J Korean Med Sci 2006; 21: 639-44
ISSN 1011-8934

Comparison of Serum Beta 2-Microglobulin and 24 hour Urinary Creatinine Clearance as a Prognostic Factor in Multiple Myeloma

A new staging system for multiple myeloma (MM) has utilized serum concentrations of beta 2-microglobulin ($S\beta_2M$) and albumin as important prognostic factors for survival. Since $S\beta_2M$ is an indicator of glomerular filtration rate, we compared the prognostic values of $S\beta_2M$ and 24-hr urinary creatinine clearance (Ccr) in patients with MM. We retrospectively reviewed the records of 170 MM patients from January 1996 to November 2003 whose 24-hr urinary Ccr was available at the time of diagnosis. We found that pretreatment $S\beta_2M$ was inversely related to Ccr (Spearman's correlation coefficient=-0.787). In univariate analysis, the hazard ratio (HR) of death was 1.043 (p<0.001) for $S\beta_2M$ and 0.985 (p<0.001) for Ccr. Multivariate analysis showed that $S\beta_2M$ (HR 1.030, p=0.010) and Ccr (HR 0.993, p=0.059) were significant prognostic factors in patients' survival. In conclusion, 24-hr urinary Ccr may be utilized for staging of patients with MM.

Key Words : *Multiple Myeloma; beta 2-Microglobulin; Glomerular Filtration Rate*

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Received : 22 September 2005
Accepted : 8 February 2006

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INTRODUCTION

Until recently, the Durie Salmon (DS) staging system was primarily used in patients with multiple myeloma (MM) (1). This staging system was designed according to cell mass, utilizing hemoglobin, serum calcium, lytic bone lesions, and M component production rates as measurements, with each stage divided into A and B subgroups according to renal function.

More recently, the Southwest Oncology Group (SWOG) introduced a new staging system with beta 2-microglobulin ($S\beta_2M$) and albumin as prognostic factors (2). The SWOG staging system has been regarded as an easy, as well as good indicator of event-free survival, first-year mortality, and long-term survival. However, the SWOG system still requires more time and practice until it becomes the standard method.

$S\beta_2M$, which is thought to reflect known tumor cell burden, has been regarded as the most important prognostic factor in MM. Although $S\beta_2M$ concentration is influenced by kidney function, multivariate analysis showed that it remains an independent prognostic factor after correction for serum creatinine concentration (3-7).

However, in patients with mild to moderate renal insufficiency, $S\beta_2M$ may be a better indicator of glomerular filtration rate (GFR) than serum creatinine (8, 9). We therefore compared $S\beta_2M$ with 24 urinary Ccr as prognostic factors in MM patients, and determined the significance of 24 hr urinary creatinine clearance (Ccr) in the staging of patients with MM.

MATERIALS AND METHODS

Subjects

We retrospectively reviewed the records of all 268 symptomatic MM patients admitted and newly diagnosed at Asan Medical Center, Seoul, Korea, from 1 January 1996 to 30 November 2003. The 24-hr urinary Ccr was available at the time of diagnosis for 170 of these symptomatic MM patients, and these 170 patients were enrolled into the study. Survival time was followed until 30 April 2005.

All the patients had symptomatic MM in accordance with the diagnostic criteria of the International Myeloma Working Group (2003) (11). These criteria are defined as: 1) M-protein in serum and/or urine; 2) bone marrow (clonal) plasma cells or plasmacytomas; 3) related organ or tissue impairment (end organ damage, including bone lesions); and 4) no minimal level of clonal bone marrow plasma cells.

Patients with nonsecretory myeloma, smoldering multiple myeloma, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes), plasma cell leukemia, light chain deposit disease, MGUS (monoclonal gammopathy of undermined significance), extramedullary plasmacytoma, a combination of other malignancies, severe trauma were excluded.

Parameters

We investigated age, sex, heavy chain types, light chain types, Durie-Salmon stage, Sβ_2M, hemoglobin, serum calcium, serum albumin, serum creatinine, and 24 hr urine creatinine clearance before chemotherapy. Sβ_2M was measured by a radioimmunoassay with ^{125}I- labeled beta 2-microglobulin.

