

Original Article

Superior myeloma response with bortezomib-based regimen in multiple myeloma patients with renal impairment

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Abstract: Objectives: We aimed at retrospectively evaluating the role of bortezomib-based, thalidomide-based, and vincristine-adriamycin-dexamethasone (VAD) regimens on the myeloma response and reversibility of renal insufficiency in 130 consecutive newly diagnosed patients with renal impairment. Methods: Between May 2005 and February 2014, 130 consecutive unselected patients with newly diagnosed multiple myeloma and RI were treated with bortezomib-based, thalidomide-based, and VAD regimen at our institute. Patients were divided into three groups according to the type of different induction regimens. Results: A myeloma response was achieved in 92.4% of patients in group B, in 75% in group T, and in 39.3% in group VAD ($P=0.000$). A complete recovery of renal function (renal complete response) was observed in 56.1% of patients treated with bortezomib, in 38.9% with thalidomide, and in 28.6% with VAD ($P=0.033$), a significant improvement of renal function (\geq renal PR [partial response]) was observed in 63.6% of patients treated with bortezomib, in 66.1% with thalidomide, and in 42.9% with VAD ($P=0.162$). Conclusion: prompt initiation of bortezomib or thalidomide based regimen for newly diagnosed myeloma patients with renal impairment, helps in achieving a rapid effective response rate and high rates of renal recovery.

Keywords: Multiple myeloma, renal impairment, bortezomib-based, thalidomide-based, vincristine-adriamycin-dexamethasone

Introduction

Acute renal insufficiency is a frequent and serious complication of multiple myeloma (MM) with approximately 15-40% renal impairment (RI) at diagnosis [1]. However, the relationship between renal impairment and survival is not yet conclusive [2-5]. Rapid diagnosis and aggressive therapy is mandated for restoration of RI; hence, treatment is challenging.

Although bortezomib- and thalidomide-based treatments have demonstrated superior results in VAD in patients with RI [6-12], there is a paucity of data on comparative studies, especially in newly diagnosed patients with RI, and the superior activity has been supported by subgroup analyses from phase III studies [13-15]. Dimopoulos reported for the first time, a retrospective comparison on the effect of thalido-

mid, bortezomib or lenalidomide regimens on renal function recovery in an unselected population of newly diagnosed myeloma patients [16]. Vincristine-adriamycin-dexamethasone (VAD) regimen is still using in China for its cost effectiveness, rapid onset, and absence of renal toxicity; although some scholars opinion that VAD is an outdated treatment. Melphalan is not available in China and lenalidomide is not yet approved for use as a first-line therapy. Although the importance of autologous stem cell transplantation (ASCT) is emphasized in China, the use of this therapy is still on a low scale. Our treatment differs from that in European and American countries, because we exclude the above agents [17].

In order to investigate this, we analyzed 130 consecutive, unselected newly diagnosed multiple myeloma patients with RI, who were treat-

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Table 1. Characteristics of 130 patients included in the analysis

	Bortezomib	Thalidomide	VAD	P
N	66	36	28	
Median ages, y	63.5	62	64	0.843
Range (Min, Max)	33, 84	33, 86	42, 78	
Age >65 y	28	13	14	0.536
Sex				0.213
Male	50	30	18	
Female	16	6	10	
eGFR (mL/min/1.73 m ²)				
Median	29.5	28.0	24.5	0.40
Range (Min, Max)	25.5, 33.6	23.1, 33.0	17.6, 31.5	
eGFR < 30 mL/min	31	19	18	0.306
Dialysis	6	3	3	0.834
Performance status ≥ 2	20	15	12	0.368
ISS stage				0.404
II	3	12	4	
III	33	54	24	
Hemoglobin < 10 g/dL	32	52	22	0.409
LDH ≥ 300 IU/l	6	21	9	0.295
Light chain only myeloma	15	27	11	0.981

Note: VAD, vincristine-adriamycin-dexamethasone; eGFR, estimated glomerular filtration rate; ISS, international staging system; LDH, lactate dehydrogenase.

ed with a novel (bortezomib or thalidomide) agents-based or conventional (VAD) regimen over the past decade, at our Institute.

Material and methods

Between May 2005 and February 2014, 130 consecutive unselective patients with newly diagnosed multiple myeloma and RI were treated with bortezomib-based, thalidomide-based, and VAD regimen at our institute. The diagnostic criteria of multiple myeloma were as outlined in the International Myeloma Working Group (IMWG) guidelines [18].

