The prognostic value of serum $\beta_2$ microglobulin compared with other presentation features in myelomatosis

(A report to the Medical Research Council's Working Party on Leukaemia in Adults)*

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Summary The levels of serum $\beta_2$ microglobulin, blood urea concentration, serum creatinine, haemoglobin and performance status have been measured in 476 patients in the Medical Research Council's 4th trial for myelomatosis. Levels of serum $\beta_2$ microglobulin were also subsequently measured in 208 patients who achieved a stable "plateau" condition. Serum $\beta_2$ microglobulin levels, uncorrected for serum creatinine, were found to be the single most powerful prognostic variable available at presentation. Multivariate analysis showed that only the addition of haemoglobin levels could improve upon this and the improvement, though statistically significant ($P=0.006$), appeared to be of much less clinical value. The prognostic value of serum $\beta_2$ microglobulin at plateau appeared to be equally large for a given difference in value, but the variability between patients was much less at that time. Serum $\beta_2$ microglobulin would appear to be a key measurement for assessing the prognosis and response to treatment in patients with myelomatosis.

There have been a large number of papers on prognostic factors for myelomatosis and at least two grouping systems (Durie & Salmon, 1975; Medical Research Council, 1980) using multiple factors have been devised. These studies indicate that the two most important presenting factors influencing survival in myelomatosis are measures of renal function such as serum urea or creatinine and the haemoglobin level. More recently a number of reports have demonstrated that serum levels of $\beta_2$ microglobulin are also important in predicting the survival of patients with myelomatosis (Norfolk et al., 1980, Child et al., 1983, Bataille et al., 1984). $\beta_2$ microglobulin is a small protein (Mol. wt 11,800) that forms the common chain of the class I major histocompatibility complex on the cell surface (Cresswell et al., 1974). The role of $\beta_2$ microglobulin in the broader context of immunology and immunopathology has been reviewed recently by Messner (1984). In disease the serum levels of $\beta_2$ microglobulin are influenced by two main factors, the production rate and its clearance from the blood by glomerular filtration; both factors can be abnormal coincidentally or independently in myelomatosis.

Previous studies have been performed on relatively small numbers of patients and further information on the relationship of $\beta_2$ microglobulin and previously identified prognostic factors is desirable. Bataille et al. (1984) have discussed the relationship between serum $\beta_2$ microglobulin and the staging system devised by Durie & Salmon (1975), and Child et al. (1983) have done a more complete multivariate analysis, but this was based on only 64 patients. Also the value of followup measurements has not been assessed on large numbers of patients.

The major prognostic variables have been measured on a large proportion of patients in the Medical Research Council's 4th trial on myelomatosis and the combined value of these variables have been assessed in this paper.

• Patients and methods

This analysis is based on the 476 patients out of

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530 randomised patients in the MRC's 4th trial for myelomatosis for whom presentation measurement of all of the following variables were available: haemoglobin, blood urea concentration, serum creatinine, performance status, and serum $\beta_2$ microglobulin ($s$-$\beta_2m$). The trial began in March 1980 and follow-up time ranged from 23 to 47 months (median 35 months). Details of the trial and the treatment arms are reported elsewhere (Medical Research Council, 1984 and in preparation, 1985). A total of 268 patients subsequently achieved a stable "plateau" condition. Until 1st October 1983 patients were randomised to stop active cytotoxic therapy after 6 months on plateau or to receive a further year's treatment. The level of $s$-$\beta_2m$ was measured at this time on 208 of the 226 patients randomized at plateau and its predictive value on further follow-up has been studied.

The $s$-$\beta_2m$ levels at presentation were measured in duplicate by a radioimmunoassay using the Phadebas $\beta_2$-micro test 100 supplied by Pharmacia Diagnostics AB, Uppsala, Sweden. Measurements of $s$-$\beta_2m$ on the plateau follow-up samples were made by radial immunodiffusion using a goat antihuman $\beta_2m$ antiserum purchased from Atlantic Antibodies. The relationship between the radioimmunoassay ($x$) and the radial immunodiffusion method ($y$) − determined on 108 samples is given by the equation:

$$y = 1.01x + 0.8$$

and the correlation coefficient was 0.989.