Treatment

Whereas patients received various treatments, they could be divided into 3 groups; those who received conservative treatment (no treatment or dexamethasone [20 mg/m^2 orally] only), those who received conventional chemotherapy (e.g., VAD, MP, high dose cytoxan plus predinisolone, and thalidomide plus dexamethasone regimens), and those who received autologous stem cell transplantation.

The MP regimen consisted of melphalan (8 mg/m^2) and prednisolone (60 mg/m^2) for 4 days; the VAD regimen consisted of vincristine (0.4 mg), doxorubicin (9 mg/m^2) for 4 days, and dexamethasone (40 mg) for 12 days. The high dose cytoxan plus prednisolone regimen consisted of cytoxan (400 mg/m^2) for 1 day and prednisolone (40 mg/m^2) for 7 days and was a variant of the VBMCP (vincristine, BCNU, melphalan, cytoxan, prednisolone) regimen. The thalidomide plus dexamethasone regimen consisted of 200 mg thalidomide orally per day plus 5 to 10 mg dexamethasone intravenously 4 times per day.

Survival time

Medical records were used to collect data. Interviews with patients' families by telephone and data from the hospital network connected to the Korean National Statistical Office were also utilized to determine the patient survival times.

Staging system

Patients were divided depending on DS stage, which was assigned by physicians who first examined them (1). Then, they were resorted by SWOG staging system according to Sβ_2M and albumin concentrations (2).

SWOG stage 1 was defined as Sβ_2M <2.5 mg/L; stage 2 as 2.5 mg/L $\leq$Sβ_2M <5.5 mg/L; stage 3, Sβ_2M $\geq$5.5 mg/L and serum albumin $\geq$3.0 g/dL; and stage 4, Sβ_2M $\geq$5.5 mg/L and albumin <3.0 g/dL.

During the course of this study, we formulated a new experimental staging system based on 24 hr urinary Ccr and serum albumin. In this system, stage 1 defined as Ccr $\geq$90 mL/min; stage 2 as 90 mL/min >Ccr $\geq$30 mL/min; stage 3 as Ccr <30 mL/min and albumin $\geq$3.0 g/dL; stage 4 as Ccr <30 mL/min and albumin <3.0 g/dL.

Statistical analysis

SPSS (version 11.0) was used to determine the means and standard deviations and medians of patient characteristics of patients and laboratory findings. One-way ANOVA and Student's t test were used to compare mean Ccr according to heavy or light chain types. An interactive graph of Ccr and Sβ_2M was drawn using a scatter plot and a logarithmic estimated curve.

The Kaplan-Meier method was utilized for survival analysis with log rank test; statistical significance was defined as p value less than 0.05.

The Cox proportional hazard model was employed for univariate analysis and multivariate analyses to confirm the significance of risk factors of death. In multivariate analysis, we used eliminated variables stepwise (backward) by a significance of less than 10%.

RESULTS

Study population

From 1 January 1996, through 30 November 2003, 289 patients with plasma cell disorders were admitted to our Center. Among them, there were 268 symptomatic MM patients. We excluded 14 patients with other monoclonal gammopathies and 7 patients with combining other malignancy or severe trauma. Gammopathies other than symptomatic multiple myeloma were 3 MUGS, 2 plasma cell leukemia, 2 smoldering MM, 2 nonsecretory MM, 1 extramedullary plasmacytoma, 1 multiple solitary plasmacytoma, and 3 POEMS. As to 170 patients, 24-hr urinary creatinine clearance was available at the time of diagnosis. Baseline characteristics and laboratory findings at the time of diagnosis are shown in Table 1.

