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ORIGINAL ARTICLE

First 100 days outcomes of cryopreserved vs non-cryopreserved stem cells autologous bone marrow transplant in multiple myeloma - a single center experience

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ABSTRACT

Objectives: To compare the first 100 days' outcomes of autologous stem cell transplantation (Auto-BMT) using cryopreserved versus non-cryopreserved grafts in multiple myeloma (MM) patients.

Methods: This prospective cohort study was conducted at a bone marrow transplant center in Rawalpindi, Pakistan, from March 2023 to March 2024. MM patients in stringent complete remission or complete remission per International Myeloma Working Group criteria were included. Patients were divided into two groups: those receiving non-cryopreserved stem cells and those receiving cryopreserved stem cells. Stem cell mobilization, collection, and preservation followed standardized protocols, with CD34+ counts and viability assessed pre-infusion. Data on patient demographics, disease characteristics, engraftment times, transplant-related complications, hospital stay duration, and outcomes at Day+100 post-transplant were collected and analyzed using SPSS 23.0.

Results: The non-cryopreserved group had a higher mean CD34 dose (5.22 × 10^6/l vs. 4.78 × 10^6/l), superior cell viability (93% vs. 84%, $p<0.01$), faster neutrophil engraftment (12 vs. 14 days, $p<0.01$), and shorter hospital stays (15 vs. 16 days, $p=0.03$). Febrile neutropenia was universal in the cryopreserved group but affected 78.6% in the cryopreserved group. Gut toxicity was more frequent in the cryopreserved group (78.6% vs. 66.7%; $p>0.05$). Mucositis incidence was higher in the cryopreserved group (64% vs. 17%,). Both groups achieved complete remission by Day+100, with no mortality or relapse.

Conclusion: NC stem cell grafts offer comparable efficacy to CryoP grafts while reducing costs and enhancing outcomes, particularly for engraftment speed and hospital stay duration. These findings support the adoption of NC protocols in resource-limited settings.

Keywords: Multiple Myeloma (MeSH); Stem Cells (MeSH); Stem Cell Transplantation (MeSH); Cryopreserved stem cells (non-MeSH); non-cryopreserved stem cells (non-MeSH); day+ 100 outcomes (non-MeSH); Pakistan (MeSH); Plasma Cells (MeSH); Anemia (MeSH); Transplants (MeSH).

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INTRODUCTION

Multiple Myeloma (MM) is characterized by the clonal proliferation of plasma cells and presents clinically with normocytic normochromic anemia, lytic bone lesions, azotemia, and hypercalcemia. It accounts for approximately 10% of hematological malignancies and 1% of all cancers worldwide.[1] Autologous bone marrow transplantation (Auto-BMT) has emerged as the standard treatment for MM patients who achieve disease remission following chemotherapy.[2] Among various techniques, cryopreservation (CryoP) of stem cells is the most commonly employed method for Auto-BMT. While effective, CryoP of stem cells using dimethyl sulfoxide (DMSO) increases the overall cost of the procedure and is associated with potential adverse effects. In contrast, the non-cryopreserved (NC) method offers a cost-effective alternative, as stem cell collection and transplantation are performed during the same hospital admission, thereby reducing procedural expenses and time.[3]

Studies conducted in developed countries have demonstrated that NC stem cell transplantation is associated with faster neutrophil recovery, fewer post-transplant complications, and shorter hospital stays.[4] However, data from developing countries, including Pakistan, remains limited. Evaluating these outcomes in the local context is essential to addressing specific healthcare challenges and establishing cost-effective, resource-appropriate treatment protocols. To address this gap, we conducted a comparative analysis of NC versus CryoP autologous graft recipients in MM patients, with the aim of optimizing treatment strategies tailored to the specific needs and conditions of the Pakistani healthcare system.

