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Serum Beta-2-microglobulin in Multiple Myeloma: Relation to Presenting Features and Clinical Status

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Abstract—*Serum beta-2-microglobulin (B2m) levels were measured in 78 patients with multiple myeloma (MM) and were compared with values for normal individuals and patients with benign monoclonal gammopathies (BMG). Serum B2m levels and values corrected for renal function were significantly higher in patients with MM at time of diagnosis than in normal individuals* ($P < 0.001$) *and were highly correlated with the total body burden of myeloma cells as derived from the staging system of Durie and Salmon. However there were no significant differences between values for BMG and low-mass MM. For patients evaluated following induction chemotherapy, there was also a clear correlation between serum B2m levels and the magnitude of tumor regression or progression* ($P < 0.05$). *During the plateau-phase, serum B2m levels remained very stable and highly correlated with the residual tumor mass* ($P < 0.001$). *It was concluded that* (1) *B2m was not a reliable marker to distinguish between BMG and low-mass MM and* (2) *B2m was a valuable marker for assessing initial tumor mass of patients with MM and response to chemotherapy (especially the plateau-phase), above all in patients with urine or low-serum monoclonal component levels.*

INTRODUCTION

BETA-2-MICROGLOBULIN (B2m) is a low molecular weight protein (MW: 11,800) synthetized by all nucleated cells and originally isolated from human urine [1]. Its structure is similar to that of constant region of immunoglobulin molecules; B2m is, in fact, the light chain of histocompatibility antigens present on the membranes of most cells [2]. Serum B2m is the free form of B2m [3]. Serum B2m levels have been shown to vary within a narrow range in normal individuals [4]. Increased levels have been associated with age [5]. The kidneys appear to play a central role in the catabolism of B2m and high serum B2m levels have been reported in patients with renal disease [6]. Increased serum B2m levels have been reported in a variety of malignant diseases [5, 7–9], most notably in multiple myeloma (MM) [7–15]. Within the plasma cell dyscrasias (PCD), serum B2m appears to be a useful marker both for the diagnosis of malignant PCD [12] and for prediction of prognosis in patients with MM, this latter feature being due to its relationship to tumor mass [12–14]. However, some discrepancy exists, probably explained by differences between age, renal status and tumor mass of studied patients.

The goal of our current and prospective study was to more fully evaluate the relationships between B2m and the main presenting features and clinical status of 78 patients with documented MM. Based upon our own and previously published data, we conclude that B2m can be a very useful marker for routine monitoring of MM, especially in patients who lack easily measurable serum monoclonal (M) components.

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MATERIALS AND METHODS

Patients

Serum B2m levels were measured in 78 patients with MM, using the diagnostic criteria of the Southwest Oncology Group [16]. The mean age (years) was 62.5 ± 10.5 and the sex ratio M/F: 0.90. Fifty-three per cent of patients had IgG myeloma, 27% IgA and 18% pure Bence–Jones. Furthermore, one patient has IgD myeloma (1%) and one had non-secretory myeloma (1%). Sixty-eight per cent had kappa subtype and 32% lambda light chain subtype. Hypercalcemia (defined as adjusted serum cal-

cium levels ≥ 2.625 mmol/l [17] was noted in 24% of cases. According to the clinical staging system of Durie and Salmon [18], 18% of patients had normal creatinine levels (defined as levels ≤ 107 μmol/l in males and ≤ 99 μmol/l in females) and 23% abnormal levels. Only 6% of our patients had serum creatinine levels ≥ 150 μmol/l (i.e., stage B [18]).

Fifty-four patients (70%) were studied both at the time of diagnosis and at various intervals during induction chemotherapy. These patients were classified according to the prognostic staging recently published by Merlini *et al.* [19]. Bone-marrow acid phosphatase staining of myeloma cells was performed in 30 out of these 54 patients at the time of presentation, according to the method of Barka and Anderson [20]. Twenty-four patients (30%) were studied only at the time of primary induction chemotherapy failure, of remission and/or relapse. At initial staging, the total body myeloma cell mass (T.B.M.C.) was assessed in each IgG and IgA myeloma according to the programs of Salmon and Wampler [21]. Tumor cell mass changes were assessed according to the programs of Salmon and Wampler for IgG/IgA myeloma [21] (considering changes in body weight, [^{131}I]-albumin plasma volume and serum monoclonal IgG/IgA rates).

