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Prognostic Significance of Pretreatment Serum β_2-Microglobulin Levels in Multiple Myeloma

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Abstract—*Pretreatment serum β_2m levels were estimated in 65 patients with multiple myeloma. After correction for changes in renal function, the level of β_2m attributable to multiple myeloma (β_2m-m) no longer correlated with the serum creatinine, but showed a strong correlation with the total body myeloma cell mass* (P = 0.002). *There was an inverse correlation between β_2m-m and the Karnofsky performance status of patients at presentation* (P = 0.001). *Patients with a pretreatment β_2m-m level of less than the median value of* 2.94 mg/l *survived significantly longer than those with a raised level* (P = 0.0008).

INTRODUCTION

β_2-MICROGLOBULIN (β_2m) is the light chain of histocompatibility antigens present on the membranes of most cells [1]. Free β_2m is released into the blood and other body fluids as a result of membrane turnover [2]. The molecular weight of β_2m is 11,800 daltons, which enables it to be freely filtered by the renal glomeruli and then catabolised by the tubules [3]. Serum levels of β_2m have been shown to rise as glomerular filtration rate falls [4]. Normal levels of serum β_2m rise slowly with age but are usually less than 3 mg/l, even in the elderly [5, 6].

Elevated serum β_2m levels have been reported in a variety of neoplastic and non-neoplastic diseases [7–13]. In 1980 Norfolk *et al.* published a preliminary report suggesting that pretreatment serum β_2m multiple myeloma may correlate with initial tumour cell mass and prognosis [14].

This paper attempts to study further the relationship between pretreatment β_2m and prognosis in a group of patients treated in a uniform manner, after correction of the β_2m levels for changes in renal function.

MATERIALS AND METHODS

Serum β_2m levels were measured in 65 patients with multiple myeloma, prior to starting chemotherapy. All patients fulfilled the diagnostic criteria of the Chronic Leukaemia/Myeloma Task Force [15]. There were 27 patients with IgG myeloma, 15 IgA, 17 Bence Jones only and 6 with non-secretory myelomas. Patients were staged according to the classification of Durie and Salmon [16]. Five patients had stage I disease, 21 stage II and 39 stage III. Thirteen patients were classified as stage B because of poor renal function (creatinine >0.18 mmol/l). Total body myeloma cell mass was assessed according to the programmes of Salmon and Wampler [17] and Durie *et al.* [18]. Bone changes seen on skeletal survey were graded as described by Durie and Salmon [16]. The Karnofsky scale was used to assess performance status [19].

Patients were treated every 4–6 weeks with combination chemotherapy (MCP), consisting of cyclophosphamide 500 mg/m^2 i.v. day 1, oral melphalan 6 mg/m^2 and prednisolone 60 mg/m^2 days 1–4 inclusive. Patients were reassessed after 1 yr. Patients who showed an objective response to therapy (reduction in myeloma protein of greater than 50%) stopped all therapy until relapse, when they were again treated with MCP. Patients who showed less than a 50% drop in their M-protein continued on chemotherapy until relapse. Patients with non-secretory myeloma stopped treatment at 1 yr, unless there was clear evidence of progressive disease on X-ray. Patients resistant to therapy with MCP were treated with either a combination of adriamycin and BCNU or vindesine and prednisolone. Patients have been followed for a median of 36 months (range 12–72 months).

Serum levels of β_2m were measured by radioimmunoassay using the Phadebas beta-2-

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microtest (Pharmacia Diagnostic, Uppsala, Sweden).

Since serum β_2m levels rise with decreasing renal function and renal complications are relatively common in patients with myeloma, allowance must be made for the contribution of poor renal function to the observed β_2m levels (β_2m-o). The level of β_2m expected for the degree of renal dysfunction (β_2m-r) was calculated from the serum creatinine level as described by Cassuto *et al.* [12], using the following formula:

$$\log_e \beta_2\text{m-r } (\mu g/ml) = 3.834 - 5.96Y + 2.49Y^2 - 0.476^3 + 0.0252Y^4,$$

where $Y = \log_e$ serum creatinine (μg/ml). The levels of β_2m attributable to myeloma (β_2m-m) was obtained by subtracting β_2m-r from β_2m-o:

$$\beta_2\text{m-m} = \beta_2\text{m-o} - \beta_2\text{m-r}.$$

Statistics

The correlation of β_2m-m with possible prognostic factors at presentation was performed by the Kendal rank correlation coefficient. Life table survival curves were compared using the log rank test [20].

RESULTS

Prior to the correction of β_2m levels for the effect of renal function, there was a strong correlation between β_2m-o and serum creatinine ($P = 0.001$). However, after correction for renal function, the β_2m-m value no longer correlated with serum creatinine. A statistically significant correlation was found between the β_2m-m levels and total body myeloma cell mass ($P < 0.002$) and an inverse correlation with Karnofsky performance status ($P < 0.001$). No correlation, however, was found between β_2m-m and the height of the M-band or degree of bone destruction assessed by skeletal survey (Table 1).

The median β_2m-m level was 2.94 mg/l. The survival of 32 patients with a β_2m-m of 2.94 mg/l or below was significantly better than the 33 patients with a higher level ($P = 0.0008$; see Fig.

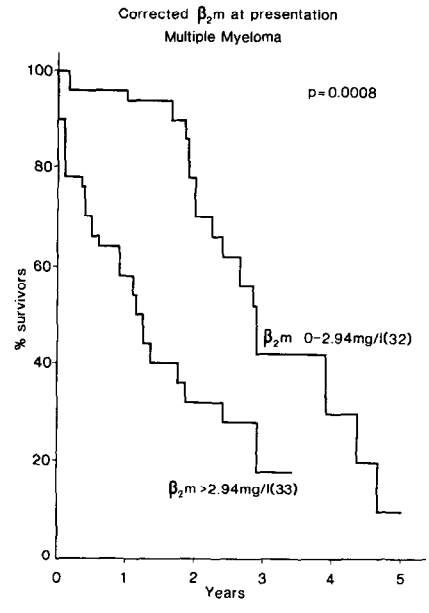

Fig. 1. The effect of pretreatment β_2m-m on survival in 65 patients with multiple myeloma.

