The outcome of autologous stem cell transplantation in patients with plasma cell disorders and dialysis-dependent renal failure

Marc S. Raab
Iris Breitkreutz
Michael Hundemer
Axel Benner
Jens Klaus
Ute Hegenbart
Thomas Moehler
Anthony D. Ho
Martin Zeier
Hartmut Goldschmidt

Patients with multiple myeloma and end-stage renal failure on dialysis are frequently not considered eligible for high-dose therapy (HDT) due to higher transplant-related mortality (TRM). Our aim was to evaluate the toxicity and survival of dialysis-dependent patients after HDT with melphalan (100 mg/m^2) compared to those of patients without renal insufficiency (melphalan 200 mg/m^2) in a matched pairs analysis of 34 patients. No significant differences were observed between hematologic toxicity, TRM or disease response. Dialysis patients showed comparable event-free and overall survival. They required significantly extended intravenous antibiotic treatment and longer hospitalization. Thus, melphalan 100 mg/m^2 is less toxic, yet equally efficient and improves the prognosis of this group of patients.

Key words: stem cell transplantation, multiple myeloma, renal failure, dialysis

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From the Department of Internal Medicine V, University of Heidelberg, Germany (MR, IB, MH, JK, UH, TM, ADH, JG); National Center of Tumor Diseases, Heidelberg, Germany (HG); Central Unit Biostatistics, German Cancer Research Center, Heidelberg, Germany (AB); Department of Intern. Medicine I, Division of Nephrology, University of Heidelberg, Germany (MZ).

Correspondence:
Marc S. Raab, MD, Dana-Farber Cancer Institute,Jerome Lipper Multiple Myeloma Center, Harvard Medical School, 44 Binney Street, Mayer Building 553 Boston, MA 02115, USA.
E-mail:
Marc_Raab@dfci.harvard.edu

Renal insufficiency is frequently observed in multiple myeloma (MM). Up to 50% of newly diagnosed patients have renal failure and about 9% require dialysis due to severe renal impairment.[1] Patients who required dialysis were reported to have a poor prognosis.[2] Although several studies have shown equivalent response rates to conventional chemotherapy in patients with mild to moderate renal insufficiency compared to those with normal renal function, the survival of myeloma patients with renal impairment is still significantly shorter.[3] The implementation of high-dose therapy (HDT) supported by autologous stem-cell transplantation (ASCT) into myeloma treatment has improved the outcome in terms of remission rates and survival.[4] The Arkansas group along with others has shown HDT to be feasible and effective in patients with renal insufficiency, even in a dialysis-dependent setting.[5,6] However, this treatment approach was associated with higher rates of toxicity and transplant-related mortality. Therefore, patients with renal insufficiency are still frequently excluded from aggressive or high-dose chemotherapy protocols. A lower dose of melphalan might be adequate for these patients, being equally effective and less toxic than standard conditioning. We aimed to evaluate this approach by comparing the toxicity and survival after HDT (melphalan 100 mg/m^2) followed by ASCT in dialysis patients with plasma cell disorders with the same outcomes in patients without renal insufficiency after standard dose conditioning in a case control approach.

Design and Methods

Between January 1996 and September 2004, 32 patients with end-stage renal failure due to myeloma were referred to our center for HDT. According to the institute's general guidelines for HDT and ASCT, patients up to the age of 65 with a WHO performance status of 0-3 were eligible, provided they did not have severe cardiac or significant hepatic dysfunction not related to MM, or active infections. Seventeen patients on maintenance dialysis met these criteria and received a single course of HDT followed by ASCT after conventional pre-treatment. Thirteen patients had MM and four patients suffered from light-chain amyloidosis with involvement of at least two organs. The clinical outcome of these 17 patients was compared to that of 17 patients without renal insufficiency (creatinine within normal limits) in a matched pairs analysis out of 500 patients having undergone HDT and ASCT at our institution between December 1996 and October 2004. The conditioning regimen of the matched controls comprised melphalan 200 mg/m^2, while the dialysis group received 100 mg/m^2. The institutional review board approved the protocol and written informed consent was obtained from all patients. For matching, the types of pre-treatment were clustered into three categories: standard induction regimens (vincristine-adriamycin-

Table 1. Patients' characteristics.

