL (n=8), ABPL (n=1), CML (n=11) and MDS (n=7). Thirty eight patients were of adult age group (>15 years of age) while the remaining 3 were of pediatric age group (<15 years of age). Median age ± SD was 28 ± 11.7 years (range 8 – 54 years).

A mean of 7.7 x 108 ± 1.5 mononuclear cells/kg were infused (range: 4.2 – 10x108/kg). The median time of WBC recovery was 19 ± 4 days (range: 15 – 23 days).

Eight patients expired by day 100, making the transplant related mortality (TRM) 19.5%. Of the remaining n=33 patients who survived beyond day 100, n=8 had relapse of primary disease, out of which n=7 patients died of relapse. Incidence of GvHD was 34.1%. It was not the cause of death in any of the patients.

The OS at a median follow up of 37 months was 67%. The median duration of OS was 53.6 months (Range: 39.2 – 68.0 months). Details of outcomes according to diagnosis are displayed in Table 1. Mean survival at day 100 according to disease is given in Table 2. The survival curves of the entire patient population and each individual diagnosis are given in Figures 1 and 2, respectively.

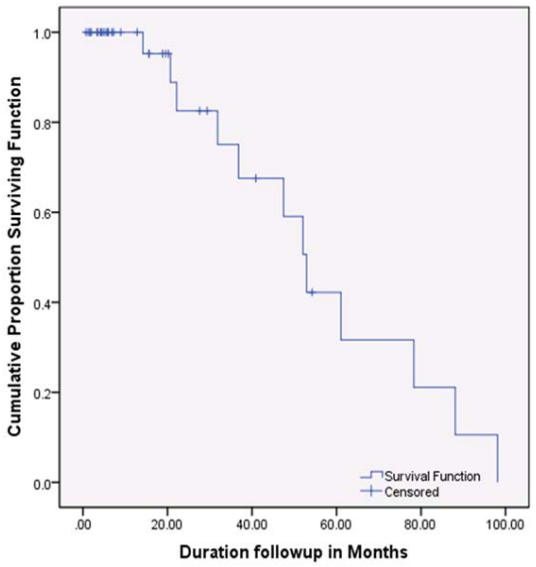

Figure 1: Median overall survival of all patients transplanted

Table 1: Outcome of allogeneic hematopoietic stem cell transplants

Diagnosis	No. of transplants	GvHD	Causes of TRM	RR/ RRM
All patients	41	14 Skin: 6, Gut: 6, Liver: 2	8 Sepsis: 3, CRT:1, Graft rejection: 1, CMV: 1, CMV+RF: 1, IC bleed+RF: 1	8/7
AML	14	5 Skin: 2, Gut: 2, Liver: 1	4 Sepsis: 1, Graft rejection: 1, CMV+RF: 1, IC bleed+RF: 1	4/4
ALL	8	4 Skin: 1, Gut: 3		2/2
ABPL	1	1 Skin: 1		0
CML	11	2 Skin: 1, Liver: 1	3 Sepsis:1, CMV:1, CRT: 1	1/1
MDS	7	2 Skin: 1, Gut: 1	1 Sepsis: 1	1/0

AML: acute myeloid leukemia, **ALL**: acute lymphoblastic leukemia, **ABPL**: acute biphenotypic leukemia, **CML**: chronic myeloid leukemia, **MDS**: myelodysplastic syndrome, **GvHD**: graft-versus-host disease, **TRM**: transplant related mortality, **RR**: relapse rate, **RRM**: relapse related mortality, **CRT**: conditioning related toxicity, **CMV**: cytomegalovirus infection, **RF**: renal failure, **IC bleed**: intracranial bleed

Table 2: Mean overall survival at day 100

Diagnosis	Estimate ± Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound
All patients	27.7 ± 4.6	18.7	36.9
AML	14.5 ± 4.6	5.6	23.4
ALL	26.2 ± 6.6	13.3	39.1
CML	33.2 ± 13.2	7.3	59.1
MDS	42.6 ± 10.2	22.5	62.7

