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Original Article

Impact of dialysis dependence on survival for multiple myeloma with renal impairment: a multicenter study in China

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Abstract: Renal impairment (RI) is a very common complication of multiple myeloma (MM) with a negative impact on survival. Herein we retrospectively analyzed 334 MM patients with renal impairment at diagnosis from three hospitals in China. All 334 patients were divided into three groups, including dialysis dependence (n=43), dialysis independence (n=42), and without dialysis (n=249). Compared with dialysis independence and without dialysis groups, dialysis dependence group had the lowest overall hematologic response (48.8% vs. 97.6% vs. 77.1%, P<0.001) and overall renal response (0.0% vs. 97.6% vs. 72.7%, P<0.001), as well as the highest early mortality within 24 months (50.0% vs. 24.4% vs. 26.3%, P=0.006). Dialysis dependence group had similar progression-free survival (24 vs. 26 vs. 27 months, P=0.231) and significantly shorter overall survival (25 vs. 69 vs. 45 months, P=0.001). Dialysis dependence was independently associated with high mortality within 24 months and shorter overall survival. In conclusion, MM patients with dialysis dependence still tend to suffer a dismal disease course, including a high probability to suffer early mortality, worse hematological and renal response, as well as shorter survival. Dialysis independence could be very promising for survival improvement.

Keywords: Multiple myeloma, renal impairment, dialysis dependence, dialysis independence, survival

Introduction

Multiple myeloma (MM) is a plasma cell neoplasm characterized by anemia, bone disease, hypercalcemia and renal damage. In China, the standardized incidence rate of MM is calculated to be about 1/100,000 person-years [1], which is much lower than that in Western countries [2, 3]. Among the newly diagnosed multiple myeloma (NDMM), 20-40% suffer from renal impairment (RI) based on different diagnostic criteria and 10% need dialysis support [4, 5]. The mechanism of RI in MM is very complicated although cast nephropathy could explain the majority of them [4]. Among MM patients with renal damage, about two-thirds have the opportunity to achieve renal recovery after bortezomib-based triplets induction regimens [6].

The prognosis for MM patients with renal damage has been improved with the introduction of novel agents, but is still worse than those with normal renal function [4, 7]. Among these patients, survival for those who had reached renal recovery or dialysis independence could be improved significantly [8, 9], while for those without renal recovery would be very poor [7, 8]. However, only a few studies focused on MM with dialysis dependence either in traditional or novel agent eras [10-13]. With the results of the limited reports, the benefit of novel agents was quite limited in these patients [11, 12], while autologous stem cell transplantation (ASCT) seemed to be promising for improving the renal response and survival of these dialysis dependence patients [14, 15]. However, for these severely renal-damaged patients, early death was a very challenging problem [5, 16]. In this

study, we retrospectively analyzed 334 NDMM patients with renal impairment at diagnosis from three Chinese hospitals to assess the survival outcomes of MM patients with dialysis dependence in novel agent era.

Methods

Patients

Between April 2004 and January 2020, 334 NDMM patients with MM-related RI (defined as serum creatine level ≥177 μmol/L and/or estimated glomerular filtration rate (eGFR) <40 ml/min) from three hospitals were enrolled in the study. RI caused by other reasons than cast nephropathy was excluded. Data were obtained from the databases of three hospitals, which were all created and maintained prospectively. MM was diagnosed based on the International Myeloma Working Group (IMWG) criteria [17]. The diagnosis of cast nephropathy was made according to clinical-biological presentation, including predominant light chain proteinuria. When urine albumin accounted for 30% of proteinuria, histologic confirmation was mandatory; otherwise, the decision for kidney biopsy was at the investigator's discretion. The study was approved by the Beijing Chaoyang Hospital Institutional Review Board and conducted in accordance with the declaration of Helsinki.

To evaluate the impact of dialysis dependence on survival, we further divided these patients into three groups, including dialysis dependence (n=43), dialysis independence (n=42), and without dialysis (n=249). Dialysis dependence was defined as dialysis support within 4 weeks after MM diagnosis without renal recovery. Dialysis independence was defined as quitting dialysis due to renal recovery after frontline treatment. Without dialysis was defined as no dialysis support at diagnosis. The evaluation of hematological response and renal response was based on the International Myeloma Working Group (IMWG) criteria [18, 19]. Follow-up data were obtained until Oct 2021, and the median follow-up period was 73 (range 17-207) months.

