Safety and efficacy of autologous stem cell transplantation in dialysis-dependent myeloma patients: the DIADEM study from the chronic malignancies working party of the EBMT

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Safety and efficacy of autologous stem cell transplantation in dialysis-dependent myeloma patients—The DIADEM study from the chronic malignancies working party of the EBMT

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The role of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) in the treatment of myeloma (MM) patients with severe and/or dialysis-dependent renal impairment remains uncertain. We report on the outcomes of 110 patients (median age 57 years) who had become dialysis-dependent pre-ASCT and who underwent a first ASCT between 1997 and 2017. Sixty-three (57%) patients had light chain MM. All patients required dialysis (94% hemodialysis and 6% peritoneal). Forty-four of 71 (62%) patients received bortezomib-based induction regimens and 42 (39%) patients had achieved at least a very good partial response (VGPR) pre-ASCT. Melphalan dosing was as follows: ≤140 mg/m^2 (82%), and >140 mg/m^2 (18%). The median PFS after ASCT was 35 months (95% CI: 21.5–42.2) and the median OS 102 months (95% CI: 70.4–129.1). At 1, 2, and 5 years after ASCT, 8% (95% CI 3–14%), 13% (6–20%), and 20% (12–29%) of patients, respectively, had achieved dialysis independence. In multivariate analyses of OS and PFS including age at ASCT, response at ASCT, and year of ASCT, younger age at ASCT and better response at ASCT (CR/VGPR/PR vs. MR/SD/progression) were significantly associated with better OS and PFS.

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INTRODUCTION

High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT) is the standard-of-care for transplant-eligible patients with multiple myeloma (MM) and the superiority of high-dose chemotherapy followed by ASCT over conventional chemotherapy has been reported in several randomized trials [1–4]. The efficacy of ASCT in MM patients with renal impairment (RI) has also been demonstrated [5–7]. MM patients with significant renal impairment, especially dialysis-dependent (DD) RI, have historically had worse outcomes compared to those with normal renal function (NRF) due to both disease characteristics and limited access to ASCT or clinical trials [8–10]. MM-related renal insufficiency is a myeloma-defining event (MDE), one of the SLiM CRAB criteria (60% or more clonal plasma cells (S), light chain (Li), MRI (M), (C)alcium (raised), (R)enal Insufficiency, (A)naemia, (B)one lesions) and is present in between 20 and 50% of MM patients at presentation, whereas 5–13% are dialysis-dependent [11, 12]. Furthermore, of the four original MDEs or CRAB criteria, renal injury was associated with the worst outcomes regarding both overall survival (OS) and treatment-related toxicity [13, 14].

Though ASCT remains the standard-of-care in the treatment of transplant-eligible MM patients, the perceived higher risk of complications in patients with RI may limit consideration of this option by some clinicians. However, MM with renal injury may in some cases reflect an increased tumour burden, which could be seen as a rationale for more intensive treatment including ASCT in suitable patients [15, 16]. Evidence in support of ASCT in this setting is inconsistent and interpretation of the data is complicated by heterogeneous datasets with regard to the definition of renal insufficiency, patient characteristics, and induction regimens, some dating to before the availability of novel agents. Improved renal function due to ASCT may lead to an improved quality of life and could be an important prognostic factor for survival [17, 18].

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Table 1. Patient, disease, and transplantation characteristics.

		N (%)
Patient sex	Male	66 (60)
	Female	44 (40)
Age at ASCT (years)	median (IQR)	56.5 (48.7–62.1)
Interval dialysis initiation—ASCT (months, *n* missing = 4, 4%)	median (IQR)	7.6 (5.5–12.4)
Timing of dialysis initiation (*n* missing = 4, 4%)	Dialysis at/after MM diagnosis	66 (62)
	Dialysis before MM diagnosis	40 (38)
Subtype at diagnosis (*n* missing = 2, 2%)	Other	45 (42)
	LCMM	63 (57)
Status at ASCT (*n* missing = 3, 3%)	CR	14 (13)
	VGPR	28 (26)
	PR	49 (46)
	MR/SD	12 (9)
	Relapse/ progression	6 (6)
Karnofsky score at ASCT (*n* missing = 22, 20%)	<80	12 (14)
	80	29 (33)
	90–100	47 (53)
Interval diagnosis—ASCT (months)	<6	27 (25)
	≥6	83 (75)
Interval diagnosis—ASCT (months)	median (IQR)	8.0 (6.0–11.7)
PI as pre-treatment before ASCT (*n* missing = 39, 35%)	no	27 (38)
	yes	44 (62)
Melphalan dose in mg/m^2 (*n* missing = 26, 24%)	≤140	69 (82)
	>140	15 (18)

ASCT autologous hematopoietic stem cell transplantation, *MM* multiple myeloma, *LCMM* light chain multiple myeloma, *CR* complete response, *VGPR* very good partial response, *PR* partial response, *MR* minor response, *SD* stable disease, *PI* proteasome inhibitor, *IQR* interquartile range, *mg* milligram.

