Original Study

# High-Dose Chemotherapy and Autologous Stem Cell Transplantation in Multiple Myeloma: A Single Institution Experience at All India Institute of Medical Sciences, New Delhi, Using Non-Cryopreserved Peripheral Blood Stem Cells

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## Abstract

**High-dose chemotherapy and autologous transplant is central to treatment of multiple myeloma (MM). To make this treatment modality possible at centers with limited resources, we highlight the use of non-cryopreserved peripheral blood stem cells (PBSC), stored at 4°C in a refrigerator, and report our results in 92 patients, which are equivalent to that of transplants with cryopreserved stem cells.**

**Background:** Intravenous high-dose melphalan has a short half-life, and application of this single drug in MM transplant favors the use of stem cells without cryopreservation, for wider use in general and in resource-limited settings in particular. **Patients and Methods:** Ninety-two patients with MM were given high-dose melphalan and rescued with granulocyte colony stimulating factor (G-CSF) mobilized noncryopreserved autologous PBSC, in our hospital during the past 18 years. Stem cells were mobilized with 4 days of G-CSF, harvested (median CD34 dose, 2.9 $\times$ $10^6$/kg) and then stored at 4°C in a refrigerator for a median of 2 days (range, 1-5 days) before reinfusion. **Results:** Median time to neutrophil (> 500/$mm^3$) and platelet (> 20,000/$mm^3$) engraftment were 10 and 14 days respectively. There was no graft failure. Mucositis grade 3/4 was seen in 66 patients (72%). Transplant-related mortality at 100 days was 3.2%. The overall response to transplant was 88% and improvement compared with pretransplant status was seen in 48%. The median overall survival (OS) and progression-free survival (PFS) were 61.7 months and 35.4 months respectively; independent predictors of survival were Eastern Cooperative Oncology Group Performance Status and hemoglobin for OS and chemosensitive disease and remission status after transplant for PFS. **Conclusion:** We conclude that high-dose chemotherapy and autologous transplant with noncryopreserved PBSC is a simple, effective, and safe method for MM with equivalent results, and that cryopreservation is not necessary. It reduces the cost of transplant and avoids dimethyl sulfoxide toxicity.

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## Introduction

Multiple myeloma (MM) is the most common indication for high-dose chemotherapy (HDC) and autologous stem cell transplant (ASCT).[1] Data from randomized[2-4] and nonrandomized studies[5,6] show that high-dose melphalan (HDM) and ASCT result in higher remission rates and prolonged survival. Most of the data on myeloma transplants is from the West. Although HDC and ASCT is now one of the most cost-effective treatments for myeloma, there are only limited reports from developing countries.[7-9]

Considering the short elimination half-life of intravenous HDM and proven viability of peripheral blood progenitor cells for 24 to 120 hours when stored at 4°C, noncryopreserved autologous stem cell graft is an attractive and simple alternative in MM when HDC is given only for 1 day. However, studies with noncryopreserved

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ASCT in MM are limited.[10-12] In this study, we report the outcome of ASCT in MM with granulocyte colony stimulating factor (G-CSF), mobilized noncryopreserved peripheral blood stem cell (PBSC) product in 92 patients in terms of feasibility, safety, and efficacy. To our knowledge, this report is the largest series of noncryopreserved ASCT in MM.

## Patients and Methods

### *Patients*

Between September 1994 and November 2012, 116 patients with MM were treated using HDM and ASCT, in the Department of Medical Oncology of Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India. Complete records of 24 patients were not available and were therefore excluded from this analysis.

### *Transplant Protocol*

Before transplant, all patients were assessed for their clinical features and treatment history, pretransplant disease status, Eastern Cooperative Oncology Group Performance Status (ECOG PS), laboratory parameters, and organ function. Scores as per the hematopoietic cell transplant comorbidity index (HCT CI) system[13] for comorbidity risk assessment were calculated retrospectively for each patient using clinical records and documented pretransplant laboratory evaluation and a score of 0 was assigned for absent information on a particular comorbidity.