Statistical analysis

Categorical variables were summarized as proportions and continuous variables were summarized as median (range). Categorical variables among different groups were compared by the χ^2 test or Fisher's exact test when appropriate. Continuous variables among groups were compared by the non-parametric Kruskal-Wallis test. Progression-free survival (PFS) was defined as the duration from the initiation of therapy to the first evidence of disease progression or death, or the last follow-up for those without evidence of progression. OS was calculated from initiation of therapy until death or the last follow-up. Survival curves of PFS and OS were plotted by Kaplan and Meier method and were compared among groups by log-rank test. For multivariate analysis, factors associated with PFS and OS were evaluated by Cox proportional hazard regression analysis, and factors associated with early mortality within 24 months and dialysis independence were introduced into a logistic regression mode. IBM SPSS v21 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Baseline characteristics

The baseline characteristics of MM patients with RI are summarized in **Table 1**. According to the results, the LDH level for patients with dialysis dependence was the highest among the three groups, however the difference did not reach statistical significance. It was reasonable that patients with dialysis dependence had the highest serum creatine level and lowest eGFR among the three groups. Gender, median age, M-protein isotype, and ISS stages were similar across the groups. No statistical differences were shown in hemoglobin, platelet, calcium and bone marrow plasma cells (BMPCs). Among 334 patients, 233 had available results of baseline cytogenetic abnormalities according to the interphase Fluorescent in Situ Hybridization (FISH) test. The cytogenetic patterns of the three groups are also exhibited in **Table 1**. According to the results, t(11;14) seemed to be more prevalent in dialysis dependence group (45.5% vs. 22.7% vs. 22.7%), however statistical difference was still not reached (P=0.067).

Baseline characteristics between dialysis dependence and independence groups had also been compared to find which type of MM-RI could realize renal recovery. However, with our results, none of the difference in base-

Table 1. The baseline characteristics of the study populations at diagnosis

Characteristics	All patients (n=334)	Dialysis dependence (n=43)	Dialysis independence (n=42)	*P* value between dialysis dependence and independence group	Without dialysis (n=249)	*P* value among all three groups
Male, n (%)	212/334 (63.5)	30/43 (69.8)	32/42 (76.2)	0.505	150/249 (60.2)	0.091
Age, y, median (range)	60 (37-85)	59 (39-80)	56.5 (43-81)	0.610	62 (37-85)	0.221
M-protein isotype						
IgG, n (%)	129/330 (39.1)	16/42 (38.1)	17/42 (40.5)	0.823	96/246 (39.0)	0.974
IgA, n (%)	61/330 (18.5)	5/42 (11.9)	9/42 (21.4)	0.242	47/246 (19.1)	0.470
IgD, n (%)	31/330 (9.4)	3/42 (7.1)	2/42 (4.8)	1.000	26/246 (10.6)	0.426
Light chain, n (%)	106/330 (32.1)	18/42 (42.9)	14/42 (33.3)	0.369	74/246 (30.1)	0.257
Others, n (%)	3/330 (0.9)	0/42 (0.0)	0/42 (0.0)	1.000	3/246 (1.2)	0.596
ISS I/II, n (%)	10/330 (3.0)	1/43 (2.3)	0/42 (0.0)	1.000	9/245 (3.7)	0.421
ISS III, n (%)	320/330 (97.0)	42/43 (97.7)	42/42 (100.0)	1.000	236/245 (96.3)	0.421
LDH, U/L, median (range)	177 (57-1099)	208 (99-488)	192 (83-416)	0.464	170 (57-1099)	0.053
Hb, g/L, median (range)	78 (35-154)	77 (49-110)	79.5 (48-121)	0.283	78 (35-154)	0.603
Platelets, 10^9/L, median (range)	155 (21-501)	124 (45-379)	154.5 (22-463)	0.212	162.5 (21-501)	0.092
Creatine, umol/L, median (range)	314.5 (92.1-1469)	701 (319-1437.3)	641.5 (247-1469)	0.689	240.5 (92.1-1077)	<0.001***
eGFR, ml/min/1.73 m^2, median (range)	17.5 (2.0-40.9)	6.8 (2.6-16.3)	8.9 (2.0-24.0)	0.169	22.7 (4.1-40.9)	<0.001***
Calcium, mmol/L, median (range)	2.3 (1.5-3.9)	2.3 (1.9-3.6)	2.3 (1.9-3.8)	0.154	2.3 (1.5-3.9)	0.374
BMPC, %, median (range)	37.5 (1.0-98.0)	38.5 (2.0-96.5)	37.3 (7.0-83.5)	0.493	37.5 (1.0-98.0)	0.838
Cytogenetic abnormalities						
t(11;14), n (%)	52/207 (25.1)	10/22 (45.5)	5/22 (22.7)	0.112	37/163 (22.7)	0.067
t(4;14), n (%)	33/211 (15.6)	1/22 (4.5)	2/22 (9.1)	1.000	30/167 (18.0)	0.178
t(14;16), n (%)	19/211 (9.0)	2/22 (9.1)	1/22 (4.5)	1.000	16/167 (9.6)	0.740
del(17p), n (%)	35/231 (15.2)	2/24 (8.3)	4/25 (16.0)	0.830	29/182 (15.9)	0.616
1q21 gain, n (%)	115/227 (50.7)	16/24 (66.7)	11/26 (42.3)	0.084	88/177 (49.7)	0.197

Abbreviation: ISS, International Staging System; LDH, lactate dehydrogenase; Hb, Hemoglobin; eGFR, estimated Glomerular Filtration Rate; BMPC, Bone Marrow Plasm Cell. ***means P<0.001.

