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Lymphoma and Myeloma

Clinical Outcomes of Autologous Hematopoietic Stem Cell Transplant in Multiple Myeloma Patients: A 5-year Experience from a Single Centre in North India

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Abstract

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Introduction Multiple myeloma (MM) forms a significant proportion of hematological malignancies. Autologous transplantation continues to be an effective consolidation strategy in resource-restricted settings such as India.

Objectives The main objective of the study was to analyze the clinical outcomes of autologous hematopoietic stem cell transplant (HSCT) in MM patients in a single tertiary care center in north India over a period of 5 years.

Materials and Methods This retrospective observational study was conducted in a tertiary care center in north India. Data of all MM patients who underwent HSCT between January 2014, and December 2018, were analyzed. The outcome of HSCT was investigated in terms of transplant-related mortality (TRM), progression-free survival (PFS), overall survival (OS), and relapse. PFS and OS were calculated by Kaplan–Meier method and differences between the groups were tested for statistical significance using the two-tailed log-rank test. Life-table method was used for the estimation of survival rate at 1, 3, 5, and 6 years.

Results Patient characteristics and survival post-transplant was similar to other published Indian studies. In total, 378 patients were diagnosed with MM in our hospital between 2014 and 2018. One hundred ninety-three patients were found to be eligible for autologous HSCT, out of which 52 ended up having a transplant giving us a high percentage (26.9%) of patients receiving a transplant in our setting. Transplant-related mortality (TRM) was nil in the present study. The mean PFS and OS were 62.8 and 70.1 months, respectively. The mean PFS and OS rates at 5 years were 75.3% and 84.2%,

Keywords

- myeloma
- multiple myeloma
- autologous transplant
- hematopoietic stem cell transplant

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respectively. The average cost estimate of HSCT in our setting was 7.2 lakh Indian national rupees.

Conclusion Autologous HSCT is a safe procedure with nil 100-day mortality in present series. Moreover, considering the cost of novel agents, autologous transplant remains a cost-effective way for prolonging remission and time-to-next treatment in India.

Introduction

Multiple myeloma (MM) forms a significant proportion of hematological malignancies in several tertiary-care centers. In several patients, high-dose chemotherapy and autologous hematopoietic stem cell transplant (HSCT) transplant is indicated.[1] Widespread use of autologous HSCT has improved survival in myeloma patients.[2,3] HSCT has been accepted as a mode of consolidation therapy for the treatment of MM worldwide.[4,5] However, it is only recently that this type of treatment has become popular in India with the first report published in 2000.[6] Though there are a few reports on autologous HSCT from India, there is perhaps, still need for further data with respect to not just clinical outcome data but also cost estimate of HSCT in resource-restricted economies such as India. We would, therefore, like to present our 5-year experience of HSCT from our center in north India.

Materials and Methods

Settings

This retrospective study included all consecutive multiple myeloma patients treated at a large tertiary-care hospital in north India, between January 2014, and December 2018. MM patients found eligible for HSCT by the transplant physician and who underwent HSCT at our center within the selected time period were included in the study. Patients who did not respond to myeloma treatment (primary refractory) and patients with plasmacytomas, and plasma cell leukemia were excluded.

All multiple myeloma (MM) patients received standard induction treatment in the form of combination of proteasome inhibitor (bortezomib), immunomodulating agent (lenalidomide), and steroid (dexamethasone).[7] In a 3-week cycle, bortezomib was given at a dose of 1.3 mg/m^2 twice weekly, lenalidomide tablets were given at a dose of 10 to 25 mg, day 1 to 14 (dose based on tolerance), and dexamethasone 40 mg once a week. Patients who failed to respond to the standard first-line therapy were started on second line (generally carfilzomib/pomalidomide/dexamethasone). Response to the induction therapy was assessed according to the International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in MM. The "fitness-for-transplant" definition in our center was in line with the internationally accepted criteria.[8] The overall fitness-for-transplant was determined by the treating physician based on age, performance status of the patient, cardiac, pulmonary, and renal functions. This percentage was derived from the ratio of patients, who underwent transplant and the total number of MM cases who were considered eligible for transplant.