Response to chemotherapy was defined as a ≥ 50% regression in the T.B.M.C. and relapse as a ≥ 50% increase in myeloma cell mass [18]. In responsive patients the plateau was defined as a ≥ 6 months steady-state phase without any significant changes in TBMC [22].

Patients were treated every 4–6 weeks with intermittent courses of a combination of cycle non-specific drugs (Melphalan, cyclophosphamide) plus prednisone with or without Vincristine, as previously described [23, 24].

Serum B2m levels were simultaneously assessed in 37 normal individuals and in 8 patients* with 'benign' monoclonal gammopathy, 6 of IgG type and 2 of IgA type. These asymptomatic patients were selected on the following criteria: (1) low and stable monoclonal protein levels (follow-up > 2 years); (2) bone-marrow plasmacytosis < 10% without atypical plasma cells; (3) normal plasma-cell bone marrow acid phosphatase staining [25]; (4) absence of urine monoclonal component ('Bence–Jones protein') and of reduced levels of normal serum immunoglobulins [16].

Methods

Serum levels were measured by a radioimmunoassay method, using the 'PHADEBAS B2-micro-test' (Pharmacia diagnostics, Uppsala, Sweden). Although the diffusion compartment of B2m was 2 to 4-fold larger than plasma volume [26] we evaluated a total serum B2m according to the following formula: SB2m × [^{131}I]-albumin plasma volume (results being given in mg per patient). Because the interpretation of high serum B2m levels was influenced by the frequent renal deficiency of the myeloma patients (23% in the current study), we used the measured B2m (M) to calculated B2m (CTD) ratio (B2m M/CTD ratio). As opposed to the measured B2m, the calculated B2m was derived from the creatinine value, as previously described by Cassuto *et al.* [12], using the following formula:

$$\log_e \text{B2m}\ (\mu\text{g/ml}) = 3.834 - 5.96\ Y + 2.94\ Y^2 - 0.476\ Y^3 + 0.0252\ Y^4$$

where $Y = \log_e$ serum creatinine (mg/ml) ($r = 0.9849$).

For statistical analysis, we used the Wilcoxon test and Student's *t* test. Bivariate analyses (= linear correlation) were performed with the Pearson correlation coefficient.

For MM, statistical analyses of uncorrected serum B2m values were carried out only for patients with normal creatinine levels (see Patients section). On the other hand, statistical analysis of B2m M/CTD ratios was carried out for all the myeloma patients.

RESULTS

Serum beta-2-microglobulin (B2m) and measured B2m (M) to calculated B2m (CTD) ratios (B2m M/CTD ratios) in myeloma patients (MM): comparison with normal individuals and benign monoclonal gammopathies (BMG)

As illustrated in Table 1, the individual values of serum B2m and B2m M/CTD ratios were significantly higher in patients with MM than in normal individuals and in patients with BMG ($P < 0.001$). These results are in agreement with previous reports, including that of Cassuto *et al.* [12]. In spite of this significant difference, normal serum B2m values were observed in 29% of myeloma patients, including 60% of low-mass myelomas. Therefore, in order to more thoroughly investigate the real discriminative interest of serum B2m in the differential diagnosis of benign and malignant PCD, we compared the serum B2m values of patients with BMG and of patients with only low-mass MM. As shown in Table 2, no difference was found between these

*Including 16 serial radioimmunoassay of serum B2m.

