Renal Insufficiency in Newly-diagnosed Multiple Myeloma: Analysis According to International Myeloma Working Group Consensus Statement

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Abstract. *Renal impairment (RI) is one of the key clinical manifestations of symptomatic multiple myeloma. However, the incidence of RI and renal response to treatment are variable depending on their definition. A total of 379 patients newly-diagnosed and treated for symptomatic myeloma at the Samsung Medical Center between January 2000 and December 2011 were retrospectively reviewed. RI and renal response were assessed according to the recent International working group (IMWG) recommendations. Out of the 379 patients, renal insufficiency was present in 117 (30.8%) and was associated with adverse clinical parameters such as anemia, elevated beta-2 microglobulin (B2M), elevated lactate dehydrogenase (LDH), hypercalcemia, and more advanced disease by the International Staging System (ISS). Out of the 85 patients who were evaluable for renal response, 58 (68.2%) showed renal response and 46 (54%) had major renal response. Less advanced disease by the International Staging System and inclusion of high-dose dexamethasone as first-line treatment were independently predictive for major renal response. Median time-to-renal response was 5.5 months, and bortezomib-containing regimen, high-dose dexamethasone, and less advanced stage disease were associated with a more rapid renal response. Conclusion: The incidence of RI in patients with newly-diagnosed multiple myeloma was 31%, and renal response was affected by the treatment and staging by the International Staging System.*

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Renal impairment (RI) is one of the key clinical manifestations that comprise symptomatic multiple myeloma (MM) and is regarded as a poor prognostic factor being associated with shorter survival or earlier death (1). The most common pathogenesis of renal insufficiency in MM is the accumulation and precipitation of monoclonal light chains in the distal tubules, resulting in renal obstruction. Other contributing factors include hypercalcemia, dehydration, co-existing infection, and nephrotoxic agents. Pathogenesis that involves the glomeruli is amyloidosis and light chain deposition disease (2-4). Recently, the wide use of high-dose chemotherapy and new drug treatment of newly-diagnosed MM has improved renal response (RR) and survival of patients with MM and RI (5-15). However, the incidence of RI and RR to the treatment vary depending on their definition. The incidence of RI at the time of diagnosis has been reported to be 20-40% (1, 16-18). M-protein related organ or tissue impairment named CRAB sign (Hypercalcemia, renal insufficiency, anemia, bone lesion) is required for the diagnosis of symptomatic myeloma and a serum creatinine level higher than 2.0 mg/dl has been easily applied to patients when defining renal insufficiency (19). However, the glomerular filtration rate varies according to age, sex and race. Recently, the International Myeloma Working Group (IMWG) recommended a new definition of RI in MM and renal response criteria (20).

The main purpose of the present study was to describe clinical features and prognostic factors related to RI of patients with newly-diagnosed MM and RR according to the IMWG recommendation.

Patients and Methods

Patients. A total of 379 patients newly-diagnosed and treated for symptomatic myeloma at the Samsung Medical Center between January 2000 and December 2011 were identified and their cases reviewed. Information on the patients' characteristics, RR and survival were obtained from review of their medical records. Patients whose myeloma was accompanied by amyloidosis or light-

chain deposit disease were excluded from the current study. This study was approved by the Institutional Review Boards (IRB) of the Samsung Medical Center (IRB No. 2013-06-016-001).

Definition of RI and RR. RI was evaluated with estimated glomerular filtration rate (eGFR) calculated by the original MDRD formula: eGFR=186×(0.742 if female)×(1.212 if Black) ×creatinine$^{-1.153}$×age$^{-0.203}$, and graded by the definition and classification of chronic kidney disease (21). Patients with stage 3 or more RI using the MDRD formula (eGFR<60 ml/min/1.73 m^2) were defined as having RI.

RR was evaluated by the IMWG consensus recommendation: complete renal response (renal CR) is sustained (*i.e.* lasting at least two months) improvement of clearance of creatinine (CrCl) from lower than 50 ml/min at baseline to more than 60 ml/min; partial renal response (renal PR) is sustained improvement of CrCl from lower than 15 at baseline to 30-59 ml/min; minor renal response (renal MR) is sustained improvement of baseline CrCl of lower than 15 ml/min to 15-29 ml/min or baseline CrCl of 15-29 ml/min to 30-59 ml/min (20). Renal CR and PR were referred to as major RR. Hematological response was assessed with IMWG criteria as described elsewhere (19).

