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Autologous Hematopoietic Stem Cell Transplantation in Dialysis-Dependent Myeloma Patients

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Abstract

We retrospectively analyzed our transplant database from 07/2000–06/2012 to identify myeloma patients who received autologous stem cell transplantation while on dialysis. 2091 patients underwent auto HCT during this period. 24 patients were dialysis dependent. The 100-day and the 6, and 12-month treatment related mortality was 0%. Overall response rate was 92%. The median PFS and OS were 1.9 years and 3.8 years, respectively.. A multivariate analysis was not performed due to the small sample size. Only 3 patients became dialysis independent posttransplant. Cardiac, gastrointestinal, genitourinary, infectious, neurologic, and pulmonary “all grade” toxicities were all higher in the Melphalan 200 group vs<200 group, however none of them was statistically significant. Due to 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.

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 hematopoietic stem cell transplantation (auto HCT)[6]. However several reports have shown that auto HCT is safe and effective in dialysis dependent myeloma patients[7,8].

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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, due to the absence of other medical etiologies explaining the renal failure, and the evidence of renal involvement from the plasma cell dyscrasia.

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 (FISH)[9,10,11,12]. This analysis was approved by the UT MD Anderson Cancer Center Institutional Review Board.

Stem cell mobilization and collection

All patients were mobilized with granulocytes colony stimulating factor (G-CSF). Peripheral blood CD34+ cell count was monitored by flow cytometry. Leukapheresis was started when the CD34+ cell count reached ≥10/μ L. Samples from leukapheresis products were collected to determine the number of CD34+ cells prior to 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 24–36 h 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 0.5×10^9/L . Platelet engraftment was defined as the first of 7 consecutive days that the platelet count exceeded 0.5×10^9/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 (CTACE) version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

Statistical methods

For associations with post-transplant dialysis status, Fisher's exact tests and Wilcoxon rank-sum tests were performed.. A Kaplan-Meier curve was used to estimate OS. All statistical analyses were performed using SAS 9.3 for Windows.

Results

Patient Characteristics

We identified 2091 multiple myeloma patients who underwent auto HCT between July 2000 to June 2012. Twenty-four were dialysis dependent (21 on hemodialysis and 3 on peritoneal dialysis), the cause of renal failure was primarily due to myeloma. 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 (ISS) 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. Table I summarizes the characteristics of the 24 patients.

Engraftment

The median collected CD34+ cell count was 8.78 (range: 3.2–52.4; missing data, n=2) × 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 engrafted. The median time to platelet (≥ 20 × 10^9/L) and neutrophil engraftment (ANC ≥ 0.5 × 10^9/L) was 12 days (range: 7–23) and 10 days (range: 9–12), respectively.

Treatment-related mortality (TRM) and Toxicity

The 100-day, 6-months, and one year treatment related mortality (TRM) were 0%. At the time of last follow-up, 13 (54.2%) patients were still alive and 11 (45.8%) had died. The primary cause of death was relapsed disease in all but one patient, who died of unknown cause. No patient died due to renal complications.

The incidence of any grade I-IV toxicity was 100% (n = 14) in the MEL 200 and 100% (n = 10) in the MEL < 200 group, Cardiac, gastrointestinal, genitourinary, infectious, neurologic, and pulmonary "all grade" toxicities were all higher in the mel 200 group vs mel <200 group, however none of them was statistically significant. Grade II mucositis was 28% (n=4) in the MEL 200 and 10% (n=1) in the MEL <200 (p>0.05). 2 patients had liver toxicity in the mel <200 group and none in the mel 200 group, p value was not statistically significant. The median hospitalization period was 25 days (range 9–49 days). Table II summarizes the toxicity per dose of Melphalan.

