Prognostic factors affecting the survival of patients with multiple myeloma

A retrospective analysis of 86 patients

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Summary

A retrospective analysis of data concerning 86 patients with multiple myeloma was carried out in order to evaluate factors affecting survival. The overall median survival was 621 days. In a univariate analysis the following factors were significantly associated with poor survival: serum creatinine $\geqslant$ 150 mmol/l, haemoglobin $<$ 11 g/dl and serum calcium values $>$ 2,75 mmol/l; and Eastern Cooperative Oncology Group performance status 3 - 4. However, age, sex, Durie and Salmon staging, lytic lesions, serum immunoglobulin concentration, urine Bence Jones protein, percentage of plasma cells in the bone marrow, proteinuria, and type of chemotherapy given were not significantly associated with survival. A strong prediction of survival was found by grouping the serum creatinine and haemoglobin levels of patients at presentation.

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Multiple myeloma is a chronic disease of the haemopoietic system characterised by clonal proliferation of B cells. The median survival of patients with multiple myeloma was approximately 6 months. However, with the introduction of chemotherapy in the management of this disease survival has increased to approximately 30 months.[1] Staging is of practical value and plays an important role in therapeutic decisions in the management of malignant disease; this is especially so in malignant disease of the haemopoietic system. It has been suggested that staging could be utilised in myeloma when making therapeutic decisions, and also for adding prognostic insight. Durie and Salmon[2] proposed a clinical staging where the myeloma cell mass was assessed by the paraprotein level in serum and urine, the extent of bone lesions, and the haemoglobin level and serum calcium values. Other investigators utilise an approach where a combination of presenting features are correlated with survival.[3-9] We analysed the data from 86 patients treated with various protocols to determine the significance of clinical features at presentation in relation to survival.

Patients and methods

Records of 86 previously untreated patients with multiple myeloma were analysed; the patients were all white, from a single institution and were seen between 1966 and 1986. Their median age was 60 years (range 31 - 77 years), and 51 were men. The diagnosis of multiple myeloma was made using the Chronic Leukemia-Myeloma Task Force criteria.[10] Using the Durie and Salmon[2] staging, 8 patients had stage I disease, 26 stage II and 52 stage III disease. Performance status (PS) was judged according to Eastern Cooperative Oncology Group (ECOG) criteria:[11] 48 patients had a good performance status (PS 1 - 2; Karnofsky 90 - 50%), and in 38 patients the PS was 3 - 4 (Karnofsky 40 - 10%).

The following treatments were given: 49 patients received melphalan and prednisone, 17 received carmustine and prednisone, 10 received a combination of carmustine + melphalan + vincristine + cyclophosphamide + prednisone, 4 received melphalan + carmustine + cyclophosphamide, 3 received melphalan + carmustine + prednisone and 3 received lomustine + prednisone. Treatments were allocated according to the randomised trials ongoing at the institution. If the patient did not fulfil the eligibility criteria of the relevant protocol, treatment was given according to the investigator's discretion.

In addition to history and clinical examination, the following investigations were performed initially and at 6 - 8-week intervals: full blood count, serum chemistry, serum and urine eletrophoresis, serum M-components and immunoglobulin quantification, bone marrow aspiration, and skeletal radiography. Other parameters, such as cell-labelling index,[12] β_2-microglobulin,[12-14] degree of infiltration on the bone marrow trephine biopsy,[15] cytogenetics and immunophenotype, light-chain excretion, and lactic dehydrogenase level, recently recognised to be of prognostic value, were not included in the analysis because they were available in only a small proportion of patients.

Statistical methods. The Kaplan and Meier life-table method was used for analysing survival.[16] Significance between curves was calculated using the Mantel-Cox and Breslow tests.[17] A Cox multivariate regression hazards analysis was done to assess the combined effect of the different clinical factors on survival.[18] All statistical tests were done by SAS and BMDP computer programs.

Results

The following parameters were found to be of prognostic significance: renal function as measured by serum creatinine value; hypercalcaemia; anaemia; hypo-albuminaemia; and ECOG PS. A multivariate regression model showed the significance as follows: serum creatinine level ($P = 0{,}0002$); serum calcium level ($P = 0{,}01$); serum albumin level ($P = 0{,}03$); and haemoglobin value ($P = 0{,}05$). In this model the PS lost its significance.

Renal function

Renal function, judged by serum creatinine values, was the most important prognostic parameter in this group of patients. Patients with a normal serum creatinine level had a median survival of 1 011 days, while the median survival of those with abnormal serum creatinine values was 216 days; this is statis-

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tically significant ($P = 0{,}00001$). The survival of patients with a serum creatinine level < 150 μmol/l compared with the survival of those with a serum creatinine level $\geqslant 150$ μmol/l is shown in Fig. 1. The serum urea value was not found to be of prognostic significance.