Statistical methods. Differences in clinical characteristics according to baseline renal function were examined using the χ^2 test or Fisher's exact test for categorical variables. The differences in continuous variables (*e.g.* age) between the groups were assessed with the Mann–Whitney test or ANOVA. For identifying attributes for major RR, univariate and multivariate analyses using the logistic regression model were performed. Time to renal response (TTRR) was also assessed, and it was calculated from the date of initiation of treatment until the date when criteria for RR were first met. In the analysis of TTRR, death before achieving RR was considered as censored event. To determine the significant factors for TTRR, univariate and multivariate analyses were performed using the Cox proportional hazard model. Survival curves for TTRR and overall survival (OS) were plotted according to the Kaplan–Meier method followed by the log-rank test. All analyses were performed using SPSS statistical software (SPSS for Windows, version 20.0; SPSS Inc Chicago, IL, USA). Throughout the analysis, a level of 5% was used to denote statistical significance.

Results

Baseline characteristics. Table I shows the characteristics of 379 patients. The median age at diagnosis was 60 (range=22-92) years. RI was present in 117 (30.8%) out of 379 newly-diagnosed patients with symptomatic MM. Precisely, there were 69 patients (18.2%) with eGFR 30-59 ml/min/1.73 m^2, 31 patients (8.2%) with eGFR 15-29 ml/min/1.73 m^2, and 17 patients (4.5%) with eGFR <15 ml/min/1.73 m^2 or on dialysis. At diagnosis, the proportion of patients who had anemia, hypercalcemia, elevated lactate dehydrogenase (LDH), elevated β2 microglobulin were 51.7%, 10.0%, 27.5% and 63.6%. Ninty-one patients (24.0%) presented with extramedullary plasmacytoma. Based on the International Staging System (ISS), 92 (24.9%), 139 (37.7%) and 138 (37.4%) patients had stage I, II and III disease. Among the patients with available baseline information on cytogenetics or fluorescence *in situ* hybridization (FISH) features, 52 patients had -13q (16.1%), 16 had -17p (8.2%), two had t(14;16) (1.4%), and 17 (11.4%) had t(4;14).

Comparison of patients' characteristics by renal function. The characteristics at presentation of patients with and without RI are given in Table I. Patients having RI were significantly older (median age 63 *vs.* 59 years old, p=0.012), had lower hemoglobin level (<10 mg/dl, p<0.001), hypercalcemia (≥11.5 mg/dl, p<0.001), abnormal LDH level (≥460 mg/dl, p<0.001), higher serum level of β-2-microglobulin (p<0.001), more plasma cells in bone marrow (p=0.019), less extramedullary plasmacytoma (p<0.001), and more advanced stage by ISS (p<0.001). However, between the groups, there was no significant difference in gender, and cytogenetic abnormalities by conventional cytogenetics or FISH.

Reversibility of RI and prognostic factors for major RR. Of all patients, 85 (22.4%) were available for assessment of RR based on their initial renal function (eGFR <50 ml/min/1.73 m^2) including 17 patients who underwent hemodialysis. There were 43 patients (50.6%) with renal CR, three patients (3.5%) with renal PR, and 12 patients (14.1%) with minor RR; 58 (68.2%) had RR and 46 (54%) had major RR. In univariate analysis, patients with initial eGFR ≥30 ml/min/1.73 m^2, less advanced ISS (stage II), hypercalcemia, more plasma cells (>70%) in bone marrow and adverse cytogenetics were more likely to achieve major RR (Table II). In addition, inclusion of high-dose dexamethasone (≥160 mg dexamethasone) as first-line treatment and PR greater hematological response to first-line treatment were favorable for major RR. In multivariate analysis, less advanced ISS (p=0.013) and inclusion of high-dose dexamethasone as first-line treatment (p=0.004) were independently predictive for major RR.

Prognostic factors for TTRR. TTRR was compared according to clinical characteristics and treatment measures (Table III). Overall, the median TTRR was estimated to be approximately 5.5 months [170 days, 95% confidence interval (CI)=147-193 days). In univariate analysis, the presence of extramedullary plasmacytoma at baseline, bortezomib-containing regimen, inclusion of high-dose dexamethasone, and PR or better hematological response to first-line treatment were associated with shorter TTRR. Among the variables, bortezomib-containing regimen and inclusion of high-dose dexamethasone as first-line treatment were associated with a more rapid RR in both univariate and multivariate analysis. Although less advanced ISS was not statistically significant in univariate analysis, it was proven to be significantly predictive for better TTRR in multivariate analysis.

