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A Real-World data of 100 Day outcomes of Multiple Myeloma patients undergoing Autologous Stem Cell Transplant using Non-Cryopreserved Stem Cells

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Abstract:

Background: The preferred treatment for newly diagnosed multiple myeloma (NDMM) patients is proteasome inhibitor-based induction followed by autologous stem cell transplant (ASCT) consolidation. Historically cryopreserved stem cells were used for ASCT in multiple myeloma (MM), however post coronavirus pandemic, non-cryopreserved stem cells are used increasingly.
Aim: To evaluate the 100 days outcome of ASCT using non-cryopreserved stem cells in MM patients.

Methods: This research included seventy patients who underwent ASCT using non-cryopreserved stem cells for MM between January 2009 and September 2023 at the department of clinical haematology and bone marrow transplant, National University of Medial Sciences, Rawalpindi Pakistan.

Results: At the time of transplant, the median age of the patients was 49.97(± 9.79) years. The ratio of male to female was 3:1. The most frequently reported symptom was backache in 49(70%) patients while anaemia was the most common laboratory abnormality in 51(73%) patients. For most of the patients (70%) Cyclophosphamide combined with granulocyte colony stimulating factor (GCSF) was used for stem cell mobilization. At the time of ASCT, 29 (43%) patients were in stringent complete remission, 37 (55%) patients were in complete remission,1(2%) was in less than partial remission. The conditioning regimen used most commonly in 60 (85%) patients was Melphalan 200 mg/m2 while Melphalan 140 mg/m^2 was used in 10 (15 %) patients. The median days for engraftment of neutrophils and platelets were 11(IQR 10.75-12) and 16 (IQR 15-18 respectively. The median duration of hospitalisation after transplant was 14 days (IQR: 13 to 16). Febrile neutropenia was documented in 54 (77%) patients, gut toxicity in 52 (74%) were most frequent complications. There was no graft failure and overall and disease-free survival was 100% at day 100.

Conclusion: Non-cryopreserved stem cells offer a cheaper, convenient and effective alternative for the cryopreserved stem cells. Non-cryopreserved stem cells were associated with rapid neutrophil and platelet engraftment and should be preferred stem cell source in resource limited centres.

Introduction

Multiple Myeloma (MM) is the second most prevalent hematologic malignancy characterised by monoclonal proliferation of plasma cell resulting in end organ damage. The median age of diagnosis in the United States of America (USA) and Europe ranges from 65 to 74 years[1-3].The preliminary treatment of recently diagnosed multiple myeloma (NDMM) is induction therapy (proteasome inhibitor-based triplet or a quadruplet incorporating anti-CD38 monoclonal antibody) followed by consolidation through autologous stem cell transplant (ASCT) [4-6].For MM patients, ASCT is most frequently employed worldwide using cryopreserved cells. Globally, treatment related mortality (TRM) 100 days post-transplant for MM patients receiving autologous HSCT has ranged between 0.0 % and 3.4% [7]. Recent data using fresh, non-cryopreserved stem cells revealed similar effectiveness and faster engraftment resulting in reduced duration of neutropenia, complications and shortened hospital stays. These benefits are especially advantageous in resource limited settings as they are likely to make ASCT procedure more cost-effective and simpler to perform. [8, 9].
The published data from developed countries has shown comparable effectiveness and safety along with faster platelet engraftment and shorter hospital stays in the patients receiving non-cryopreserved stem cells[10-12]. For ASCT in MM, 100-day outcome is important because conditioning toxicity, graft failure and infectious complications are the main reason for transplant related mortality and 100-day outcome is a feasible time point to evaluate these complications. The aim of this study is to evaluate the 100-day outcome of ASCT for MM using non-cryopreserved stem cells.

