Evaluation of serum β2-microglobulin as a prognostic indicator in myelomatosis

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Summary Serum β2-microglobulin (β2-m) is frequently increased in patients with myelomatosis. The possibility that it could provide a biochemical indicator of prognosis was tested in a group of 129 patients from 3 centres, all serum analyses being carried out in one laboratory by radioimmunoassay. A strong association between the pretreatment serum β2-m level and survival was demonstrated, the data for the 2 main subgroups being very similar. In further detailed analyses of 64 patients, serum β2-m proved to be a stronger indicator of prognosis than current "standard" clinical and laboratory data, including stage determined by the method of Durie and Salmon and the combination of haemoglobin level and blood urea. The association between serum β2-m and survival remained close after treatment as indicated by the findings at one year. The serum β2-m in myeloma reflects the tumour mass and also reduced glomerular filtration when renal failure supervenes. It is concluded that the β2-m is a powerful prognostic indicator in myelomatosis and of considerable value in the investigation of patients with the disease.

Beta 2-microglobulin (β 2-m) forms the light chain moiety of HL-A (loci A, B, C). Cell membrane turnover is the principal source of free β2-m in blood plasma and body fluids (Cresswell et al., 1974). The serum level is raised in a variety of malignancies and appears to be a reflection of tumour load in many patients with lymphomas and myelomatosis, (Amlot et al., 1978; Child et al., 1980; Cooper et al., 1981; Bataille et al., 1981; Norfolk et al., 1980), though its exact cellular origin is as yet uncertain.

It has been suggested that serum β2-m may be of value as a prognostic indicator in myelomatosis (Norfolk et al., 1980). Sixty-four patients with this disease presenting to two centres were therefore investigated in order to compare the prognostic information provided by this single protein measurement with that obtained from existing staging systems, other clinical features and "standard" laboratory measurements. To confirm the results relating survival to serum β2-m an additional group of 65 patients from a third centre were investigated.

Patients and methods

All new patients diagnosed as having myelomatosis at Leeds General Infirmary between January 1975 and April 1981 (48 patients) and at Bradford Royal Infirmary between November 1979 and April 1981 (16 patients), who fulfilled the accepted diagnostic criteria for myelomatosis (Chronic Leukaemia—Myeloma Task Force, 1973) were included in the analyses. These 64 patients are referred to as Group A. A complementary study was made using data on 65 patients with myelomatosis under the care of the Department of Medical Oncology, Christie Hospital and Holt Radium Institute, Manchester, who presented between August 1974 and December 1979. These patients are referred to as Group B. The stage and renal grade for each patient were determined according to the system of Durie and Salmon (1975); the distribution within the 2 main sub-groups is shown in Table I. The Phadebas β2-Micro test (Pharmacia, Uppsala, Sweden) was used to measure serum β2-m, which rises slightly with age but in normal people it rarely exceeds 3 mg l⁻¹. This level has been taken as the upper limit of normal appropriate for the age of patients studied. Measurements were made before treatment was started and at 3, 6 and 12 months from diagnosis. All serum β2-m measurements were carried out in one laboratory (Unit for Cancer Research, University of Leeds). The details of treatment are not relevant but most patients were treated with various combinations of melphalan, cyclophosphamide and prednisolone.

Statistical methods:

A multivariate regression model (Cox, 1972) was
Table I Distribution of patients according to serum $\beta_2$-m levels, stage* and renal grade*

| Stage and renal grade | Group A (Leeds & Bradford) | Group B (Manchester) |
|-----------------------|-----------------------------|----------------------|
|                       | Serum $\beta_2$-m mg l$^{-1}$ | Serum $\beta_2$-m mg l$^{-1}$ | |
| $\leq 4.0$            | 4.1–10.0                     | $>10.0$               | |
| IA                    | 15                           | 0                    | 0 |
| IB                    | 0                            | 0                    | 0 |
| IIA                   | 14                           | 5                    | 1 |
| IIIB                  | 3                             | 7                    | 2 |

*System of Durie & Salmon (1975).

Results

The distribution of patients according to serum $\beta_2$-m levels (in 3 bands because of the relatively small numbers per stage) for each stage and renal grade is presented in Table I. A tendency for serum $\beta_2$-m to increase with stage is seen, all 20 patients with stage I disease having serum $\beta_2$-m levels $\leq 4.0$ mg l$^{-1}$ and 55 of 67 patients with stage III disease having serum $\beta_2$-m levels $>4$ mg l$^{-1}$.

Serum $\beta_2$-m vs. survival:

The levels of serum $\beta_2$-m at first presentation and the median survival of subsets, designated by the initial $\beta_2$-m are shown in Table II. There was a close similarity in the pattern of results for the 2 patient groups. The remainder of the analyses refer to Group A patients.