Table I. *Baseline characteristics and comparison of characteristics by renal function.*

Baseline characteristics	Number (%) total N=379	eGFR <60 mL/min/ 1.73 m^2 (N=117)	eGFR ≥60 mL/min/ 1.73 m^2 (N=262)	*p*-Value
Age years				
Median (range)	60 (22-92)	63 (30-92)	59 (22-86)	0.012
≤65	237 (62.5%)	65 (55.6%)	172 (65.6%)	0.067
>65	142 (37.5%)	52 (44.4%)	90 (34.4%)	
Gender				
Male:female	34 (57.6%): 25 (42.4%)	63 (53.8%): 54 (46.2%)	132 (50.4%): 130 (49.6%)	0.579
Ineternational staging system at diagnosis[a]				
Stage I	92 (24.9%)	6 (5.1%)	86 (32.8%)	<0.001
Stage II	139 (37.7%)	22 (18.8%)	117 (44.7%)	
Stage III	138 (37.4%)	85 (72.6%)	53 (20.2%)	
Baseline laboratory finding#				
Anemia, number (%)	196 (51.7%)	81 (69.2%)	115 (43.9%)	<0.001
Hypercalcemia, number (%)	38 (10.0%)	26 (22.2%)	12 (4.6%)	<0.001
Elevated LDH[b], number (%)	95 (27.5%)	45 (38.5%)	50 (19.1%)	<0.001
Elevated B2M[c], number (%)	236 (63.6%)	107 (91.5%)	129 (49.2%)	<0.001
Bone marrow plasma cell[d]				
<30%	129 (32.9%)	28 (23.9%)	101 (38.7%)	0.019
30-70%	165 (43.7%)	58 (49.6%)	107 (41.0%)	
>70%	84 (22.2%)	31 (26.5%)	53 (20.3%)	
Extramedullary plasmacytoma				
Yes	91 (24.0%)	13 (11.1%)	78 (30%)	<0.001
Cytogenetic abnormalities[e]				
Any abnormality	116 (36.0%)	37 (36.6%)	79 (35.7%)	0.901
del 13q	52 (16.1%)	18 (17.8%)	34 (15.4%)	0.625
del 17p in FISH[f]	16 (8.2%)	4 (6.5%)	12 (9.0%)	0.780
t (14;16) in FISH[g]	2 (1.4%)	0 (0.0%)	2 (2.1%)	0.545
t (4;14) in FISH[h]	17 (11.4%)	7 (13.7%)	10 (10.2%)	0.590

Number of available patients: a=369, b=345, c=371, d=378, e=322 (conventional cytogenetics), f=195, g=145, h=149. #Anemia, hemoglobin <10 g/dL; hypercalcemia, calcium >10 mg/dl; elevated lactate dehydrogenase (LDH), > upper limit of normal for LDH (460 mg/dl); elevated beta-2 microglobulin (B2M) ≥3.5 mg/l.

Survival. During a median follow-up period of 60.0 months, the median OS of 379 patients was assessed as 45.7 months (95% CI=38.7-52.7 months). OS was significantly different according to the grade of RI (p=0.019) (Figure 1A). OS of patients who achieved major RR was longer than that of non-responders (median of 40.2 months *vs*. 24.8 months), but was not statistically significant (p=0.286) (Figure 1B).

Discussion

The incidence of RI in MM varies from series to series (20). This is primarily caused by the different definition of RI in each series. Serum creatinine has been often used to define RI (18, 22), and Dimopoulos *et al*. reported that 21% of new patients with MM presented with renal failure (defined by serum creatinine ≥2 mg/dl) in their large-scale data (23). Recently, the IMWG stated the eGFR using the MDRD formula as a recommended method for the assessment of renal function in MM (20). In this study, we assessed the incidence of RI according to the recent IMWG recommendation, and RI was observed in approximately 30% of new patients with MM. Given that there were 31% of patients with abnormal renal function of serum creatinine ≥1.5 mg/dl in the aforementioned study by Dimopoulos *et al*. (23), it is assumed that an eGFR <60 ml/min/1.73 m^2 is likely to be matched with creatinine ≥1.5 mg/dl at a rough estimate in patients with MM.