Patients and methods

This single-centre retrospective study was conducted at the department of Clinical Haematology and Bone Marrow Transplant of National University of Medical Sciences, Rawalpindi Pakistan. The study was approved by the hospital ethics committee and adhered to the principles of the Declaration of Helsinki. The study data was gathered from the hospital registrations and patient clinical records [13]. Patients receiving ASCT between January 2009 and September 2023 were included in the study. Patients receiving cryopreserved stem cells or those with incomplete data about the source of stem cells were excluded from the study. Chemotherapy + granulocyte colony stimulating factor (G-CSF), G CSF alone, and G-CSF+ Plerixafor were the mobilisation protocols used. Peripheral blood stem cell (PBSC) apheresis was done using the COBE spectra PBSC system. The target CD34 cell dose was ≥ 2 x 10^6 /kg as per institutional practice. Patients who did not achieve an adequate cell dose had apheresis the next day or until target CD 34 dose was achieved [14]. CD34 dose calculation was done on a 10 colour Beckman Coulter flow cytometer. Afterward, the harvested product was stored at 4°C in the blood bank's walk-in cooler, a routine storage area for packed red blood cell concentrates. Melphalan was administered the same day in the evening. Melphalan 200 mg/m2 was most frequently used while140 mg/m^2 dosage was prescribed to patients who were frail or had concomitant renal failure. Stem cell infusion was done 24 hours post melphalan administration. Patients were given G-CSF from day +8 until neutrophil engraftment which was defined as the duration from the day of stem-cell transplant to the first of three consecutive days with an absolute neutrophil count (ANC) greater than or equal to 0.5 x10^9/l. The period from the day of stem-cell infusion to day with a platelet count more than 20x 10^9/l without transfusion in the past seven days was defined as platelet engraftment. Febrile neutropenia was defined as absolute neutrophil counts below 500 cells/ul with a fever above 38°C[15, 16]. The failure to achieve neutrophil engraftment by day 28 post stem cell infusion was defined as graft failure. Data analysis was done through SPSS version 25.0. In descriptive analysis, percentage and frequency was calculated for categorical variables and mean ± standard deviation or median with interquartile range (IQR) for the continuous variables.

Results

Our study comprised 70 patients with a median age of 49.97(± 9.79) years. Majority (76%) were males, and 36% patients had concomitant plasmacytoma. Patterns of clinical presentation pre transplant is summarised in Table 1.Patients were stratified according to ISS staging and included 21(30%) patients with ISS stage 1, 17(24%) ISS II and 18(26%) were ISS III while 14(20%) patients had ISS stage unknown at outset. The first line treatment most commonly administered pre-transplant was Bortezomib, Lenalidomide and dexamethasone (VLd) in 34(49.3%) patients followed by Bortezomib, Cyclophosphamide and dexamethasone(VCd) in 24 (34.8%) and Bortezomib, Thalidomide dexamethasone(VTd) in 2 (2.9%) patients.

For mobilization, the strategy used was Chemotherapy+G-CSF for 44(63%), G-CSF Plerixafor for 25(36%) while 1(1%) of the patient was mobilised with G-CSF alone. At the time of transplant 29(43%) patients were in stringent complete remission(sCR), 37(55%) patients were in complete remission (CR) and 1(2%) patient was having stable disease (SD). The protocol used for Conditioning regimen was Melphalan (Mel) 200 mg/m2 in 60(85%), Mel 140 mg/m2 in 10(14%) of the study population. The median CD 34 dose achieved was 3.90 x10^6/kg (IQR :2.99-5.58). The median day for neutrophils and platelet engraftment were 11 (IQR:10.75-12.00) and 16 days (IQR:15.00-17.00) and median hospital stay was 14 days (IQR: 13 to 17). Most common complication post-transplant was febrile neutropenia in 54 (77%) followed by gut toxicity in 52 (74%). Post transplant complications are enlisted in Table 1. Antibiotics for febrile neutropenia were used for a median of 7 days (IQR 4-12 days).

The treatment-related mortality (TRM) at day 100 was zero (0%) and one of the patients was lost to follow-up in the first 100 days of transplant.