Table 2. Treatment strategies of the study populations

Treatments	All patients (n=334)	Dialysis dependence (n=43)	Dialysis independence (n=42)	Without dialysis (n=249)	*P* value
Induction regimens					
PI based, n (%)	279 (83.5)	36 (83.7)	38 (90.5)	205 (82.3)	0.446
IMiDs based, n (%)	36 (10.8)	5 (11.6)	1 (2.4)	30 (12.0)	0.169
PI + IMiDs based, n (%)	16 (4.8)	1 (2.3)	3 (7.1)	12 (4.8)	0.583
Conventional therapy, n (%)	2 (0.6)	1 (2.3)	0 (0.0)	1 (0.4)	0.278
ASCT, n (%)	66 (19.8)	0 (0.0)	13 (31.0)	53 (21.3)	0.001**
Conditioning regimens					
Melphalan alone, n (%)	57 (86.4)	-	10 (76.9)	47 (88.7)	0.268
Other regimens, n (%)	9 (13.6)	-	3 (23.1)	6 (11.3)	0.268

Abbreviation: PI, Proteasome inhibitors; IMiDs, Immunomodulatory drugs; ASCT, autologous stem cell transplantation. **means P<0.01.

Table 3. The best response of the study populations

Characteristic	All patients (n=334)	Dialysis dependence (n=43)	Dialysis independence (n=42)	Without dialysis (n=249)	*P* value
Hematologic response, n (%)					
sCR	31 (9.3)	2 (4.7)	9 (21.4)	20 (8.0)	
CR	93 (27.8)	3 (7.0)	15 (35.7)	75 (30.1)	
VGPR	56 (16.8)	1 (2.3)	9 (21.4)	46 (18.5)	<0.001***
PR	74 (22.2)	15 (34.9)	8 (19.0)	51 (20.5)	
SD	58 (17.4)	17 (39.5)	1 (2.4)	40 (16.1)	
Unknown	22 (6.6)	5 (11.6)	0 (0.0)	17 (6.8)	
At least VGPR	180 (53.9)	6 (14.0)	33 (78.6)	141 (56.6)	<0.001***
ORR	254 (76.0)	21 (48.8)	41 (97.6)	192 (77.1)	<0.001***
Renal response, n (%)					
RenalCR	121 (36.2)	0 (0.0)	13 (31.0)	108 (43.4)	
RenalPR	51 (15.3)	0 (0.0)	16 (38.1)	35 (14.1)	
RenalMR	50 (15.0)	0 (0.0)	12 (28.6)	38 (15.3)	<0.001***
No response	110 (32.9)	43 (100.0)	1 (2.4)	66 (26.5)	
Unknown	2 (0.6)	0 (0.0)	0 (0.0)	2 (0.8)	
MRR	172 (51.5)	0 (0.0)	29 (69.0)	143 (57.4)	<0.001***
RenalORR	222 (66.5)	0 (0.0)	41 (97.6)	181 (72.7)	<0.001***

Abbreviation: sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minimum response; SD, stable disease; MRR, major renal response; ORR, overall response rate. ***means P<0.001.

line characteristics had reached statistical significance between the two groups, indicating that baseline characteristics were insufficient to predict renal recovery.

Treatment

The treatment strategies for the three groups of patients are shown in **Table 2**. With the results, 83.5% of patients received bortezomib-based induction, while 10.8% of patients received immunomodulatory drugs (IMiDs)-based induction. A small proportion of patients (4.8%) received combinations containing bortezomib and IMiDs. Only 2 patients (0.6%) received conventional therapy. Induction regimens were comparable among the three groups. ASCT was performed in 66 patients. Among them, 6 patients received double ASCT and 3 received ASCT as salvage therapy. In dialysis dependence group, none received ASCT. Most patients (86.4%) received single-agent melphalan as conditioning regimen before ASCT, while the others received melphalan in combination with bortezomib, busulfan plus cyclophosphamide or BEAM (carmustine, eto-

Table 4. The early mortality of the study populations

Early mortality, n (%)	All patients	Dialysis dependence	Dialysis independence	Without dialysis	*P* value
2 months	28/334 (8.4)	6/43 (14.0)	2/42 (4.8)	20/249 (8.0)	0.297
6 months	39/334 (11.7)	9/43 (20.9)	2/42 (4.8)	28/249 (11.2)	0.061
12 months	64/334 (19.2)	14/43 (32.6)	6/42 (14.3)	44/249 (17.7)	0.050
24 months	94/323 (29.1)	21/42 (50.0)	10/41 (24.4)	63/240 (26.3)	0.006**

Note: Early mortality is defined as death ratio within the specific duration after the start of treatment. **means P<0.01.