Table 2 shows the mean Ccr of each type. The mean Ccr in patients with free light chain was lower than those of the heavy and light chain type groups. Mean Ccr of patients with free light chain was 36.2 mL/min, whereas those of patients with IgG type and IgA were 54.9 mL/min and 62.2 mL/min (p=0.005), respectively. However, mean Sβ_2M of patients

Table 1. Baseline characteristics of the patients

	Mean±SD or Median (Range) (n=170)
Age (yr)	60.0 (29-80)
Sex (male:female)	107:63
Hemoglobin (g/dL)	9.1±2.3
Serum calcium (mg/dL)	9.5±1.8
Serum creatinine (mg/dL)	1.5 (0.5-17.6)
Serum beta 2-microglobulin (μg/mL) (n=167)	5.5 (1.2-48.4)
Serum albumin (g/dL)	3.2±0.8
Creatinine clearance (mL/min)	47.8 (0.2-140.7)

according to heavy chain types was not significantly different (p=0.156).

Of the 170 patients, 28 patients were managed conservatively, 92 patients were treated with conventional chemotherapy, and 50 patients received high-dose chemotherapy with autologous stem cell transplantations. The first-line chemotherapy regimens consisted of VAD in 94 patients, MP in 41, cytoxan plus prednisolone in 4, thalidomide plus dexamethasone in 1. The chemotherapy regimen was unidentified in 2 patients.

We could definitively identify cause of death only if patients died in hospital, although we attempted to interview by telephone family members of patients who died outside of hospital to exclude death by accidental trauma. Of the 51 patients who died in hospital, 28 died of sepsis, 9 of respiratory failure, 4 of heart failure, 2 of major bleeding, 1 of arrhythmia, 3 of acute renal failure, 1 of acute myocardial infarction, 1 of subdural hemorrhage, and 2 of hepatic failure.

Among the 268 symptomatic MM patients, only 3 patients had hemodialysis before diagnosis because of acute renal failure; these patients did not have any other specific etiology, such as diabetes mellitus or hypertension. In all 3 persons, Ccr was measured at diagnosis, and all 3 were enrolled in this study.

Univariate and multivariate analysis

Univariate analysis showed that age, serum calcium, serum creatinine, Sβ_2M, Ccr, free light chain type, and treatment modalities were significant prognostic factors, using both the continuous and dichotomous methods (Table 3). The conservative management group had a shorter life expectancy than both the conventional chemotherapy group (hazard ratio [HR] 2.021, p=0.004) and the autologous transplantation group (HR 9.020, p<0.001). However, Sβ_2M concentration was not significant in univariate analysis of 104 patients with Ccr ≥30 mL/min (HR 1.001, p=0.982) (Table 4).

Multivariate analysis of prognostic factors using the Cox proportional hazard model showed that serum Sβ_2M, creatinine clearance, and treatment modalities were significant prognostic factors in continuous method (Table 6). Ccr was of borderline significance and was not eliminated by backward stepwise calculation if p=0.10. Using the dichotomous method, however, the result was somewhat different. If the Ccr cut-off value was 30 mL/min and that of Sβ_2M was 5.5 mg/L, Ccr and treatment were significant, but Sβ_2M concentration was not. This discrepancy was due to the close relationship of Sβ_2M and Ccr, making it difficult to determine a standard cutoff value using the dichotomous method.

Table 2. Types of heavy chains and light chains

	No.	Ccr (mean±SD) (mL/min)	No.	Sβ_2M (mean±SD) (μg/mL)
Heavy chain				
IgG	68	54.9±37.9	67	9.9±11.4
IgA	36	62.2±35.7	36	8.1±9.2
Free light chain	50	36.2±31.0*	48	13.3±11.4
IgD	14	50.3±36.7	14	10.5±8.2
IgM	1	(102.6)	1	(2.6)
biclonal	1	(86.2)	1	(4.1)
		p=0.005		p=0.156
Light chain†				
Lambda	86	50.1±37.8	84	10.5±10.6
Kappa	83	51.9±35.7	82	10.4±11.1
		p=0.751		p=0.961

*p<0.05 between patients with IgG type and free light chain type, or between IgA type and free light chain type, †One with only IgG heavy chain type was excluded.