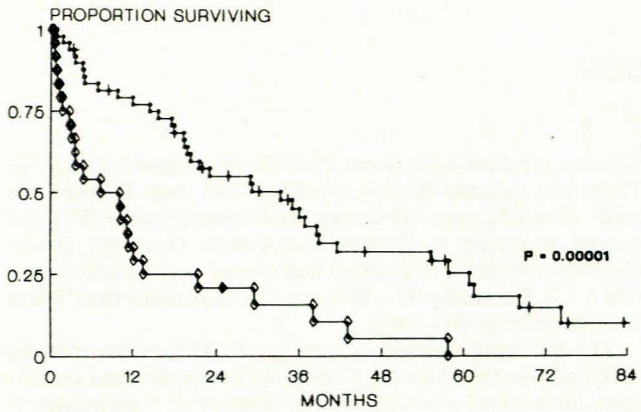

Fig. 1. Survival of patients according to serum creatinine values (.—. = < 150 μmol/l ◆—◆ = ⩾ 150 μmol/l).

Anaemia

Anaemia was another variable with prognostic significance. Patients with a haemoglobin value $\geqslant 11$ g/dl had a median survival of 885 days, which was significantly better than the median survival of 209 days for patients with a haemoglobin value < 11 g/dl ($P = 0{,}0001$) (Fig. 2).

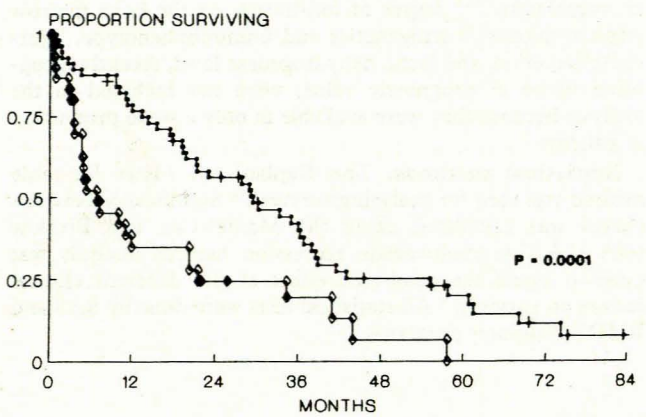

Fig. 2. Survival of patients according to haemoglobin values, (◆—◆ = haemoglobin < 11 g/dl; .—. = haemoglobin ⩾ 11 g/dl).

Hypercalcaemia

Thirty per cent of patients in this series presented with a raised serum calcium level. This subgroup of patients had a median survival of 346 days, which was significantly poorer than the median survival of 706 days among the patients who were normocalcaemic on presentation ($P = 0{,}01$) (Fig. 3).

Hypo-albuminaemia

Hypo-albuminaemia was another prognostic variable significantly associated with poor survival. The hypo-albuminaemic

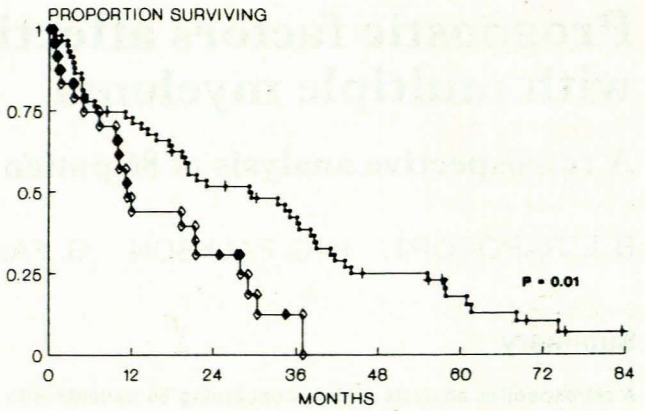

Fig. 3. Survival of patients according to serum calcium values (normocalcaemic = .—.; hypercalcaemic = ◆—◆).

group had a median survival of 222 days v. 889 days of those who were normo-albuminaemic at presentation. This difference ($P = 0{,}0001$) is shown in Fig. 4.

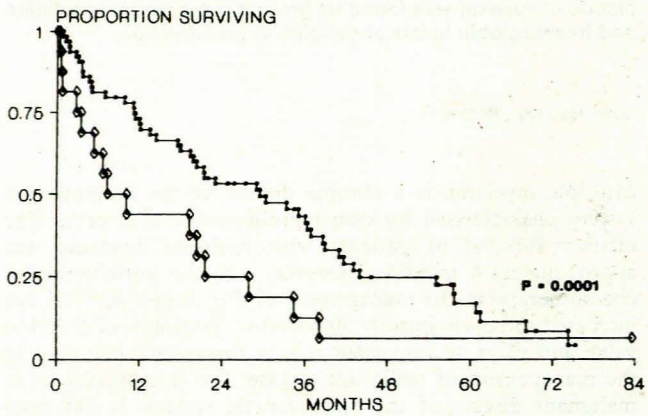

Fig. 4. Survival of patients according to serum albumin values (.—. = normo-albuminaemic; ◆—◆ = hypo-albuminaemic).