Table 5. Effect of baseline characteristics and response on early mortality within 24 months (n=323)

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age ≥60 vs. <60 years	1.069	0.661-1.729	0.786			
Hb <8 vs. ≥8 g/dl	0.956	0.589-1.552	0.855			
BMPC ≥30 vs. <30%	2.001	1.164-3.441	0.012*	1.901	1.094-3.305	0.023*
Light chain plus IgD vs. others	1.212	0.742-1.980	0.442			
LDH ≥250 vs. <250 U/L	1.659	0.928-2.963	0.087			
High risk FISH vs. not	1.910	0.950-3.843	0.069			
Dialysis dependent vs. not	2.849	1.471-5.518	0.002**	2.408	1.198-4.839	0.014*
ASCT vs. not	0.360	0.170-0.766	0.008**	0.459	0.211-0.999	0.050

Note: Light chain plus IgD, defined as M protein type; High risk FISH, defined as the presence of any of del17p, t(4;14), t(14;16) and/or 1q21 gain. Abbreviations: OR, odds ratio; Hb, hemoglobin; BMPC, bone marrow plasma cells; LDH, lactate dehydrogenase; ASCT, autologous stem cell transplantation. *means P<0.05, **means P<0.01.

poside, cytarabine and melphalan) respectively. Conditioning regimens were still comparable between dialysis independence group and without dialysis group.

Response to first line treatment

Hematological response: Hematological response to first-line treatment was assessed in dialysis dependence, dialysis independence and without dialysis groups respectively. The proportion of patients with stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), as well as at least VGPR and overall response rate (ORR) as best response to first-line treatment are shown in **Table 3**. A huge discrepancy was observed in the proportion of ORR (48.8% vs. 97.6% vs. 77.1%, P<0.001) and at least VGPR in the three groups (14.0% vs. 78.6% vs. 56.6%, P<0.001). According to the results, dialysis dependence patients were difficult to reach deep hematological responses than the other two groups of patients.

Renal response: Renal response to first-line treatment was also assessed in all three groups respectively. The proportion of patients with complete response (CR), partial response (PR), minor response (MR), no response, as well as major renal response (MRR) and overall renal response (ORR) as the best response to first-line treatment are shown in **Table 3**. In dialysis dependent group, none had reached renal response at any degree. The dialysis independence group was observed to have the highest renal ORR (97.6%) and MRR (69.0%) among the three groups.

Early mortality

Early mortality within 2, 6, 12 and 24 months were compared between the groups (**Table 4**). With the results, the dialysis dependence group exhibited the highest early mortality. Although it did not reach statistical differences within 2, 6 and 12 months, early mortality within 24 months of patients with dialysis dependence was significantly higher than in the other two groups (50.0% vs. 24.4% vs. 26.3%, P=0.006). With univariate analysis, high proportion of BMPC, dialysis dependent and non-ASCT were associated with early mortality within 24 months. Among these, high proportion of BMPC (P=0.023) and dialysis dependent (P=0.014) were independently related to early mortality

Table 6. Effect of baseline characteristics and response on dialysis independence (n=85)

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age ≥60 vs. <60 years	0.777	0.327-1.848	0.569			
Hb <8 vs. ≥8 g/dl	0.654	0.277-1.545	0.333			
BMPC ≥30 vs. <30%	0.628	0.253-1.558	0.316			
Light chain plus IgD vs. others	0.615	0.258-1.466	0.273			
LDH ≥250 vs. <250 U/L	0.818	0.294-2.280	0.701			
High risk FISH vs. not	0.294	0.080-1.080	0.065	0.605	0.098-3.726	0.588
Less than vs. at least VGPR for best R	0.051	0.016-0.160	<0.001***	0.026	0.004-0.165	<0.001***

Note: Light chain plus IgD, defined as M protein type; High risk FISH, defined as the presence of any of del17p, t(4;14), t(14;16) and/or 1q21 gain. Abbreviations: OR, odds ratio; Hb, hemoglobin; BMPC, bone marrow plasma cells; LDH, lactate dehydrogenase; VGPR, very good partial response; R, hematologic response. ***means P<0.001.

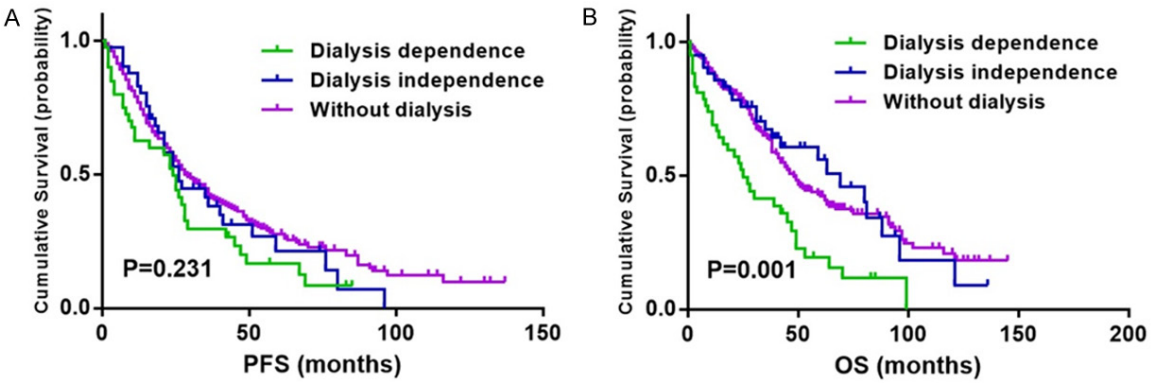

Figure 1. PFS (A) and OS (B) of MM patients with RI according to dialysis dependence, dialysis independence and without dialysis.

within 24 months in multivariate analysis (**Table 5**).