Table 1: Pre- transplant presentation and Post-transplant complications

			n	%
Pre- transplant Presentation	**Back ache**	**Yes**	49	70
		no	21	30
	Anemia	**Yes**	51	73
		no	19	27
	Azotemia	**Yes**	24	34
		no	46	66
	Pathological fracture	**Yes**	16	23
		no	54	77
	Hypercalcemia	**Yes**	10	15
		no	60	85
Post-transplant complications	**Mucositis**	**yes**	42	60
		no	28	40
	Febrile neutropenia	**yes**	54	77

	no	16	23
Perianal pain	**yes**	7	10
	no	62	90
Gut toxicity	**yes**	52	74
	no	18	26
Others complications	**yes**	10	14
	no	60	86

By using spearman's correlation, there was a weak and inverse correlation between hospital stay and age (r= - 0.1, p=0.37) (Figure 1). Meanwhile, there was no correlation among hospital stay time with CD34 dose (r= 0.0, p= 0.51), neutrophil engraftment days (r= - 0.0, p= 0.49) and platelets engraftment days (r= 0.0, p= 0.51). There were significant association with moderate inverse correlation found between CD34 dose and neutrophil engraftment days (r= - 0.3, p= 0.01) (Figure 2), although weak inverse correlation between CD34 dose and platelets engraftment days (r= - 0.1, p= 0.23) (Figure 3) and no correlation between CD34 dose with age (r= -0.0, p=0.71)