AML: acute myeloid leukemia, **ALL**: acute lymphoblastic leukemia, **CML**: chronic myeloid leukemia, **MDS**: myelodysplastic syndrome

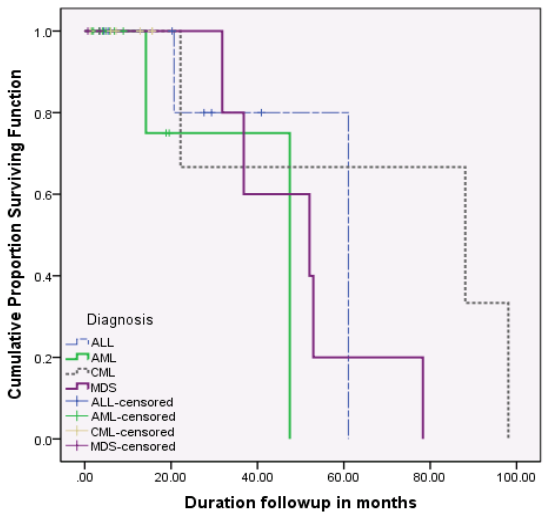

Figure 2: Median overall survival according to diagnosis

DISCUSSION

Combination chemotherapy with antineoplastic agents is the mainstay of treatment for hematological malignancies, inducing remission in a majority of patients.[14] However, relapse of underlying malignancy is a common occurrence, resulting in failure of treatment after chemotherapy. Neutropenia complicated by sepsis and other infections, bleeding, anemia and tumor lysis related metabolic derangements are other causes accounting for morbidity and mortality in such patients.[6, 15] Allo-HSCT has proven to be a superior treatment modality in terms of OS and disease-free survival in randomized control clinical trials[16, 17] when compared with combination chemotherapy alone.

Allo-HSCT was commenced at our center in April 2004. The stem cell transplant unit comprises of highly qualified medical specialists and specially trained nursing staff, HEPA air filters with positive pressure ventilation, infection control protocols and extensive laboratory and blood bank services. Treatment is offered for both benign as well as malignant hematological conditions.[18]

Several complications ensue after allo-HSCT, leading to substantial morbidity and mortality in these patients. Following bone marrow ablation to engraftment and hematopoietic recovery, profound compromise of the immune system leaves patients

vulnerable to fatal infections. After hematopoietic recovery, donor T-lymphocytes in the graft recognize the host tissues as foreign and initiate an immune mediated inflammatory response, giving rise to GvHD, which itself is a feared and potentially fatal complication following allo-HSCT if not treated properly. Despite its dangerous and potentially lethal clinical course, milder forms of GvHD are often welcomed. A certain aspect of GvHD, known as graft-versus-leukemia effect, attacks and destroys any remaining cancer cells in the body and accounts for the highly curative potential of allo-HSCT.[3] Nevertheless, GvHD remains a noteworthy cause of morbidity and mortality following transplantation. The opposite is also an important, albeit infrequent, cause in treatment failure in which the host body rejects the stem cell graft, leading to graft failure.[2-4] Graft failure was the cause of TRM in one of our patients, and has been reported as a cause of mortality at a few other centers.[9, 11, 19]

In our study, sepsis and CMV infection were the major causes of TRM within the first 100 days. Infectious complications have already been previously reported to be the major causes of death in patients undergoing allo-HSCT in Pakistan,[5-7] as well as other countries in the region, like China[9] and Iran.[10] Some western countries have also reported infections and sepsis as the chief reasons for mortality,[12, 20, 21] but in some instances, GvHD has proven to contribute equally or more to TRM than infections or other post-transplant complications.[5-7, 11, 19, 22] Although graft failure was the cause of TRM in one of our patients, GvHD was not the cause of TRM in any patients in our study.