Response and survival

The median follow up is 1.1 (range: 0.2 – 7) years. Overall response rate [Complete response (CR) + Very good partial response (VGPR) + Partial response (PR)] was 92% (N=22/24, 95% CI: 0.81–1.00). Six patients (25%) achieved CR. The rates of VGPR and PR

were 29.2% (N=7) and 37.5% (N=9), respectively. Two patients (8.3%) had stable disease (SD). After a median follow up of 1.1 years (range: 0.2 – 7) the median PFS and OS were 1.9 years (95% CI: 0.9–4.7) and 3.8 years (95% CI: 1.1–4.9), respectively (Figures 1 & 2). Melphalan dose was not observed to be significantly associated with OS or PFS. A multivariate analysis was not performed due to the small sample size and only 11 events.

Dialysis independence

At the time of last follow-up, only 3 patients (13%) had become dialysis independent at one month, 13 months and 32 months post transplant. We did not find any variable associated with of becoming dialysis independent.

Discussion

Renal failure in myeloma patients is a frequently encountered problem. The prognosis in these patients is generally poor and often these patients are considered unfit for HDT and auto HCT. Patients on dialysis present a unique problem, as there is no consensus regarding the optimal conditioning regimen. While some trials using standard chemotherapy have shown that recovery of renal function in MM patients is associated with improved survival[14,15,16,17], there is little evidence to predict if dialysis dependent patients become dialysis independent after auto HCT. In this study, we report on the feasibility and toxicity of auto HCT in dialysis dependent myeloma patients in a large cohort of patients treated at a single center.

There is conflicting data as to whether melphalan dose reduction is required prior to auto HCT in patients with renal failure including those requiring dialysis. In a report by Tricot et al. melphalan pharmacokinetics were not adversely affected by impaired renal function[18]. Melphalan was not removed by dialysis, however, the authors concluded that the short half-life of melphalan in water and its binding to dialysis tubing could have contributed to lack of detection in dialysate.

In a report by Badros et al., 81 myeloma patients in renal failure, including 38 on dialysis underwent auto HCT, melphalan dose was reduced to 140 mg/m^2 in the last 21 patients due to excessive toxicity[8]. In another report, a TRM of 50% was seen in dialysis dependent myeloma patients who received MEL 200[19]. This led authors to recommend a reduction in melphalan dose in patients with renal failure. In a matched pair analysis by Raab et al., toxicity, TRM and survival were similar in dialysis dependent myeloma patients who received auto HCT with MEL 100 compared to patients without renal failure who received auto HCT with MEL 200[20]. In our study, the TRM was 0 at 12-months regardless of melphalan dose used. There was a statistically insignificant trend towards greater non hematologic toxicity in MEL 200 group. However, the response rate and survival was not affected by the melphalan dose used. Due to lack of a clear survival benefit with higher dose melphalan and potential of higher toxicity in this group of patients, it seems reasonable to recommend a melphalan dose reduction to 140 mg/m^2 in patients with dialysis dependent renal failure.

We also explored dialysis independence after auto HCT. Only 3 patients in our group had improved renal function and no longer required dialysis. We did not detect any variable, which predicted a better renal outcome after auto HCT. This experience is similar to that reported in the literature. In a study by Badros et al, 2 of 27 patients discontinued dialysis after auto HCT[8]. Similarly, in the report by Knudsen et al, none of the 8 patients on hemodialysis at the time of auto HCT went off dialysis after transplant[19]. Also in report by Raab et al., 2 of 17 patients recovered from dialysis-dependency[20]. In summary, the current data is indicative of an often continued need of renal replacement therapy in myeloma patients who are dialysis dependent at the time of auto HCT.

We did not observe any impediment to hematopoietic progenitor cells (HPC) mobilization by dialysis. All patients in our study were able to collect sufficient number of HPCs for auto HCT with a median of 2.5 apheresis days. This is in line with our historical experience in the non-dialysis patients[21].