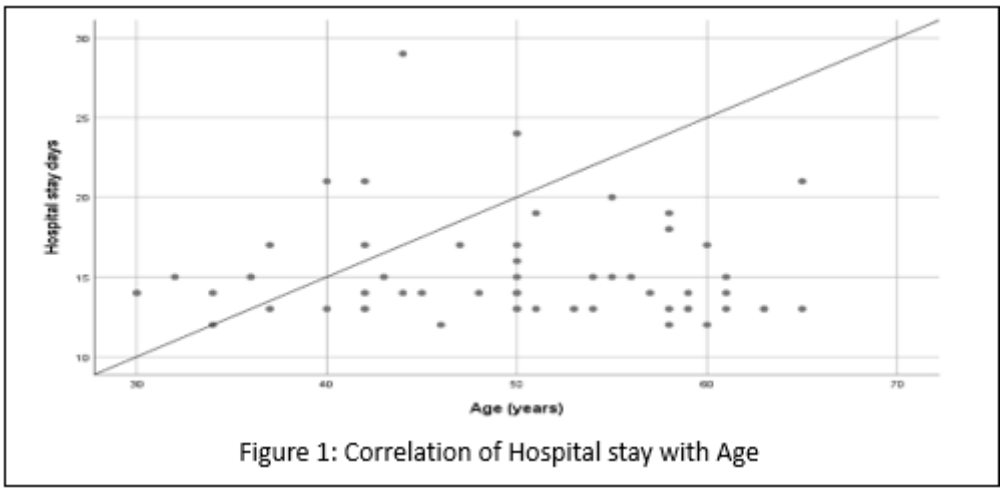

Figure 1: Correlation of Hospital stay with Age

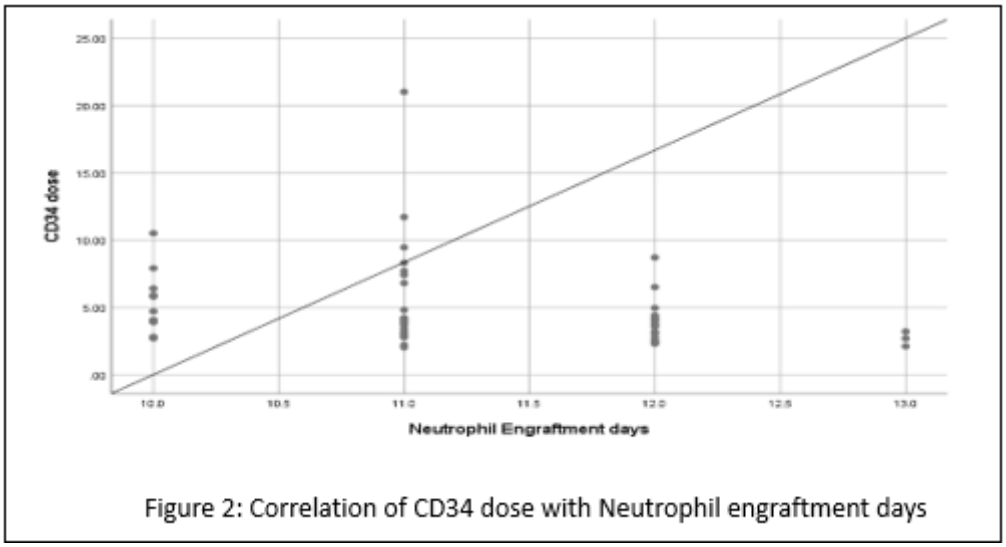

Figure 2: Correlation of CD34 dose with Neutrophil engraftment days

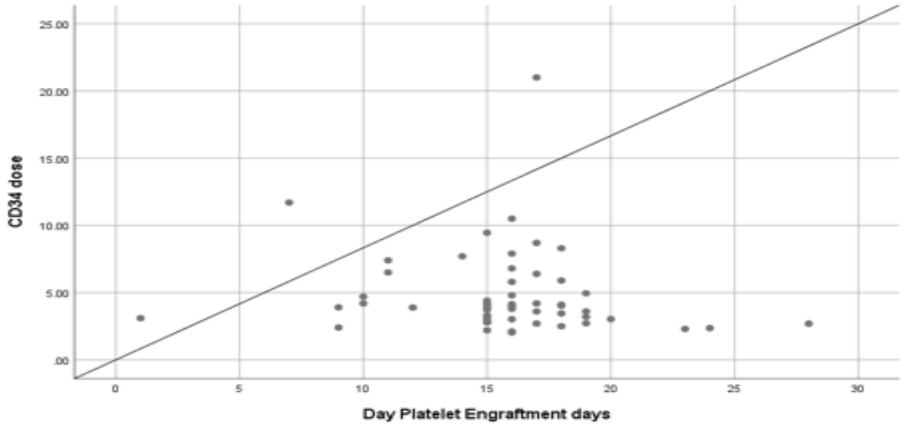

Figure 3: Correlation of CD34 dose with platelet engraftment days

Discussion

This analysis focused on the early outcomes of ASCT using non-cryopreserved stem cells in MM patients. Our patients were followed up to day +100 in terms of their platelets and neutrophil engraftment, transplant related mortality, its associated complications and duration of hospitalisation. The mean age of the patients was 49.97 years, with males constituting 76% and females 24%. In the research by Piriyakhuntorn et al., the average ages were 54.9 years for the cryopreserved group and 55.7 years for the non-cryopreserved (NC) group, with 57.7% females and 42.3% males in the NC group, while the cryopreserved group had an equal distribution of 50% females and 50% males. Another study by Uysal et al. reported a mean age of 59 years for the cryopreserved group and 56 years for the NC group, with gender stratification showing 38% females and 61% males in NC group, and 47.3% females and 52.7% males in the cryopreserved group[11, 13].

Patients were categorized based on ISS staging, that included 21 (30%) with ISS stage I, 17 (24%) in ISS stage II, and 18 (26%) were ISS stage III. Additionally, 14 patients (20%) had an unknown ISS stage at the beginning of treatment. In study by Piriyakhuntorn, P., et al., the patients were classified in NC group as 30.8% with ISS stage I, 38.5% in ISS stage II, and 30.8% patients had ISS stage III while the cryopreserved group included patients having ISS stage I 18.8%, ISS stage II 43.7% patients while 37.5% patients were staged as ISS III. In the same way, another study was published by Uysal, A., et al., wherein the patients were separated into two groups according to their cryopreservation status. In the NC group, 15.6% were classified as ISS stage I, 41.1% as ISS stage II, and ISS stage III included 43.3%. In contrast, the cryopreserved group comprised 23.4 % of patients in ISS stage I, 31.9% in ISS stage II, and 44.7 % in ISS stage III. The median dose of CD 34 achieved was 3.90 $x10^6$/kg. Piriyakhuntorn, P., et al., and Joseph, J., et al., employed cryopreservation after stem cells collection, resulting in a median CD 34 dose 4.7 $x10^6$/kg and 4.32 $x10^6$/kg [11, 13, 14]