In our series, the overall TRM was 19.5%. Studies conducted at other centers offering stem cell transplantation in Pakistan have shown TRM of 22.7%,[5] 32.6%[7] and 14.3%.[6] After reviewing the outcomes of the first 10 years of allo-HSCT done for hematological malignancies in Pakistan, Shamsi et al[8] found the overall TRM to be 18%. Chen et al [9] from China reported TRM of 15.66%, while Nagafuji et al[23] stated TRM of 8.5% in Japanese patients. A multicenter study conducted by EBMT[12], including patients from several countries like Italy, Turkey, Finland etc., described TRM of 14.7%, while Ringdén et al,[24] in another multicenter study, in patients with AML and ALL, from several countries found TRM to be as high as 29%. These figures from national and international centers, as well as several others, are comparable to the TRM at our center. For example, TRM of 24.2% was observed in large cohort of patients published by the IBMTR and EBMT.[25]

Relapse/progression of primary malignancy after allo-HSCT is not an infrequent occurrence and is a noteworthy cause of treatment failure, morbidity and mortality. Previous studies from Pakistan have reported relapse rates of 4.5%[5], 14%[7] and 14.3%.[6] In these studies, relapse was mostly observed in patients with acute leukemias, and these patients also had a higher rate of relapse related mortality in comparison to CML and MDS. Same was the case in our study, where n=8 patients (19.5%) had relapse of primary disease, out of which n=7 died of the relapse. Six of these patients had acute leukemias. Similar rates of relapse have been reported from India,[11] Iran[10] and China[9] i.e. 16.7%, 11.4% and 21.76%, respectively. These figures are comparable to rates described from other countries like Japan[23] and Brazil[22], i.e. 24.4% and 16.7%, respectively. However, lower relapse rates have been observed in several multicenter studies from western countries, ranging from 8.2% to 14.1%.[12, 20, 25] Ringdén et al[24] have described a relapse rate as high as 40% in one multicenter study, although this study comprised of patients with AML and ALL only, accounting for the high incidence of relapse due to the aggressive nature and clinical course of these malignancies. In most of the aforementioned studies, most patients died of relapse of primary disease, majority of which were patients with AML or ALL.[9, 10, 12, 20, 22, 24]

International CIBMTR data[26] has shown CML to be associated with the best prognosis following allogeneic stem cell transplantation, with an OS of up to 62.9%. Data from Pakistan is very encouraging, showing similar trends in OS and low relapse rate among CML patients after transplantation. Hashmi et al[5] and Ullah et al[7] showed an OS of 77.2% and 69.7% in CML, respectively. There was only 1 case of relapse of CML after transplant in each series, making relapse incidence of 4.5% and 3%, respectively. In our series the median duration of OS was 88 months in

patients with CML. Only 1 out of 11 patients (9%) relapsed and eventually succumbed to the disease. Similarly, low relapse rates and increased OS have been observed in India, where OS was 50% with a relapse rate of 6.7% i.e. n=2 patients.[11] Iranian patients with CML showed an OS of 75% with no cases of relapse,[10] whereas Chinese patients had an OS of 83.87% at 5 years with only n=1 of these dying of the relapse.[9] Similar results have been reported from the western world. Oehler et al[27] from United States of America (USA) reported an OS of 81% with a relapse rate of 3.1%(n=1). An EBMT trial[12] showed OS of 80% and 71% at 1 year and 3 years post-transplant, respectively. Couban et al[20] reported an OS of 79% at the end of 3 years in patients from Canada and New Zealand. A study from Germany has reported an OS of 94.6% with relapse incidence of 3%(n=1).[28] Imamura et al[29] reported an OS of 53.3% from Japan. Relapse rate in CML patients in another paper published by the IBMTR and EBMT was 4.2%.[25]