Mobilization was done using granulocyte colony-stimulating factor at a dose of 10 µg/kg body weight before harvest. Pre-peripheral blood (PB) CD34+ cell count was done on the fourth day of mobilization. Four patients with PB CD34+ $<$ 10 cells/µL received plerixafor (CXCR4 chemokine inhibitor) for mobilization. Harvest was performed on the fifth day. All procedures were done by apheresis machine (COM.TEC Fresenius Kabi, Germany). A dose of 5 million CD34+ cells/kg body weight was targeted with minimum of 2 million CD34+ cells/kg body weight. Melphalan was administered on the evening of successful harvest at a dose of 200 mg/m^2 unless renal impairment where it was reduced to 140 mg/m^2. The harvest product was infused after a gap of 24 hours from the time of melphalan administration.

Neutrophil engraftment was defined as absolute neutrophil count of 500 cells/mm^3 (0.5×10^9/L) or greater for 2 consecutive days. Platelet engraftment was defined by the achievement of a continued platelet count of 20,000/mm^3 (20×10^9/L) or greater for 2 consecutive days, at least 7 days from the last platelet infusion. Those who did not engraft up until the 28th day were considered as "engraftment failure."

After successful engraftment, patients continued to receive lenalidomide until progression. Patients with 17 p deletion were given bortezomib.

Transplant-related mortality (TRM) was defined as deaths within first 100 days of transplant due to toxicity of the pre-transplant therapy and/or pre-transplant conditioning regimen. Progression-free survival (PFS) was defined as the length of time from the start of the treatment to the time of relapse measured in months. Overall survival (OS) was defined as the length of time from the date of the start of the treatment of disease to the last known follow-up, when the patients were still alive and was measured in months. For evaluation of effect of age on survival, transplanted patients were stratified into two groups: $<$60 and $>$60 years. The PFS rate was defined as the percentage of patients whose disease did not show any signs of progression and remained stable after HSCT. The OS rate was defined as the percentage of the patients in the study cohort who were still alive for a certain period of time after HSCT.

Primary outcome was measured by TRM, PFS, OS, and relapse. Secondary outcome was measured by the response

to the treatment in terms of complete remission (CR) and very good partial response (VGPR).

The total cost of autologous HSCT, including cost of mobilization, peripheral blood stem cell collection, conditioning, stem cell infusion, drugs, laboratory investigations, hospital stay was retrieved from the hospital information system (HIS). The cost was obtained for all patients, who underwent HSCT. The cost of the course of second line of treatment with daratumumab (anti-CD38 monoclonal antibody) was obtained from the hospital pharmacy and compared with HSCT costs.

Data of all patients diagnosed with MM, eligible for HSCT and those who underwent autologous HSCT between 2014 and 2018 were retrieved from HIS. HSCT patient's follow-up data including engraftment, survival (TRM, PFS, and OS) and relapse data were collected. All data were analyzed systematically. Follow-up was done until January 2021. We did not include staging or prognostic FISH information in our analysis.

The analysis included profiling of patients on different demographics parameters and treatment outcomes (survival and relapse-free survivals). The Shapiro–Wilk test was used to test the normal distribution of the data. Quantitative data are presented in terms of median and inter-quartile range (IQR). Qualitative/categorical data are presented as absolute numbers and percentages and OS were calculated using the Kaplan–Meier method and differences between groups were tested for statistical significance using the two-tailed log-rank test. Life table method was used for the estimation of survival rate at 1, 3, 5, and 6 years. A p-value < 0.05 was considered statistically significant. The median and the range of cost of treatment were calculated. The SPSS software version 24.0 (Statistical Package for the Social Sciences; IBM Bengaluru, India) was used for statistical analysis.

This study was ethically approved by the institutional review board (IRB) on November 18, 2019 (reference number MICR: 1034/2019). The waiver of patient consent was obtained from the IRB due to the retrospective nature of the study.

Results

In total, 378 patients were diagnosed with MM between 2014 and 2018. Also, 193 patients were eligible for HSCT as determined by the treating physician. Out of the 193 transplant-eligible patients, 52 ended up having a transplant giving us a baseline percentage (26.9%) of MM patients, eventually receiving HSCT in our setting.