METHODS

This prospective cohort study was conducted at the Department of Clinical Hematology, Armed Force Bone Marrow Transplant Centre, Combined Military Hospital Rawalpindi, Pakistan between March 2023 and March 2024. Ethical approval was obtained from the hospital's ethical committee and institutional review board (Ref: IRB-019/AFBMTC/Approval/2022). Informed consent was obtained from all

participants in accordance with the principles outlined in the Declaration of Helsinki.

The study included patients in Stringent Complete Remission (SCR) or Complete Remission (CR) based on the International Myeloma Working Group (IMWG) criteria.[5] Patients who did not meet the criteria for CR were excluded.

The variables analyzed included patient demographics (age, gender), International Staging System (ISS) stage at diagnosis, paraprotein type, pre-transplant chemotherapy response, time interval to Auto-BMT and remission status, transplant indications, and stem cell characteristics. Specific stem cell parameters assessed were the type of mobilization protocols, cellular product viability, CD34+ cell dose, graft preservation method (CryoP vs. NC), days to cellular engraftment, post-transplant complications, length of hospital stay, and Day +100 outcomes. Outcomes were measured as Overall Survival (OS) and Progression-Free Survival (PFS). OS was defined as the duration from diagnosis to the last follow-up, while PFS was defined as the time from initiation of treatment to documented disease progression. These data points were evaluated to assess the comparative efficacy and safety of cryopreserved versus non-cryopreserved stem cell grafts in patients undergoing Auto-BMT for MM.

Stem cell mobilization regimens, processing and transplant protocol: The majority of patients in both cohorts were given induction chemotherapy containing Bortezomib (V) with either Lenalidomide (L) or cyclophosphamide (Cy) containing regimens. Two patients, who were treated with induction chemotherapy in other hospitals and later referred to our institute, had received either a Melphalan (M) + Thalidomide (T) or Cy + T containing regimens based on their respective hospital guidelines. Refractory, relapsed patients were managed with either a carfilzomib (K) and/or Pomalidomide (P) containing chemotherapy regimens based on exposure and response to prior chemotherapy regimen and patient's comorbidities. Stem cell mobilization was done using either a Cy + Granulocyte-Colony Stimulating Factor [GCSF] (Cyclo-G) or Plerixafor + GCSF (G-Plerixafor) followed by peripheral blood stem cell collection (PBSC) using COBE spectra PBSC system. The Cyclo-G protocol consisted of Cy 1.5g/m^2 for 1 day followed by GCSF 10mcg/kg for the next 4-5 days until peak white cell count is attained followed by PBSC. G-Plerixafor protocol incorporated GCSF 10mcg/kg for 5 days and Plerixafor 240mcg/kg 12 hours before PBSC. For NC cohort of patients PBSC were collected on day -3. In both cohorts the conditioning chemotherapy regimen consisted of IV Melphalan 200mg/m^2 on day-1 and stem cells were infused after 24 hours on day 0.

In the CryoP cohort, stem cell collection was acquired on 1 or more separate admissions as per mobilization regimen and stem cell collection was done. Both cohorts received GCSF 5-10mcg/kg starting Day + 8 until neutrophil engraftment.

The stem cell's CD34 cell count was measured by flow cytometry on the morning of the planned apheresis day. Spectra Optia Apheresis System was used for apheresis procedures. Patients with a suboptimal < (2.0 x 10^6/kg) CD34 cell collection underwent 2nd apheresis session on the following day. In the NC cohort, stem cells were stored in the stem cells lab refrigerator at -4°C. In the CryoP cohort, DMSO was added to the PBSC and stored in liquid nitrogen at -190°C. Pre-infusion thawing was done at the patient's bedside using a 37°C water bath. Cell viability was confirmed by trypan blue exclusion test before the start of conditioning protocols.