Although the pathology of renal disease in MM is heterogeneous and may involve a variety of different mechanisms, RI in MM generally reflects that patients may have a higher tumor burden and more advanced disease (17, 23, 24). Accordingly, we confirmed that the presence of RI is positively correlated with prognostically-relevant adverse clinical parameters: anemia, elevated β2-microglobulin, elevated LDH, hypercalcemia, and more advanced disease by ISS. This is not a new finding in the field, but it is notable that RI defined by eGFR using the MDRD formula, which is the currently recommended method, is well-correlated with disease aggressiveness and physiological properties.

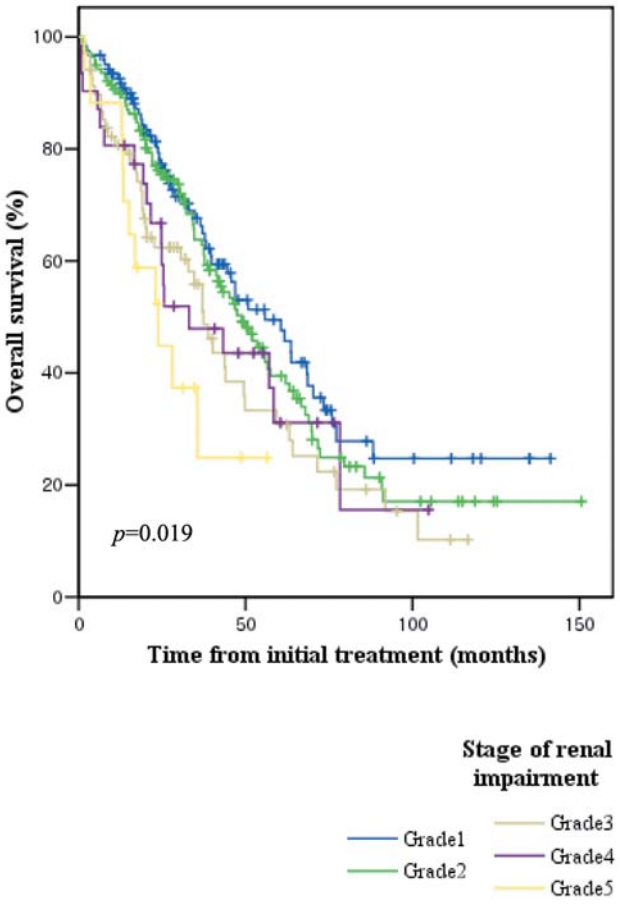
Table II. *Prognostic factors for major renal response.*

Variable	Total number	Major renal response number (%)	Univariate *p*-Value	Multivariate	
				p-Value	OR (95% CI)
Age (years)					
≤65	50	31 (67.4%)	0.083	0.962	-
>65	35	15 (32.6%)			
Gender					
Male	47	29 (61.7%)	0.121	0.877	-
Female	38	25 (44.7%)			
eGFR					
≥30	37	25 (67.6%)	0.031	0.300	-
<30	48	21 (43.8%)			
ISS					
I, II	12	10 (83.3%)	0.037	0.013	0.014 (0.000-0.407)
III	71	34 (47.9%)			
Anemia					
Hb ≥10	21	13 (61.9%)	0.411	0.513	-
Hb <10	64	33 (51.6%)			
Hypercalcemia					
Ca ≤11.5	61	28 (45.9%)	0.019	0.172	-
Ca >11.5	24	18 (75.0%)			
LDH					
normal	41	21 (51.2%)	0.552	0.267	
elevated	38	22 (57.9%)			
BM plasma cell					
≤70 (%)	62	29 (46.8%)	0.030	0.241	
>70 (%)	23	17 (73.9%)			
EMP					
No	76	38 (50.0%)	0.055	0.199	
Yes	9	8 (88.9%)			
Cytogenetics					
Normal	49	22 (44.9%)	0.030	0.659	
Abnormal	25	18 (72.0%)			
First-treatment					
Chemotherapy	64	31 (48.4%)	0.176	0.294	
Imid	15	10 (66.7%)			-
Bortezomib	6	5 (83.3%)			-
High-dose dex.					
Yes	50	34 (68.0%)	0.003	0.004	0.023 (0.002-0.304)
No	35	12 (34.3%)			
Hematological response					
≥PR	46	31 (67.4%)	0.009	0.181	-
No response	39	15 (38.5%)			

eGFR, Estimated glomerular filtration rate; ISS, international staging system; LDH, lactate dehydrogenase; BM, bone marrow; EMP, extramedullary plasmacytoma; dex, dexamethasone; Hb, hemoglobin; Ca, calcium; Imid, immunomodulary drug (either thalidomide or lenalidomide); PR, partial response; OR, odds ratio; CI, confidence interval.