We, therefore, evaluated the safety and efficacy of ASCT in MM patients with DD RI who underwent ASCT in EBMT-affiliated centres between 1997 and 2017 inclusive.

METHODS

This is a retrospective, multicentre, registry-based analysis approved by the Chronic Malignancies Working Party of the EBMT. The EBMT is a non-profit, scientific society representing more than 600 transplant centres, mainly in Europe. Data are entered, managed, and maintained in a central database with internet access; each EBMT centre is represented in this database. EBMT centres commit to obtaining informed consent according to the local regulations required for the reporting of pseudonymized data. Information was first sought on patients registered in the database as (1) having had a first ASCT for MM between 1997 and 2017 inclusive and (2) having a serum creatinine concentration >3 mg/dL (>265 umol/L) at the time of diagnosis or pre-ASCT. Centres were approached for additional data regarding dialysis (creatinine values at diagnosis and transplant, dialysis dependency at diagnosis/transplant (yes/no), date of dialysis initiation and cessation, and type of dialysis (hemodialysis/peritoneal)). Patients from centres that responded to the data request were included in the final analysis after verification that dialysis was initiated prior to the ASCT. Baseline patient characteristics at diagnosis, treatment regimens, and clinical outcomes were collected using standardized report forms.

The primary objective of this retrospective study was to assess the OS, progression-free survival (PFS), early non-relapse mortality, and cumulative incidence of cessation of dialysis after ASCT. The starting point for the time-to-event analyses was the date of ASCT, and patients who were alive without a (competing) event were censored at the date of last follow-up. For OS, the event was defined as death regardless of cause, whereas, for PFS, the event was disease progression or death, whichever occurred first. OS and PFS were analysed using the Kaplan-Meier method. The cumulative incidences of cessation of dialysis and death before the dialysis cessation were analysed together in a competing risks framework. If dialysis was stopped within two weeks of death, it was not regarded as cessation of dialysis. Subgroup differences in time-to-event outcomes were assessed using log-rank or Gray's tests, where appropriate. All estimates were reported with (95% CI) confidence intervals.

Cox proportional hazards regression analysis was used to assess the association of baseline characteristics and cessation of dialysis after ASCT (as a time-dependent variable) with death, and progression. Simon-Makuch curves starting at one year after ASCT and including cessation of dialysis as a time-dependent variable were used to obtain OS and PFS probabilities for the (hypothetical) subgroups of patients with dialysis at 1 year, and without dialysis at 1 year and never thereafter. A landmark analysis starting at 100 days after ASCT was performed to assess the association between the best response at three months and achievement of dialysis independence. Median follow-up after ASCT was calculated using the reverse Kaplan-Meier (KM) method. All analyses were performed in R version 3.6.3 (REF: R Core Team. A language and environment for statistical computing. R Foundation for Statistical Computing. 2020. Available from: https://www.r-project.org/) using 'survival', 'cmprsk' and 'prodlim' packages.

RESULTS

A total of 91,421 adult MM patients were registered in the EBMT database as having undergone ASCT between 1997 and 2017 inclusive. Of these, a total of 1218 underwent a first ASCT with a reported serum creatinine concentration >3 mg/dL (>265 umol/L) at diagnosis or pre-ASCT. Further data on dialysis was requested on these 1218 patients. Information was received on 446 patients of whom 124 patients (28%) had received dialysis and 332 (72%) had not. After verification of the dialysis initiation and stop dates in relation to the date of ASCT, 110 patients from 44 EBMT registered centres were ultimately included in the analysis.