Outcomes: The primary outcomes of this study were neutrophil and platelet engraftment, measured in days. Neutrophil engraftment was defined as achieving an absolute neutrophil count (ANC) > 0.5 × 10^9/L for three consecutive days, while platelet engraftment was defined as achieving a platelet count > 20 × 10^9/L for more than seven days without transfusion.[6]

The secondary outcomes included cell viability and post-transplant complications such as febrile neutropenia, defined as a single oral temperature > 101°F or a temperature > 100.4°F sustained for over an hour, with an ANC < 0.5 × 10^9/L or an expected decline to < 0.5 × 10^9/L within 48 hours.[7] Additional complications assessed were mucositis, graded according to the WHO criteria,[8] and gut toxicity, evaluated using the NCI CTCAE v5.0 guidelines.[9] Other secondary outcomes included the length of hospital stay (total days until discharge), transplant outcomes at Day +100, and survival metrics such as Progression-Free Survival (PFS) and Overall Survival (OS).

Post-Auto-BMT Cytomegalovirus (CMV) surveillance was conducted using Polymerase Chain Reaction (PCR) testing to monitor and manage any potential viral reactivation or complications. These outcomes were analyzed to comprehensively assess the efficacy, safety, and feasibility of cryopreserved versus non-cryopreserved stem cell grafts in the context of autologous transplantation for Multiple Myeloma.

Statistical analysis: Data analysis was performed using SPSS version 23.0. Frequencies and percentages were calculated for categorical variables, while means and standard deviations were computed for continuous variables. Univariate Chi-square analysis was employed to compare the CryoP and NC groups and evaluate their association with the study variables. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 20 patients underwent autologous stem cell transplantation for MM. The mean age of the cohort was 52 ± 8.3 years. Among these, cryopreserved stem cells were infused in 6 patients (30%), while 14 patients (70%) received non-cryopreserved stem cells. The mean CD34+ cell dose was 5.22 × 10^6/L (IQR 2.0 × 10^6/L–12.0 × 10^6/L) in the NC group and 4.78 × 10^6/L (IQR 3.0 × 10^6/L–8.0 × 10^6/L) in the CryoP group.

The mean cellular viability was 93% (IQR 91%–96%) in the NC cohort compared to 84% (IQR 82%–88%) in the CryoP cohort. The mean time for neutrophil and platelet engraftment across the entire cohort was 12 ± 1.6

Table I: Demographic data of multiple myeloma cases (n=20)

Variable		Cryopreserved (CryoP) [Frequency (n=6) %]	Non-cryopreserved (NC) [Frequency (n=14) %]
Age groups (years)	<40	0	1(7)
	41-50	2 (33)	5 (36)
	51-60	2 (33)	7 (50)
	>60	2 (33)	1 (7)
Patient Gender	Male	3 (50)	9 (64)
	Female	3 (50)	5 (36)
ISS-Stage	I	3 (50)	5 (36)
	II	0	4 (28)
	III	3 (50)	5 (36)
Paraprotein Type	IgG Kappa	2 (33)	8 (57)
	IgG Lambda	1 (16)	6 (43)
	IgA Lambda	1 (16)	0
	IgA Kappa	2 (33)	0
Induction Chemotherapy	VLD	3 (50)	8 (57)
	VCD	2 (33)	5 (36)
	MPT	1(16)	0
	CTD	0	1(7)
Response to Induction Chemotherapy	sCR	2 (33)	5 (36)
	CR	0	4 (28)
	VGPR	1 (16)	1 (7)
	Partial Response	3 (50)	4 (28)
Second Line Treatment	VLD	2 (33)	3 (21)
	KPD	2 (33)	0
	KRD	0	2 (14)
	None	2 (33)	9 (64)
Response to Second line Treatment	sCR	1 (16)	0
	CR	4 (66)	4 (28)
	VGPR	0	0
	Partial Response	0	1 (7)
	Not applicable	1(16)	9 (64)

days and 15 ± 5.1 days, respectively. Patients in the NC group had a mean hospital stay of 15 ± 4.2 days, whereas those in the CryoP group remained hospitalized for a mean of 16 ± 3.2 days.

The overall survival (OS) and progression-free survival (PFS) for the entire cohort were 29 months and 15.8 months, respectively (Table I).