In our research, found the median duration for neutrophil and platelet engraftment as 11 and 16 days respectively This aligns with the findings of Castellanos et al., who observed similar engraftment times of 11 days for neutrophils and 12 days for platelets using cryopreserved stem cells. Likewise, Piriyakhuntorn, P., et al. reported neutrophil and platelets engraftment in 10.5 and 12 days respectively, also utilizing cryopreserved stem cells. Conversely, Al Saleh, A.S., et al. conducted comparison of platelets in two cohorts receiving melphalan on days -1 and -2 with NC stem cells resulting in platelets engraftment at 17 days in the first cohort consistent with our observations [11, 15, 16].

In our study, the Day 100 transplant related mortality (TRM) was zero percent and all patients were alive and disease free at day 100. Different studies have documented TRM of 0-3.7%. Kumar, L., et al. compared TRM for patients with early and late transplant and found day 100 TRM of 3.5% early vs 3.7% late in early vs late transplant, similar findings were observed in another study by same author having Day 100 TRM of 3.1%. Contrary to that Turunen, A., et al. and Lemieux, C., et al. recorded death rate zero% in first 100 days of Auto HSCT [17-20].The comparison suggests that non-cryopreserved stem cell infusion is safe and feasible treatment option as compared to historically used cryopreserved cells.

We found that the median hospital stay after transplant for our patients was 14 days. Similarly, Zheng-Lin, B., et al., Marini, J., et al. reported median length of hospital stay as 15 and 15.5 days respectively in their cohorts using fresh stem cells. Contrary to that in studies with cryopreserved stem cells source, Piriyakhuntorn, P., et al. reported median time for hospital stay as 33 days including the duration from day of admission till discharge while most of the studies calculated hospital stay from day of transplantation till discharge. In the same way Voloshin, S., et al. reported median length of hospital stay as 16 days. Our patients had less hospital stay then other cohorts using cryopreserved stem cells[11, 21-23].

The transplant period was complicated by Mucositis in 42(60%) , Febrile neutropenia in 54(77%), Peri anal pain in 7(10%), Gut toxicity in 52(74%) and other complications (hypokalaemia , azotaemia) in 10(14%) patients .In comparison, the study using cryopreserved stem cell source by Piriyakhuntorn, P., et al. documented infectious complications of 16% while Sarmiento, M., et al reported infectious complications of 92% in his study population. In the same study, Mucositis was observed in 64% patients of the cryopreserved cohort. Similarly, Yadav, N., et al. reported 58% of patients having mucositis post-transplant using cryopreserved stem cells.[11, 24, 25]

Our study had certain limitations that included a small sample size, being conducted at a single centre and the need for follow-up with longer period to assess the effects of overall survival (OS), disease free survival (DFS) and immune reconstitution.

Conclusion:

Non-cryopreserved stem cells offer a cheaper, convenient and effective alternative for the cryopreserved stem cells. Non-cryopreserved stem cells were associated with rapid neutrophil and platelet engraftment and should be preferred stem cell source in resource limited centres.

Declaration of interests
It is declared by the authors that they have no recognized competing financial interests or personal relationships that might have seemed to influence the work presented in this paper.

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Author Contributions:
Qudratullah contributed from data collection, methodology, manuscript writing to the publication in all steps. Hira has done statistical analysis and manuscript review. Ibaad has written the abstract, part of discussion and reviewed the manuscript. Raheel Iftikhar supervised the manuscript from study design, data collection, results and through final submission.

Conflicts of interest: The authors declare that they have no relevant financial or non-financial interests to disclose.

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