Table 1. Comparison of serum B2M in normal individuals, patients with benign monoclonal gammopathies (BMG) and untreated multiple myeloma (MM)

Clinical status (No. of evaluable normal individuals and patients)	Serum B2M (μg/ml): mean values ± S.D. (median values)	Serum B2M M/CTD ratio: mean values ± S.D. (median values)
Normal individuals ($n = 37$)	1.64 ± 0.40 (1.6)	1.03 ± 0.31 (0.95)
Benign monoclonal gammopathies ($n = 8$)	2.31 ± 0.52 (1.7)*	0.94 ± 0.19 (0.85)*
Untreated multiple myeloma ($n = 54$)	4.34 ± 2.79 (3.1)†	2.05 ± 1.22 (2)†

*Not significantly different to normal individuals.
†Significantly different to normal individuals ($P < 0.001$).

Table 2. Comparison of serum B2M in normal individuals, patients with benign monoclonal gammopathies (BMG) and patients with untreated low mass multiple myeloma (MM)

Clinical status (No. of evaluable controls and patients)	Age (years): mean values ± S.D. (median age)	Serum B2M (μg/ml) mean values ± S.D. (median values)	Serum B2M M/CTD ratios: mean values ± S.D. (median values)
Normal individuals ($n = 37$)	60.8 ± 8.9 (58)	1.64 ± 0.40 (1.6)	1.03 ± 0.31 (0.95)
Benign monoclonal gammopathies ($n = 8$)	61.7 ± 10*(57)	2.31 ± 0.52* (2.1)	0.94 ± 0.19* (0.85)
Untreated low mass myelomas ($n = 9$)	55.89 ± 17.52* (50)	2.09 ± 0.74* (1.9)	1.10 ± 0.26* (1.1)

*Not significantly different to normal individuals.

two groups. It was concluded that if high serum B2m levels were in favor of a malignant PCD, normal levels did not exclude the diagnosis of myeloma at all.

Serum beta-2-microglobulin (B2m); total serum beta-2-microglobulin (TB2m) and measured B2m (M) to calculated B2m (CTD) ratios (B2m M/CTD ratios) in myeloma patients (MM): relation to presenting features

As shown in Tables 3, 4 and 5, serum B2m, TB2m and B2m M/CTD ratios were related to hemoglobin level, serum calcium and M-component G or A levels, to the extent of lytic bone lesions and initial staging. Finally, a strong positive correlation was found with the myeloma cell mass ($P < 0.001$), the highest values of B2m being observed in patients with high tumor mass (i.e., stage III). Furthermore, an inverse correlation was found between B2m and polyclonal immunoglobulin M levels measured by nephelometry in IgG, IgA and pure Bence–Jones myelomas ($P < 0.05$). This was expected considering that polyclonal IgM levels were directly related to myeloma cell mass, the lowest values being observed in patients with the highest tumor mass ($P < 0.01$). These data are in agreement with previous reports, including the recent report of Pruzanski *et al.* [27].

A further and more detailed investigation revealed that after correction for the myeloma cell mass, relationship between serum B2m levels and M-components levels IgG or IgA was not significant any more. Furthermore, no difference in serum B2m levels was found between IgG, IgA and Bence–Jones types and between kappa and lambda light chain subtypes. These data are in agreement with previous studies of B2m production *in vitro* by human myeloma cell lines [28, 29]. In these studies no correlation between the capacity to

Table 3. Bivariate analysis between serum B2M and presenting features of patients with multiple myeloma (MM)

Bivariate analysis: Pearson correlation coefficient (No. of patients‡)	Serum B2M levels†	T B2M levels	B2M M/CTD ratios‡
Hemoglobin ($n = 40$)	−0.64***	−0.58***	−0.38**
Serum calcium ($n = 40$)	0.36*	0.31^{NS}	0.21^{NS}
IgG/IgA monoclonal protein ($n = 33$)	0.54***	0.51**	0.33**
T.B.M.C.§ ($n = 33$)	0.61***	0.54**	0.41**

†Patients with normal creatinine levels (see Patients and Methods section).
‡All patients.
§Total body myeloma cell mass (see Patients and Methods section and references [18, 21]).
Significant to $*P < 0.05$; $**P < 0.01$; $***P < 0.001$; NS: not significant.