International CIBMTR data[26] has shown lower survival rates in patients with AML (42.7%) and ALL (41.4%) after allo-HSCT. Data from Pakistan shows similar trends in survival among patients with either AML or ALL post-transplant. Ullah K et al[7] showed an OS of 37.5% in patients with acute leukemias. In this series survival was 100% in n=3 AML patients. However, relapse rate and relapse related mortality was observed in 100% of the n=5 patients with ALL. In our series the median duration of OS for patients with AML and ALL was 47 and 61 months, respectively. Four out of n= 14 patients with AML and two out of n=8 patients with ALL had relapse of underlying malignancy (relapse rates 28.6% and 25%, respectively). All n=6 of these patients eventually died of relapse. In India, patients with acute leukemias had an OS of 51.1%, however, in this study; ALL was associated with comparatively better outcomes than AML, with a higher OS (70% vs. 45.7%). The relapse rate, however, was lower among AML patients in comparison to patients with ALL (22.9% vs. 40%).[11] In Iran, patients with acute leukemias showed an OS of 71.2% (AML 79.4% and ALL 55.6%). Lower relapse rates were observed in AML as compared to ALL (20.6% vs. 33.3%).[10] Mortality was 100% among relapsed patients. Imamura et al from Japan[29] also reported better outcomes in patients with AML when compared with ALL (OS of 44.2% and 33.7%). Similar results have been demonstrated in the western world. An EMBT trial[12] showed OS of 65.7% and 54.1% with relapse rates of 35.3% and 47% at 1 year and 3 years post-transplant, respectively. In this trial, AML was associated with better outcomes in terms of OS and relapse rate in comparison to ALL. A multinational study supported by EBMT[24] reported an OS of 50% in patients with acute leukemia with a relapse rate of 40%. Patients with AML had better outcomes when compared to those with ALL in terms of OS (53% vs. 47%) and relapse rate (34.9% vs. 53.6%). Relapse rate in another paper published by IBMTR and EBMT was 12.5% in patients with acute leukemias.[25]

International CIBMTR data[26] has shown the lowest survival rates in MDS when compared with other myeloid malignancies, with the OS after allogeneic stem cell transplant being 40%. Data from Pakistan shows similar trends in survival among patients with either AML or ALL after transplantation. Out of the two patients with MDS transplanted in the study published by Ullah K et al,[7] one patient died of veno-occlusive disease of the liver, whereas the other patient survived without relapse of primary disease. In our series the median duration of OS was 52 months in patients with MDS. Only one patient died during the pre-engraftment phase due to E. coli sepsis. In India, two out of the eight patients with MDS that were transplanted survived with an OS of 25%. However, the follow up duration for these patients was very short.[11] Iravani et al from Iran[10] showed results similar to Ullah K et al from Pakistan. One out of the two patients with MDS expired due to GvHD. The other patient was surviving without relapse of primary disease. Imamura et al[29] reported an OS of 37.3% in MDS patients from Japan. Similar results have been demonstrated in the western world. An EMBT trial[12] showed OS of 50% and 38% at 1 year and 3 years post-transplant, respectively. Couban et al[20] reported a comparatively higher OS of 61% at the end of 3 years in MDS patients from Canada and New Zealand.

In our study, the OS at a median follow up of 37 months was 67%, which is comparable to survival trends reported previously from other centers in

Pakistan. For example, Ullah K et al[7] reported an OS of 65.1% at the end of 5 years of follow up. Similarly, Hashmi et al[5] and Shamsi et al[6] described OS of 77.2% at a median follow up of 212 days and 66.7% at a median follow up of 678 days, respectively. A review of the data from the first decade from centers across Pakistan showed an OS of 54%.[8] These findings are comparable to those in neighboring countries. While OS in our patients was relatively higher than in India (OS of 48.2%),[11] higher survival rates have been reported in Iranian patients (OS of 71% at a median follow up of 17months)[10] and Chinese patients (OS of 73.49% at the end of 5 years of follow up). [9] The Japanese cohorts have shown an OS of 50.2% at the end of 3 years.[23] Patients from Brazil showed an OS of 47% at 1000 days follow up.[22] Finally, CIBMTR[26] has shown a total of OS of 46.5% in patients undergoing allo-HSCT for hematological malignancies, a survival rate lower than what has been reported in this study.

CONCLUSION

Allo-HSCT is a very effective treatment option for patients with hematological malignancies who have HLA matched donors. The median time to engraftment was 19 days. The TRM was 19.5%, with infectious complications being the leading cause of death in our patients. Although the incidence of GvHD is similar to figures reported in other studies, none of our patients died of GvHD. OS at a median follow up of 37 months was 67%. These figures contribute to our national data and are comparable to previous studies reporting similar outcomes in Pakistan and international literature.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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