Hematopoietic Stem Cell Transplant for Hematological Malignancies: Experience from a Tertiary Care Center in Northern India and Review of Indian Data

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Abstract

Hematopoietic stem cell transplantation (HSCT) is the preferred treatment for high-risk and relapsed/refractory hematological malignancies. Moreover, with the improved supportive care and increasing acceptance of haploidentical transplantsations as an alternative treatment modality, more patients are opting for HSCT as a definite treatment for hematological malignancies. We report here the real-world data and outcome of HSCT done for hematological malignancies at our transplant center. Five hundred and sixteen patients underwent HSCT from August 2010 to November 2019. The most common indications for allogeneic and autologous HSCT were acute myeloid leukemia and multiple myeloma, respectively. The 5-year overall survival and disease-free survival for all transplants were 65% and 33%, respectively. Though outcome of matched sibling donor allogeneic transplant is better than haploidentical donor (HID) transplant, patients having only HID can still be considered for allogeneic HSCT for high-risk diseases. The most common cause of death was infections followed by relapse of the disease.

Keywords
- leukemia
- lymphoma
- myeloma
- matched sibling donor
- allogeneic
- haploidentical
- stem cell transplant
- overall survival
- infections
- GVHD

Introduction

Hematopoietic stem cell transplantation (HSCT) is the preferred treatment for high-risk and relapsed/refractory (RR) hematological malignancies. Acute myeloid leukemia (AML) and multiple myeloma (MM) are the most common hematological malignancies requiring HSCT. There is scarcity of data on the feasibility and the outcome of autologous and
allogeneic stem cell transplant from the developing countries. We report here the real-world data on the outcome of HSCT done at our transplant center.

Materials and Methods

Five hundred and sixteen patients who underwent HSCT at BLK Super Speciality Hospital, New Delhi, India, from August 2010 to November 2019, were evaluated retrospectively using hospital information system and medical records. Informed consent was taken from all patients, and the study was approved by hospital ethical committee and institutional review board. The transplants were conducted in high-efficiency particulate air-filtered rooms. All patients received conditioning regimens as per transplant protocols and transplant physician’s discretion depending upon the type of disease and patient’s performance status.

Conditioning intensity was defined as per the Consensus Center for International Blood and Marrow Transplant Research criteria. \(^1\) Myeloablative conditioning (MAC) regimens were defined by busulfan (Bu) dose \(> 6.4 \text{ mg/kg intravenously}\), whereas reduced intensity conditioning (RIC) regimens were defined by Bu dose \(\leq 6.4 \text{ mg/kg intravenously}\) and melphalan (Mel) \(\leq 150 \text{ mg/m}^2\text{ intravenously}\). The various RIC conditioning regimens used were fludarabine (Flu)/Mel (Flu 30 mg/m\(^2\text{ intravenously for 5 days and Mel 140 mg/m}^2\text{ intravenously for 1 day}), Flu/Bu (Flu 30 mg/m\(^2\text{ intravenously for 5 days and Bu 3.2 mg/kg/day intravenously for 2 days}), Flu/Ara-C/idarubicin/Mel (Flu 30 mg/m\(^2\text{ intravenously for 5 days, cytarabine 2 g/m}^2\text{ intravenously for 5 days, idarubicin 8 mg/m}^2\text{ intravenously for 3 days, and Mel 140 mg/m}^2\text{ intravenously for 1 day}), and Flu/cyclophosphamide (Cy) (Flu 30 mg/m\(^2\text{ intravenously for 5 days and Cy 60 mg/kg intravenously for 2 days}). MAC regimen included Bu/Cy (Bu 3.2 mg/kg/day intravenously for 4 days and Cy 60 mg/kg intravenously for 2 days), Cy/total body irradiation (TBI) (Cy 50 mg/kg intravenously for 3 days and TBI 200 cGy twice daily for 3 days), and Flu/Bu4 (Flu 40 mg/m\(^2\text{ intravenously for 4 days and Bu 3.2 mg/m}^2\text{ intravenously once daily for 4 days}).