RI was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² using the simplified Modification of Diet in Renal Disease (MDRD) formula [19].

We used an eGFR < 60 ml/min/1.73 m² as a cutoff to define at least moderate renal dysfunction in patients with newly diagnosed myeloma, based on the definition of moderate renal dysfunction by National Kidney Foundation Kidney Disease Outcomes Quality Initiative [20].

Patients were divided into three groups according to the type of different induction regimens. Group VAD included 28 patients; group T included 36 patients who received a thalidomide-based regimen such as TD (T with dexamethasone); CTD (cyclophosphamide and TD); T-VAD; and group B included 66 patients who received a bortezomib-based regimen such as VD; VTD; or VCD. Four patients opted for ASCT after induction, three with bortezomib-based regimen and one with VAD regimen. Besides antimyeloma treatment, in all patients additional measures were taken that included intravenous hydration alkalization of urine, correction of hypercalcemia, and discontinuation of all nephrotoxic agents and administration of antibiotics

as prophylaxis. Renal dialysis was offered when indicated.

The degree of restoration of renal function was evaluated according to recently proposed criteria [5, 21]. Myeloma responses were based on the IMWG Uniform Response Criteria [22].

Differences among various groups were compared with the χ^2 -test for categorical variables (using Fisher's exact test when appropriate) and with the Mann-Whitney test or analysis of variance (ANOVA) for continuous variables. Logistic regression analysis was used for multivariate analysis by entering all significant variables ($P < 0.05$), which were associated with renal response. Time to renal response was calculated from the date of initiation of treatment, until the date when criteria for renal response were first met. Data of patients who died before renal response were censored during analysis. Survival was evaluated from the date of treatment initiation until the date of death or last follow-up, and was plotted by the Kaplan-Meier method. Log-rank test analysis was used for the difference between the various survival curves and the multi-factor analy-

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Table 2. Myeloma response to different induction therapy

Response/regimen	Bortezomib-	Thalidomide-	VAD	P
N	66	36	28	0.000
≥ VGPR	29 (43.9)	7 (19.4)	2 (7.1)	
PR (%)	23 (34.8)	15 (41.7)	9 (32.1)	
MR (%)	9 (13.6)	5 (13.9)		
ORR (%)	61 (92.4)	27 (75)	11 (39.3)	
NR (%)	5 (7.6)	9 (25)	17 (60.7)	
Median overall survival, Months (95% confidence interval)	79 (67.4-90.6)	71 (33.5-108.5)	39 (33.3-44.7)	0.007

Note: VAD, vincristine-adriamycin-dexamethasone; VGPR, very good partial response; PR, partial response; MR, minimal response; NR, no response; ORR, objective response rate.

Table 3. Comparative response based on the extent of renal impairment

Response/Outcome, n (%)	Moderate RI eGFR ≥ 30 mL/min to < 60 mL/min (n=62)	Severe RI eGFR < 30 mL/min (n=68)	P
Overall response	54 (87.1%)	45 (66.2%)	0.043
≥ Very good partial response	22 (35.5%)	16 (23.5%)	
Partial response	25 (40.3%)	22 (32.4%)	
Minor response	7 (11.3%)	7 (10.3%)	
Response not evaluable	8 (12.9%)	23 (33.8%)	
Time to major renal response (months)	1.89	1.90	>0.05
Median overall survival, Months (95% Confidence interval)	74 (55.6-92.4)	50 (22.7-77.3)	0.012

Note: eGFR, estimated glomerular filtration rate; RI, renal impairment.

Table 4. Myeloma response and renal response

Myeloma response	n	Renal Response, %, (n)				P
		CR	PR	MR	NR	
≥ VGPR	38	63.1 (24)	10.5 (4)	15.8 (6)	10.5 (4)	0.001
PR	47	46.8 (22)	21.3 (10)	17.0 (8)	14.9 (7)	
MR	14	35.7 (5)	0 (0)	14.3 (2)	50 (7)	
Response not evaluable	31	25.8 (8)	9.7 (3)	12.9 (4)	51.6 (16)	

Note: CR, complete response; PR, partial response; MR, minimal response; NR, no response.

sis in the survival curve used the Cox regression.

Results

Patients

Baseline characteristics of the entire patient population are presented in **Table 1**. All of the patients should be collected medical history include hypertension, diabetes and chronic renal failure et al. 14 (10.8%) patients underwent a kidney biopsy.