Performance status

In a univariate analysis the PS was of significant prognostic importance. The median survival of patients with a good PS

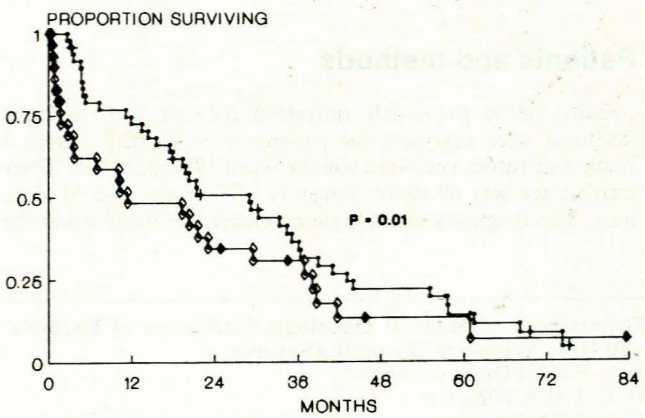

Fig. 5. Survival of patients according to ECOG PS (.—. = PS 1 and 2; ◆—◆ = PS 3 and 4).

was 662 days. This was significantly better than the 341 day median survival of those with a poor PS ($P = 0,01$) (Fig. 5).

Durie and Salmon staging

The pretreatment stage of each patient was assessed according to the Durie and Salmon classification.[2] Difference in survival for the three stages was not statistically significant ($P = 0,79$). Median survival of 8 patients with stage I disease was 1 178 days, of 26 patients with stage II disease 620 days, and of 52 patients with stage III disease 621 days (Fig. 6).

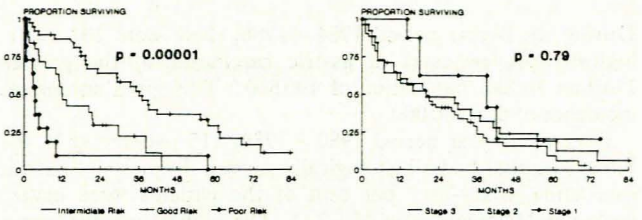

Fig. 6. Comparison of survival according to the Durie and Salmon [2] (right) staging system and haemoglobin and creatinine levels (left) combined.

Haemoglobin and creatinine values combined

A combination of the haemoglobin and serum creatinine values recorded at presentation was compared in three groups. The first group had a haemoglobin value $\geqslant$ 11 g/dl and a serum creatinine level $\leqslant$ 149 μmol/l, the second group had a haemoglobin value $<$ 11 g/dl and a serum creatinine level $\geqslant$ 150 mmol/l; the third group of patients were those who had either a normal haemoglobin value with an abnormal serum creatinine level or an abnormal haemoglobin value with a normal serum creatinine level. The median survivals were 925 days, 109 days and 360 days respectively. The survival curves are shown in Fig. 6 and demonstrate a significant difference between the three groups ($P = 0,00001$).

Other parameters

The following parameters did not significantly affect survival: age; sex; number of lytic lesions; uric acid levels; paraprotein type; paraprotein levels; Bence Jones proteinuria; proteinuria $>$ 1 g/24 h; and the type of cytostatic treatment administered.

Discussion

This study was undertaken in order to analyse the prognostic significance of the most common features and complications of multiple myeloma. It demonstrated the importance of evaluating presenting features in relation to patient survival. Analysis of data shows that several clinical parameters are associated with poor prognosis. Clinical features with prognostic significance were, in order of importance: abnormal renal function; anaemia; hypo-albuminaemia; hypercalcaemia; and impaired PS. However, in a Cox multivariate regression model of clinical features, the PS lost its significance.

In an analysis of 485 patients with multiple myeloma the British Medical Research Council's (BMRC) Working Party on Leukaemia in Adults reported similar results.[3] These investigators found that the three major determinants of prognosis were the blood urea concentration, the haemoglobin concentration and the clinical PS; they divided patients into those with a good, intermediate and poor prognosis. We found that serum creatinine value is more accurate for assessing renal function than serum urea. Fluctuation of the serum urea level occurs during dehydration, a complication often encountered in patients with multiple myeloma.

The importance of PS as a predictive discriminant of survival was documented by the BMRC series as well as the Argentine Group for the Treatment of Acute Leukemia (GATLA).[5,8] GATLA analysed 410 patients treated on two different protocols; the most important predictors of survival were impaired PS and bone marrow infiltration with more than 40% plasma cells.

The importance of estimating the pretreatment tumour cell mass was previously demonstrated by Salmon and Smith[19] and confirmed by Woodruff *et al.*[20] This mathematical calculation was based on the rate of paraprotein production by the myeloma cells on a culture media. In our patients paraprotein levels did not correlate with survival.

In the analysis of our data the staging system of Durie and Salmon[2] was not of statistically significant prognostic importance.

In conclusion, we found that presenting features can be practically utilised and are of better prognostic value in patients with multiple myeloma than the staging system proposed by Durie and Salmon.[2] This finding agrees with that of the BMRC and other investigators.[3-9]

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