The most common post-transplant complications observed were febrile neutropenia in 17 patients (85%), gut toxicity in 15 patients (75%), and mucositis in 10 patients (50%). All patients in the CryoP group experienced febrile neutropenia, while the majority of patients in the NC group (64.3%; 9/14) had mucositis. Cytomegalovirus (CMV) reactivation was not observed in either cohort.

At Day +100, all patients in both groups achieved complete remission (CR), with no deaths or disease relapse reported.

Chi-square analysis was performed to evaluate factors influencing transplant outcomes in the CryoP and NC groups. Patients receiving NC stem cells had significantly higher cell viability (≥90% in all patients) compared to those receiving CryoP stem cells (<90% in 100% of cases, 6/6; $P < 0.01$). Early neutrophil engraftment (<12 days) was significantly more frequent in the NC group (71%; n=10/14) compared to the CryoP group (0%; n=0/6; $P < 0.01$). Mucositis incidence was higher in the NC group (64%; n=9/14) compared to the CryoP group (17%; n=1/6; $P = 0.05$).

Regarding hospital stay duration, all CryoP recipients had hospital stays longer than 14 days (100%; n=6/6), whereas only half of the NC group (50%; n=7/14) experienced similar lengths of stay ($P = 0.03$) [Table II].

DISCUSSION

This study compared cryopreserved and non-cryopreserved autologous stem cell transplantation in multiple myeloma patients, focusing on the critical first 100 days post-transplant, which encompass stem cell engraftment and hematopoietic reconstitution. NC stem cell recipients demonstrated higher cell viability (≥90%), faster neutrophil engraftment (<12 days in

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Disease Relapse	Yes	1(16)	2 (14)
	No	5 (83)	12 (86)
Salvage Treatment	VLD	1 (16)	0
	KPD	0	1(7)
	KRD	0	1(7)
	Not applicable	5 (83)	12 (86)
Auto-BMT Indication	Relapse Disease	1(16)	2 (14)
	Refractory Disease	3 (50)	3 (21)
	Primary Disease	2 (33)	9 (64)
Disease Status at Auto-BMT	sCR	3 (50)	2 (14)
	CR	3 (50)	12 (86)
Time interval between diagnosis and Auto-BMT	<6 months	1 (16)	2 (14)
	6-12 months	2 (33)	8 (86)
	>12 months	3 (50)	4 (28)
Mobilization Protocol Used	G-Pleraxifor	4 (66)	11 (79)
	Cyclo-G	2 (33)	3(21)

*ISS (International staging system), IgG Kappa (Immunoglobulin G kappa Light Chain), IgG Lambda (Immunoglobulin G Lambda Light Chain), IgA Kappa (Immunogl-obulin A Kappa Light Chain), IgA Lambda (Immunoglobulin A Lambda Light Chain), VLD (Bortezomib, Lenalidomide, Dexamethasone), VCD (Bortezomib, Cycloph-osphamide, Dexamethasone), MPT (Melphalan, Prednisolone, Thalidomide), CTD (Cyclophosphamide, Thalidomide, Dexamethasone), KPD (Carfilzomib, Pomalido-mide, Dexamethasone), KRD (Carfilzomib, Lenalidomide, Dexamethasone), sCR (Stringent Complete remission), CR (Complete Remission), VGPR (Very Good Par-tial Response), G-Pleraxifor (Granulocyte-Colony Stimulating Factor+ Pleraxifor), Cyclo-G (Cyclophosphamide + Granulocyte-Colony Stimulating Factor)

Table II: Chi-square analysis of patients receiving NC vs CryoP stem cells (n=20)

Variable		Cryopreserved (CryoP) n=6(%)	Non-cryopreserved (NC) n=14(%)	p-value
CD34 dose groups	<4 x 10^6/kg	2 (33)	5 (38)	0.91
	≥4 x 10^6/kg	4 (67)	9 (64)	
Stem cells Viability	<90%	6 (100)	0	<0.01
	≥90%	0	14	
Neutrophil engraftment days	<12	0	10 (71.4)	<0.01
	≥12	6	4 (28.6)	
Platelet engraftment days	<15	5 (83.3)	8 (57.1)	0.26
	≥15	1 (16.7)	6 (42.9)	
Febrile Neutropenia incidence	yes	6 (100)	11(78.6)	0.21
	No	0	3(21.4)	