The response rate with novel agents in myeloma patients with severe renal impairment is approximately 82%[22]. We noticed an encouraging overall response rate of 92% and a CR rate of 25% in our patients. This is similar to that reported after auto HCT in myeloma patients with normal renal function[20,24,25,26]. Similarly, in the era of novel agents, the median OS of myeloma patients with severe renal impairment has increased to 2.6 years compared to 1.5 years in the period 1990 – 1994[23]. The median OS in our cohort was 3.8 years (95% CI: 1.1- 4.9). Overall, our data suggest that the toxicity is low and excellent response rate and long-term survival can be expected after auto HCT in dialysis dependent myeloma patients, at a price of longer hospitalization as shown here (25 days, range 9–49 days), which probably was related to the higher degree of mucositis in the dialysis population, (and subsequently higher infectious complications), and the fluid-balance and electrolytes disturbance in this population.

There are several potential limitations of our study including the retrospective nature, lack of a matching control and heterogeneity of patients. Since this was not an intention-to-treat analysis the total number of dialysis dependent myeloma patients who did not receive auto HCT is unknown. Furthermore, due to limited number of events, a comprehensive multivariate analysis for survival could not be conducted. However, our data suggest that while the chances of becoming dialysis independent after auto HCT are low, the myeloma specific response rate is similar to that seen in patients with normal renal function. In addition, the TRM remains low and survival is at least comparable to that seen with non-transplant treatment options reported in literature[27].

In conclusion, dialysis dependent renal failure alone should not be an exclusion criterion for auto HCT. Prospective randomized studies in eligible patients with severe renal failure or on dialysis may help optimize the timing and dosage of melphalan, with a view to potentially improving renal function and minimizing treatment related toxicity.

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Clinical Practice Points

Approximately 5% of these patients are dialysis-dependent. 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, and also in part to reluctance in the use of intensive chemotherapy. Therefore, patients with dialysis dependent renal failure are frequently considered unfit for high-dose therapy (HDT) and autologous hematopoietic stem cell transplantation (auto HCT). The existing data suggest that melphalan dose reduction to 140 mg/m^2 is less toxic than 200 mg/m^2. We report the outcomes of 24 patients who underwent autologous stem cell transplant for multiple myeloma while dependent on hemodialysis; our results support the safety and efficacy of intensive chemotherapy followed by autologous stem cell transplant. We suggest that patients with dialysis dependent renal failure should be considered for high dose chemotherapy followed by autologous stem cell transplant.