The non-myeloablative haploidentical donor (HID) transplant protocol consisted of Flu/Cy/TBI (Cy 14.5 mg/kg/day intravenously for 2 days, Flu 30 mg/m\(^2\text{/day intravenously on days 5 and TBI 200 cGy on day –1}), whereas the myeloablative HID transplant protocol consisted of Flu/Bu/Cy (Flu 25 mg/m\(^2\text{ intravenously for 5 days, Bu 110 mg/m}^2\text{ intravenously for 4 days, and Cy 14.5 mg/kg for 2 days}). Donor-specific antibodies were done using single bead assay for all patients undergoing HID transplants.

For autologous HSCT, MM patients received Mel 200 mg/m\(^2\) (11 patients received Mel 140 mg/m\(^2\)) and lymphoma patients received BEAM (BCNU 300 mg/m\(^2\) on day –6; etoposide 200 mg/m\(^2\) on days –5 to –2 [total dose 800 mg/m\(^2\)], cytarabine 200 mg/m\(^2\) twice daily on days –5 to –2 [total dose 1600 mg/m\(^2\)], and Mel 140 mg/m\(^2\) on day –1) as conditioning regimens before transplant. Stem cells were infused on day 0. For myeloma patients peripheral blood hematopoietic stem cells (PBSCs) were noncryopreserved and for lymphoma patients PBSCs were cryopreserved.

PBSC harvest was done in blood bank and bone marrow harvest was done in the operation theater under general anesthesia. Posttransplant graft versus host disease (GVHD) prophylaxis included methotrexate, cyclosporine, or post-transplant cyclophosphamide (50 mg/kg on day +3 and day +4 posttransplant), tacrolimus, and mycophenolate mofetil as per protocol. All patients received antimicrobial prophylaxis including fluconazole (200 mg once a day orally), acyclovir (400 mg twice a day orally), and co-trimoxazole, and treatment of febrile neutropenia as per hospital policy. Engraftment was defined by absolute neutrophil count more than 500/\(\mu\)L for three consecutive days and platelet counts more than 20,000/\(\mu\)L for 7 days after last platelet transfusion. GVHD was graded as per Glucksberg criteria and was treated with intravenous methylprednisolone accordingly. After discharge the patients were regularly followed up in outpatient clinics.

Statistical Analysis

Survival analysis was done using Kaplan–Meier curve analysis using MedCalc version 2.0. Multivariate analysis was performed using Cox proportional regression analysis and log rank test for patients undergoing autologous and allogeneic transplants. Statistical calculation for comparison between matched sibling donor (MSD) and HID HSCT was done using chi-square test or Student’s t-test as required.

Results

Out of the 516 patients, who underwent HSCT for hematological malignancies, 348 were males and 168 were females. Median age was 43 years (range: 2–75 years) (Table 1). Two hundred fifty-eight (50%) patients underwent autologous HSCT. Among allogeneic HSCT, 181 were MSD HSCT, 64 were HID HSCT, and 13 were matched unrelated donor (MUD) HSCT. The most common indication for allogeneic HSCT was AML (32.4%) and the most common indication for autologous HSCT was MM (35.8%). The most common RIC regimen used was Flu/Mel, and the most common MAC regimen used was Bu/Cy (Table 1). Grade 1 acute GVHD and grade 2 to 4 acute GVHD developed, respectively, in 4.3 and 26.8% patients undergoing allogeneic HSCT. All patients with grade 2 to 4 GVHD were treated with intravenous methylprednisolone 1 mg/kg twice a day as first line treatment. Second line treatment included etanercept (0.4 mg/kg twice a week), ruxolitinib (5–10 mg twice a day), or methotrexate. About 11% patients responded to steroids whereas 36.1% patient required two or more lines of treatment. Chronic GVHD was seen in 16.3% patients. Cytomegalovirus (CMV) reactivation was seen in 31.2% of patients and the patients were treated with intravenous ganciclovir (5 mg/kg twice daily) followed by oral valganciclovir. The 5-year overall survival (OS) and disease-free survival (DFS) for all HSCTs were 65 and 33%, respectively. Table 2 and Figs. 1 and 2 show the disease-specific 5-year OS and DFS. Among allogeneic HSCT patients, the 5-year OS was significantly better in the MSD group compared with the HID group (53.6% vs. 21.7%, \(p < 0.001\)), though the 5-year DFS was not significantly different.
between the two groups (42% vs. 35.7%, \( p = 0.247 \)). The overall mortality was 30.8%. The most common cause of death was infection followed by relapse of the disease. Seven patients developed proven or probable fungal pneumonia based on bronchoalveolar lavage or chest computed tomography scan findings. Five patients developed posterior reversible encephalopathy syndrome and there was no death due to bleeding. Gram-negative bacterial infection was seen in 18.4% of patients and the most common bacteria grown were *Escherichia coli*, *Pseudomonas aeruginosa*, Klebsiella, and Enterococcus. Day +100 transplant-related mortality (TRM) of the total cohort was 16.6%.