Myeloma response and renal response

A myeloma response was achieved in 92.4%, 75%, and 39.3% of patients in group B, T, and VAD, respectively (P=0.203) (**Table 5**).

and VAD, respectively (P =0.000; **Table 2**). Patients with moderate RI were associated with a significantly higher myeloma response than that with severe RI, P=0.043 (**Table 3**).

There was a significant difference in the rates and quality of renal response among patients with different quality of myeloma response (**Table 4**): renal CR rates for patients who achieved ≥ VGPR, PR, MR or NR were 63.1% vs. 46.8% vs. 35.7% vs. 25.8%, P < 0.05, respectively. The VGPR, PR, MR or NR rates for myeloma patients were 89.4%, 85.1%, 50% or 48.4%, respectively (P < 0.05). Some patients who did not achieve a myeloma PR improved their renal function (6/14) to achieve a renal PR of 42.9%, in group T and group B, and 25% in group VAD.

Therapies and renal response

An improvement of renal function (that is, at least renal MR) was observed in 77.3%, 77.8%, and 60.7% of patients in in group B, T, and VAD, respectively (P=0.203) (**Table 5**).

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Table 5. Renal responses according to primary therapy with thalidomide-, bortezomib- or VAD regimens

	Bortezomib- 66	Thalidomide- 36	VAD 28	P-value
Baseline eGFR (ml/min/1.73 m ²), median (range)	29.5 (25.5-33.6)	28.0 (23.1-33.0)	24.5 (17.6-31.5)	0.40
Best eGFR, median (range)	62.36 (47.1-77.6)	60.0 (45.4-74.5)	50.3 (34.7-65.9)	0.646
Renal response (≥ renal MR)	51 (77.3)	28 (77.8)	17 (60.7)	0.203
Major renal response (≥ PR)	42 (63.6)	22 (66.1)	12 (42.9)	0.162
Renal CR	37 (56.1)	14 (38.9)	8 (28.6)	0.033*
Baseline eGFR for patients who achieved renal CR, median (range)	37.1 (32.3-41.8)	37.5 (29.8-45.2)	42.25 (28.4-56.0)	0.644
Best eGFR for patients who achieved renal CR, median (range)	90.6 (66.8-114.4)	89.0 (64.5-113.5)	83.8 (62.9-104.7)	0.957
Time to major renal response (months)	1.74	2.08	2.09	>0.05

Note: VAD, vincristine-adriamycin-dexamethasone; eGFR, estimated glomerular filtration rate; MR, minimum response; PR, partial response; CR, complete response. *P < 0.05.

Table 6. Univariate and multivariate analysis for factors associated with major renal response (At least renal partial response)

	Univariate		Multivariate	
	Exp (B) (95% CI)	P-value	Exp (B) (95% CI)	P-value
Age < 65 years	2.027 (10.985-4.172)	0.055	1.677 (0.729-3.858)	0.224
eGFR ≥ 30 ml/min	4.24 (1.954-9.204)	0.000	3.62 (1.583-8.279)	0.002
Myeloma response ≥ PR	5.891 (2.674-12.976)	0.000	5.167 (2.268-11.772)	0.000
Bortezomib and thalidomide	2.183 (1.058-4.505)	0.035	1.24 (0.472-3.254)	0.662
VAD	0.359 (0.152-0.844)	0.019	0.691 (0.216-2.211)	0.533

Note: eGFR, estimated glomerular filtration rate; PR, partial response rate; VAD, vincristine-adriamycin-dexamethasone.