Of note, extramedullary plasmacytoma is negatively-linked with RI in this study. In general, extramedullary disease is regarded as a poor prognostic factor in MM accompanied by shorter progression-free survival and OS even in the era of novel agents (25-27). We do not know exactly where this discrepancy came from, but it is assumed that this in part implies a gap between the extent of systemic disease (responsible for production of monoclonal light- chain) and the extramedullary plasmacytoma formation. In cases of light chain deposition disease or amyloidosis, which usually exhibit mild or moderate plasma cell infiltration in bone marrow, they also do not follow the principles of positive correlation between RI and advanced disease (22, 28, 29).

Recently, new criteria for the assessment of RR in MM have been proposed (20). Improvement of renal function has been assessed based on this new criteria in a series of studies (15, 30), and it was proven that cases of major RR (renal PR and renal CR) were most frequently observed in patients



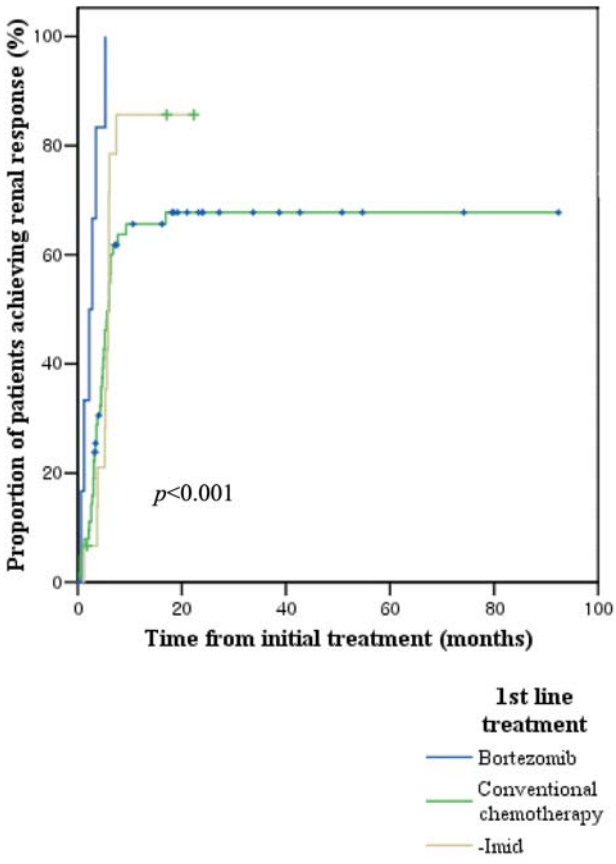


Figure 2. *Time-to-renal response according to first-line treatment.*

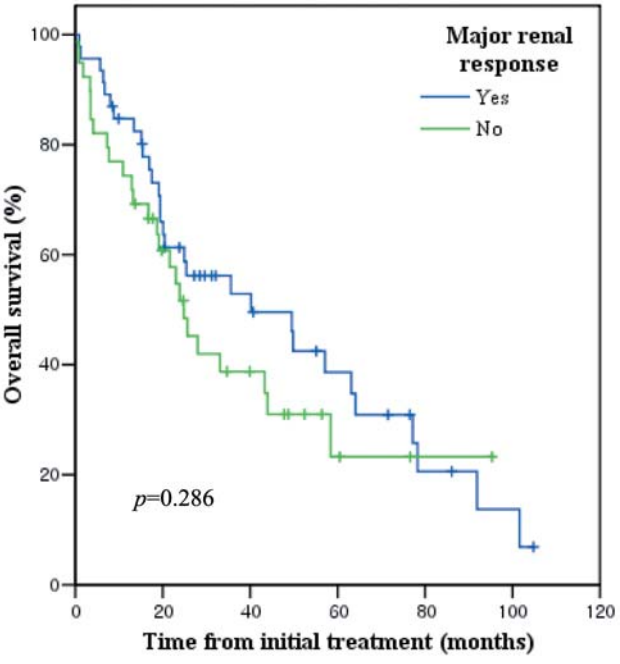


Figure 1. *Overall survival according to initial renal function (A) and to achievement of major renal response (B).*