Dialysis independence

In our cohort, a total of 85 patients received dialysis at diagnosis, among which 42 patients (49.4%) had achieved renal recovery after first-line treatment and became dialysis independent. Factors related to dialysis independence were investigated. According to the results, only at least VGPR for best hematological response was associated with dialysis independence both in univariate and multivariate analysis (**Table 6**), indicating that only deep hematologic response could be the predictor for dialysis independence.

Survival outcomes

The median PFS and OS for the whole cohort were just 26 months (95% CI, 23.0-29.0 months) and 44 months (95% CI, 39.1-48.9 months) respectively. There were no differences in median PFS [24 (95% CI: 19.3-28.7) vs. 26 (95% CI: 19.0-33.0) vs. 27 (95% CI: 22.3-31.7) months, P=0.231] among the three groups (**Figure 1**). Multivariate analysis showed that none of these baseline characteristics were associated with PFS (**Table 7**). As the aspect of OS, patients with dialysis dependence had the shortest OS of only 25 months among three groups [25 (95% CI, 16.7-33.3) vs. 69 (95% CI, 44.0-94.0) vs. 45 (95% CI, 38.0-52.0) months, P=0.001]. Further multivariate analysis confirmed that dialysis dependent (P=0.004) was independent predictive factor for shorter OS in our patient cohort (**Table 8**).

Discussion

In this multicenter retrospective study, we investigated the clinical manifestation and survival of MM patients with dialysis dependence, who was found to have lower hematological and renal responses, high early mortality within

Table 7. Effect of baseline characteristics and response on PFS (n=334)

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age ≥60 vs. <60 years	1.127	0.880-1.445	0.343			
Hb <8 vs. ≥8 g/dl	1.006	0.782-1.295	0.960			
BMPC ≥30 vs. <30%	1.272	0.975-1.661	0.077	1.304	0.981-1.735	0.068
Light chain plus IgD vs. others	1.078	0.838-1.387	0.559			
LDH ≥250 vs. <250 U/L	1.368	1.007-1.859	0.045*	1.322	0.960-1.820	0.087
High risk FISH vs. not	1.081	0.775-1.508	0.647			
Dialysis dependent vs. not	1.362	0.948-1.958	0.095	1.259	0.846-1.872	0.256
ASCT vs. not	0.806	0.585-1.110	0.186			

Note: Light chain plus IgD, defined as M protein type; High risk FISH, defined as the presence of any of del17p, t(4;14), t(14;16) and/or 1q21 gain. Abbreviations: PFS, progression-free survival; HR, hazard ratio; Hb, hemoglobin; BMPC, bone marrow plasma cells; LDH, lactate dehydrogenase; ASCT, autologous stem cell transplantation. *means P<0.05.

Table 8. Effect of baseline characteristics and response on OS (n=334)

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age ≥60 vs. <60 years	1.272	0.968-1.672	0.085	1.280	0.948-1.727	0.107
Hb <8 vs. ≥8 g/dl	1.133	0.860-1.492	0.375			
BMPC ≥30 vs. <30%	1.435	1.065-1.935	0.018*	1.381	1.021-1.867	0.036*
Light chain plus IgD vs. others	1.108	0.840-1.460	0.468			
LDH ≥250 vs. <250 U/L	1.316	0.946-1.831	0.103			
High risk FISH vs. not	1.012	0.696-1.472	0.950			
Dialysis dependent vs. not	1.950	1.353-2.811	<0.001***	1.782	1.208-2.629	0.004**
ASCT vs. not	0.727	0.508-1.042	0.083	0.886	0.595-1.320	0.552

Note: Light chain plus IgD, defined as M protein type; High risk FISH, defined as the presence of any of del17p, t(4;14), t(14;16) and/or 1q21 gain. Abbreviations: OS, overall survival; HR, hazard ratio; Hb, hemoglobin; BMPC, bone marrow plasma cells; LDH, lactate dehydrogenase; ASCT, autologous stem cell transplantation. *means P<0.05, **means P<0.01, ***means P<0.001.

24 months, as well as shorter OS than other MM patients with RI. Only at least VGPR for the best hematological response could be the predictor for dialysis independence. Dialysis dependence was found to have an independent negative impact on overall survival in our patient cohort.

Although the survival of patients with RI had improved significantly in novel agent era, early death was still a predominant problem. As previously reported, 12% MM patients with severe RI (eGFR <30 ml/min/1.73 m^2) died within 2 months after induction therapy [20]. More importantly, the introduction of novel agents had not changed the high early mortality in these patients [21]. A recent study had shown that the negative impact of RI on survival could be consistent during the 3 years following MM diagnosis. Notably, RI was strongly associated with excess mortality in the first 6 months after diagnosis, with a relative risk of excess mortality >4 in the first month [7]. But few researches had focused on the early death risk of dialysis dependence in MM. Our study showed dialysis dependence group had higher early mortality compared with the other two groups, with an early mortality as high as 14.0% within 2 months. And even after two years from MM diagnosis, the negative impact of dialysis dependence on early mortality still continued. Dialysis dependence was proved to be related to early death within 24 months in the multivariate analysis. Thus, the prognosis was dismal for dialysis-dependent MM patients who failed to get renal recovery after front-line treatment.