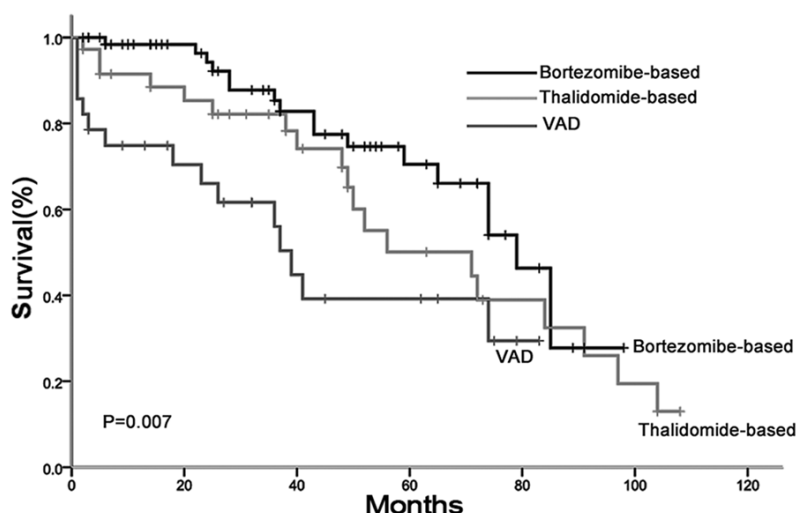


Figure 1. Prognostic value of bortezomib-based vs. thalidomide-based regimens vs. vincristine-adriamycin-dexamethasone regimen in newly diagnosed multiple myeloma patients with renal impairment; the median survival was 79 months, 71 months and 39 months, respectively.

We focused more on renal PR and renal CR, as this improvement of renal function was of greater clinical relevance. Thus, renal PR were observed in 63.6%, 66.1%, and in 42.9% in group B, T, and VAD, respectively (P=0.162), whereas renal CR was achieved in 56.1%,

38.9%, and 28.6% patients in group B, group T, and group VAD, respectively (P=0.033) (Table 2). Among 12 patients who required dialysis, five patients (one from group T and four from group B) became dialysis independent.

The median time for achieving a renal PR was 1.74 months, 2.08 months, and >2.09 months for patients in group B, T, and VAD, respectively (P>0.05). An eGFR ≥ 30 mL/min correlated with time to major renal response than eGFR < 30 ml/min (1.89 vs. 1.90 months) (P>0.05). There

were no correlations between myeloma major response and time to renal major response.

Prognostic factors for major renal response

An eGFR of ≥ 30 mL/min, age < 65 years, and myeloma response ≥ PR associated with a

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Table 7. Factors associated with overall survival

	Univariate		Multivariate	
	Exp (B) (95% CI)	P-value	Exp (B) (95% CI)	P-value
Age < 65 years	0.706 (0.408-1.220)	0.212	0.752 (0.428-1.323)	0.323
eGFR ≥ 30 ml/min	0.484 (0.271-0.864)	0.014	1.248 (0.629-2.475)	0.526
Myeloma response (≥ PR)	0.194 (0.105-0.358)	0.000	0.205 (0.108-0.390)	0.000
Bortezomib and thalidomide	0.509 (0.286-0.906)	0.022	0.782 (0.390-1.566)	0.487
VAD	2.419 (1.303-4.490)	0.005	2.153 (1.146-4.044)	0.017
Renal response (≥ PR)	0.449 (0.238-0.845)	0.013	1.598 (0.824-3.100)	0.166
LDH ≥ 300 IU/L	1.721 (0.923-3.209)	0.088	1.656 (0.860-3.187)	0.131

Note: CI, confidence interval; eGFR, estimated glomerular filtration rate; PR, partial response; VAD, vincristine-adriamycin-dexamethasone; LDH, lactate dehydrogenase.

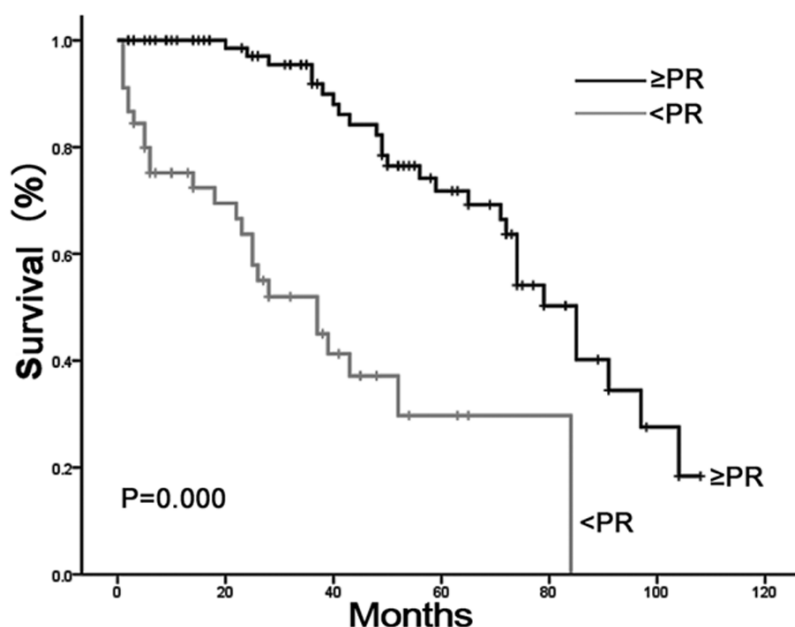


Figure 2. Prognostic value of myeloma response ≥ PR vs. < PR in newly diagnosed multiple myeloma patients with renal impairment, the median survival was 85 months and 37 months, respectively.