Table II Median survival in relation to pre-treatment serum $\beta_2$-m levels

| Serum $\beta_2$-m mg l$^{-1}$ | $\leq 3.0$ | 3.1–6.0 | 6.1–10.0 | $>10.0$ | |
|-------------------------------|-----------|---------|---------|---------|
| Group A (64 patients)         | 25        | 16      | 8       | 15      | |
| Median survival (months)      | 50        | 22      | 18      | 11      | |
| Group B (65 patients)         | 14        | 26      | 7       | 18      | |
| Median survival (months)      | 35        | 24      | 16      | 11      | |

The probability of survival given the initial value of serum $\beta_2$-m as calculated from Cox's regression model is shown in Table III. The figure shows the estimated survival of patients with "high" (12.0 mg l$^{-1}$) and "low" (2.5 mg l$^{-1}$) $\beta_2$-m levels at diagnosis with the 95% confidence bands.

Comparison between serum $\beta_2$-m and standard data:

The relationship between the pre-treatment serum $\beta_2$-m and survival was compared with standard clinical and laboratory data obtained at presentation. The significance levels of these associations are presented in Table IV which shows that the serum $\beta_2$-m level had the strongest relationship with survival. Once allowance for $\beta_2$-m had been made, the standard data (sex, light chain class, age, stage, stage and renal grade, blood urea, haemoglobin level) contributed no further prognostic information (i.e. statistically non-significant). The effect of adding serum $\beta_2$-m to the
SERUM $\beta$-2-MICROGLOBULIN IN MYELOMATOSIS 113

Table III  Probability of surviving (95% confidence limits) given the initial value of serum $\beta$2-m as calculated from Cox's regression model

| Initial value of serum $\beta$2-m mg l$^{-1}$ | Survival time |
|---------------------------------------------|---------------|
|                                             | 2.0 | 4.5 | 8.0 | 15.0 |
| 5 months                                    | 0.95 | 0.89 | 0.82 | 0.68 |
|                                             | (0.98,0.88) | (0.95,0.80) | (0.90,0.68) | (0.82,0.47) |
| 12                                          | 0.91 | 0.80 | 0.68 | 0.48 |
|                                             | (0.96,0.81) | (0.88,0.68) | (0.79,0.52) | (0.66,0.26) |
| 18                                          | 0.80 | 0.60 | 0.40 | 0.17 |
|                                             | (0.89,0.65) | (0.72,0.45) | (0.55,0.24) | (0.36,0.05) |
| 24                                          | 0.71 | 0.46 | 0.24 | 0.07 |
|                                             | (0.83,0.53) | (0.60,0.30) | (0.39,0.12) | (0.12,0.01) |
| 38                                          | 0.64 | 0.36 | 0.16 | 0.03 |
|                                             | (0.78,0.44) | (0.52,0.20) | (0.32,0.02) | (0.15,0.001) |
| 60                                          | 0.40 | 0.12 | 0.02 | 0.0 |
|                                             | (0.65,0.14) | (0.35,0.01) | (0.17,0.003) | (0.05,0.00) |

Figure 1  Estimated survival of patients with “high” (12.0 mg l$^{-1}$) and “low” (2.5 mg l$^{-1}$) serum $\beta$2-m levels at diagnosis, with 95% confidence bands.

model after accounting for the standard data is shown in Table V. Haemoglobin and blood urea were both, as expected, indicators of prognosis but they were not individually or together as powerful as serum $\beta$2-m; the addition of serum $\beta$2-m to the model gave a significant result even after haemoglobin and blood urea had been taken into account. Similarly, clinical stage and survival showed a relationship which was significantly enhanced by the addition of serum $\beta$2-m (Table V). By including the serial measurement of serum $\beta$2-m made at 3, 6 and 12 months after diagnosis as well as the initial measurement, a highly significant result was obtained ($P < 0.001$) but only slightly more powerful than that using the initial measurement alone. The measurements of serum $\beta$2-m alone, at 12 months from diagnosis, in Cox's model carried significant prognostic information ($P < 0.005$).

Discussion

The staging of myelomatosis has, in recent years, been dominated by the system of Durie and Salmon (1975) which has been shown to give a good correlation between stage and survival (Woodruff et al., 1979) but which has been criticised because it allocates a high proportion of cases to Stage III
Table V Significance of including serum β2-m after clinical features/laboratory measurements have been accounted for.

|                          | P       |
|--------------------------|---------|
| Age + serum β2-m         | <0.001  |
| Stage* + serum β2-m      | <0.001  |
| Stage* and renal grade* + serum β2-m | <0.001 |
| Blood urea + serum β2-m  | <0.001  |
| Haemoglobin + serum β2-m | <0.005  |
| Blood urea + haemoglobin + serum β2-m | <0.01 |

*System of Durie & Salmon (1975).