Informed written consent was obtained from all patients. A central venous access (Hickman, subclavian line, or peripherally-inserted central catheter) was put in place. G-CSF, at a dose of 5 μg/kg twice daily subcutaneous, was injected for 4 days to mobilize PBSC; these were harvested using leukapheresis and used as the source of stem cells for all patients. PBSC products were stored at 4°C in a conventional blood bank refrigerator for a median of 2 days (range, 1-5 days). Stem cell yield of the harvest was determined according to mononuclear cell count and $CD34^+$ cell count using flow cytometry. The goal for pheresis was to collect an average of $2 \times 10^6$/kg CD34 stem cells, but for some patients for whom CD34 count could not be done or yield too low (during the initial period of start of the transplant facility), mononuclear cell count was taken as a surrogate marker of stemness.

HDM was administered at a median dose of 200 mg/m$^2$ (range, 140-200 mg/m$^2$) on Day −1. After infusion of the stem cells (on Day 0); all patients were observed for toxicities and febrile complications which were managed as per standard guidelines and institutional protocol. Patients received G-CSF 300 μg once a day starting on Day 1 after infusion of stem cells until the time of engraftment. Platelet and blood transfusion (irradiated products, 25 Gy) was given as required during the course. All patients remained hospitalized until engraftment and until the time deemed clinically suitable for discharge. Follow-up information was collected by review of outpatient follow-up records and patients were contacted in phone calls and by letter. No patient underwent a second or tandem transplant in this study cohort.

### *Outcome Evaluation and Study Definitions*

The International Myeloma Working group (IMWG) Uniform Response criteria, 2006 were applied for evaluation of disease status and response.[14] For the purpose of analysis, patients who achieved complete response (CR), very good partial response (VGPR), or a partial remission (PR) were regarded to have chemosensitive disease. Patients with stable, progressive, or refractory disease before transplant were defined to have chemoresistant disease.

Neutrophil engraftment was defined as the first of 3 consecutive days with achievement of absolute neutrophil count of $\geq 500/cm^3$ and no subsequent decline. Platelet engraftment was defined as the first of 3 consecutive values of platelet count $\geq 20{,}000/cm^3$ with transfusion independence. The standard definition for febrile neutropenia was used and febrile episodes were classified according to Immunocompromised Host Society consensus conference and the European Society of Clinical Microbiology and Infectious Diseases guidelines into clinically documented infections, microbiologically documented infections, and fever of unknown origin.[15,16] Regimen-related organ toxicities, evaluated in the first 100 days, were graded using the Seattle criteria.[17] The maximum toxicity score was the highest score reached in any single organ system. Cumulative toxicity score was the sum of the highest score observed in each organ at any time. We studied the association of various pretransplant factors with final cumulative toxicity scores to find factors predictive of a higher score and greater organ toxicity. Length of hospital stay was defined as the time from the day of infusion of stem cell product to the day of hospital discharge. Transplant-related mortality (TRM) was taken as death from any cause other than disease relapse or progression occurring within the first 100 days after ASCT. Relapse or progression was defined as worsening of the disease status from that at the time of transplant and meeting the IMWG criteria[14] for progressive disease, or the start of a new definitive therapy at any time after transplant. Progression-free survival (PFS) was defined from the time of transplant until relapse or progression. Toxic deaths, deaths not related to disease, and second malignancies were censored for PFS. Overall survival (OS) was measured from date of transplant to death from any cause.

### *Statistical Analysis*

Descriptive statistics were used for baseline characteristics, transplant-related factors, and posttransplant outcome. Differences in the distribution of variables between patient subsets were analyzed using Pearson $\chi^2$ test/correlation test/$t$ test. Response rate to transplant was assessed using the McNemar test for paired categorical data. OS and PFS were estimated using the Kaplan-Meier method. Log-rank test was used to determine differences in survival and events. Median follow-up time was calculated using the Kaplan-Meier method for potential follow-up.[18] Cox regression (univariate and multivariate) method for proportional hazard was used to identify significant predictors of survival outcome. All statistical analyses were 2-sided and performed at the 5% significance level. Data were censored for survival analysis on December 31, 2012. SPSS v 16.0 was used for analysis.

## Results

Of a total of 116 patients with MM who underwent HDM and noncryopreserved autologous PBSC transplant at our center during the past 18 years, this report includes 92 patients; of whom, 61 were men (66%) and 31 were women (34%). Median age of the study group of 92 patients was 51 years (range, 22-65 years) and the male