Table 3. Hazard ratio in univariate analysis

	Continuous	Dichotomous	
	HR, p value	Cutoff value	HR, p value
Age (yr)	1.038, p<0.001	≥60 <60	1.972, p<0.001
Sex (male:female)		Male female	1.075, p=0.711 NS
Hemoglobin (g/dL)	0.954, p=0.259 NS	≥9.0 <9.0	0.850, p=0.386 NS
Serum calcium (mg/dL)	1.106, p=0.026	≥10.0 <10.0	1.524, p=0.045
Serum creatinine (mg/dL)	1.101, p<0.001	≥1.5 <1.5	2.077, p<0.001
Serum beta 2- microglobulin (μg/mL)	1.043, p<0.001	≥5.5 <5.5	2.097, p<0.001
Serum albumin (g/dL)	0.916, p=0.469 NS	≥3.0 <3.0	0.987, p=0.944 NS
Creatinine clearance (mL/min)	0.985, p<0.001	≥30 <30	0.361, p<0.001
Heavy chain type*		Only light Heavy and light chain	1.525, p=0.032
Light chain type		Kappa Lambda	0.753, p=0.135 NS
Treatment modalities			p<0.001

HR, hazard risk of death; NS, not significant.
*heavy chain type, Free light chain type vs. both heavy and light chain type.

Table 4. Hazard ratio in univariate analysis if Ccr ≥30 mL/min

	Continuous	Dichotomoud	
	HR, p value	Cutoff value	HR, p value
Sβ_2M (μg/mL)	1.001, p=0.982	≥5.5 <5.5	1.114, p=0.736
Ccr (mL/min)	0.987, p=0.015	≥90 <90	0.499, p=0.034

Sβ_2M, Serum beta 2-microglobulin; Ccr, Creatinine clearance; HR, hazard risk of death.

Table 5. Multivariate analysis by Cox proportional hazard model (backward)

	Continuous				Dichotomous*		
	Hazard ratio	Confidence interval	Significance		Hazard ratio	Confidence interval	Significance
Sβ_2M	1.030	1.007-1.053	p=0.010	Ccr ≥30	0.403	0.275-0.591	p<0.001
Ccr	0.993	0.986-1.000	p=0.059†	Treatment‡ 1),3)	7.945	4.052-15.577	p<0.001
Treatment‡ 1),3)	8.642	4.389-17.018	p<0.001	Treatment‡ 2),3)	3.717	2.147-6.435	p<0.001
Treatment‡ 2),3)	3.866	2.210-6.760	p<0.001				

†Borderline significant and not eliminated backward stepwise calculations at a significance of 10%; ‡Treatments; 1) Conservative management, 2) Conventional chemotherapy, and 3) Autologous stem cell transplantation.
*Dichotomous: Cutoff values were Ccr ≥30 or <30 mL/min and Sβ_2M ≥5.5 or <5.5 μg/mL.
Dichotomous results could not be accepted with confidence because the change in cutoff value of Ccr led to different outcomes. For example, if the cutoff value of Ccr was ≥50 or <50 mL/min and if Sβ_2M ≥5.5 or <5.5 μg/mL, Sβ_2M, treatment modalities, heavy chain type, serum calcium became significant prognostic factors. This result might be caused by the close relationship between Sβ_2M and Ccr.

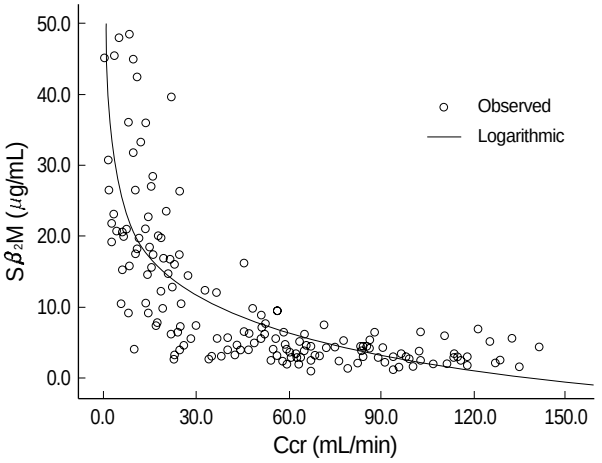

Fig. 1. Relationship of beta 2-microglobulin and 24 hr urinary creatinine clearance before chemotherapy.