71% vs. 0%), and shorter hospital stays (>14 days in 50% vs. 100%). While febrile neutropenia was common in both groups, mucositis was more frequent in the NC cohort. At Day +100, all patients achieved complete remission without disease relapse or mortality. These findings highlight the clinical and logistical benefits of NC transplantation in resource-limited settings.

Cellular viability and potency are critical for achieving successful hematopoietic reconstitution, as delays can directly impact transplant outcomes. Recognizing that various factors influence the potency and quantity of stem cells in patients with hematological malignancies, we specifically focused on comparing stem cell graft preservation methods. Our analysis revealed that NC stem cells demonstrated higher viability, facilitated earlier hematopoietic reconstitution, and reduced hospital stay durations compared to CryoP stem cells, albeit with a higher incidence of mucositis.

As previously noted, stem cell viability significantly impacts the regeneration of blood progenitor cells. In this study, NC stem cells demonstrated superior viability, with >90% viability observed in all 14 patients (14/14) compared to <90% viability in all 6 patients (6/6) who received CryoP stem cells (P < 0.01). A previous study done by Noiperm P, et al., in 2022 demonstrated a cellular viability of 99.1% for NC stem cells in MM.[10] This could be due to NC stem cells avoiding the damage that can occur during freezing and thawing.[11] In addition to demonstrating superior viability, the use of NC stem cells offers a cost-effective alternative for autologous stem cell transplants in resource-limited countries, eliminating the need for expensive preservation methods without compromising clinical outcomes.[12]

With regards to cellular regeneration, we observed an early neutrophil recovery <12 days in 70% (10/14) in NC vs 0% (0/6) in the CryoP group (P=0.03). Early neutrophil engraftment is associated with a decrease in post-transplant infection complications, as demonstrated by Pessoa in 2022.[13] We believe a smaller number of stem cell

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Febrile Neutropenia duration (days)	<3 days	2 (33.3)	6 (42.9)	0.32
	≥3 days	4 (66.7)	5 (35.7)	
	Not occurred	0	3 (21.4)	
Gut Toxicity incidence	Yes	4 (66.7)	11(78.6)	0.57
	No	2 (33.3)	3 (21.4)	
Gut Toxicity Grade	Grade I	1(16.7)	5 (35.7)	0.23
	Grade II	1(16.7)	3 (21.4)	
	Grade III	1(16.7)	2 (14.3)	
	Grade IV	1(16.7)	1(7.1)	
	No	2 (33.3)	3 (21.4)	
Mucositis Incidence	Yes	1(16.7)	9 (64.3)	0.05
	No	5 (83.3)	5 (35.7)	
Mucositis Grade	Grade I	1(16.7)	4 (28.6)	0.23
	Grade II	0	2 (14.3)	
	Grade III	0	3 (21.4)	
	Grade IV	0	0	
	No	5 (83.3)	2 (35.7)	
CMV Reactivation	Yes	0	0	N/A
	No	6 (100)	14 (100)	
Disease Status at Auto-BMT	sCR	3 (50)	2 (14)	0.09
	CR	3 (50)	12 (86)	
Time interval between diagnosis and Auto-BMT	<6 months	1(16)	2(14)	0.59
	6-12 months	2 (33)	8(86)	
	>12 months	3(50)	4(28)	
Duration of Hospital stay (days)	<14	0	7(50)	0.03
	≥14	6 (100)	7(50)	

*sCR (Stringent Complete remission), CR (Complete Remission), VGPR (Very Good Partial Response), CMV (Cytomegalovirus), Auto-BMT (Autologous Bone Marrow Transplant)

loss by NC techniques helps achieve a higher CD34 infusion dose therefore, leading to rapid engraftment. Since none of our patients failed to engraft in the two cohorts, we believe both techniques are safe to be practised in clinical scenarios where the NC stem cell graft cannot be used because of any impediment in stem cell transplant.

