Original Study

Autologous Hematopoietic Stem Cell Transplantation in Dialysis-Dependent Myeloma Patients

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Abstract

Retrospective analysis of 24 patients who underwent autologous stem cell transplant for multiple myeloma while dependent on hemodialysis. All patients were engrafted. The 100-day and the 6-month treatment related mortality was 0%. The incidence of grade II to IV nonhematological toxicity was similar across different melphalan doses. Overall response rate was 92% (complete response = 25%, very good partial response = 29.2%, and partial response = 37.5%).

Background: We retrospectively analyzed our transplant database from July 2000 to June 2012 to identify myeloma patients who received autologous stem cell transplantation while dialysis-dependent. **Patients:** 2091 patients underwent autologous high-dose therapy during this period. Twenty-four patients were dialysis-dependent. **Results:** The 100-day and the 6, and 12-month treatment-related mortality was 0%. Overall response rate was 92%. The median progression-free survival and overall survival were 1.9 years and 3.8 years, respectively. A multivariate analysis was not performed because of the small sample size. Only 3 patients became dialysis-independent after transplantation. Cardiac, gastrointestinal, genitourinary, infectious, neurologic, and pulmonary "all grade" toxicities were all higher in the melphalan 200 group versus < 200 group, however, none of them were statistically significant. **Conclusion:** Because of a lack of clear survival benefit with higher-dose melphalan and potential higher toxicity in this group, it is reasonable to use lower-dose melphalan in dialysis-dependent myeloma patients.

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Introduction

The incidence of renal insufficiency at presentation is approximately 30% in patients with multiple myeloma (MM).[1] Approximately 5% of these patients are dialysis-dependent.[2] Several factors contribute to renal injury in MM patients, including monoclonal light chain-induced proximal tubular damage, light chain cast nephropathy, interstitial nephritis, hypercalcemia, dehydration, infection, hyperuricemia, and the use of nephrotoxic drugs. In addition, amyloid deposition and plasma cell infiltration are less frequent causes for renal impairment. Presence of renal dysfunction is associated with poor survival. This can be attributed to an increased risk of early death, association of renal dysfunction with advanced disease,[1,3,4] and also in part to reluctance in the use of intensive chemotherapy.[5] Therefore, patients with renal failure are frequently considered unfit for high-dose therapy (HDT) and autologous (auto) hematopoietic stem cell transplantation (HCT).[6] However, several reports have shown that auto HCT is safe and effective in dialysis-dependent myeloma patients.[7,8] The existing data suggest that melphalan dose reduction to 140 mg/m^2 is less toxic than 200 mg/m^2 and support the low incidence of developing dialysis independence after auto HCT.[7,8]

In this study we report our experience with myeloma patients who had dialysis-dependent renal failure at the time of auto HCT. All patients included in this study had renal failure attributed to plasma cell dyscrasia, because of the absence of other medical etiologies to explain the renal failure, and the evidence of renal involvement from the plasma cell dyscrasia.

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Patients and Methods

Patients

We retrospectively analyzed our transplant database from July 2000 to June 2012 to identify all myeloma patients who received auto HCT while they were dialysis-dependent. High-risk chromosomal abnormalities were defined as deletion of chromosome 13 detected on conventional cytogenetics or t(4;14), t(14;16), abnormalities of chromosome 1, hypodiploidy, and del17p detected on conventional cytogenetics or fluorescence in situ hybridization.[9-12] This analysis was approved by the University of Texas M.D. Anderson Cancer Center institutional review board.

Stem Cell Mobilization and Collection

All patients received granulocyte colony stimulating factor for stem cell mobilization. Peripheral blood CD34-positive ($CD34^+$) cell count was monitored using flow cytometry. Leukapheresis was started when the $CD34^+$ cell count reached $\geq 10/\mu L$. Samples from leukapheresis products were collected to determine the number of $CD34^+$ cells before cryopreservation, and yields were calculated per kilogram of body weight.