Correlation of beta 2-microglobulin and creatinine clearance

When we drew a scatter plot of Sβ_2M and Ccr prior to the start of chemotherapy (Fig. 1), we found that pretreatment Sβ_2M was inversely related to Ccr (Spearman's correlation efficient -0.787, p<0.001).

Stage

Fig. 2 shows survival curves relative to DS stage and SWOG stage. Because we enrolled only patients whose DS stage was recorded by doctors at the time of diagnosis, the total number according to DS stage was 147 (95 dead, 52 alive). Because Sβ_2M was not checked in 3 patients in the study group, the total number according to SWOG stage was 167 (112 dead, 55 alive).

Median overall survival times according to DS stage were 919 days for stage 1 (n=11), 1011 days for stage 2 (n=17), 925 days for stage 3A (n=66), and 380 days for stage 3B (n=53).

Median survival times according to SWOG stage were 1475 days for stage 1 (n=18), 917 days for stage 2 (n=65), 453 days for stage 3 (n=57), and 152 days for stage 4 (n=27) (log rank test <0.0001).

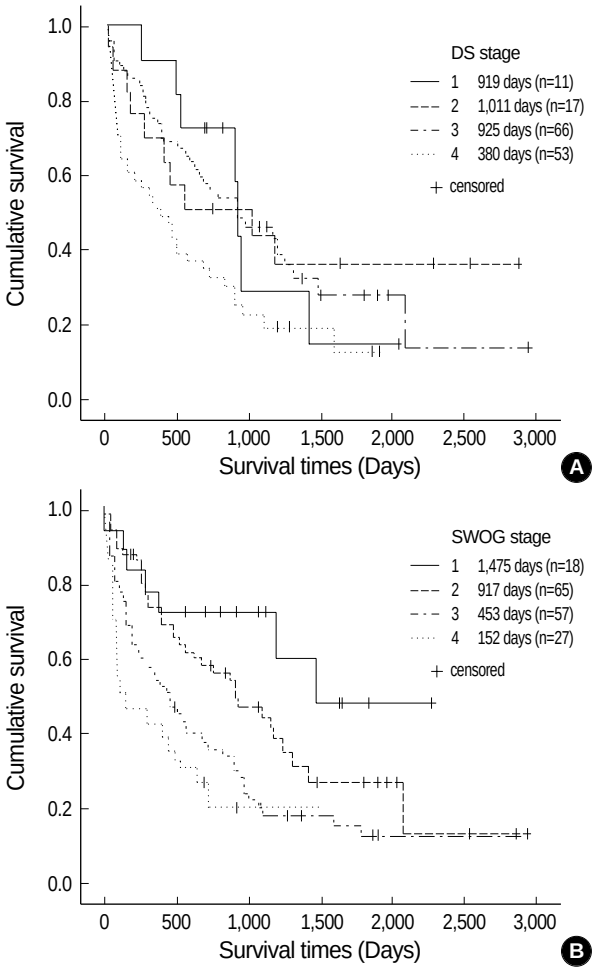

Fig. 2. Survival curves according to DS stage (A) and SWOG stage (B) with serum beta 2-microglobulin and serum albumin.

Possible staging system

Univariate analysis showed that, as Ccr increased, patient

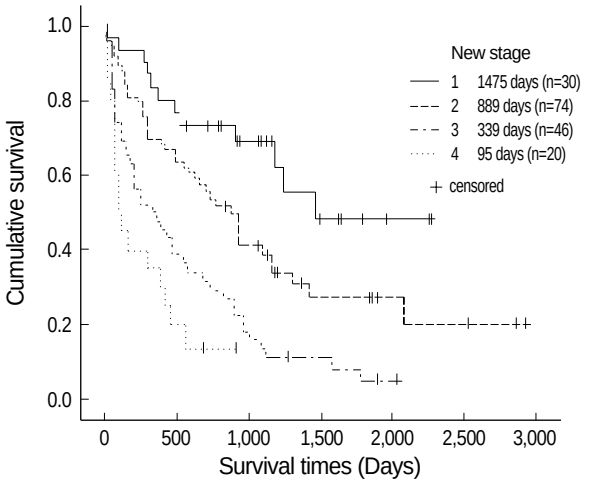

Fig. 3. Survival curves according to new staging system with Ccr and serum albumin.

