Original Study

# Autologous Stem Cell Transplantation for Multiple Myeloma: Identification of Prognostic Factors

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## Abstract

**Currently, high dose chemotherapy supported by autologous stem cell transplantation (ASCT) is considered a standard treatment approach for multiple myeloma (MM) patients aged 65 years or younger. To evaluate the predictors of outcome after ASCT, we analyzed results of 170 patients. Pretransplant chemosensitive disease and achievement of complete response (CR) were associated with improved outcome.**

**Introduction:** The purpose of this study was to evaluate the effect of prognostic factors on the outcome of patients with MM after ASCT. **Patients and Methods:** We analyzed results of 170 consecutive patients (121 male and 49 female) of MM who underwent ASCT. Patients' median age was 52 years (range, 26-68 years). High dose melphalan (200 mg/m$^2$) was used for conditioning. One hundred thirty-two patients (77.6%) had evidence of chemosensitive disease before transplant. Response was assessed using European Group for Blood and Bone Marrow Transplantation criteria. **Results:** Post ASCT 44.7% of patients achieved CR, 24.7% had very good partial response (VGPR), and 21.2% had partial response (PR). Presence of pretransplant chemosensitive disease (CR, VGPR, and PR) and transplant within 12 months of diagnosis for years before 2006 were associated with higher response rates on multivariate analysis. At a median follow-up of 84 months, median overall (OS) and event-free survival (EFS) is 85.5 and 41 months, respectively. Estimated OS and EFS at 60 months is 62 $\pm$ 0.04% and 41 $\pm$ 0.04%, respectively. Patients who responded to transplant (CR, VGPR, and PR) had a longer OS ($P < .001$) and EFS ($P < .001$). Additionally, patients who achieved CR post transplant had a longer OS ($P < .001$) and EFS ($P < .001$). Patients who received novel agents for induction pretransplant had a longer OS ($P < .001$) and EFS ($P < .002$). **Conclusion:** Outcome after ASCT is better for myeloma patients with pretransplant chemosensitive disease and those who achieve CR after transplant.

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**Keywords:** Chemosensitive disease, Complete response, Novel Agents, Serum M protein, Transplant outcome

## Introduction

High-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (ASCT) is currently a standard treatment approach for multiple myeloma (MM) patients aged 65 years or younger.[1,2] A number of nonrandomized,[3,4] randomized,[5-9] and population-based studies[10] and metaanalyses[11,12] have suggested that this approach is associated with improved response rates, and event-free survival (EFS) compared with conventional chemotherapy. These studies were done before newer and more potent novel agents (eg, immune modulators: thalidomide and lenalidomide, proteasome inhibitors—bortezomib) were routinely used. Higher response rates achieved with use of novel agents, followed by consolidation with ASCT[13-15] has led to search for predictors of outcome post ASCT. We started our autologous stem cell transplant program in 1990; our initial results with conventional chemotherapy for induction and ASCT have been reported earlier.[16] We have now updated our experience and analyzed data on 170 patients of MM treated with ASCT. This report describes the results.

## Patients and Methods

Between April 1990 and June 2010, 170 patients with MM underwent ASCT. Patient characteristics are shown in Table 1. Patients age ranged from 26 to 68 years (median 52 years). There

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**Table 1 Patient Characteristics**

| | |
|---|---|
| **Patients, N** | 170 |
| **Age (Years) Median (Range)** | 52 (26-68) |
| **Sex, M:F** | 121:49 (71.2% vs. 28.8%) |
| **Myeloma Subtype, n (%)** | |
| IgG κ | 83 (50) |
| IgG λ | 35 (21) |
| IgA κ | 09 (5.4) |
| IgA λ | 09 (5.4) |
| Kappa light chain only | 11 (6.6) |
| Lambda light chain only | 13 (7.8) |
| Nonsecretory | 03 (1.8) |
| Subtype not known | 03 (1.8) |
| **Renal Function at Diagnosis, n (%)** | |
| Normal | 131 (76.6) |
| Abnormal (serum creatinine ≥ 2 mg) | 39 (23.4) |
| **Stage at Diagnosis (n = 168)** | |
| IA | 3 |
| IIA | 4 |
| IIIA | 121 (72.6%) |
| IIIB | 39 (23.2%) |
| **First-Line Treatment Before Transplant, n (%)** | |
| Alkylating agents | 26 (15.3) |
| VAD | 78 (45.9) |
| Novel agents | 66 (38.8) |
| Chemosensitive disease | 132 (77.6) |
| Chemoresistant or refractory disease | 38 (22.4) |
| **Interval From Diagnosis to Transplant (Months)** | |
| Mean | 15.2 |
| Median | 10 |
| Range | 3-128 |