Besides early death risk, dialysis dependence also had a negative impact on overall survival. In traditional agent era, the prognosis for MM

with dialysis was very poor. In Haynes RJ etc.' study, the median OS was only 10.2 months for 107 patients with 88 requiring dialysis [16]. In another study, the median OS was 20 months in 20 patients with dialysis dependence [10]. In novel agent era, the outcome for patients with dialysis dependence had not been improved obviously. One study from Ireland showed that from 1995 to 2012, despite the stable increase of survival for the total MM patient population, patients with dialysis support within 4 weeks of diagnosis had not benefitted from the treatment of bortezomib plus dexamethasone [22]. Median OS was just 6 months for patients with dialysis throughout 2007-2012 [22]. Another study from England showed the median OS was 14 months in 2010 for these patients [5]. According to a study from French, novel agents led to better dialysis independence, but did not improve the survival of patients with severe renal failure [23]. Similarly, in the nationwide Dutch population-based study, 278 patients with dialysis received the Bortezomib-based regimens and achieved a median OS of only 1.74 years [12]. Our results showed that MM with dialysis dependence had the shortest median OS of 25 months, compared with 69 months for the dialysis independence and 45 months for without dialysis group respectively. The correlation between dialysis dependence and short OS was also confirmed by multivariate analysis in our study, which was in accordance with previous studies. However, the survival for patients with dialysis in our study seemed to be longer than in previously studies. One possible explanation for dialysis dependence with a relatively longer OS in our study is that the majority of patients received the bortezomib-based triplets induction therapy. According to a study focusing on double versus triple bortezomib-based regimen in MM patients with renal damage, bortezomib-cyclophosphamide-dexamethasone triplet regimen seemed to be better than bortezomib-dexamethasone regimen among patients with acute kidney injury stage 3, in spite of statistical significance not reached [24]. Under such circumstances, triplet regimens deserved to be further investigated for patients with dialysis. In addition, recent studies showed ASCT was safe and effective for MM with dialysis [14]. Although it was not performed in our dialysis-dependent patient cohort, according to these studies, ASCT should be considered for MM with dialysis based on careful selection in order to further improve the prognosis.

It is quite certain that novel agents could increase the ratio of dialysis independence, while there were still some controversies over the impact of novel agents on survival for MM with dialysis. The reported ratio of dialysis independence varies between 19% and 76% in novel agent era [14, 23, 25]. And limited reports showed ASCT seemed to be possible to increase the ratio of dialysis independence further [26, 27]. In our study, 49.4% (42/85) of patients achieved dialysis dependence after bortezomib-based triplets therapy, which was in accordance with previous researches. Another interesting question is the impact of dialysis independence on survival. It has been confirmed that renal response could further improve survival [28, 29]. Furthermore, Punit Yadav etc.' study showed MM with dialysis independence would have excellent long-term outcomes with a median OS was 64.1 months [30]. With our results, the median OS was 69 months for dialysis independence group, which was very close to the aforementioned results. Therefore, dialysis independence patients seemed to have better survival, which deserved to be further confirmed in prospective studies. In addition, only at least VGPR for hematologic response could predict the dialysis independence in our study. The Mayo clinic found that the rapid decrease of serum free light chain was relevant to renal recovery [31]. But it was unfortunate that the majority of our patients had not received successive tests of serum free light chain, which was the main limitation of this retrospective study.

In conclusion, in novel agent era, MM patients with dialysis dependence still tend to suffer a dismal disease course, including a high probability to suffer early mortality, worse hematological and renal response, as well as shorter survival. Compared with mild or moderate MM-related RI, dialysis independence could be very promising for survival improvement.

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Disclosure of conflict of interest

None.

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References

[1] Gao W, Zheng Y, Zhang R, Liu G, Jian Y, Zhou H, Zhang Z, Chen S, Wu S and Chen W. Incidence of multiple myeloma in Kailuan cohort: a prospective community-based study in China. Cancer Epidemiol 2022; 78: 102168.

[2] Turesson I, Velez R, Kristinsson SY and Landgren O. Patterns of multiple myeloma during the past 5 decades: stable incidence rates for all age groups in the population but rapidly changing age distribution in the clinic. Mayo Clin Proc 2010; 85: 225-230.

[3] Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF and Melton LJ 3rd. Incidence of multiple myeloma in Olmsted County, Minnesota: trend over 6 decades. Cancer 2004; 101: 2667-2674.

[4] Gavriatopoulou M, Terpos E, Kastritis E and Dimopoulos MA. Current treatments for renal failure due to multiple myeloma. Expert Opin Pharmacother 2016; 17: 2165-2177.

[5] Evison F, Sangha J, Yadav P, Aung YS, Sharif A, Pinney JA, Drayson MT, Cook M and Cockwell P. A population-based study of the impact of dialysis on mortality in multiple myeloma. Br J Haematol 2018; 180: 588-591.