survival time increased. Furthermore Sβ_2M was closely related with Ccr. We therefore formulated a new staging system based on Ccr instead of Sβ_2M, plus serum albumin (Fig. 3). According to this system, stage 1 is Ccr $\geq$90 mL/min; stage 2 is 90 mL/min > Ccr $\geq$30 mL/min; stage 3 is Ccr <30 mL/min and albumin $\geq$3.0 g/dL; stage 4, Ccr <30 mL/min and albumin <3.0 g/dL.

Applying this system, we found that 30 patients (12 dead, 18 alive) were stage 1, 74 (44 dead, 30 alive) were stage 2, 46 (42 dead, 4 alive) were stage 3, and 20 (17 dead, 3 alive) were stage 4.

According to this staging system, the median survival times were 1,475 days for stage 1, 889 days for stage 2, 339 days for stage 3, and 95 days for stage 4 (log rank test <0.0001).

DISCUSSION

In MM, the importance of Sβ_2M has led to the introduction of the SWOG staging system. In an attempt to determine the relationship between Sβ_2M and kidney function and to choose a more significant prognostic factor, we were unable to find any study that included both 24 hr urinary Ccr and Sβ_2M as prognostic factors. Thus, to our knowledge, this study is the first to include both of these as prognostic factors.

We found that in MM, Sβ_2M and Ccr were more closely related than we expected. Multivariate analysis showed that Sβ_2M, Ccr, and treatment modalities were independent prognostic factors. Thus, the results of this study suggest that Ccr is a new, powerful prognostic factor in the patients with MM. Moreover, this finding indicates that Ccr can be incorporated into a discrete new staging system for MM.

It was interesting that Sβ_2M was not significant in patients whose Ccr was greater than 30 mL/min. That is, the incremental addition of Sβ_2M concentration was not a significant prognostic factor if kidney function was relatively good. Thus, the effect of Sβ_2M on patient survival might be mainly due to declining kidney function.

Our new staging system used Ccr instead of Sβ_2M. The latter is not likely to be a specific tumor marker in MM. This finding indicates that patient survival is related to the decreased excretion of Sβ_2M rather than to its overproduction. There is evidence that Sβ_2M reflects glomerular filtration rate in many situations, although it also reflects tumor cell mass (9-11). Although our Kaplan-Meier curves of stages relative to Ccr and serum albumin concentrations were discrete, they were unable to show that Ccr was a more significant prognostic factor than Sβ_2M. These two factors, plus serum creatinine, are related, and other conflicting factors affect survival, thus making interpretation difficult. Differences in mean Ccr between patients with both heavy and light chains and those with only free light chains may be related to different survival times. Although the SWOG staging system has been regarded as easier and likely to supersede the DS staging system, it is cautious to determine the superiority between the two staging systems. Serum albumin was not a significant prognostic in univariate analysis, but, in the SWOG staging system, it was important in sorting patients with advanced stage MM.

Our study had several limitations. First, we may have included patients who died accidentally, since the causes of death of patients who died outside the hospital could not be determined. Second, this retrospective study did not include important parameters such as performance status, C reactive protein, chromosome 13 abnormality, and plasma cell labeling index (12, 13).

In conclusion, we found that in patients with MM, Sβ_2M was an independent significant prognostic factor in multivariate analysis that included Ccr. Although closely related to Sβ_2M, Ccr was also a significant prognostic factor that could replace Sβ_2M in staging systems of MM. Mean Ccr differed among heavy chain types, and these differences were likely related to different survival times.

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