higher probability of renal PR. B group was associated with a higher rate of renal CR than that with T group (56.1% vs. 38.9%, $P < 0.05$). However, the results of renal PR were comparable between the B and T group (63.6% and 66.1%, $P > 0.05$). The VAD regimen elicited the least response among the three groups. An eGFR of ≥ 30 mL/min and myeloma response ≥ PR were independently associated with a higher probability of major renal response in the multivariate analysis (Table 6).

Renal impairment and survival

The median follow-up for all patients was 36.5 (range, 1-108) months and the median survival

was 74 months. The median survival for patients in the B, T, and VAD groups was 79 months, 71 months, and 39 months, respectively ($P = 0.007$). Figure 1. The median survival for patients with degree of renal response was listed in graph 3. Because RI in patients with myeloma is associated with an increased risk of early death due to various complications, we examined the rates of early death. Six patients (4.6%) died within two months of treatment initiation, and the causes of death are 3 cases of pulmonary infection, 1 case of heart failure, 1 case of myocardial infarction and 1 case of cerebral hemorrhage, respectively;

the corresponding frequencies in groups B, T, and VAD were 0%, 2.8% and 17.9%, respectively ($P < 0.05$). However, early deaths occurred in 4.4% of patients with an eGFR of < 30 mL/min as compared to 4.8% of patients with an eGFR of ≥ 30 mL/min ($P > 0.05$).

Univariate analyses revealed that baseline level of eGFR ≥ 30 mL/min, myeloma response ≥ PR, therapy with new agents, and renal minimal response were associated with significantly longer overall survival (OS). Further multivariate analyses identified that a myeloma response ≥ PR and VAD therapy were independent prognostic factors (Table 7; Figure 2). The median

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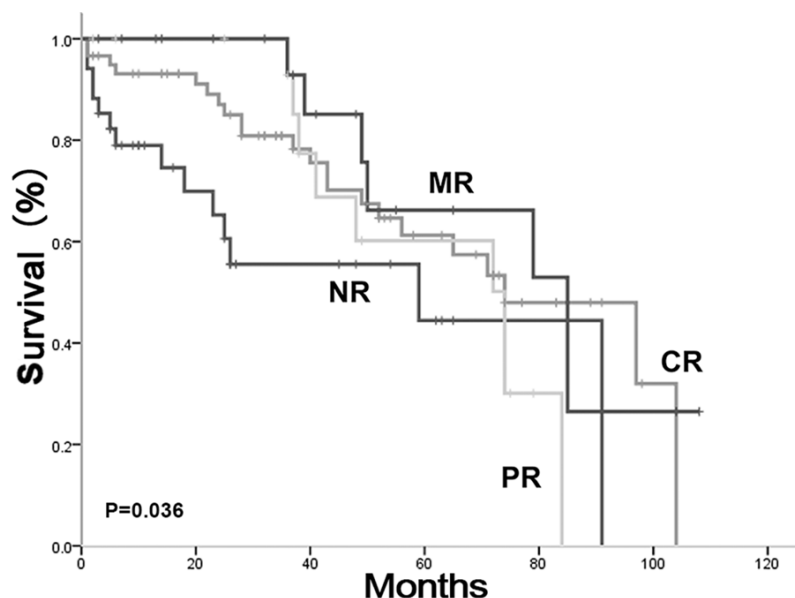


Figure 3. Overall survival according to the degree of renal response, the median survival was 74 months, 74 months, 85 months and 59 months in renal CR, PR, MR and NR, respectively.

survival was 74 months, 74 months, 85 months and 59 months in renal CR, PR, MR and NR, respectively, $P < 0.05$ (Figure 3).

Adverse events

The most common side effects in T group included grade 1 peripheral neuropathy (2%), constipation (3%), tremor (1%), and lethargy (1%). There were no reports of deep venous thrombosis. The most common side effects in B group included peripheral neuropathy (grade 3, 4: 10%; grade 1, 2: 30%) and herpes zoster in nearly 20% patients.

All adverse events were known side effects and were manageable. The main side reaction in the VAD group was loss of hair, phlebitis, infections and mild upset gastro-intestinal.

