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Allogeneic peripheral blood stem-cell transplantation and long-term survival outcomes - A retrospective observational study

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Abstract

Allogeneic hematopoietic stem cell transplantation (allo-HCT) has been extensively investigated as a potentially curative treatment option for hematological malignancies and other cancers. The current study aimed to investigate the long-term survival outcomes after allo-HCT. We retrospectively analyzed the long-term survival outcomes of patients who received allo-HCT from April 2015 to March 2021 at the Department of Haematology, SMS Hospital for different malignancies. Data from 51 patients with a mean age of 18.7 ±10.79 years who underwent peripheral blood allo-HCT as their first transplant were included for analysis. The average follow-up period was 30 months with a mortality rate of 23.52% (n=12). Overall, 39 patients were still alive and complete response was observed in 36 (92.3%) of patients. In summary, this retrospective study evidenced that peripheral blood (PB) derived allo-HCT has some survival advantages and can be successfully performed with the appropriate conditioning regimen and graft versus host disease (GVHD) prophylaxis.

Keywords: allogeneic transplantation, peripheral blood stem-cell transplantation, conditioning regimen, retrospective observational study, survival outcomes

1. Introduction

Hematologic malignancies (HMs) are heterogeneous disorders that accounts for 6.5% of all cancers around the globe and the incidence continues to rise (1). Although the treatment strategies for HMs have gained tremendous headway, the morbidity and mortality rate attributed to HMs still remain substantial (2). At this juncture, hematopoietic stem cell transplantation (HCT) using hematopoietic progenitor cells from a donor (allogeneic HCT) or the patient (autologous HCT) is a potential therapy, including HMs (3). However, transplantation type also significantly impacts the clinical outcomes in patients. In general, malignancy type, age of the recipient, status and stage of disease, and graft versus host disease (GVHD) effects are the factors to be considered for selection of transplantation type (4).

Although autologous stem cell transplantation (auto-HCT) offers lower treatment related mortality (<5%), rapid immune reconstitution, and lower risk of GVHD. On downside, auto-HCT has a higher relapse rate for disease dissemination due to contamination of autograft with clonogenic tumor cells(4). Allo-HCT includes irradiation-based conditioning regimens (non-myelo-ablative or ablative), and infusion of alloreactive HCT (for anti-tumoral effect and active immunological effect). In myelo-ablative regimen patients, 15–25% of early mortalities were reported to be due to GVHD, immunosuppression-induced infections, and drug-induced toxicities (5). Therefore, allo-HCT can be preferentially recommended only in patients with high-risk features after relapse, or after initial chemotherapy (6). Allo-HCT also offers a lower risk for disease recurrence and long-term survival benefits due to immune graft-versus-malignancy effect (4, 7, 8). However, the therapeutic potential of allo-HCT remains limited by both acute and chronic GVHD (9, 10). Besides, there have been many changes in transplantation practices over the past decade. Therefore, in the current study we investigate new insights into long-term survival after allo-HCT.

2. Matherials and Methods

2.1. Study design and population

In this single-center observational study, data on patient with specific cancer types (Table 1) who underwent allo-HCT at Department of Haematology of SMS Hospital from April 2015 to March 2021 were collected from the medical records and analyzed retrospectively. Before initiation, the study was cleared by IRB. Patient informed consents were taken from all the participating patients.

2.2. Data collection

Data collected for analysis included the patients' clinical characteristics such as age, gender, histological subtype of cancer, disease status, transplantation type and chronological

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order, conditioning regimens, acute GVHD (aGVHD) and chronic GVHD (cGVHD), cause of death, etc. The major patient dependent factors for allo-HCT include age, ECOG status, donor availability, and unfavorable prognostic factors (response to chemotherapy, bone marrow involvement, etc) Patients with missing required data were excluded.