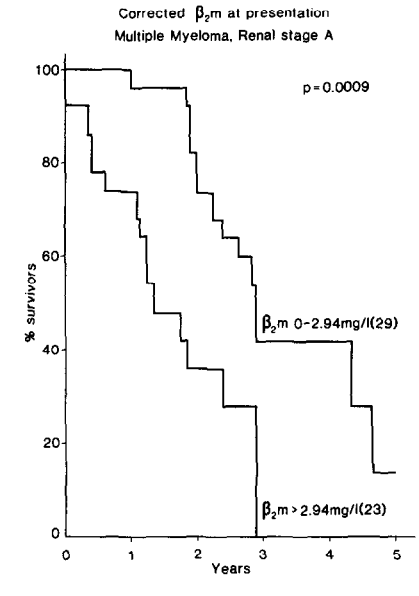

Fig. 2. The effect of pretreatment β_2m-m on survival in 52 patients with renal stage A myeloma (serum creatinine <0.18 mmol/l).

Table 1. Correlation of levels of serum β_2m-m with other variables at presentation of multiple myeloma

Variable	No. of patients	τ*	P
Karnofsky performance status	65	-0.3	<0.001
Total body myeloma cell mass	59	0.3	<0.002
Myeloma protein band height	42	0.02	N.S.
Serum creatinine	65	0.03	N.S.
X-ray change†	65	0.1	N.S.

*Kendal rank correlation coefficient.

†Scale: 0 = normal bones; 1 = osteoporosis; 2 = lytic bone lesions; 3 = extensive skeletal destruction and major fractures.

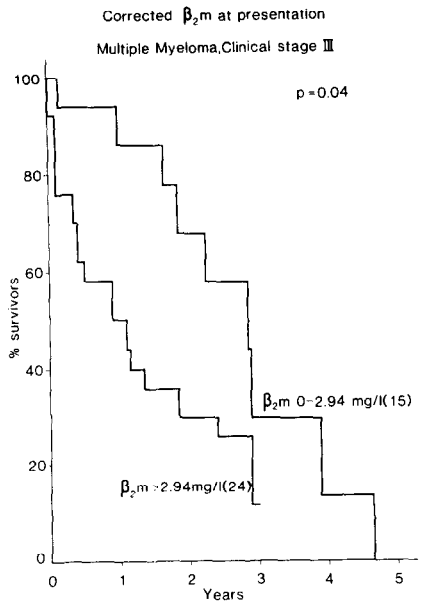

Fig. 3. The effect of pretreatment β_2m-m on survival in 39 patients with stage III myeloma.

1). Of the 52 patients with a relatively normal renal function (Salmon and Durie, group A, serum creatinine <0.18 mmol/l), the 29 patients with a β_2m-m of 2.94 mg/l or less had a significantly longer survival ($P = 0.0009$) than the 23 patients with an elevated level (see Fig. 2). β_2m-m level was not of prognostic significance for the 13 patients with impaired renal function (Salmon and Durie [16], group B, serum creatinine >0.18 mmol/l).

The prognostic significance of β_2m-m levels in stages I and II disease is difficult to assess because of the low numbers within each stage; however, the 15 stage III patients with β_2m-m levels of 2.94 mg/l or below survived significantly longer than the 24 patients with a β_2m level of >2.94 mg/l ($P = 0.04$) (see Fig. 3).

DISCUSSION

Renal function is an important prognostic factor for patients with multiple myeloma [16]. The relationship of serum β_2m levels to renal function makes it important to correct for the contribution due to renal impairment before assessing the prognostic value of pretreatment serum β_2m. Otherwise the measured serum β_2m level may simply reflect the prognostic significance of a test of renal function. The observed β_2m level (β_2m-o) correlated closely with serum creatinine, but after correction using Cassuto's formula, β_2m-m levels no longer related to the serum creatinine.

The pretreatment β_2m-m levels showed a strong correlation with total body myeloma cell mass and an inverse correlation with Karnofsky performance status. In patients suffering from multiple myeloma, an increase in tumour cell mass is likely to be associated with a decrease in performance status. Norfolk *et al.* [14] demonstrated that the uncorrected β_2m levels related to the clinical stage of disease. However, advancing stage is usually associated with a higher proportion of patients with impaired renal function [21]. Bataille *et al.* [22] attempted to overcome this problem by correcting for the effect of renal function using the formula proposed by Cassuto *et al.* [12], and found a strong correlation between the corrected β_2m level and the calculated total body myeloma cell mass. The correlation of β_2m with stage of disease has also been demonstrated in Hodgkin's disease and non-Hodgkin's lymphoma [12, 23, 24].

In the preliminary report of Norfolk *et al.* [14], the pretreatment uncorrected β_2m level was of prognostic significance in the 36 patients studied. Details of treatment received were not given. In this study of 65 patients treated in a uniform manner by the same physician (JHS), the β_2m-m level was of clear prognostic value for the group as a whole, for patients with relatively normal renal function and in stage III disease. The ability to divide stage III disease is important, since the Durie and Salmon staging classification allocates a high proportion of cases into this group.

This study confirms the preliminary report of Norfolk *et al.* [14] that pretreatment serum β_2m is of prognostic significance in multiple myeloma, even after correction for renal impairment.

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