Abbreviations: AL = amyloid light chain; CR = complete response; PR = partial response; VAD = vincristine, doxorubicin, dexamethasone; VGPR = very good partial response.
Four patients had primary AL amyloidosis. Chemosensitive defined as CR, VGPR, and PR, combined; chemoresistant defined as stable and progressive disease combined.

were 121 male and 49 female patients. The database was maintained prospectively.

Before transplant, patients had received induction therapy either using VAD (vincristine, doxorubicin, dexamethasone; n = 78), novel agents (thalidomide and dexamethasone, or lenalidomide and dexamethasone, or bortezomib and dexamethasone; n = 66), or alkylating agents (VMCP [vincristine, melphalan, cyclophosphamide, and prednisolone] or MP [melphalan and prednisolone], n = 26); 42.4% of patients received more than 1 line of regimen. One hundred thirty-two patients (77.6%) had chemosensitive disease (including complete response [CR], very good partial response [VGPR], and partial response [PR]) before ASCT. Thirty-nine patients (23.4%) had renal insufficiency at diagnosis and 16 (9.4%) had renal dysfunction at the time of transplant. Four patients had primary amyloid light chain (AL) amyloidosis (Table 1).

### *Transplant Protocol*

Briefly, all patients were initially reviewed in the weekly 'Bone Marrow Transplant Clinic' in which the procedure, potential risks and benefits were explained to patients and family members. Initial evaluation included: history, physical examination, staging according to Durie-Salmon, and International Staging System (ISS). Details of previous treatment were recorded. Investigations including hemogram, differential count, renal and liver function tests, bone marrow examination, skeletal survey, serum and urine electrophoresis, immunofixation studies, serum β-2 microglobulin and immunoglobulin levels (quantitative) were done in all patients. Written informed consent was obtained.

During follow-up patients were seen in the 'Transplant Clinic' initially monthly, then bi-to tri-monthly for 3 years, then every 6 months thereafter. Follow-up information is available for all patients. Transplant cost was met by the individuals, government support, medical insurance, and charitable organizations.

*Stem Cells.* The source of stem cell was bone marrow in the first 7 patients; for the next 163 patients granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood stem cells were harvested. A median of 2 leukapheresis were done (range, 1-3). A sample of stem cells was obtained and total cell counts were determined using an automated cell counter and the differential cell count was done manually. For CD34 counts cells were labeled with florescence 4 conjugated anti-CD34 and analyzed using a fluorescence-activated cell sorter scan flow cytometer to yield an absolute $CD34^+$ counts. Stem cells were kept at 4°C or were cryopreserved at −80°C using cryoprotectant mixture of 7.5% dimethyl sulfoxide (DMSO), albumin, and saline. Stem cells were transfused intravenously 24 hours after high dose melphalan. The viability of cells was determined by trypan blue dye exclusion test.

*Conditioning Regimen.* The myeloablative regimen consisted of melphalan (GlaxoSmithKline, UK) 200 mg/$m^2$ slow intravenous (I.V.) push on day 1 followed by forced alkaline diuresis. Four patients with AL amyloidosis, and 16 patients with renal insufficiency at the time of transplant received melphalan 120-150 mg/$m^2$. Autologous blood stem cells were reinfused on day 0 through a central venous catheter (Hickman) preceded by pheniramine maleate 50 mg I.V.

*Supportive Care and Monitoring.* All patients received growth factors G-CSF 5 μg/kg daily subcutaneously on day +1 and onwards until engraftment. Patients were admitted in an isolation room and reverse barrier nursing was practiced. All patients received antimicrobial prophylaxis-ciprofloxacin, fluconazole/itraconazole and acyclovir. Packed red blood cells and platelet transfusions were administered to maintain a hemoglobin level >8 g/dL and a platelet count $>10 \times 10^9$/L. All the blood products transfused during the post-transplant period were irradiated with 25 Gy. Patients received broad-spectrum antibiotics for fever; amphotericin B was added, if patients had persistent fever after 4-5 days of intravenous antimicrobial therapy.