Conditioning Regimen and Supportive Care

The conditioning regimen for all patients consisted of melphalan (14 patients received melphalan 200 mg/m^2, 7 patients received melphalan 140 mg/m^2, and 3 patients received melphalan 180 mg/m^2) given over 1 or 2 days, at the discretion of the treating physician, stem cell infusion was preceded by dialysis 24 to 36 hours after melphalan. Supportive care was given according to existing institutional protocols.

Engraftment, Toxicity, Response, and Progression

Neutrophil engraftment was defined as the first of 3 consecutive days that the absolute neutrophil count (ANC) exceeded $0.5 \times 10^9/L$. Platelet engraftment was defined as the first of 7 consecutive days that the platelet count exceeded $0.5 \times 10^9/L$, independent of platelet transfusions. Response and progression were measured according to International Myeloma Working Group uniform response criteria.[13] Toxicity was measured according to Common Terminology Criteria for Adverse Events version 4.0 (*http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf*).

Statistical Methods

For associations with dialysis status after transplantation, Fisher exact tests and Wilcoxon rank-sum tests were performed. A Kaplan–Meier curve was used to estimate overall survival (OS). All statistical analyses were performed using SAS 9.3 for Windows.

Results

Patient Characteristics

We identified 2091 MM patients who underwent auto HCT between July 2000 to June 2012. Twenty-four were dialysis-dependent (21 who were receiving hemodialysis and 3 who were receiving peritoneal dialysis), the cause of renal failure was primarily because of myeloma. A conditioning regimen for all patients was melphalan 200 mg/m^2 (MEL 200) or melphalan < 200 mg/m^2 (MEL < 200). The median age was 53 (range, 29-70) years. The median time interval between diagnosis and HCT was 337 days. Overall, 54% (n = 13) had International Staging System stage III disease and 83.3% (n = 20) had high-risk cytogenetics. Four (16.7%) patients had concomitant amyloidosis. Only 8.7% (n = 2) received maintenance therapy. The induction regimen was bortezomib-based in all patients. In Table 1 the characteristics of the 24 patients are summarized.

Engraftment

The median collected $CD34^+$ cell count was 8.78 (range, 3.2-52.4; missing data, n = 2) $\times 10^6/kg$. The median number of apheresis days required to achieve the target collection was 2.5 (range, 1-7; missing data = 2). All patients were engrafted. The median time to platelet ($\geq 20 \times 10^9/L$) and neutrophil engraftment

Table 1 Patient and Disease Characteristics (n = 24)

Variable	Value
Age at Time of Transplant, Years	53 (29-70)
Sex	
Male	15 (62.5)
Female	9 (37.5)
Histology/Myeloma Subtype	
Amyloidosis	4 (16.7)
Ig-A	4 (16.7)
Ig-G	7 (29.1)
Light chain only	8 (33.3)
Plasma cell leukemia	1 (4.16)
International Staging System Stage at Diagnosis	
Stage I	1 (4.16)
Stage II	1 (4.16)
Stage III	13 (54)
Unknown	9 (37.5)
High-Risk Cytogenetics	
No	20 (83.3)
Yes	4 (16.7)
Duration of Dialysis Before Transplant (Days)	235 (1-1481)
Stem Cell Mobilization	
Granulocyte colony stimulating factor	24 (100)
Melphalan Dose	
200	14 (58.3)
180	3 (12.5)
140	7 (29.2)
Neutrophil Engraftment Time, Days	10 (9-12)
Platelet Engraftment Time, Days	10 (9-12)
Maintenance Therapy	
Missing	1 (4.16)
No	21 (87.5)
Yes	2 (8.3)
CR, Very Good PR, PR	17 (71)
Refractory Disease After Initial Induction	3 (12.5)
Relapsed Disease	4 (16.5)

Data are presented as n (%) or median (minimum-maximum).