In multivariate analysis, for allogeneic HSCT, factors impacting OS were chronic GVHD (\( p = 0.0272 \)), engraftment (\( p < 0.0001 \)), and Eastern Cooperative Oncology Group (ECOG) status (\( p = 0.0302 \)), while diagnosis, acute GVHD, donor source, graft source, mucositis, veno-occlusive disease, and CMV reactivation were not significant. For DFS, significant factors were chronic GVHD (\( p = 0.0064 \)) and engraftment (\( p < 0.0001 \)), while acute GVHD, ECOG status,
graft source, mucositis, veno-occlusive disease, and CMV reactivation were not significant. Primary graft rejection was seen in three patients that underwent HID, two with AML and one with acute lymphoblastic leukemia (ALL).

Discussion

India has a large population of 1.39 billion as per estimates in 2021, with increasing proportion of patients being diagnosed with hematological malignancies, requiring HSCT. In India, approximately 19,421 HSCT have been done till 2019 according to the Indian Society for Blood and Marrow Transplantation Registry (ISBMTR-2020). In 2019 alone 2,932 HSCT were performed in India and about one-third of those who underwent allogeneic HSCT were HID HSCT. With the increasing acceptance and availability of better supportive care, increasing number of patients are undergoing HSCT in developing countries, with improved outcomes and lesser cost of transplant.² In our cohort of patients, MM was the most common indication for autologous HSCT followed by Hodgkin lymphoma (HL), whereas AML was the most common indication for allogeneic HSCT followed by ALL. There is scarcity of multicenter data from India, with only few single-center studies available (►Table 3).

Multiple Myeloma

MM is still the most common indication for autologous HSCT worldwide and in India. Various studies have been reported from the Indian subcontinent. Malhotra et al have reported the median OS of 76.7% and progression-free survival (PFS) of 55.8% at 6.5 years.³ Kumar et al have reported an estimated OS at 10 and 15 years of 40.4 and 17.7%, respectively, and day + 100 TRM of 5.2%.⁴ Kulkarni et al have reported 5-year OS and PFS of 61.6 and 37.2%, respectively, and TRM of 2.86%.⁵ In our cohort of myeloma patients, the 5-year OS and DFS were 82.3 and 29.3%, respectively, with mean DFS of approximately 44 months.