Early engraftment also helped in hospital admission duration in NC group. i.e. <14 days in 50% (7/14) vs 0% (0/6) in the Cryo group (P=0.03). A Similar study done by Araújo AB, et al., in 2022 showed a shorter duration of hospital stay for patients receiving NC stem cells.[14] Cryopreservation may introduce engraftment delays or complications requiring extended inpatient care. This in turn makes NC a preferred technique where hospital admission cost is a limiting factor.

Our study also revealed comparable rates of early transplant-related complications between the two groups. Febrile neutropenia was observed in all CryoP recipients compared to 78.6% (n=11/14) of NC recipients. Similarly, gut toxicity occurred in 78.6% (n=11/14) of the NC group versus 66.7% (n=4/6) of the CryoP group, though neither difference was statistically significant. However, the incidence of mucositis was significantly higher in the NC group at 64% (n=9/14) compared to 17% (n=1/6) in the CryoP group (P = 0.03).

Contrary to our findings, previous studies have reported a lower incidence of mucositis in patients receiving NC stem cells compared to CryoP stem cells in multiple myeloma.[15] We hypothesize that the faster engraftment associated with NC stem cells leads to accelerated and more intense cell growth in the oral and gastrointestinal lining. When combined with the strong chemotherapy regimens administered prior to transplantation, this rapid growth may result in greater irritation and tissue damage, exacerbating mucositis. Additionally, quicker immune recovery might trigger stronger inflammatory responses in these tissues, further aggravating the condition.

At 100 days post-transplant, overall survival was comparable between the CryoP and NC groups, demonstrating that both methods are effective in the short term. The decision between CryoP and NC stem cell transplantation involves weighing logistical, economic, and clinical factors. NC transplants provide benefits such as faster engraftment and shorter hospital stays but require precise timing and coordination since the stem cells must be used fresh. In contrast, CryoP transplants offer greater flexibility in scheduling and are particularly advantageous when there is a delay between stem cell collection and transplantation.

CONCLUSION

Both cryopreserved and non-cryopreserved (NC) stem cell transplants are effective for multiple myeloma, achieving comparable short-term survival rates. However, NC

transplants offer faster recovery due to higher stem cell viability, reducing hospital stays and associated costs.

This study highlights NC transplants as a cost-effective alternative, particularly in resource-limited settings, with benefits like faster engraftment and shorter hospitalization. However, the higher incidence of mucositis in the NC group calls for further research to optimize protocols. Larger studies with extended follow-up are needed to validate these findings and evaluate long-term outcomes.

Limitations of the study & future recommendations

This study's small sample size and single-center design limit its generalizability. The 100-day follow-up period was insufficient to evaluate long-term outcomes such as sustained progression-free survival, overall survival, and late complications. The observed higher incidence of mucositis in the NC group warrants further investigation through larger, randomized trials to better understand this complication. Additionally, the lack of quality-of-life assessments and consideration of potential confounders, such as variations in conditioning regimens, restricts the comprehensiveness of the findings.

Future research should focus on multicenter studies with extended follow-up to assess long-term outcomes and validate these findings. Incorporating quality-of-life and cost-effectiveness analyses would provide a more comprehensive evaluation of CryoP and NC transplant methods. Moreover, optimizing transplant protocols to minimize complications, particularly mucositis, remains a priority for improving patient outcomes.

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AUTHORS' CONTRIBUTIONS

Following authors have made substantial contributions to the manuscript as under:

AS, IH, Qu & MNA: Acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

MAK: Conception and study design, critical review,approval of the final version to be published

JUR & HJ: Analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest, whether financial or otherwise, that could influence the integrity, objectivity, or validity of their research work.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

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