Results

The performance of the major prognostic factors, considered separately, are shown in Table I. The largest $\chi^2$ values (and hence greatest predictive power) were obtained from the uncorrected $s$-$\beta_2m$ values ($\chi^2 = 58.2$, $P < 0.0001$). The differences are illustrated graphically in Figure 1. We found the correction factor for renal failure recommended by Cassuto et al. (1978) to be inaccurate and unnecessarily complicated. Study of 50 individuals with non-neoplastic conditions who were attending hospital for renal disease and who possessed varying degrees of renal failure indicated that a simple linear relationship on a log-log scale between serum creatinine and $s$-$\beta_2m$ was adequate ($R^2 = 0.95$). The estimated regression line was

$$\log_{10}(s$-$\beta_2m) = 1.77 + 1.15 \log_{10}(s$-creat)$$

where $s$-$\beta_2m$ was measured in mg/l$^{-1}$ and creatinine in mM (Figure 2). This simple correction is of a similar form to that originally proposed by Revillard & Vincent (1978) who obtained

$$\log_{10}(s$-$\beta_2m) = -0.29 + 0.81 \log_{10}(s$-creat)$$

(whence creatinine is expressed in mg 100 ml$^{-1}$).

Corrected $s$-$\beta_2m$ levels were computed by subtracting this value from the observed levels. This led to negative values in some cases, as would be
Table I  Survival according to the major prognostic factors

| Variable     | Levels      | N  | O  | O/E |
|--------------|-------------|----|----|-----|
| s-β2m        | <4 mg l⁻¹   | 144| 64 | 0.61|
|              | 4-5.9       | 94 | 51 | 0.84|
|              | 6-9.9       | 128| 86 | 1.17|
|              | 10-19.9     | 57 | 40 | 1.54|
|              | >20         | 53 | 42 | 2.42|

χ² = 58.21, P < 0.0001
χ² (in patients with creatinine < 130 mM) = 10.41, P = 0.001
χ² (in patients with creatinine > 130 mM) = 24.15, P < 0.0001

s-β2m corrected (see text)
< 0 mg l⁻¹  155| 77 | 0.77|
0-1.9       | 140| 83 | 0.92|
2-3.9       | 65 | 41 | 1.12|
4-5.9       | 48 | 29 | 1.07|
>6          | 68 | 53 | 1.85|

χ² = 22.69, P < 0.0001
χ² (in patients with creatinine < 130 mM) = 9.48, P = 0.002
χ² (in patients with creatinine > 130 mM) = 11.97, P = 0.0005

Prognostic groups (see MRC 1980)
good         | 111| 44 | 0.54|
intermediate | 267| 170| 1.06|
poor         | 98 | 69 | 1.67|

χ² = 36.05, P < 0.0001

Blood urea concentration
< 8 mM       | 317| 171| 0.82|
8-14.9       | 99 | 67 | 1.27|
> 15         | 60 | 45 | 2.11|

χ² = 36.31, P < 0.0001

Serum creatinine
< 130 mM     | 278| 147| 0.80|
130-199      | 109| 71 | 1.10|
> 200        | 89 | 65 | 1.88|

χ² = 32.53, P < 0.0001

Haemoglobin
< 75 g l⁻¹   | 61 | 43 | 1.69|
75-99        | 124| 92 | 1.48|
> 100        | 291| 148| 0.76|

χ² = 35.84, P < 0.0001

The table gives numbers of patients (N), numbers of deaths (O), and the observed-to-expected ratio (O/E) for each level of each factor. A χ² for trend across levels (1 df) is also given.

expected since the corrected value gives the excess over that which would be expected in a normal population and statistical fluctuations imply this will be negative some of the time. These corrected levels were found to be much less predictive of survival than the uncorrected values (χ² = 22.69, Table I). The other major prognostic factors, e.g. blood urea (or serum creatinine), haemoglobin, and the composite prognostic groups based on urea, haemoglobin and performance status (Medical Research Council, 1980) were also much less predictive than s-β2m (Table I). These classical factors all had about the same χ² (trend) values, but of them, the prognostic grouping was probably the most useful, because of the more even splitting of the patients into different groups.

The prognostic value of s-β2m was seen in all three prognostic groups (Table II), and in fact was most apparent in the good and intermediate prognostic groups (χ² = 13.30, P = 0.0003 and χ² = 12.38, P = 0.0004, respectively).

Some effect was also seen in the poor prognosis group (χ² = 4.81, P = 0.03).