Discussion

The incidence of renal insufficiency in patients with newly diagnosed multiple myeloma was 24.3% over the last decade in our center, which included consecutive, unselected patients who received similar supportive care from a single center. At our center, the condition of 9.2% of the patients progressed to severe renal failure, warranting dialysis support. 59 patients achieved renal CR after chemotherapy, so their RI was believed due to myeloma; in the 71

patients who did not gain CR, 12 patients were verified their RI were related to myeloma by kidney biopsy, only 8 patients had hypertension and/or diabetes history and 1 had chronic renal failure, others had not any history of chronic disease, so RI in the 9 patients could not ascribed to the myeloma completely. The myeloma response rate in group B was significantly higher than that in group T and group VAD. The extent and type of renal response significantly correlated with the extent of myeloma response; the higher the myeloma response, the better the renal response.

Multivariate analysis showed that a baseline eGFR ≥ 30 mL/min and myeloma response higher than PR was one of the main factors affecting the recovery of renal function (\geq PR). The result of this study was consistent with the results reported by Kastiris et al. [23] that response to therapy (\geq PR) was a crucial factor in the reversal of renal insufficiency with either thalidomide or bortezomib. Only four patients received additional ASCT, and advancing age, economical status, and the living conditions in China could be possible reasons.

VAD has been the preferred first-line treatment for patients with renal failure [24, 25]. Our study indicated that VAD therapy was inferior to novel agent-based therapies, both in terms of myeloma response and renal response. Although this result is consistent with previous research [6-12, 26], this study was limited by the fact that our patients were consecutive and were included without screening; most of them cannot be included in any clinical trials, and hence, our data is objective and not entirely representative.

Bortezomib-based therapy was the preferred and recommended treatment of myeloma patients with renal failure, in many studies [13, 21, 27]. Bortezomib could potentially inhibit the cytokine-mediated inflammatory damage in the

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kidney microenvironment [28, 29]. Dimopoulos [16] reported that bortezomib plays a significant role in the recovery of renal function, and patients on bortezomib-based therapy, with an eGFR \geq 30 mL/min, age < 65 years, and myeloma response showed a higher probability of renal response in multivariate analysis. According to our data, the median survival time is similar between renal CR and renal PR (79 months and 74 months, respectively, $P > 0.05$), though there is no difference in overall response (CR+PR) of renal response among the three groups, bortezomib-based regimens elicited a favorable renal CR.

The myeloma response rate of at least PR in patients treated with thalidomide-based regimens was comparable to that in patients with normal renal function [22]. In addition, the rate of renal recovery was superior in thalidomide-based regimens in another report [30]. Our analysis suggests that thalidomide-based regimens are still one of the most useful treatment options for patients with newly diagnosed myeloma along with renal insufficiency.

According to a previous study, early deaths may occur in one-third of the newly diagnosed myeloma patients presenting with renal failure [27]. Only 4.6% myeloma patients with RI died within the first 2 months after initiation of therapy at our center, and subgroup analysis revealed that this rate was as high as 17.9% in the VAD groups. According to previous reports, the presence of renal impairment in patients with multiple myeloma is associated with poor survival [2, 4, 31-39], and the reversibility of renal function was associated with improved survival compared with patients with irreversible renal failure [2, 32-34]. In this study, a myeloma response higher than PR and VAD therapy were independent prognostic factors of overall survival. Further, the median survival times in the novel agent groups were 79 months and 71 months as compared to current reports of survival time in patients with multiple myeloma in published literature [40]. Thus, novel agents should be recommended as first line therapy for rapid and optimum control of the disease in patients presenting with RI. Of the 130 consecutive newly diagnosed multiple myeloma patients with renal impairment patients enrolled in this retrospective study, fluorescence in situ hybridization (FISH) analy-

ses for changes in 13q14, 1q21, 14q32 and 17p13 loci were available only in 83 patients, and hence, we were unable to derive any meaningful conclusions with respect to the chromosome influence on myeloma effect, recovery of renal function, and survival time.

In conclusion, improvement in RI is not an independent adverse prognostic factor in MM patients with a novel agent based regimen such as thalidomide or bortezomib. For newly diagnosed myeloma patients, with RI, bortezomib- or thalidomide-based regimens should be initiated promptly to achieve rapid and effective myeloma response rates and high rates of renal recovery.

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Disclosure of conflict of interest

None.

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