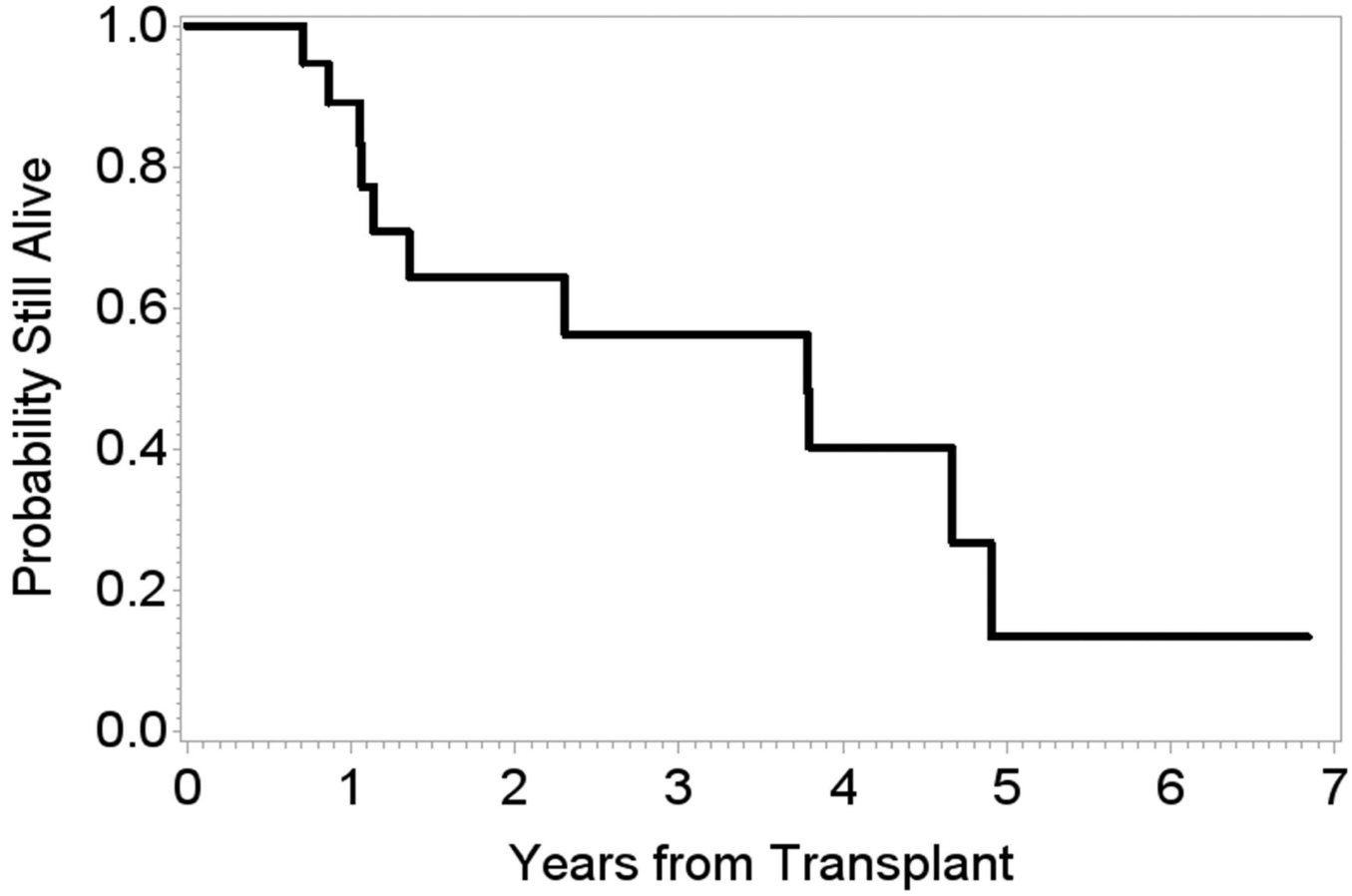

Figure 1.
Overall Survival (N=24, 11 deaths). The median overall survival time was 3.8 years (95% CI: 1.1- 4.9).