[6] Dimopoulos MA, Roussou M, Gavriatopoulou M, Psimenou E, Eleutherakis-Papaiakovou E, Migkou M, Matsouka C, Mparmparousi D, Gika D, Kafantari E, Ziogas D, Fotiou D, Panagiotidis I, Terpos E and Kastritis E. Bortezomib-based triplets are associated with a high probability of dialysis independence and rapid renal recovery in newly diagnosed myeloma patients with severe renal failure or those requiring dialysis. Am J Hematol 2016; 91: 499-502.

[7] Courant M, Orazio S, Monnereau A, Preterre J, Combe C and Rigothier C. Incidence, prognostic impact and clinical outcomes of renal impairment in patients with multiple myeloma: a population-based registry. Nephrol Dial Transplant 2021; 36: 482-490.

[8] Sharma R, Jain A, Jandial A, Lad D, Khadwal A, Prakash G, Nada R, Aggarwal R, Ramachandran R, Varma N and Malhotra P. Lack of renal recovery predicts poor survival in patients of multiple myeloma with renal impairment. Clin Lymphoma Myeloma Leuk 2022; 22: 626-634.

[9] Faguer S and Roussel M. 'Patients with multiple myeloma have excellent long-term outcomes after recovery from dialysis-dependent acute kidney injury'. Eur J Haematol 2016; 96: 547-548.

[10] Torra R, Bladé J, Cases A, López-Pedret J, Montserrat E, Rozman C and Revert L. Patients with multiple myeloma requiring long-term dialysis: presenting features, response to therapy, and outcome in a series of 20 cases. Br J Haematol 1995; 91: 854-859.

[11] Murphy PT, Baldeo C, O'Kelly P, Sargant J, Thornton P, McCloy M, Conlon P, Magee C, Denton M and Quinn J. Dialysis-dependent renal failure at diagnosis continues to be associated with very poor outcome in multiple myeloma. Br J Haematol 2014; 165: 890-891.

[12] Oortgiesen BE, Azad R, Hemmelder MH, Kibbelaar RE, Veeger NJGM, de Vries JC, van Roon EN and Hoogendoorn M. The impact of the introduction of bortezomib on dialysis independence in multiple myeloma patients with renal impairment: a nationwide Dutch population-based study. Haematologica 2018; 103: e311-e314.

[13] Dimopoulos MA, Roussou M, Gavriatopoulou M, Fotiou D, Ziogas DC, Migkou M, Panagiotidis I, Eleutherakis-Papaiakovou E, Kanellias N, Psimenou E, Marinaki S, Bacharaki D, Mparmparoussi D, Matsouka C, Giannouli S, Terpos E and Kastritis E. Outcomes of newly diagnosed myeloma patients requiring dialysis: renal recovery, importance of rapid response and survival benefit. Blood Cancer J 2017; 7: e571.

[14] Waszczuk-Gajda A, Lewandowski Z, Drozd-Sokołowska J, Boguradzki P, Dybko J, Wróbel T, Basak GW, Jurczyszyn A, Mądry K, Snarski E, Frączak E, Charliński G, Feliksbrot-Bratosiewicz M, Król M, Matuszkiewicz-Rowińska J, Klinger M, Krajewska M, Augustyniak-Bartosik H, Kościelska M, Rusicka P, Dwilewicz-Trojaczek J and Wiktor Jędrzejczak W. Autologous peripheral blood stem cell transplantation in dialysis-dependent multiple myeloma patients-DAUTOS Study of the Polish Myeloma Study Group. Eur J Haematol 2018; 101: 475-485.

[15] Augeul-Meunier K, Chretien ML, Stoppa AM, Karlin L, Benboubker L, Diaz JMT, Mohty M,

Yakoub-Agha I, Bay JO, Perrot A, Bulabois CE, Huynh A, Mercier M, Frenzel L, Avet-Loiseau H, de Latour RP and Cornillon J. Extending autologous transplantation as first line therapy in multiple myeloma patients with severe renal impairment: a retrospective study by the SFGM-TC. Bone Marrow Transplant 2018; 53: 749-755.

[16] Haynes RJ, Read S, Collins GP, Darby SC and Winearls CG. Presentation and survival of patients with severe acute kidney injury and multiple myeloma: a 20-year experience from a single centre. Nephrol Dial Transplant 2010; 25: 419-426.

[17] Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, Kumar S, Hillengass J, Kastritis E, Richardson P, Landgren O, Paiva B, Dispenzieri A, Weiss B, LeLeu X, Zweegman S, Lonial S, Rosinol L, Zamagni E, Jagannath S, Sezer O, Kristinsson SY, Caers J, Usmani SZ, Lahuerta JJ, Johnsen HE, Beksac M, Cavo M, Goldschmidt H, Terpos E, Kyle RA, Anderson KC, Durie BG and Miguel JF. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014; 15: e538-548.

[18] Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, Gertz M, Dimopoulos M, Westin J, Sonneveld P, Ludwig H, Gahrton G, Beksac M, Crowley J, Belch A, Boccadaro M, Cavo M, Turesson I, Joshua D, Vesole D, Kyle R, Alexanian R, Tricot G, Attal M, Merlini G, Powles R, Richardson P, Shimizu K, Tosi P, Morgan G and Rajkumar SV; International Myeloma Working Group. International uniform response criteria for multiple myeloma. Leukemia 2006; 20: 1467-1473.