treated with bortezomib compared to conventional chemotherapy or Immunomodulatory drugs (IMiDs, such as thalidomide or lenalidomide) treatment. In accordance with previous reports, our data also support the benefit of bortezomib use for new patients with MM with RI. All six patients receiving first-line bortezomib showed RR, and five of them showed major RR. Although there was no significant statistical difference in the proportion of major RR between treatment groups, which might be attributed to too small a number of patients who received bortezomib as a first-line treatment (N=6, 1.6% of total 379 patients), it seems that the use of bortezomib-based regimen was much superior to conventional chemotherapy (48.4% of major RR) or to immunomodulatory drug (66.7% of major RR) for achieving major RR. Additionally, TTRR was significantly shorter in these patients when compared to patients treated with conventional chemotherapy or immunomodulatory drug-based first-line therapy (Figure 2). Before the novel agents, high-dose dexamethasone-based regimens were usually used as initial management of new patients with MM with RI

Table III. *Prognostic factors for time-to-renal response.*

Variables	Median TTRR, days (95% C.I)	Univariate *p*-Value	Multivariate	
			p-Value	HR (95% CI)
Age (years)				
≤65	172 (146-198)	0.776	0.820	-
>65	163 (77-249)			
Gender				
Male	160 (138-182)	0.426	0.813	-
Female	187 (160-214)			
eGFR				
≥30	160 (137-183)	0.745	0.242	-
<30	183 (153-213)			
ISS				
I, II	98 (56-140)	0.075	0.015	0.209 (0.059-0.737)
III	183 (163-203)			
Anemia				
Hb ≥10	113 (85-141)	0.131	0.615	-
Hb <10	176 (154-198)			
Hypercalcemia				
Ca ≤11.5	183 (168-198)	0.374	0.986	-
Ca >11.5	160 (147-173)			
LDH				
Normal	149 (93-205)	0.809	0.818	
Elevated	176 (153-199)			
BM plasma cell				
≤70 (%)	176 (151-201)	0.337	0.983	
>70 (%)	160 (129-191)			
EMP				
No	172 (149-195)	0.048	0.846	
Yes	117 (105-129)	0.486		
Cytogenetics				
Normal	172 (145-199)	0.082	0.195	
Abnormal	160 (115-205)			
1st treatment				
Chemotherapy	184 (152-216)	0.001	0.015	
Imid	183 (170-196)	0.459	0.887	-
Bortezomib	66 (11-121)	<0.001	0.004	7.639 (1.931-30.225)
High-dose dexa				
Yes	161 (137-185)	0.040	0.011	0.297 (0.116-0.760)
No	235 (0-670)			
Hematologic response				
≥PR	160 (141-179)	0.037	0.068	-
no response	207 (162-252)			

eGFR, Estimated glomerular filtration rate; ISS, international staging system; LDH, lactate dehydrogenase; BM, bone marrow; EMP, extramedullary plasmacytoma; dex, dexamethasone; Hb, hemoglobin; Ca, calcium; Imid, immunomodulary drug (either thalidomide or lenalidomide); PR, partial response; HR, hazard ratio; CI, confidence interval.

(10). Inclusion of high-dose dexamethasone as a front-line treatment is likely still to be effective in this era of novel agents, leading to 81.3% of RR in this group of patients who received immunomodulatory drug or bortezomib with concomitant ≥160 mg dexamethasone. Moreover, high-dose dexamethasone treatment also contributed to achieving more rapid RR.

OS was significantly affected by the grade of initial RI, the lower the grade, the more inferior the survival outcome was (p=0.019). However, OS was not statistically different neither between those with RR and those without (p=0.159) or between major responders and non-major responders (p=0.286). Because RR was closely associated with systemic response, the fact that RR did not translate into significant improvement of OS was a

little perplexing. The relationship between renal response and survival was also analyzed in a previous study (15), showing no correlation between them. It is rather confusing whether there is really no association between RR and survival, or whether statistical insignificance was caused by the definition of RR. Because the choice of cut off value for defining RR is rather arbitrary, it might obscure the truth.

In summary, the incidence of RI in patients with newly-diagnosed MM was 31% according to the methods by recent consensus recommendation. RI at diagnosis was relevant to adverse clinical parameters, and had an impact of worse OS. RR was affected by the treatment, and ISS, but was not translated into significant improvement of OS. TTRR was significantly shorter in patients who were treated with a bortezomib-containing first-line regimen.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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