Longer term predictive value
It has previously been observed (Buckman et al., 1982; Medical Research Council, 1984) that prognostic variables in myelomatosis, especially those related to renal function, are of less prognostic value in long term follow-up than in the period immediately after diagnosis. The χ² trend
Table II  The predictive value of s-β2m for survival in different prognostic groups

| Good prognosis patients | N | O | O/E |
|-------------------------|---|---|-----|
| Level                   |   |   |     |
| <4 mgL⁻¹                | 63| 21| 0.77|
| 4–5.9                   | 31| 11| 0.93|
| 6–9.9                   | 11|  7| 1.94|
| 10–19.9                 |  5|  4| 3.47|
| >20                     |  1|  1|18.08|

χ² (trend) = 13.30, P = 0.0003

Intermediate prognosis patients

| Level               | N | O | O/E |
|---------------------|---|---|-----|
| <4 mgL⁻¹            | 74| 39| 0.70|
| 4–5.9               | 58| 37| 0.97|
| 6–9.9               | 87| 61|1.14|
| 10–19.9             | 29| 18|1.16|
| >20                 | 19| 15|2.07|

χ² (trend) = 12.38, P = 0.0004

Poor prognosis patients

| Level               | N | O | O/E |
|---------------------|---|---|-----|
| <4 mgL⁻¹            |  7|  4| 0.70|
| 4–5.9               |  5|  3| 0.77|
| 6–9.9               | 30| 18| 0.72|
| 10–19.9             | 23| 18| 1.13|
| >20                 | 33| 26| 1.40|

χ² (trend) = 4.81, P = 0.03

Adjusted summary χ² (trend) = 24.80, P < 0.0001

Table III  The predictive value of various presenting features for survival in the IVth Myelomatosis trial

| Feature           | χ² (trend) all patients | χ² (trend) patients surviving at least 1 year |
|-------------------|-------------------------|---------------------------------------------|
| Blood urea        | 36.31                   | 4.12                                        |
| Serum creatinine  | 32.53                   | 3.92                                        |
| Haemoglobin       | 35.84                   | 7.22                                        |
| Prognostic group  | 36.05                   | 5.07                                        |
| s-β2m (uncorrected) | 58.21                 | 8.00                                        |
| s-β2m (corrected) | 22.69                   | 4.31                                        |

values are shown for prediction of survival after 1 year in all patients who survived that long in Table III. Uncorrected s-β2m (χ² = 8.00, P = 0.005) and haemoglobin (χ² = 7.22, P = 0.007) are seen to be the most important predictors.

Follow-up measurements of s-β2m

Of the 268 patients achieving a stable plateau phase in their disease, a total of 226 were re-randomized for maintenance therapy. Two hundred and eight had s-β2m measured at the time of the second randomization. The value of this measurement in determining subsequent survival is shown in Table IV and Figure 3. The follow-up samples were analysed both as absolute levels and as a percentage of the presentation level. The absolute levels were predictive of subsequent survival (χ² = 11.35, P = 0.0008) whereas the percentage fall conveyed no prognostic information (χ² = 0.79, P = 0.4).

Table IV  Prognostic value of s-β2m level taken at “plateau” phase

| Variable                | Levels               | N | O | O/E |
|-------------------------|----------------------|---|---|-----|
| s-β2m                   | <3 mgL⁻¹             | 37|  9| 0.53|
| (uncorrected)           | (at plateau)         |   |   |     |
| 3–3.9                   | 81                   | 30|  94|
| 4–4.9                   | 34                   | 11|  88|
| >5                     | 56                   | 25|  1.83|
| ratio of s-β2m          | <60%                 | 48| 15|  0.86|
| at plateau to           |                      |   |   |     |
| presentation level      | 60-100%              | 77| 26|  0.96|
| >100%                  | 79                   | 32|  1.12|

χ² = 11.35, P = 0.0008

Abbreviations are as in Table I.

Figure 3 Survival probabilities according to uncorrected levels of serum β2-microglobulin measured at plateau phase in 208 patients who achieved this condition. Numbers in parentheses indicate numbers of patients in each group. χ² (trend) = 12.52; P = 0.0004.

The levels were generally less varied than at presentation and the number of patients and follow-up time was less than for presentation analyses so that it is not possible to compare χ² values to judge the relative usefulness of the follow-up measurement compared to the presentation.
sample. However the regression coefficient attached to log(s-β2m) is not significantly different in the presentation and follow-up samples (z = 1.45, P = 0.15) (Table V, Model III).