Table 1 demonstrates patient characteristics at time of ASCT. The median age was 57 years (interquartile range (IQR), 49–62 years) and 66 (60%) patients were male. The Karnofsky Performance Score (KPS) was reported as ≥90 in 53% of patients. Regarding MM subtype, 63 (57%) patients had light chain MM (LCMM; 40 kappa and 23 lambda). A total of 103 patients (94%) required hemodialysis and seven (6%) peritoneal dialysis. As first-line induction therapy, 44 of 71 (62%) patients had received bortezomib-based regimens. Forty-two (39%) patients had achieved at least a very good partial response (VGPR) pre-ASCT. The median time from MM diagnosis to ASCT was 8.0 months (IQR, 6.0–11.7). Regarding conditioning chemotherapy, melphalan dosing was as follows; ≤140 mg/m^2 (82%), and >140 mg/m^2 (18%).

The median age at ASCT in the melphalan >140 mg/m2 dose group was 58.0 (IQR 50.3–62.6) years and was higher than the median age in the melphalan ≤140 mg/m2 group (56.1, IQR 48.5–60.5). However, the proportion of patients <55 years of age at ASCT was similar (47% in >140 mg/m2 and 48% in ≤140 mg/m2 group). The 5-year NRM in those with >140 mg/m2 was 14% (95% CI 0–33%) and compares to 12% (95% CI 3–20%) in those with ≤140 mg/m2 (Gray's test $p = 0.58$).

The median follow-up post-ASCT was 56.8 months (IQR 26.1–87.8 months). The median times to neutrophil (≥0.5×10^9/L) and platelet (≥20×10^9/L) engraftment were 12 (IQR 11–13) and 14 (IQR, 12–19) days, respectively. The 30-day and 100-day non-relapse mortality rates were 2% (95% CI 0–4%) and 7% (95% CI 2–11%), respectively. Of the 73 patients for whom data on best response assessed at 100 days was available, 34 had a CR or VGPR

(47%, 95% CI 35–59%). At 1, 2, and 5 years, 8% (95% CI 3–14%), 13% (95% CI 6–20%), and 20% (95% CI 12–29%) of patients, respectively, had achieved dialysis independence. A total of seven additional patients stopped dialysis but died within two weeks and were therefore not considered to have achieved dialysis independence. Finally, in a univariable analysis of dialysis cessation factors, patients who had achieved at least a VGPR pre-ASCT had a lower cumulative incidence of dialysis independence at 5 years after ASCT (9%, 95% CI 0–20%) when compared to patients who had achieved less than VGPR (27%, 95% CI 5–39%, Gray's test $p = 0.03$).

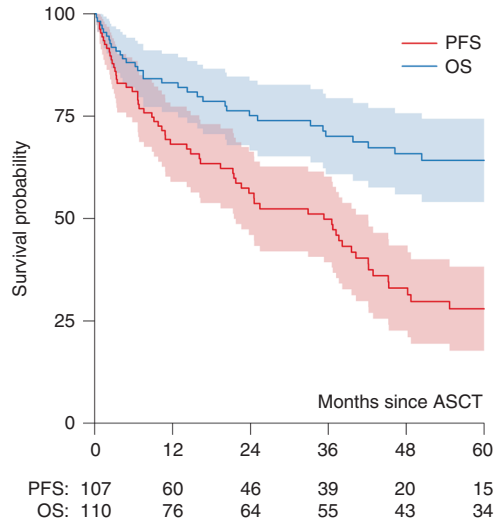

Fig. 1 Progression-free survival (PFS) and overall survival (OS). Numbers below the graph shows the number of patients at risk. Relapse status was unknown in 3 patients, hence the PFS curve contains data from 107 patients. ASCT autologous stem cell transplantation.

The median PFS was 35 months (95% CI: 21.5–42.2) and the 5-year PFS 28% (95% CI: 18–38%) (Fig. 1). The median OS was 105 months (95% CI: 70.4–129.1) and the 5-year OS post-ASCT 64% (54–74) (Fig. 1). Regarding the years of transplantation, no significant differences were observed in either PFS (log-rank $p = 0.78$) or OS (log-rank $p = 0.85$) between patients undergoing ASCT between 1997 and 2007 as opposed to between 2008 and 2017; the 5-year PFS probabilities were 26% (95% CI 6–47%) and 28% (16–40%) and the 5-year OS probabilities were 64% (95% CI 43–86%) and 64% (53–76%), respectively (Table 2). The probability of PFS 5 years following ASCT was higher in those who had achieved either a CR, VGPR, or PR (31%), (95% CI 20–43%) compared to those with MR/SD/progression at ASCT (9%, 95% CI 0–25%, log-rank $p = 0.01$). The 5-year PFS was also higher in patients aged <55 years at ASCT (33%, 95% CI 17–48%) compared to those aged ≥55 years (26%, 95% CI 12–40%, log-rank $p = 0.13$). Stopping dialysis was not significantly associated with improved OS (Mantel-Byar $p = 0.80$) or PFS (Mantel-Byar $p = 0.94$).