Patients	*Dialysis group (n=17)*	*Matched controls (n=17)*	*p value*	*Relapse therapy, on dialysis (n=5)*
Age at ASCT (years)*	**57 (39–65)**	**59 (43–64)**		61 (46–66)
Salmon-Durie Stage I/II/III/amyloidosis	**2/1/10/4**	**2/1/10/4**		1/0/4/0
Monoclonal protein				
AL/G/A/D/BJ	**4/2/3/1/7**	**4/2/3/1/7**		0/1/1/0/3
Pre-treatment				
1/2/3 regimens	**1/11/5**	**1/11/5**		0/0/2/2/1
β-2 MG/Dx (mg/L)*	15.0 (2.8–68.8)	2.1 (1.2–3.9)		14.8 (8.5 - 15.4)
β-2 MG/ASCT (mg/L)*	28.5 (12.7–97.0)	2.4 (1.5–10.2)		18.9 (9.0 - 34.7)
Albumin/Dx (mg/dL)*	38 (17–51)	43 (25–54)		45 (44 - 51)
Albumin/ASCT (mg/dL)*	33 (18–46)	39 (17–45)		30 (26 - 43)
Gender (female/male)	8/9	5/12		2/3
Cycles of pre-treatment*	4 (1–10)	5 (1–12)		8 (5–20)
Patients with PD during induction treatment	2	2		
Toxicity				
Days until WBC >1×10^9/L*	13 (8–24)	13 (7–21)	0.73	13 (12–14)
Days until PLT >20×10^9/L*	12 (2–28)	11 (0–17)	0.94	13 (7–14)
No. of PLT transfusions*	3 (1–16)	3 (0–6)	0.14	2 (1–6)
No. of erythrocyte transfusions*	4 (2–16)	2 (0–12)	0.12	3 (0–16)
Days of total parent. nutrition*	4 (0–30)	1 (0–15)	0.38	2 (0–19)
Days of fever*	3 (0–20)	2 (0–9)	0.16	3 (2–3)
Days on i.v. antibiotics*	10 (0–22)	6 (0–16)	**0.04**	10 (8–15)
Days on i.v. antimycotics*	0 (0–14)	0 (0–10)	0.36	
Days in hospital*	19 (13–63)	17 (13–22)	**0.04**	17 (13–39)
Response + survival				
PR/CR (prior ASCT)	6/0	9/2		
PR/CR (post ASCT)	9/4	10/4		
Event-free survival/months*	23.4	18.3	0.71	
Overall survival/months*	35.6	52.3	0.44	
Transplant-related mortality	1/17	1/17		
Est. median follow-up/months	35	35		

*ASCT: autologous blood stem cell transplantation; β2-MG: β2-microglobulin; Dx: diagnosis; PD: progressive disease; PR: partial remission; CR: complete remission; WBC: white blood cell count; PLT: platelets: parameters used for matching are given in bold; *: median (range).*

dexamethasone and related regimens), melphalan-prednisone, and relapse treatment (thalidomide-cyclophosphamide-etoposid-dexamethasone), with the last being used for patients transplanted in second response following relapse during induction therapy.

Given the unusual distribution of immunoglobulin subtypes due to the focus on severe renal impairment we used an extensive matching algorithm in order to reach the greatest similarity possible. We applied matching on the estimated propensity score for age at ASCT and the number of previous treatment regimens. Exact matching was used on stage (Durie-Salmon), immunoglobulin subtype, and type of previous regimen. The propensity score is the probability that a unit receives treatment (here being the dialysis patient), given the covariates. Matched pairs analysis was performed using the Wilcoxon signed rank test for quantitative data. Survival analysis and the analysis of time-to-event data for matched pairs was done using Cox's proportional hazards model. We modeled the potential *clustering* of event times within pairs of patients by using a group-specific random effect or frailty term in the proportional hazards model.[7] To be more precise we fitted a shared γ frailty model using a penalized likelihood on the hazard function.[8]

Results and Discussion

Patients' characteristics

The patients' characteristics are presented in Table 1. It is worth noting that 65% of patients in the dialysis group had either Bence-Jones type MM (n=7) or AL-amyloidosis (n=4), reflecting the known high nephrotoxic potential of these subtypes of plasma-cell disorders.[9,10] Apart from the matching criteria, β2-microglobulin was markedly increased while albumin was decreased in dialysis-dependent patients, consistent with retention and loss, respectively, of these proteins in the setting of renal failure.

Renal failure requiring dialysis occurred a median of 4.5 months (range 1–8) prior to ASCT. Two patients recovered from dialysis-dependency 5 and 6 months post-ASCT.

Hematopoietic engraftment and toxicity

Statistically significant differences were not seen in the number of days until hematologic recovery, days with fever, or days with total parenteral nutrition (Table 1). Dialysis patients did, however, require significantly extended intravenous antibiotic treatment and a longer time in hospital (p=0.04). A tendency towards extended intravenous nutrition reflects the more severe mucositis observed in dialysis patients despite the already reduced dose of melphalan (100 mg/m^2) which, in turn, led to prolongation of hospitalization. However, this indicates the equal potency of this conditioning regimen in dialysis patients.

Transplant-related mortality

There was one transplant-related death (cardiac arrest) among the 17 patients in the dialysis group and one (due to sepsis) in the matched controls. This is in contrast to other reports, in which transplant-related mortality rates for dialysis patients reached 17%,[11] 29%,[6] and 50%.[12] However, patients in those reports had been treated with higher doses of melphalan (140 mg/m^2 or 200 mg/m^2, respectively).