In the study cohort, more than two-third of patients who underwent transplant were males (37 patients, 71.2%), the rest were females. The age of the patient in the study ranged from 32 to 69 years with a median of 55.5 years. The majority of patients were in the age group of 51 to 60 years (28 patients, 53.8%), followed by 12 (23.1%) and 10 (19.2%) patients in the age groups of 61 to 70 and 40 to 50 years, respectively. Also, 42.3% (22) of patients who underwent HSCT had blood group O followed by 28.84% (15) of patients with blood group B and 25% (13) and 3.84% (2) patients with blood groups A and AB, respectively. Out of 52 transplanted patients, all relevant data were available for 50 patients; these 50 patients were profiled for the analysis of disease status at the time of transplant, disease status at last follow-up and TRM, PFS, and OS.

HPCs were harvested on the fifth day of mobilization. The median peripheral blood pre-CD34+ cell count was 38 cells/μL with a range of 6 to 256 cells/μL. The total blood volume (TBV) processed varied from 1.3 to 8, the median being 3.2. The median total cell dose collected was 6.06 million CD34+ cells/kg with a range from 1.73 to 31.75 million CD34+ cells/kg. The median product volume collected was 457 mL (150–1,000 mL).

The vast majority of patients, i.e., 31 out of 50 (62%), were in CR and VGPR and 19 (38%) patients in PR at the time of transplant.

The median follow-up was 33.6 months (1.3 months–78.3 months). The median time for neutrophil and platelet engraftment was 11 and 11.5 days, respectively. There was no TRM (first 100 days post-transplant) in the cohort. The mean overall survival (OS) was 70.1 months (95% CI: 63.8–76.4) (►Fig. 1). Stratification by age revealed that the mean OS was longer in younger patients (< 60 years) (OS = 70.3 months; 95% CI: 63.1–77.4) in comparison with patients ≥ 60 years (OS = 56.1 months; (95% CI: 52.0–60.2). However, this was not statistically significant (Log rank Mantel–Cox = 0.057; p-value = 0.811). The post-transplant six-year OS rate was 84.2% (at 1, 3, 5, and 6 years was 98.0%, 91.2%, 84.2%, and 84.2%, respectively). The mean PFS was 62.8 months (95% CI: 55.2–70.4 months) (►Fig. 2). The PFS rate at 6 years was 75.3% (at 1, 3, 5, and 6 years were 87.1%, 75.3%, 75.3%, and 75.3% respectively). None of the patient developed any secondary malignancy during the follow-up.

On follow-up, it was found that 64% (32) of the patients were in CR, 6% (3) patients were in VGPR at follow-up, whereas 20% (10) patients had relapsed, and 10% (5) patients had died due to relapse and subsequent infections in the cohort.

The median cost of HSCT in our hospital setting was found to be 7.2 lakhs (range: 6–20 lakhs). The course of treatment with daratumumab was 14 lakhs (drug cost) for induction therapy over 2 months and another 14 lakhs for next 4 months for consolidation therapy.

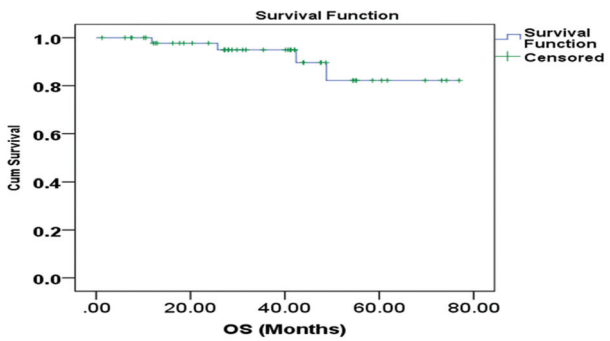

Fig. 1 Kaplan–Meier curve for overall survival.

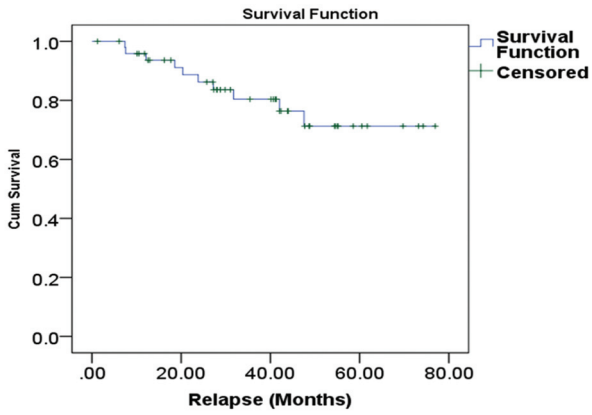

Fig. 2 Kaplan–Meier curve for progression-free survival.