As shown in Fig. 2, there was no difference in the cumulative incidence of dialysis independence at 5 years after ASCT between patients who achieved a best response of at least VGPR at day 100 compared to patients with other responses (12%, 95% CI 0–24% vs. 13%, 95% CI 0–27%, respectively, Gray's test $p = 0.85$). In

Table 2. Estimates of probabilities (95% confidence intervals) for overall survival (OS) and progression/relapse-free survival (PFS) at 5 years after autologous hematopoietic stem cell transplantation (ASCT).

		OS (%)		PFS (%)	
		5-year probability (95% CI)	*p*	5-year probability (95% CI)	*p*
Age at ASCT	<55 years	75 (63–88)	0.07	13 (17–48)	0.13
	≥55 years	54 (39–69)		26 (12–40)	
Sex	Male	64 (51–76)	0.37	29 (15–42)	0.87
	Female	66 (50–82)		27 (11–43)	
Year of ASCT	1997–2007	64 (43–86)	0.85	26 (6–47)	0.78
	2008–2017	64 (53–76)		28 (16–40)	
Interval diagnosis -ASCT in months	<6	57 (33–80)	0.48	8 (0–22)	0.08
	≥6	66 (55–78)		33 (21–45)	
Prior PI treatment	Yes	67 (52–82)	0.99	35 (16–54)	0.87
	No	64 (46–83)		27 (11–43)	
Response at ASCT	CR/VGPR/PR	68 (58–79)	0.11	31 (20–43)	0.01
	MR/SD/ progression	38 (7–69)		9 (0–25)	
Melphalan dose in mg/m^2	<140	62 (49–75)	0.59	25 (13–38)	0.31
	≥140	79 (59–100)		16 (0–44)	
Karnofsky score at ASCT	≤80	65 (48–82)	0.50	26 (9–42)	0.96
	90 or 100	56 (40–72)		30 (14–46)	
Type of disease	LCMM	70 (57–83)	0.22	33 (19–47)	0.33
	Other	58 (42–74)		21 (6–35)	
Dialysis cessation*	Yes	81 (61–100)	0.80	43 (20–90)	0.94
	No	76 (66–89)		39 (26–59)	

P-values were obtained using the log-rank test.
*Probability estimates obtained with Simon-Makuch methods (starting at 12 months after ASCT) including dialysis cessation as a time-dependent variable, *p*-values obtained with Mantel-Byar test.
ASCT autologous hematopoietic stem cell transplantation, *LCMM* light chain multiple myeloma, *CR* complete response, *VGPR* very good partial response, *PR* partial response, *MR* minor response, *SD* stable disease, *PI* proteasome inhibitor, *mg* milligram.