Table 4. Relation of serum B2M to the extent of lytic bone lesions in patients with multiple myeloma (MM) at time of presentation

Graded bone lesions† (No. of patients)‡	Serum B2M (μg/ml): mean values ± S.D. (median values)	T B2M (mg): mean values ± S.D. (median values)	B2M M/CTD ratios: mean values ± S.D. (median values)
Grade 0 ($n = 9$)	2.30 ± 0.93§* (1.9)	7.96 ± 4.20 (6.92)§**	1.18 ± 0.36§** (1.07)
Grade 2 ($n = 16$)	4.20 ± 3.47‖* (2.9)	13.24 ± 8.03 (9.40)	3.09 ± 4.88‖*** (1.66)
Grade 3 ($n = 16$)	5.60 ± 2.07 (5.5)	19.75 ± 10.18 (18.17)	2.40 ± 1.26 (2.14)

†According to the clinical staging system of Durie and Salmon [18]. No patients with Grade 1 were observed in this study.
‡Patients with normal creatinine levels (see Patients and Methods section).
§Significantly different to Graded 2 lytic bone lesions.
‖Significantly different to Graded 3 lytic bone lesions.
$*P < 0.01$; $**P = 0.05$; $***P < 0.05$.

Table 5. Relation of serum B2M to initial staging of patients with multiple myeloma (MM)

Initial staging† (No. of patients‡)	Serum B2M (μg/ml): values ± S.D. (median values)	T B2M (mg): mean values ± S.D. (median values)	B2M M/CTD ratios: mean values ± S.D. (median values)
Stage I ($n = 8$)	2.09 ± 0.74§**** (1.9)	6.62 ± 2.46§* (6.29)	1.10 ± 0.26§**** (1.1)
Stage II ($n = 11$)	2.99 ± 1.04‖**** (2.7)	11.73 ± 7.21‖** (8.64)	1.66 ± 0.58‖*** (1.50)
Stage III ($n = 21$)	5.89 ± 2.98 (5.5)	16.98 ± 6.81 (17.5)	2.42 ± 1.35 (2.0)

†According to the clinical staging system of Durie and Salmon [18].
‡Patients wiht normal creatinine levels (see Patients and Methods section).
§Significantly different to stage II patients.
‖Significantly different to stage III patients.
$*P = 0.05$; $**P = 0.02$; $***P < 0.02$; $****P < 0.01$.

secrete B2m and immunoglobulin was found. Neither was there any correlation between B2m secretion and the class of immunoglobulin produced [29]. In the current study 12% of our patients with IgG or IgA myelomas had normal or subnormal serum B2m levels (i.e., $\leqslant 3$ μg/ml) in spite of high tumor mass, and were considered as low B2m producers. On the other hand, a similar percentage of patients was found with unexpected high serum B2m levels in comparison with their tumor mass and were considered as high B2m producers. Further *in vitro* and *in vivo* investigations will be necessary to confirm such data. At the present time, a search for any special clinical features that might identify these subgroups was impossible, considering the small number of patients in each subgroup.

In spite of a good relationship between serum B2m levels and myeloma cell mass, B2m was found not to be well related to disease activity. Indeed, after correction for the myeloma cell mass, no relationship was found with uric acid levels, acid phosphase activity and with the MWJ staging of prognostic value [19].

Serum beta-2-microglobulin (B2m) and measured B2m (M) to calculated B2m (CTD) ratios (B2m M/CTD ratios) in myeloma patients (MM): relation to clinical status

The most striking finding was the close relationship between the percentage of regression or progression of myeloma cell mass (i.e., T.B.M.C.) and that of both serum B2m levels ($P < 0.05$) and B2m M/CTD ratios ($P < 0.001$). As illustrated in Table 6, response to induction chemotherapy was marked by a significant regression of serum B2m levels, in complete agreement with regression of myeloma cell mass. Indeed, in responsive patients to chemotherapy, serum B2m levels remained closely related to residual tumor mass ($P < 0.001$). Of particular interest, the plateau-phase, following a $\geqslant 75\%$ regression of tumor mass, was characterized by very low and stable values of serum B2m levels: 91% of normal values (i.e., $\leqslant 2.6$ μg/ml); mean values $\pm$ S.D. = 2.16 ± 0.47 μg/ml. On the other hand, primary treatment failure with progressive disease or relapse was marked by a significant increase of serum B2m levels over the initial or remission levels. Of interest, in pure Bence-Jones myelomas response to induction chemotherapy, assessed on clinical improvement, correction of anaemia and hypoalbuminemia and regression of Bence-Jones protein, was marked by a significant fall of