Table 1. Baseline patient characteristics, transplant, and treatment data

Characteristics	Number of patients (n=51), %
Age (years ± SD)	18.7(±10.79)
Sex	
Men	34 (66.67)
Women	17 (33.33)
Acute graft versus host disease (GVHD)	
Yes	27 (52.94)
No	24 (47.05)
Chronic GVHD	
Yes	05 (9.80)
No	46 (90.19)
Time in days (range)	618(8-1920)
Status at last follow-up	
Dead	12 (23.52)
Alive	39 (76.47)
Cause of Death (n=12)	
Renal failure	3 (25)
Infection	2 (16.66)
GVHD	5 (41.66)
Progressive disease (PD)	2 (16.66)
If Alive (n=39)	
Complete hematologic remission	36 (92.30)
Relapse	3 (7.69)
Chronological number of transplant - 1st transplant	51
Type of Transplant - Allogenic	
Allogeneic (matched donor)	42 (82.35)
Haploidentical	9 (17.64)
Donor	
Identical sibling	30 (58.82)
Matched/Mismatched relative	21 (41.17)
Type	
Peripheral blood	51
Aplastic Anemia (AA)	24 (47.05)
Acute myeloid leukemia (AML)	8 (15.68)
Thalassemia	5 (9.80)
Myelodysplastic syndromes (MDS)	5 (9.80)
Acute lymphocytic leukemia (ALL)	3 (5.88)
CML with blast crisis	2 (3.92)
Chronic myeloid leukaemia (CML)	1 (1.96)
Dyskeratosis congenita	1 (1.96)
Congenital dyserythropoietic anemia (CDA) type II	1 (1.96)
Acute promyelocytic leukaemia (APML)	1 (1.96)
Status at transplant	
1st Complete hematologic remission	6 (11.76)
First relapse	14 (27.45)
Not applicable	31 (60.78)
Diagnosis - conditioning regimen used	
Flu-Cy-ATG-Fludarabine+Cyclophosphamide+anti-thymocyte globulin	23 (45.09)
Bu-Flu – Busulfan+Fludarabine	15 (29.41)
Flu-Mel – Fludarabine+Melphalan	7 (13.72)
Melphalan	2 (3.92)
Cy-TBI – Cyclophosphamide and total body irradiation	1 (1.96)
Bu-Flu-ATG – Busulfan+Fludarabine+ anti-thymocyte globulin	1 (1.96)
Bu-Cy-MTX–Busulfan+ Cyclophosphamide+Methotrexate	1 (1.96)
Flu-Cy-MTX–Fludarabine+Cyclophosphamide+Methotrexate	1 (1.96)

2.3. Statistical analysis

Descriptive statistics were used to summarize the data using SPSS 22 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patients and transplant characteristics

Baseline patient characteristics, transplant, and treatment data are presented in Table 1. Of the 51 included patients for analysis, 34 (66.67%) were female and 17 (33.33%) were male and the mean age was 18.7 ±10.79 years. Further, all the included patient underwent peripheral blood allo-HCT (PBHCT, matched donor (82.3%) and haploidentical (17.64%) as first transplant. Majority of the included patients were diagnosed with aplastic anemia [24 (47.05%)] followed by acute myeloid leukemia [8 (15.68%)]. At the time of transplant, around 11.6% and 27.5% were in complete response (CR) and first relapse, respectively. Further, Flu-Cy-ATG – Fludarabine + Cyclophosphamide + anti-thymocyte globulin was used as conditioning regimen in majority of the patients (45.09%) followed by Bu-Flu – Busulfan + Fludarabine (29.41%).

3.2. Post-transplant outcomes

At a mean follow-up date 30 months' post-transplantation, 39 patients were still alive and CR was observed in 36 (92.3%) of patients. Further, 12 (23.52%) were succumbed and the causes of deaths were related majorly to GVHD [5 (41.66%)] followed by infection and progressive disease, 16.6 % each.