Discussion

MM a plasma cell dyscrasia, accounts for ~10% of all hematological malignancies.[9] Autologous HSCT is a vital component of management of MM, and it is only recently that it has gained popularity in India. In our study, out of 193 transplant-eligible patients, 52 (26.9%) had a transplant. This was real-world data, outside the realm of clinical trials on percentage (26.9%) of eligible patients who eventually underwent HSCT from a single center. The majority of patients (71.2%) who underwent transplant in our settings were male, which is similar to other published studies from India.[9,10] The male predominance in our data possibly reflects the society's attitude providing greater privileges to men as compared with women, even with respect to "access to treatment." In our opinion, it does not reflect the pattern of myeloma presentation or increased incidence in the male gender. The median age at diagnosis in the present study was 55.5 years, which is comparable to other Indian studies.[9,10] However, this is decade earlier as compared to the western world.[9,11]

The median time for neutrophil and platelet engraftment was 11 and 11.5 days, respectively, which was similar to other published reports.[10,12] CR and VGPR rates were substantially higher post-HSCT transplant (70%) as compared with what they were before transplant (62%). More than two-third of the patients were in CR and VGPR at follow-up post-transplant. These improved remission rates were similar to three previous published reports from India.[13–15]

In our study, there was no TRM that meets the current standard of 1% or less.[16] The mean PFS and OS at a median follow-up of 33.6 months were 62.8 months and 70.1 months, respectively. The long-term survival of our patient cohort post-transplant was comparable to survivals achieved in large randomized controlled trials.[17] Our PFS data also corroborate with PFS achieved in large trials.[7,17,18] The survival data in our study, shown in ►Table 1, are comparable to other published reports from India and demonstrate beyond doubt that autologous HSCT is a safe and feasible treatment modality for MM in resource-restricted countries such as India. The non-relapse mortality of the transplant procedure was nil. All deaths ($n = 4$) reported were due to relapse and subsequent complications. Our data throw up no additional safety concerns in the autologous HSCT setting.

The treatment cost data of HSCT versus second-line therapy are useful in the context of resource-restricted economies such as India. The present study has shown that PFS is ~5 years after autologous HSCT in MM patients. HSCT is, therefore, a useful modality to delay the time-to-next treatment. An autologous HSCT costed ~7 lakh Indian rupees (~10,000 USD) in our corporate hospital setting. Costs may be lower by around 20 to 30% in a government or government-supported charitable hospital, whereas the second-line therapy with daratumumab costs ~14 to 15 lakh Indian rupees (~20,000 USD) for induction therapy over a period of 2 months and another 14–15 lakh Indian rupees (~20,000 USD) for the consolidation over the next 4 months. Therefore, HSCT is far more cost-effective in comparison to daratumumab.

One of the limitations of the present study was that FISH data for the patients could not be obtained and analyzed. HCT-CI (Hematopoietic Cell Transplantation Co-morbidity Index) and risk stratification of MM patients were not performed. Large prospective multicentric study on HSCT in MM patients including FISH data, HCT-CI, and risk stratification should be performed.

Table 1 Comparison of results with previous Indian studies

References	Median follow-up (months)	Median OS (months)	Median PFS	TRM	OS rate at 5 years	PFS at 5 years
Present study ($n = 50$)	33.6	70.1	62.8	0	84.2%	75.3%
Lalit et al, 2019[9] ($n = 349$)	73	90	41	5.2%	60.8%	40.6%
Aggarwal et al,2009[10] ($n = 225$)	54	128.3	73.8	2.1%	NA	NA
Bagal BP, 2012[19] ($n = 61$)	NA	NA	NA	8%	73%	33%
Kulkarni et al, 2018[13] ($n = 245$)	40.7	NA	NA	2.86%	61.6%	37.2%

Abbreviation: NA, not available.
n: sample size.

Conclusion

Autologous HSCT is a safe procedure with nil 100-day mortality in the present series. Moreover, considering the cost of novel agents, autologous transplant remains a cost-effective way for prolonging remission and time-to-next treatment in this part of the world.

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None.

Conflict of Interest
None declared.

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