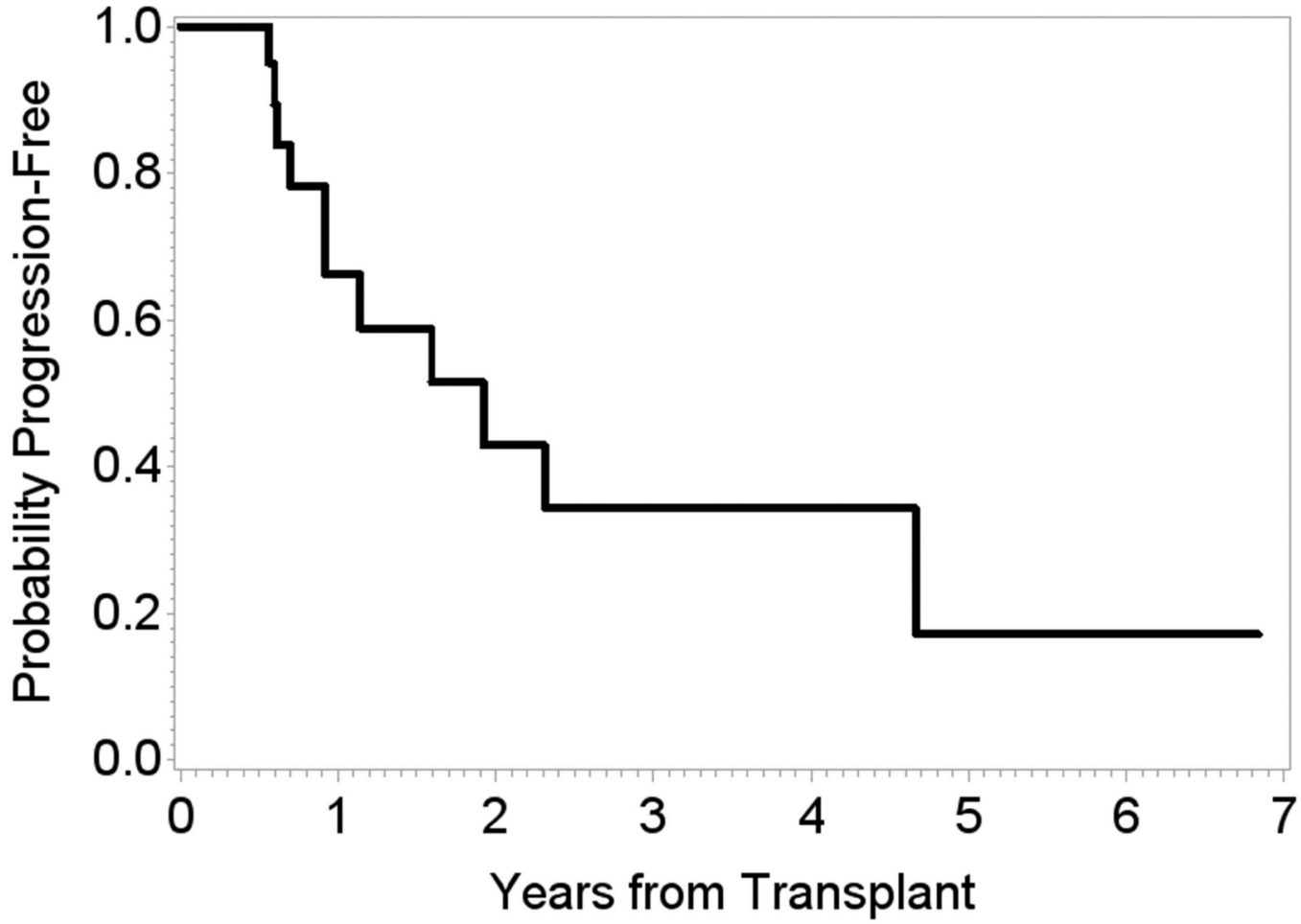

Figure 2.
Progression-Free Survival (N=24, 11 deaths or progressions). The median PFS time was 1.9 years (95% CI: 0.9- 4.7).

Table I

Patient and Disease Characteristics (N=24)

Variable	Category	Count (%) or Median (Min, Max)
Age at 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 prior to transplant (days)		235 (1 – 1481)
Stem cell mobilization	G-CSF	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, VGPR, PR		17(71%)
Refractory disease after initial induction		3(12.5%)
Relapsed disease		4(16.5%)

Table II

Rate of toxicity by total dose of melphalan (N=24)

	Total Melphalan Dose		p-value
	200 (n=14)	<200 (n=10)	
Grade I-IV toxicity	14 (100%)	10 (100%)	1.0000
Any cardiac toxicity	10 (71%)	2 (20%)	0.6404
Any gastrointestinal toxicity	14 (100%)	7 (70%)	1.0000
Any genitourinary toxicity	5 (35%)	0 (0%)	0.2801
Any liver toxicity	0 (0%)	2 (20%)	0.0543
Any infectious toxicity	8 (57%)	4 (40%)	0.6404
Any neurologic toxicity	6 (42.8%)	0 (0%)	0.2770
Any pulmonary toxicity	3 (21%)	1 (10%)	1.0000