Confirmation of the utility of the International Staging System and identification of a unique pattern of disease in Brazilian patients with multiple myeloma

Multiple myeloma (MM) is one of the most frequent hematologic malignancies, and its incidence varies worldwide. Except for occasional case series or correlative biological studies, little is known about the incidence and clinical features of MM in Latin America. In Brazil, national estimates for the incidence of MM are currently unavailable. Sixteen Brazilian institutions provided information on patients diagnosed with MM between 1998 and 2004. The investigators included all patients whose charts were available. All patients were undergoing care at these institutions. The diagnosis was based on the new criteria,[1] and/or standard clinical, laboratory and radiographical features, as well as on bone marrow findings compatible with MM. Since the majority of patients had Durie-Salmon stage (DSS) III, the diagnosis was not in doubt. Patients' data were obtained from institutional charts, and were entered on a web-based system specifically designed for the study under the auspices of the International Myeloma Foundation. We collected information regarding the demographical features of the patient, date of diagnosis, stage according to the DSS[2] and ISS,[3] type of monoclonal component, results of pertinent laboratory tests, type of treatment administered, and date of last follow-up or death. From 1998 to 2004, the patients who were not candidates for high-dose chemotherapy (i.e., those who presented with poor performance status or for whom high-dose chemotherapy was not available) were treated with melphalan and prednisone.

The database was analyzed in August 2006. A total number of 1,112 patients were included. χ^2 tests were used for the comparisons between proportions. Survival, defined from the date of diagnosis until death, was analyzed by the Kaplan-Meier method[4] and survival curves were compared using the log-rank test.[5] Patients who were alive on the last visit or who were lost to follow-up were censored for survival analyses. Significant baseline univariate predictors of survival in the Kaplan-Meier analyses were considered for inclusion in a Cox regression model.[6] Backward selection of all factors was used, and a variable was retained in the model if the associated two-sided p value was ≤0.05. All statistical tests were two-sided, and final p values ≤0.05 were considered significant.

Main demographical and clinical features of the patients are shown in Table 1. The median follow-up was 20.5 months, and the estimated median overall survival was 57.7 months. At the time of the analysis, 392 patients (35.3%) were already deceased. Overall survival was analyzed according to DSS and ISS (Figure 1, Panels A and B). There was a statistically significant difference between the overall survival of patients with MM in stages I, II and III according to both staging systems (p<0.001). With DSS, however, there was a considerable overlap between the survival curves for patients in stage I and II (Figure 1, Panel A). The median overall survival for patients in DSS I and II had not been reached at the time of the analysis; for patients in stage III, the median overall survival was 52.1 months. After 5 years, the estimated proportions of survival for patients in DSS stages I, II and III were 73.3%, 54.7% and 44.3% respectively.

Table 1. Patients' characteristics (n=1112).

Characteristic	*Information available (N)*	*N (%)*
Age, median (range)	1112	60.5 years (28 – 94)
Sex	1112	
Female		553 (49.7)
Male		559 (50.3)
Ethnicity	1112	
Caucasian/mixed		926 (83.3)
African		176 (15.8)
Other		10 (0.9)
Creatinine	1004	
> 2 mg/dL		231 (23)
≤ 2 mg/dL		773 (77)
Immunoglobulin (Ig) isotype	926	
IgG		570 (61.5)
IgA		181 (19.5)
IgM		3 (0.3)
Light-chain only		112 (12.1)
Non-secretory		40 (4.3)
Hemoglobin	1007	
<10 g/dL		585 (58)
Bone lesions	1043	
Absent		155 (14.9)
Present		888 (85.1)
Durie-Salmon stage	1066	
I		68 (6.4)
II		182 (17.1)
III		816 (76.5)
International Staging System stage	756	
I		152 (20.1)
II		368 (48.7)
III		236 (31.2)
Hypercalcemia	1003	
Absent		764 (76.2)
Present		239 (23.8)
High-dose chemotherapy	1057	
Yes		270 (25.5)
No		787 (74.5)

The survival curves for patients in ISS stages I, II and III are clearly distinct, with no overlap until 100 months of follow-up (Figure 1, Panel B). In addition, 20.1%, 48.7% and 31.2% of patients were in ISS I, II and III respectively. Corresponding proportions in the ISS database were 28.9%, 37.5% and 33.6% respectively.[3] The median overall survival for patients in ISS stage I had not been reached at the time of the analysis; for patients in stages II and III, median overall survival was 65.5 and 26.0 months respectively. Corresponding figures in the original ISS database were 62, 44 and 29 months respectively. After 5 years, the estimated proportions of survival for patients in ISS stages I, II and III were 68.2%, 52.7% and 30.4% respectively.