Table 6. Relation of serum B2M to myeloma cell mass (TBMC) changes during chemotherapy in Stage III patients with multiple myeloma (MM)

Clinical status* (No. of available couples of SB2M-TBMC)	Serum B2m (μg/ml): mean values + S.D. (median values) (%of normal values $\leqslant 2.6$)	T.B.M.C. ($\times 10^{12}$): mean values $\pm$ S.D. (median values)
Initial staging (III) ($n = 16$)	5.94 ± 3.24 (4.4)(6%)	2.28 ± 0.34 (2.31)
Primary treatment failure with regression $< 50\%$ ($n = 39$)	3.52 ± 0.67 (3.4)†(23%)	1.39 ± 0.21 (1.30)†
Regression $\geqslant 50\%$ ($n = 52$)	2.34 ± 0.71 (2.2)‡(75%)	0.71 ± 0.37 (0.54)‡
$\geqslant 50\%$ ($n = 20$)	2.73 ± 0.91 (2.6)(50%)	1.11 ± 0.20 (1.07)
$< 75\%$	§	§
$\geqslant 75\%$ ($n = 32$)	2.16 ± 0.47 (2)§(91%)	0.40 ± 0.29 (0.48)§
Progressive disease/relapse ($n = 12$)	5.42 ± 1.93 (4.8)(0%)	2.45 ± 1.49 (2.09)

*Patients with normal creatinine levels and available sequential tumor mass (TBMC) (see Patients and Methods section).

†Significantly different to initial staging and relapse: $P < 0.001$.

‡Significantly different to initial staging/relapse: $P < 0.001$ and to regression $< 50\%$: $P < 0.001$ (TBMC).

§Significantly different to regression $> 50\% < 75\%$: $P < 0.01$ (Serum B2M) and $P < 0.001$ (TBMC).

serum B2m levels, followed by a plateau-phase in some patients. The interest of serum B2m to assess response to chemotherapy, plateau and relapse is well illustrated in Figs. 1 and 2 concerning 2 representative patients with IgA kappa and pure Bence–Jones lambda MM. On the other hand, serum B2m was found not to be valuable to detect early relapse in comparison with M-component. Indeed, in spite of the small number of patients we studied in relapse, serum B2m level and M-component level changes often occurred simultaneously.

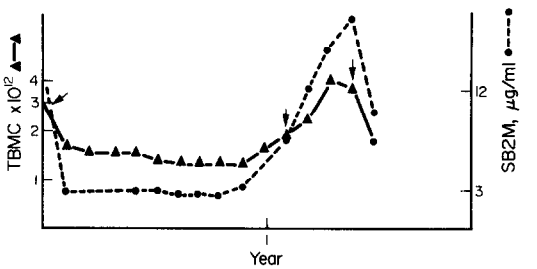

Fig. 1. Partial response with subsequent relapse in a patient with IgA kappa myeloma. Abbreviations used: T.B.M.C.: total body myeloma cell mass; SB2M: serum beta-2-microglobulin levels. ← indicates a new induction chemotherapy.