[19] Dimopoulos MA, Sonneveld P, Leung N, Merlini G, Ludwig H, Kastritis E, Goldschmidt H, Joshua D, Orlowski RZ, Powles R, Vesole DH, Garderet L, Einsele H, Palumbo A, Cavo M, Richardson PG, Moreau P, San Miguel J, Rajkumar SV, Durie BG and Terpos E. International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment. J Clin Oncol 2016; 34: 1544-1557.

[20] Augustson BM, Begum G, Dunn JA, Barth NJ, Davies F, Morgan G, Behrens J, Smith A, Child JA and Drayson MT. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002--Medical Research Council Adult Leukaemia Working Party. J Clin Oncol 2005; 23: 9219-9226.

[21] Dimopoulos MA, Delimpasi S, Katodritou E, Vassou A, Kyrtsonis MC, Repousis P, Kartasis Z, Parcharidou A, Michael M, Michalis E, Gika D, Symeonidis A, Pouli A, Konstantopoulos K, Terpos E and Kastritis E. Significant improvement in the survival of patients with multiple myeloma presenting with severe renal impairment after the introduction of novel agents. Ann Oncol 2014; 25: 195-200.

[22] Pozzi S, Bari A and Sacchi S. Dialysis-dependent renal failure at diagnosis continues to be associated with very poor outcome in multiple myeloma--response to Murphy et al. Br J Haematol 2014; 165: 892.

[23] Laforet M, Jourde-Chiche N, Haddad F, Sallee M, Stoppa AM, Brunet P, Dussol B, Burtey S and Gondouin B. Evolution in the treatment of multiple myeloma and impact on dialysis independence: data from a French cohort from 1999 to 2014. Blood Cancer J 2016; 6: e409.

[24] Bridoux F, Arnulf B, Karlin L, Blin N, Rabot N, Macro M, Audard V, Belhadj K, Pegourie B, Gobert P, Cornec Le Gall E, Joly B, Karras A, Jaccard A, Augeul-Meunier K, Manier S, Royer B, Caillot D, Tiab M, Delbes S, Suarez F, Vigneau C, Caillard S, Arakelyan-Laboure N, Roos-Weil D, Chevret S and Fermand JP; MYRE study group. Randomized trial comparing double versus triple bortezomib-based regimen in patients with multiple myeloma and acute kidney injury due to cast nephropathy. J Clin Oncol 2020; 38: 2647-2657.

[25] Zannetti BA, Zamagni E, Santostefano M, De Sanctis LB, Tacchetti P, Mancini E, Pantani L, Brioli A, Rizzo R, Mancuso K, Rocchi S, Pezzi A, Borsi E, Terragna C, Marzocchi G, Santoro A and Cavo M. Bortezomib-based therapy combined with high cut-off hemodialysis is highly effective in newly diagnosed multiple myeloma patients with severe renal impairment. Am J Hematol 2015; 90: 647-652.

[26] Lazana I, Floro L, Christmas T, Shah S, Bramham K, Cuthill K, Bassett P, Schey S, Kazmi M, Potter V, Pagliuca A, Streetly M and Benjamin R. Autologous stem cell transplantation for multiple myeloma patients with chronic kidney disease: a safe and effective option. Bone Marrow Transplant 2022; 57: 959-965.

[27] St Bernard R, Chodirker L, Masih-Khan E, Jiang H, Franke N, Kukreti V, Tiedemann R, Trudel S, Reece D and Chen CI. Efficacy, toxicity and mortality of autologous SCT in multiple myeloma patients with dialysis-dependent renal failure. Bone Marrow Transplant 2015; 50: 95-99.

[28] Dimopoulos MA, Roussou M, Gkotzamanidou M, Nikitas N, Psimenou E, Mparmparoussi D, Matsouka C, Spyropoulou-Vlachou M, Terpos E and Kastritis E. The role of novel agents on the reversibility of renal impairment in newly diagnosed symptomatic patients with multiple myeloma. Leukemia 2013; 27: 423-429.

[29] Gonsalves WI, Leung N, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Dingli D, Kapoor P, Go RS, Lin Y, Russell SJ, Lust JA, Zeldenrust S, Kyle RA, Gertz MA and Kumar SK. Improvement in renal function and its impact on survival in patients with newly diagnosed multiple myeloma. Blood Cancer J 2015; 5: e296.

[30] Yadav P, Hutchison CA, Basnayake K, Stringer S, Jesky M, Fifer L, Snell K, Pinney J, Drayson MT, Cook M and Cockwell P. Patients with multiple myeloma have excellent long-term outcomes after recovery from dialysis-dependent acute kidney injury. Eur J Haematol 2016; 96: 610-617.

[31] Hutchison CA, Cockwell P, Stringer S, Bradwell A, Cook M, Gertz MA, Dispenzieri A, Winters JL, Kumar S, Rajkumar SV, Kyle RA and Leung N. Early reduction of serum-free light chains associates with renal recovery in myeloma kidney. J Am Soc Nephrol 2011; 22: 1129-1136.