**Multivariate analysis**

The relative merits of s-β2m, creatinine, haemoglobin and performance status were studied by means of a stepwise proportional hazards regression model. The levels of s-β2m and creatinine were put on a logarithmic scale (base 10), haemoglobin levels were on a linear scale, and performance status was coded as a dichotomy: asymptomatic or minimal symptoms vs restricted activity or bedridden. The results are summarized in Table V. Levels of s-β2m clearly emerge as the most important prognostic factor and are highly significant in the univariate model (Model I, χ² = 62.06, P < 0.0001). The regression coefficient for log(S-β2m) was 1.366 suggesting that a doubling of S-β2m leads to a 50% increase in the rate of death. The only other variable which provided additional information was haemoglobin (Model II, χ² = 7.50, P = 0.006). Although clearly statistically significant, this improvement would not appear to be sufficiently great to be clinically helpful, and our data suggest that measured s-β2m levels alone are likely to be enough to predict the prognosis in the majority of patients. The estimated predictor of prognosis took the form

\[ 1.156 \log(s-\beta2m) - 0.007 \text{Hb} \]

with large values implying a poorer prognosis. The median value was 0.13 and the upper and lower quartiles were 0.50 and −0.23 respectively.

**Discussion**

The earliest studies of the levels of s-β2m in benign and malignant disease found that s-β2m was frequently raised in myelomatosis (Evrin & Wibell, 1973, Shuster et al., 1976, Kin et al., 1977). Norfolk et al. (1980) reported that in 37 patients the pretreatment level of s-β2m was an important prognostic factor. They took 4 mg/l⁻¹ as a discriminant level and found that patients presenting with a s-β2m > 4 mg/l⁻¹ had a median survival of 6 months, and those < 4 mg/l⁻¹ had a median survival of 15 months. They confirmed the earlier observations by a survey of 156 patients and drew attention to the combined influences of a raised s-β2m due to renal insufficiency and hyperproduction. Revillard & Vincent (1976, 1978) observed a simple linear relationship on a logarithmic scale between serum creatinine and s-β2m in patients with non-neoplastic conditions. Cassuto et al. (1978) devised a polynomial equation to correct for the GFR and observed that in myelomatosis s-β2m levels were increased in patients with a high tumour mass. Several investigators (Bataille et al., 1982, 1984, Scarffe et al., 1983) have used Cassuto’s correction when examining the relationship between s-β2m and prognosis in myelomatosis. Others have reported the prognostic value of the uncorrected s-β2m level and have shown that it provides information which was not obtainable from previously recognized prognostic factors (Child et al., 1983; Bataille et al., 1983).

Sequential measurements of s-β2m have been reported to carry prognostic information (Child et al., 1983; Bataille et al., 1984). Bataille et al. (1984) observed s-β2m levels closely correlated with the

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**Table V** Summary of the multivariate analysis

| Variable                      | Coefficient | Standard error | χ² (to remove) |
|-------------------------------|------------|----------------|----------------|
| Model I                       |            |                |                |
| log(s-β2m)                    | 1.366      | 0.166          | 62.06          |
| haemoglobin                   | 1.156      | 0.186          | 36.01          |
| performance status            | χ² to enter=2.81 |
| Model II                      |            |                |                |
| log(s-creat)                  |            |                |                |
| Model III                     |            |                |                |
| log(s-β2m) at plateau         | 2.179      | 0.536          | 13.03          |
| (N = 208)                     |            |                |                |

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chemotherapy response in 70 out of 80 patients and was comparable with the assessment of response based on change of paraprotein level. Norfolk et al. (1980), Child et al. (1983), Bataille et al. (1984) and Garewal et al. (1984) have observed that the plateau phase of the disease is associated with s-β2m levels that tend to stabilize, usually below 6 mg{l}^{-1}. The terminal events in myelomatosis have been observed to be associated with an upswing in the levels of s-β2m (Norfolk et al., 1980, Bataille et al., 1984).

Our studies confirm these observations, both at initial diagnosis and during follow-up. We have found that the presentation level of serum β2 microglobulin is the single most important prognostic variable currently available. The uncorrected values are more predictive than the corrected ones, probably because they include a contribution due to renal failure, as assessed by elevated serum creatinine which itself has a negative influence on survival. Little further information appears to be available from simple measurements of renal function, but haemoglobin levels do provide some further independent prognostic information. It should be noted, however, that special attention was paid to management of renal failure in the trial analysed in this paper. Patients in this trial presenting in renal failure fared better than equivalent patients in earlier trials (Medical Research Council, 1984).

The variability of s-β2m at follow-up is much less than at presentation, but the prognostic significance of specific levels appears to be similar to that at presentation. We are encouraged by our findings in patients assessed when in plateau phase and by reports in the literature that sequential s-β2m levels can be used to monitor the disease (Norfolk et al., 1980; Bataille et al., 1984). Regularly repeated measurements of s-β2m during follow-up are included in the Medical Research Council’s current (fifth) trial. Our objective is to relate the rate of change of s-β2m to the evolution of the disease and to investigate its value as an indicator of response to treatment.

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