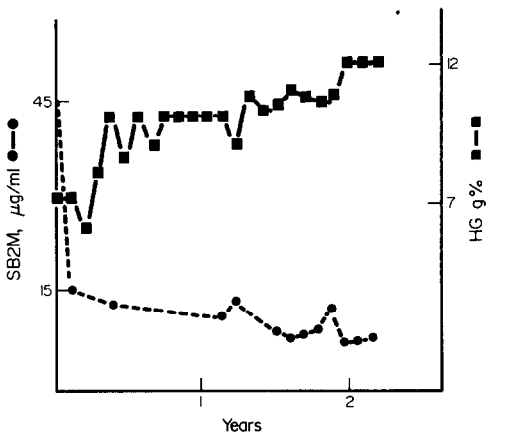

Fig. 2. Fast objective response to induction chemotherapy in a patient with high mass lambda myeloma (lambda protein < 500 mg/day in urine): fast decrease of serum beta-2-microglobulin levels (SB2M) associated with a fast correction of anemia (HG: hemoglobin levels).

DISCUSSION

Recent studies have shown that myeloma cell mass can be accurately predicted from extent of bone lesions, hemoglobin levels, serum calcium levels and the levels of monoclonal component in serum and urines [18], and that tumor cell mass changes could be detected from changes in monoclonal component production [18, 21]. In daily routine, however, assessment of myeloma cell mass and of tumor cell mass changes during treatment was less accurate, difficult or impossible in myelomas with pure Bence–Jones protein or in myeloma without monoclonal protein.

Several recent works have reported higher serum B2m levels in patients with MM than in normal controls [7–15] and a relation of serum B2m levels to initial staging. Furthermore, few works investigated interest of serum B2m for both discriminative diagnosis with benign monoclonal gammopathies (BMG) [11, 12] and prognosis of MM [14].

We have presented here results of a prospective study concerning serum B2m in 78 MM, in comparison with both normal controls and BMG, while considering age and renal status of all controls/patients and while considering myeloma cell mass. Indeed, in this study, B2m (in terms of serum B2m levels and B2m M/CTD ratios) was shown to be highly related to tumor cell mass and B2m changes during treatment to tumor cell mass changes during chemotherapy. This was well illustrated by normal B2m levels observed in patients without osteolytic lesion and/or low-cell mass and in patients in plateau following an objective response to chemotherapy. On the other hand, the highest values were observed in patients with extensive skeletal destruction and major fractures and/or high tumor mass at initial staging, or in patients in relapse or with primary treatment failure. Of major interest, and as already described for human myeloma cell lines [28, 29] and by Norfolk *et al.* [14] in patients with MM, no correlation was found between B2m secretion and the class of immunoglobulin produced. In particular, patients with pure Bence–Jones protein had similar serum B2m levels to IgG and IgA (after correction for cell mass) and demonstrated similar changes in response to chemotherapy. Therefore, it was logical to suggest that in such patients, B2m might be a better tool than Bence–Jones protein estimation for assessing both response to treatment and the plateau-phase.

Moreover, we have investigated the value of B2m in the discrimination of BMG and MM. Considering age, renal status and myeloma cell mass, as illustrated in Table 2, it was impossible to separate normal individuals, patients with BMG and patients with low-mass myeloma. Such results were not surprising, as recent studies have shown that only markers closely related to plasma-cell activity, such as [^{3}H]-thymidine labelling indices [30, 31] or acid phosphatase activity of myeloma cells [25, 32], were really helpful in the differential diagnosis of BMG and MM.

Up to now, myeloma has been characterized by different biological and cytological tumor markers (i.e., monoclonal components). Some of them are related to myeloma cell mass, such as osteoclast activating factor [33]. Others are more related to disease activity, independently of tumor mass, such as labelling index [30] and acid phosphatase activity of myeloma cells [32]. Both are useful for prognosis. Based on our own and previously published data, we can conclude that serum B2m is a simple and reliable non-specific marker of myeloma cell mass, useful in the management of multiple myeloma, especially pure Bence–Jones myelomas. Furthermore, we emphasized the interest of the B2m M/CTD ratio in patients with impaired renal function, as previously described by Cassuto *et al.* [12]. Finally, the total serum B2m was found to be of poor practical value and appeared to have no especial merit as a discriminant compared to serum B2m. This is easily explained by the fact that the diffusion compartment of B2m is 2 to 4-fold larger than plasma volume [26]. Further investigations (*in vitro* studies) will be necessary to clarify the real significance of low/high B2m production observed in some patients with MM.

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