Lymphoma

The age-adjusted incidence rates for non-Hodgkin lymphoma (NHL) in men and women in India have been reported at 2.9/100,000 and 1.5/100,000, respectively.⁶ Approximately 50 to 60% of patients with diffuse large B cell lymphoma (DLBCL) achieve and maintain complete remission after first-line therapy, whereas 30 to 40% relapse and 10% have refractory disease.⁷ High-dose therapy followed by autologous stem cell transplant (HDT-ASCT) is the mainstay of therapy for RR-DLBCL. The landmark PARMA trial has established HDT-ASCT as the standard of care for RR-DLBCL.⁸ In a study from India, in patients with B cell NHL treated with chemotherapy (CHOP ± R), 4-year OS and event-free survival (EFS) were 64.7 and 54%, respectively.⁹ RR-NHL remains the major cause of morbidity and mortality.¹⁰ In a study by Kumar et al, in a similar cohort of patients treated with autologous HSCT, estimated 5-year OS and EFS for patients with RR- HL and NHL were 54.34 and 34.3%, respectively, and TRM was 7%.¹¹ In our study, the 5-year OS and DFS for RR-HL were 83 and 29.5% and for RR-NHL were 65 and 38%, respectively, and are comparable to that reported in literature.¹²,¹³

Acute Myeloid Leukemia

Allogeneic HSCT is the preferred treatment for intermediate- and high-risk AML and for RR-AML. In a study by Ganapule et al, which included 254 consecutive patients who underwent allogeneic-HSCT for AML, the 5-year OS and EFS were 40.1 and 38.7%, respectively.¹⁴ In the studies comparing RIC versus MAC from the Indian subcontinent, Ganapule et al has reported better OS and EFS with RIC regimen compared with MAC but this was not found in a study by Sharma et al, from similar cohort of patients.¹⁴,¹⁵ Among children (age < 18 years) with AML who underwent allogeneic HSCT, Arora et al have reported 5-year OS and EFS of 36.3 and 33.3%, respectively.¹⁶

In allogeneic HSCTs, matched donor HSCTs are still preferred over HID-HSCTs; however, advances in graft techniques and pharmacological prophylaxis of GVHD have reduced the risks of graft failure and GVHD after HID-HSCT and have made haploidentical stem cell source a viable
alternative for patients lacking an human leukocyte antigen-matched donor.\(^{17}\) There are no published randomized comparisons of HID HSCT versus MSD HSCT. Wang et al have compared the outcomes of HID and MSD HSCT groups, the 3-year OS rates were 79 and 82\%(p = 0.36), and DFS rates were 74 and 78\%(p = 0.34), respectively, and the cumulative incidences of relapse were 15 and 15\%(p = 0.98), and the nonrelapse mortality rates were 13 and 8\%(p = 0.13), respectively.\(^{18}\) In a large retrospective study by Ringdén et al, there was no statistically significant difference in probability of relapse between the MSD group when compared with the HID HSCT group but the leukemia-free survival was superior in the MSD group.\(^{19}\) Nataraj et al studied MSD and HID HSCT in 122 patients, and there were 38\% deaths in MSD and 50\% deaths in HID HSCT \(p = 0.245).^{20}\) A study by Jaiswal et al on HID in pediatric acute leukemia have reported 2-year OS of 64.3\%.\(^{21}\) In our study, the outcome of HID HSCT was inferior compared with MSD HSCT. The OS in the MSD group was significantly lower in HID compared with MSD (21.7% vs. 52.6%, \(p < 0.001\)). This difference was attributed probably to increased risk of infections in the HID transplant. Sepsis was the cause of death in 22\% of MSD compared with 37.5\% of HID HSCT.

Though this real-world data shows variable results of HID compared with MSD transplant, HID HSCT is still a viable treatment option for high-risk patients who either lack an MSD or for those whom a MUD cannot be found or mobilized timely.\(^{22}\) Better understanding of the role of T cells,\(^{23}\) B cells,\(^{24}\) and antigen presenting cells in the pathophysiology of rejection, and acute and chronic GVHD, has improved the management of transplant-related complications.

### Conclusion

Autologous and allogeneic HSCTs are the curative treatment options for many high-risk and RR hematological malignancies. Though outcome of MSD allogeneic transplant is better than HID transplant, patients having only HID can still be considered for allogeneic HSCT for high-risk diseases. Infections and relapse of the disease post-HSCT are still the major obstacles in the successful outcome of HSCT.

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Ethics Committee Approval
The protocol and informed consent was approved by the Hospital ethical committee. Informed consent was taken from all the patients.

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Conflict of Interest
None declared.

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