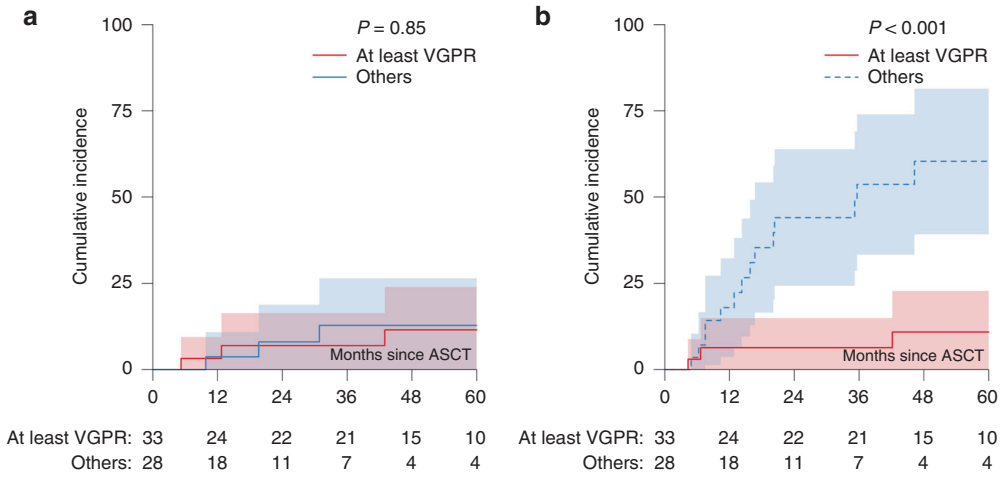

Fig. 2 Incidence of dialysis independence and death before dialysis independence. Cumulative incidence of **a** dialysis independence and **b** death before dialysis independence according to best response at 3 months after at ASCT. Landmark analysis from 3 months after ASCT. ASCT autologous stem cell transplantation.

Table 3. Hazard ratios (HR) and 95% confidence intervals (CI) obtained using multivariable Cox proportional hazards regression on overall survival (OS) and progression-free survival (PFS).

	OS		PFS	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
Age at ASCT (per 10-year increase)	1.71 (1.10–2.64)	0.02	1.32 (1.00–1.75)	0.05
Year of ASCT				
1997–2007	1		1	
2008–2017	1.31 (0.55–3.14)	0.54	1.09 (0.59–2.02)	0.78
Response at ASCT				
CR or VGPR	1		1	
Other	2.58 (1.06–6.25)	0.04	2.43 (1.26–4.70)	0.008

contrast, significantly fewer patients died before achieving dialysis independence in those who achieved at least a VGPR compared to other responses (11%, 95% CI 0–23% vs. 60%, 95% CI 39–81%, respectively, Gray's test $p = 0.001$).

In a MVA analysis assessing the effect of (1) age at ASCT, (2) response at ASCT, and (3) the era of ASCT on PFS and OS, younger age at ASCT and a better response at ASCT (CR/VGPR/PR vs. MR/SD/progression) were significantly associated with better OS and PFS (Table 3).

DISCUSSION

To the best of our knowledge, the EBMT DIADEM study represents the largest analysis of ASCT outcomes in DD RI MM patients to date. The median PFS was 35 months and 5-year PFS 28%. The median OS was 105 months with 5- and 10-year OS post-ASCT of 64% (95% CI 54–74) and 38% (18–57), respectively. While inferior to the median PFS of 67.5 months and 5-year OS of 80.7% achieved in the transplant arm of the recently reported DETERMINATION trial, they remain robust responses for a retrospective study over two decades. These improved outcomes of late are likely attributable to more potent induction and the uniform use of maintenance treatment until disease progression. Of particular note, about 20% of patients in our study achieved dialysis-independence post-ASCT, an outcome likely to confer an improved quality-of-life. In MVA, older age was associated with both a shorter PFS and OS. With regard to pre-ASCT response, superior responses pre-ASCT (CR, VGPR, or PR vs. Other) were associated with improved PFS and OS.

Previous reports by St Bernard et al. observed a median OS of 69 months in 33 DD MM patients, comparable to their overall institutional outcomes [19]. Mahindra et al. performed a CIBMTR study analyzing ASCT outcomes based on the degree of renal impairment. They found that in the severe renal insufficiency group, the 5-year PFS and OS rates in the 'Mel140' cohort were 25% (11–41%) and 63% (46–80%), respectively, whereas for patients receiving 'Mel200', they were 32% (11–58%) and 55% (31–77%), respectively [12].

Raab et al. reported an analysis of 34 DD pts and matched pairs without RI and observed comparable estimated post-transplant PFS (23.4 vs. 18.3 months) and OS (35.6 vs. 52.3 months; p=ns) [15]. Despite the greater toxicity seen in DD patients in a similar Polish matched-pair analysis, these events did not significantly affect either the PFS or OS [16].

As a benchmark for expected outcomes in MM patients following ASCT, Auner et al. compared survival rates in the EBMT database following conditioning with either Mel140 or Mel200 [7]. The median OS was not reached for the Mel140 cohort and was 78 months for the Mel200 cohort; the median PFS was 29 months in the Mel140 group and 26.3 months in the Mel200 group [5]. OS and PFS in our DD MM patients, therefore, appear to be comparable to outcomes seen in unselected MM patients undergoing ASCT from the EBMT Registry. No significant differences in either PFS or OS were observed when comparing the 1997–2007 and 2008–2017 cohorts: 5-year PFS 26% (95% CI 6–47) vs. 28% (95% CI 16–40, $p = 0.78$) and 5-year OS 64% (95% CI 43–86) vs. 64% (95% CI 53–76, $p = 0.85$), respectively. It might have been expected that more patients would have achieved dialysis independence following the availability of bortezomib-containing induction. However, it should be noted that bortezomib was introduced at different times in the countries involved in this analysis. It has been reported previously that following induction with bortezomib-based regimens, dialysis-independence can be achieved in 13–50% of patients [20, 21] and that they are associated with superior OS when compared with non-bortezomib-based chemotherapy (83 vs. 36%, $p = 0.02$). It should be noted, however, that a significant number of patients remain DD even after treatment with bortezomib and they are included in