The differences between the survival of our patients in stages I and II and the corresponding patients from the original ISS database may reflect patient selection, treatment modalities, or be due to chance. Our database contains a lower proportion of patients in stage I, and a higher proportion in stage II, but these differences are unlikely to have contributed to the longer overall survival observed in the current study. In the ISS database, 26.1% of patients received high-dose chemotherapy within nine months of diagnosis, figures very similar to those found in the present study (25.5%). We, therefore, cannot explain the survival difference observed for patients in this study and patients included in the ISS database.

Table 2. Multivariate prognostic model for mortality.

Variable	Category	Hazard ratio	95% confidence interval	p value
Hypercalcemia	Absent	1.00		
	Present	2.47	1.86-3.28	<0.001
ISS stage	I	1.00		
	II	1.22	0.79-1.88	0.364
	III	2.40	1.55-3.72	<0.001
Age	≤ 60 years	1.00		
	> 60 years	1.54	1.18-2.01	0.002
Durie-Salmon stage	I	1.00		
	II	0.97	0.44-2.12	0.939
	III	1.28	0.63-2.60	0.501

ISS: International Staging System.

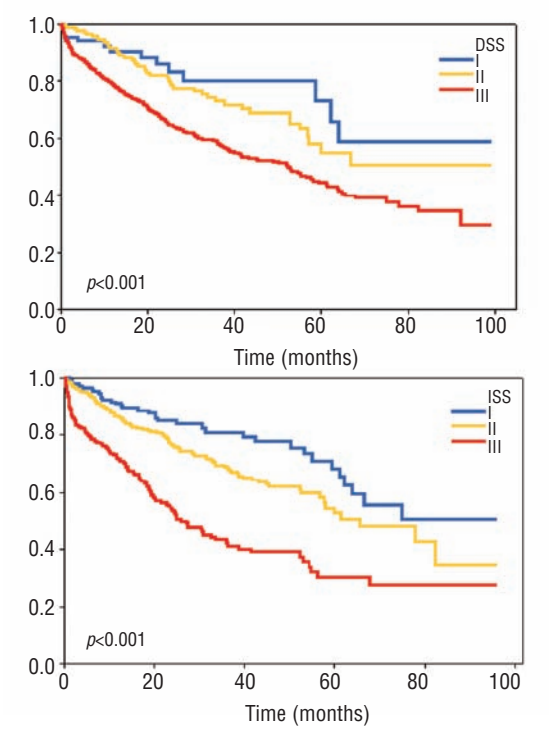

Figure 1. Overall survival according to the Durie-Salmon Staging (DSS) system (Panel A, N=1,066) and to the International Staging system (ISS; Panel B, N=756).

Interestingly, no patients from Brazil or any other Latin American countries were included in the original ISS database.

When survival was analyzed according to other potential prognostic factors, age >60 years (52.1 *vs.* 65.5 months for those with age ≤60 years), presence of hypercalcemia (21.3 *vs.* 63.9 months for those with normal serum calcium) and receipt of high-dose chemotherapy (82.2 *vs.* 43.5 months for patients not treated with high-dose chemotherapy) were found to be significantly associated with increased mortality (p<0.001 in all cases). Age and receipt of high-dose chemotherapy were correlated: 83.0% of patients undergoing high-dose chemotherapy were aged ≤60 years, whereas 62.9% of patients not treated with high-dose chemotherapy were aged > 60 years (p<0.001).

The multivariate prognostic model included patients' baseline variables that were associated with mortality in the Kaplan-Meier univariate analyses. Only hypercalcemia, ISS stage III and age were independent predictors of mortality (Table 2). According to the model, DSS had no independent prognostic role when hypercalcemia, ISS and age were considered simultaneously.

The current study, which is the largest case series of MM in Brazil, identifies the unique aspect of the pattern of disease for Brazilian myeloma patients, with hypercalcemia as the main risk. It recognizes the feasibility of large, collaborative, observational studies between various tertiary-care hematology centers, and confirms that ISS is indeed a more useful prognostic index than the DSS system in Brazilian patients.

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