Multiple Myeloma

Evaluation of five staging systems in 470 patients with multiple myeloma

We evaluated the prognostic significance of five staging systems in 470 consecutive, previously untreated patients with multiple myeloma diagnosed between 1989 and 2006. The five staging systems were those proposed by Durie and Salmon, Bataille *et al.*, the South West Oncology Group, Weber *et al.* and the International Staging System. This last proved to be superior to the others.

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The wide range in survival rates in multiple myeloma (MM) establishes the need for a staging system (SS) with prognostic reliability. Since 1975, the Durie-Salmon SS (DS SS) has been a widely accepted classification of MM patients, despite its lack of reproducibility, problematic designation of bone disease and failure to identify prognostic groups in patients under conventional or high-dose therapy.[1-3] In the meantime, the prognostic significance of β-2 microglobulin (β_2m) and albumin (levels) became evident. β2m reflects tumor burden and renal function and emerged in several studies as a most powerful predictor of survival.[4,5] Albumin levels correlate inversely with the levels of interleukin-6, a major growth and survival factor of myeloma cells, thus indicating disease severity and proliferative rate.[6] The prognostic power of the combination of β2m and albumin was recognized and subsequently employed in the simpler SS of Bataille *et al*. (BSS), the South West Oncology Group (SWOG SS) and most recently in the International Staging System (ISS) (Table 1).[7-9] Weber *et al*., in an early attempt to validate the ISS, questioned the need to use albumin in their model (WSS), since they demonstrated similar results using β_2m alone in identical cut-offs with ISS (Table 1).[10]

Table 1. Myeloma staging system based on the combination of B2m and albumin or β2m alone.

	BSS	*SWOGSS*	*ISS*	*WSS*
Stage I	β2m <6mg/L, alb >3g/dL	β2m <2.5mg/L	β2m <3.5mg/L, alb ≥3.5g/dL	β2m <3.5 mg/L
Stage II	β2m ≥6mg/L, alb >3g/dL	2.5mg/L β2m <5.5mg/L	neither stage I nor III	3.5mg/L β2m <5.5mg/L
Stage III	alb ≥3g/dL	β2m ≥5.5mg/L, alb ≥3g/dL	β2m ≥5.5mg/L	β2m ≥5.5mg/L
Stage IV		β_2m ≥5.5mg/L, alb <3g/dL		

The aim of the present study was to evaluate and compare the prognostic significance of these five SS in 470 consecutive, previously untreated MM patients diagnosed in our department between 1989 and 2006. Ninety-two (19.6%) patients received high-dose therapy followed by autologous stem cell transplantation and the remaining 378 (80.4%) were treated with conventional chemotherapy. All patients were classified according to each SS and survival was estimated according to Kaplan-Meier method. Survival differences between stages were assessed using the log-rank test.

The median follow-up was 36 months (range: 1-180) and the median overall survival for all patients was 40 months (95% CI: 36-44). One hundred and seventy-six patients (37.4%) are still alive, 274 (58.3%) have died and 20 (4.3%)

Table 2. Distribution and median overall survival of 470 MM patients according to the DS SS, BSS, SWOG S, ISS and WSS.

	DS SS		*BSS*		*SWOG SS*		*ISS*		*WSS*	
Stage	*N (%)*	*OS (95%CI) months*	*N (%)*	*OS (95%CI) months*	*N (%)*	*OS (95%CI) months*	*N (%)*	*OS (95%CI) months*	*N (%)*	*OS (95%CI) months*
I	38 (8.1)	75 (62-78)	270 (57.4)	53 (44-62)	73 (15.5)	76 (67-85)	135 (28.7)	76 (66-86)	177 (37.4)	64 (54-74)
II	131 (27.9)	47 (37-57)	79 (16.8)	25 (21-31)	229 (48.7)	45 (41-49)	168 (35.7)	40 (35-45)	126 (26.8)	43 (38-48)
III			121 (25.7)	19 (13-23)	98 (20.8)	23 (18-28)	167 (35.5)	23 (19-27)	167 (35.5)	23 (19-27)
IIIA	231 (49)	38 (35-41)								
IIIB	70 (15)	24 (16-32)								
IV					70 (14.8)	21 (15-27)				

OS, overall survival.
DSSS: pI,II=0.007, pI,IIIA=0.0003, pI,IIIB <0.0001, pII,IIIB <0.0001, pIIIA,IIIB=0.0007, but pII,IIIA=0.06; BSS: pI,II <0.0001, pI,III <0.0001, but pII,III=0.11; SWOGSS: pI,II=0.008, pI,III <0.0001, pI,IV <0.0001, pII,III <0.0001, pII,IV <0.0001, but pIII,IV=0.59; ISS: pI,II <0.0001, pI,III <0.0001 and pII,III <0.0001; WSS: pI,II=0.001, pI,III <0.0001 and pII,III <0.0001.

were lost during the follow-up. The distribution and median overall survival of the patients according to each SS are presented in Table 2. In practice, the difference between the ISS and the WSS is that patients with β2m <3.5 mg/L and albumin <3.5 g/dL are classified in stage II according to the ISS, while according to the WSS they are in stage I. There were 42 such patients in our study: when these patients were analyzed separately in order to determine in which prognostic group they practically belong, their median overall survival was 40 months, (95%CI: 32-48) not being statistically significantly difference from that of stage II patients of either SS (p>0.7).

Classification according to the DS SS, the BSS and the SWOG SS yielded a heterogeneous distribution of our patients among the three stages of each SS, with the majority of the patients classified in DS SS IIIA, BSS I and SWOG SS II. Application of the ISS and WSS produced the most homogeneous distribution of patients. There was no statistically significant difference in survival between patients in DS SS II and DS SS IIIA. Overall survival was also similar between patients in BSS II and BSS III and between those in SWOG SS III and SWOG SS IV, leading us to the conclusion that albumin seems to lose its prognostic value at high cut-off levels of β2m. The ISS and WSS demonstrated the best discriminatory efficacy, since significant differences in survival were found between all three stages.

The median overall survival of our patients in stage I, according to the DS SS, SWOG SS and ISS, is identical, exceeding 6 years. The BSS and WSS seem to do these patients a prognostic injustice by decreasing their expected survival by 2 years and 1 year, respectively. In the case of BSS, this difference indicates that 6 mg/L is an exceedingly high cut-off level of β2m for identifying low-risk patients. In the case of WSS, the difference is due to the mistaken inclusion of patients with β2m <3.5 mg/L and albumin <3.5 g/dL in stage I, since according to their median overall survival of 40 months, they do, in fact, belong to stage II.

Stage II patients had a similar survival of around 3.5 years in all SS with the exception of the BSS. In fact, in our study BSS II patients belonged to a more advanced stage, since their short survival of 2 years is not significantly different from that of BSS III patients, corresponding at the same time to the survival of DS SS IIIB, SWOG SS III or IV, ISS III and WSS III patients.

In conclusion, our study confirms the superiority of the ISS over the DSSS and previous prognostic classifications based on the combination of β2m and albumin. The ISS proved to be the only simple, reproducible alternative with high prognostic power, definitely able to gain wide clinical applicability.

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