Response and survival after ASCT

The response rate after ASCT, defined according to the EBMT guidelines, was similar in both groups.[13] After an estimated median follow-up time of 35 months, the dialysis patients showed a comparable estimated post-transplant event-free (23.4 vs. 18.3 months, p=0.71) and overall survival (35.6 vs. 52.3 months, p=0.44) (Figure 1). In both groups together, the primary cause of death during follow-up was terminal disease progression (5 patients). Another two patients had septic shock following relapse treatment, while two died of unknown causes. Of note, no deaths due to dialysis-associated causes were observed. This is in line with results from other groups reporting similar survival data in patients with renal insufficiency who were or were not dialysis-dependent.[6,12,14]

Relapsed patients

Five out of the 17 dialysis patients underwent second HDT and ASCT after a median of 11 months because of relapse. These 5 patients developed comparable toxicities although no statistical evaluation was performed due to the limited number. One of the five relapsed dialysis patients died after the second ASCT due to sepsis.

Patients not eligible for HDT and ASCT

Fifteen dialysis-dependent patients were considered not eligible for HDT followed by ASCT according to the inclusion criteria mentioned above. The majority had a poor performance status while three were excluded because they were >65 years old. The median age at the start of treatment was 56 years (range 39-73). All

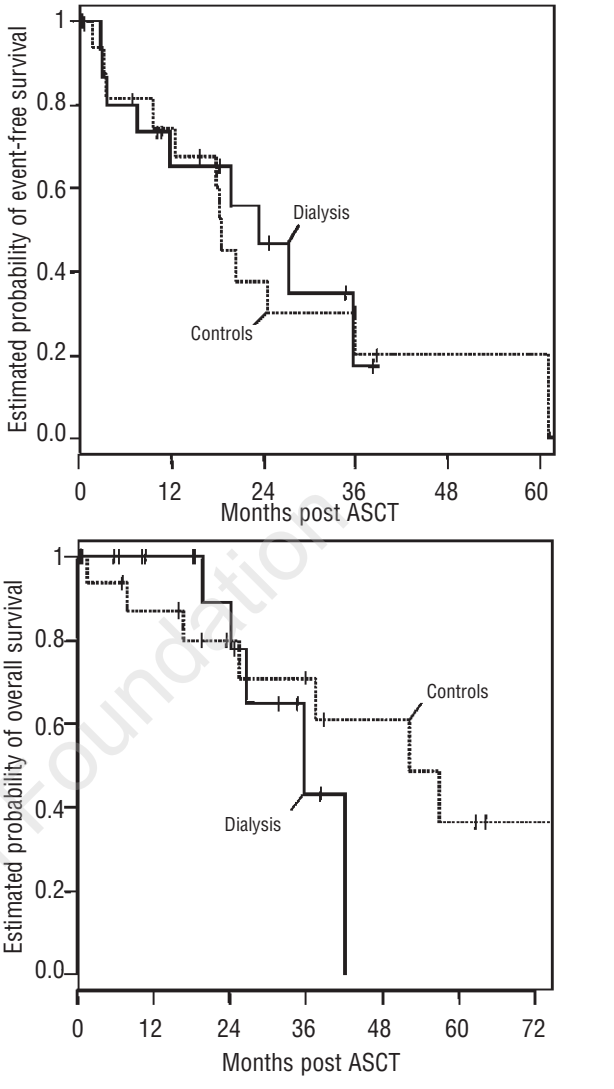

Figure 1. Estimated event-free and overall survival for dialysis-dependent patients (dialysis) and their matched controls without renal insufficiency (controls).

patients in this group were referred to their regional health care centers for further treatment and received a median of four cycles of conventional chemotherapy (range 1-19). These patients had a poor median overall survival after starting treatment (15 months, range 1-101), which is not unexpected given their unfavorable status prior to therapy.

In conclusion, in our matched-pairs analysis, HDT in 17 patients with MM and light-chain amyloidosis on chronic dialysis caused slightly more toxicity than in the matched controls. However, no significant differences were detected in transplant-related mortality, event-free survival, and overall survival. In the light of these favorable findings, we recommend a reduced dosage of melphalan (100 mg/m^2), which appears to be equally effective, to avoid excessive toxicity. This is in line with the

Italian guidelines for disease management in multiple myeloma, suggesting a dose-reduction of melphalan for patients with renal impairment.[15]

Even in relapse treatment, dialysis should not constitute a criterion for exclusion from high-dose therapy and autologous stem cell transplantation. Prospective randomized trials in patients with severe renal failure are mandatory to further optimize treatment-related toxicity and improve the outcome of this frequently neglected group of patients.

MR: collected and analyzed the data and wrote the paper; IB: collected the data and was responsible for data management; AB: did the statistics and wrote part of the paper; MH: took care of patients, reviewed and discussed the paper; TM: took care of patients, and reviewed and discussed the paper; ADH: supervised patient care and was responsible for treatment concept; MZ: provided expert opinion and reviewed the paper; HG: took care of patients, reviewed and discussed the paper, and was responsible for the treatment concept.

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