this analysis. For such patients who remain DD, our findings suggest that they may well benefit from proceeding to ASCT.

Even in the era of modern targeted therapies, the ability of high-dose therapy to deepen responses in DD MM patients should be appreciated. Augeul-Meunier et al. from the French transplant registry found that 43% of the DD patients achieved CR after ASCT, whereas prior to ASCT, only 5% of patients achieved CR [6]. In our cohort, there was a deepening of responses post ASCT (39% >=VGPR pre-ASCT, 47% at Day +100). Badros et al. analysed 81 MM patients with a creatinine concentration >177 umol/l, including 38 DD MM patients. The TRM was 6% and 13% after the first and second auto-SCT, respectively. The CR rates following the first and second ASCT were 26% and 38%, respectively; these rates being similar to CR rates of 22% and 45% for patients with normal renal function undergoing single and tandem SCT, respectively [5].

An important finding of our study regards the number of patients who became dialysis independent after ASCT: 20% of patients at 5 years post-ASCT. This is an important observation as it has often been considered that patients who remain on dialysis following induction are highly unlikely to recover thereafter. A number of factors including dehydration, hypercalcemia, concomitant nephrotoxic drugs, and infection are frequently associated with reversible tubular injury in patients with MM, but these factors can additionally trigger tubulointerstitial lesions associated with cast nephropathy in patients who are at risk. Previous studies reporting on dialysis independence following ASCT have demonstrated rates of between 5–12% on average [7, 12, 16, 19]. Dialysis imposes a considerable burden on patients, requiring prolonged hospital visits three times each week. Dialysis dependence has been reported to be associated with increased morbidity, a lower quality of life (QOL), and an increased economic burden; coming off HD is therefore highly desirable [22].

There is a paucity of evidence regarding the factors that determine dialysis independence after ASCT in DD MM patients. We observed that dialysis independence occurred more frequently, and dialysis was stopped sooner, in the group who had not achieved at least a VGPR following induction and before the transplant. It is possible that in patients who had not yet achieved a VGPR, the nephrotoxic process was more reversible but required the deeper remission achieved following high-dose chemotherapy. It should be acknowledged, however, that the benefit conferred by autologous stem cell transplantation in deepening responses post-induction in this retrospective cohort might now be achieved by more potent induction regimens incorporating monoclonal antibodies. Alternatively, some of the responding patients in VGPR may have subsequently had non-MM-related RI which, once established, can be more difficult to reverse. It should also be noted that the 30-day and 100-day non-relapse mortality rates were 2% (95% CI 0–4%) and 7% (95% CI 2–11%), respectively. This late mortality after the first month is higher than expected. However, given the relatively small numbers involved in this study, it may have been a chance finding.

The limitations of our study are those inherent to a retrospective, registry-based study. Transplant decisions and their timing in this population will have been based on physician and patient preferences, MM disease characteristics, patient characteristics, and the availability of renal support services. Moreover, induction regimens changed considerably over the two decades covered in this study. Nonetheless, our analysis shows that ASCT in selected DD MM patients is feasible, induces a modest deepening of responses, and can result in dialysis-independence in 20% of patients after five years.

DATA AVAILABILITY

The final analysis dataset is available upon request to the Working Party chair.

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AUTHOR CONTRIBUTIONS

AW-G designed the study, interpreted the data, and wrote the first draft of the manuscript. The data was extracted and compiled by TS and the statistical analysis performed by LG and LCDW. PJH, MB, DPMcL, and SS interpreted the data and edited the manuscript. AI, ZNO, JAS, MA, CEB, JN, MS, SP, VP, AG, TC, GVG, JML, TK, JD-S, KR, and IYA reviewed the manuscript and provided clinical data. All authors approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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