4. Discussion

Since its first application in 1957 between identical twins, the field of allo-HCT has made ground-breaking progress (11). Among various transplantation methods, peripheral blood stem cell transplantation has become preferred stem cell source largely replacing bone marrow due to its ease of collection and quicker engraftment kinetics. In the recent with the existing literature support, the use of Allo-HCT using hematopoietic progenitor cells has increased greatly as a potentially curative therapy for many nonmalignant disorders and life-threatening cancers. The Allo-HCT has the advantage over other techniques such as autologous transplantation in terms of its contaminating tumor cells free grafts and lower risk for disease recurrences, respectively. The allo-HCT outcomes have also improved over the years due to a variety of factors - including transplant techniques, matching of donor-recipient, and better patient selection (12). On the downside, allo-HCT is still associated with some potentially fatal complications such as GVHD, graft failure, and regimen-related organ toxicity (4). Overall, allo-HCT advantages outweighed its disadvantages and emerged as preferred transplantation technique. Over the

years, its usage was also projected to be increased proportionally with the advancement of technology, where patients were received a risk-adapted, individualized multidisciplinary follow-up care.

As per literature, large number of our patients also underwent matched unrelated or related donor HCT, to avoid allogeneic transplant related risks and for best possible outcomes (12). However, long-term follow-up reports from Hilgendorf et al. (13) have reported that patients who received a transplant before the age of 35 years were observed to have faced greater challenges in terms of long term complications. Such complications were quite evident in our patient population too, due to their lower age during the time of transplantation. Such chief risk factors reported from the studies and from our patient experiences were observed to be age, GVHD, infections, and progressive disease (7, 9, 10, 13).

A retrospective analysis from the EBMT registry have measured the non-relapse mortality over the years and it was observed to be decreased over time: 29.7% from 1980 through 1989 to 12.2% in 2010 through 2016 (14). Similar results were reported from our study but with a slight increase in mortality, possibly related to the lower age of patients at the time of transplantation. On contrary, in a retrospective study conducted by Greco et al. (15) a long-term disease remission with improved outcomes were reported in younger patients, especially in terms of toxicities and non-relapse mortality. Whereas, the prominence of GVHD and infections as a cause of death was no surprise and has also been noted earlier in multiple studies (7, 10). So clinically in allo-HCT, an emphasis on controlling and reducing GVHD should remain as high priority. Simultaneously, extra care should be taken in all the patients during the pre and post transplantation to avoid any such infections and their related deaths caused due to the insufficient immunologic recovery (7, 16, 17).

Overall, the literature suggests that the better supportive therapy, advanced intensive care medicine (to control infectious diseases, GVHD, etc), reduction in the intensity of conditioning regimens, adapted treatment protocols for induction/conditioning, improved risk stratification, and patient selection can play a likely vital role in contributing to better outcomes and survival pre and post allo-HCT. It was also evident from the literature that patients who underwent transplantation and survived the first 5 years without any recurrence of original disease were also projected to have high life expectancy (10).

Nevertheless, the limitations of the present study include its retrospective nature, small sample size, and non-heterogeneity.

In summary, this retrospective study evidenced the lower risk of disease recurrence and survival advantage in patients treated with PB-derived allo-HCT by successfully adapting the appropriate conditioning regimen and GVHD prophylaxis. PB-derived allo-HCT can also be preferentially recommended in patients with high-risk features after relapse, or after initial chemotherapy. Nonetheless, to optimise long-term outcomes and to avoid late life-threatening complications, regular follow-ups are highly recommended. In future prospective comparative studies, the role of each transplant modality in different subsets of patients receiving different conditioning regimens should be defined along with long-term follow-up outcomes.

Conflict of interest

The authors declared no conflict of interest.

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Authors' contributions

Concept: M.K., J.Y., Design: M.K., J.Y., Data Collection or Processing: M.K., S.J., A.M., K.G., R.K., L.M., S.K., J.Y.; Analysis or Interpretation: M.K., J.Y.; Literature Search: M.K., J.Y.; Writing: M.K.

Ethical Statement

This study was approved by the Institutional Review Board and Ethics Committee of SMS Hospital, Jaipur as part of project in accordance with the 1964 Helsinki declaration and later amendments. As the study was retrospective, there was no study-specific consent. All patients granted verbal or written consent prior to and investigation or treatment.

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