(Parker & Malpas, 1979). The Medical Research Council group found that the blood urea and the haemoglobin level were the most significant parameters in assessing the prognosis of myeloma patients and together with performance status they form the basis of the system of staging which they adopted. (Medical Research Council, 1980).

The results of the present study have shown that serum β2-m measured at presentation has a strong association with survival, the data for 2 comparable groups of patients being very similar. The additional analyses revealed that the serum β2-m was a better guide to prognosis than the other "standard" clinical and laboratory data, whether derived from the combination of haemoglobin level and blood urea or stage based on the system of Durie & Salmon (1975).

The haemoglobin level is likely to be related to marrow involvement and therefore, tumour load, whilst blood urea reflects the renal effects of myelomatosis, probably light chain excretion. The level of β2-m in serum, reflecting myeloma cell mass but also rising as the glomerular filtration rate falls, represents the net effect of tumour mass together with a contribution from reduced filtration in patients with impaired renal function. The serum β2-m continues to give powerful prognostic information after the institution of treatment as demonstrated by the findings at one year. This reinforces earlier observations that the prognosis for patients whose serum β2-m levels fall and stabilise at normal or near normal levels after treatment is better than for patients with persistently high or rising levels (Norfolk et al., 1980).

It is concluded that the serum β2-m at diagnosis carries more prognostic information than any of the commonly used indicators in myelomatosis and should, therefore, have a valuable role in the investigation of patients with this disease and their stratification for clinical trial purposes. The use of a single simple measurement has obvious attractions.

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References

AMLOT, P.L. & ADINOLFI, M. (1978). β2-microglobulin, a tumour marker of lymphoproliferative disorder. Lancet, ii, 476.

BATTLEUR, R., MAGUB, M., SANY, J. & 4 others. (1981). β2-microglobulin sérique au cours de myélome multiple. Rev. Rhum. Mal. Ostéartic., 48, 235.

BRESLOW, N. (1974). Covariance analysis of censored survival data. Biometrics, 30, 80.

CHILD, J.A., SPATI, B., ILLINGWORTH, S. & 6 others. (1980). Serum β2-microglobulin and C-reactive protein in the monitoring of lymphomas. Cancer, 45, 318.

CHRONIC LEUKAEMIA-MYELOMA TASK FORCE. (1973). Proposed guidelines for protocol studies II. Plasma cell myeloma. Cancer Chemother. Rep. 4, (Suppl.), 145.

COOPER, E.H. & CHILD, J.A. (1981). Serum β2-microglobulin in the assessment of lymphoid neoplasia: a review. Tumour Diagnostik, 2, 167.

COX, D.R. (1972). Regression models and life tables (with discussion). J. R. Statist. Soc. B, 34, 187.

CRESWELL, P., SPRINGER, T., STROMINGER, J.L., TURNER, M.J., GREY, H.M. & KULO, R.T. (1974). Immunological identity of the small subunit of HL-A antigens and β2-microglobulin and its turnover on the cell membrane. Proc. Natl. Acad. Sci., 71, 2123.

DURIE, B.G.M. & SALMON, S.E. (1975). A clinical staging system for multiple myeloma. Cancer, 26, 842.

KALBFLEISCH, J.D. & PRENTICE, R.L. (1980). The Statistical Analysis of Failure Time Data. New York: Wiley.

MEDICAL RESEARCH COUNCIL (1980). Prognostic features in the third MRC myelomatosis trial. Br. J. Cancer, 42, 831.

NORFOLK, D.R., CHILD, J.A., COOPER, E.H., KERRUISH, S. & MILFORD WARD, A. (1980). Serum β2-microglobulin in myelomatosis: a potential value in stratification and monitoring. Br. J. Cancer, 42, 510.

O'QUIGLEY, J. (1982). Regression models and survival prediction. Statistician, 32, 107.

PARKER, D. & MALPAS, J.S. (1979). Multiple myeloma. J. R. Coll. Phys. (London) 13, 146.

PETO, R., PIKE, M.C., ARMITAGE, P. & 7 others. (1977). Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part 2—Analysis and examples. Br. J. Cancer, 35, 1.

TSIATIS, A.A. (1981). A large sample study of Cox's regression model. Ann. Statist., 9, 93.

WOODRUFF, R.K., WADSWORTH, J. MALPAS, J.S. & TOBIAS, J.S. (1979). Clinical staging in multiple myeloma. Br. J. Haematol., 42, 199.