Prognostic factors in multiple myeloma

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Summary

All patients with multiple myeloma seen over a 9-year period at Tygerberg Hospital were studied retrospectively. Presentation data of 144 patients, as well as individual laboratory results were included in the survival analysis. Cox's proportional hazard model (a non-parametric multivariate regression method) was used to predict survival and divide patients into prognostic groups. The relationship between pairs of variables at the time of diagnosis was investigated. The survival of groups of patients was compared using the generalized Wilcoxon and Savage tests. The association of the following factors with prognosis were again substantiated: haemoglobin; serum creatinine, urea and albumin; percentage of plasma cells in the bone marrow aspirate and trephine biopsy specimen; and the number of lytic lesions on skeletal radiography. The following factors were not substantiated: serum uric acid, light-chain proteinuria, age at presentation of the disease and IgG rather than the IgA class. In addition, a higher serum monoclonal peak size at presentation of the disease, and a more rapid fall in the abnormal serum monoclonal peak within the first 40 days after commencing treatment were associated with a significantly longer survival.

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Certain clinical parameters have been assumed to be important for prognosis in patients with multiple myeloma, and have been related to the tumour-load. Such factors include pretreatment levels of haemoglobin,[1,2] serum urea, serum creatinine,[3,4] serum uric acid,[2,4] serum calcium,[1,4] serum M-protein,[1,5] serum albumin,[2] the presence and type of light-chain proteinuria (kappa or lambda),[5] proteinuria other than light chains,[5] the percentage of plasma cells in the bone marrow aspirate,[4] the number of lytic bone lesions seen on radiography,[1] age at presentation of the illness[2] and the general clinical status.[6] Salmon and Smith[7] used direct[8] and indirect[9] methods for the calculation of the tumour cell mass in multiple myeloma in 1970, and they described three clinical stages. Their work was based on experimental studies by Hobbs.[5] Woodruff *et al.*[1] used this staging system in a clinical evaluation and they demonstrated highly significant differences in the survival of patients with low, intermediate and high tumour cell mass. These results were also corroborated in other clinical series.[4,8] The Acute Leukemia Group B[10] in 1975 and Matzner *et al.*[2] in 1977 reported that patients with IgA myeloma had a significantly shorter survival than those with IgG, but this could not be substantiated in other series.[11] Patients on therapy with a fast fall in tumour size survived for a shorter period than those who responded more slowly.[12] Pennec *et al.*,[13] however, in a large multicentric study, could not demonstrate any significant differences in the survival of these three 'stages' of multiple myeloma. According to them, only the haemoglobin level is significant as a 'classic' criterion of survival. They recognized that kidney failure, thrombocytopenia, fever, increased percentage of plasma cells in the bone marrow and higher age were significant factors associated with shorter survival. Bernstein and Humes,[14] however, pointed out that kidney failure with multiple myeloma is reversible in 55% of patients. Treatment of hypercalcaemia and/or chemotherapy for the illness is associated with reversibility of kidney failure in 88% of cases and thus improved survival. The association with survival has already been identified for some of these prognostic factors, but further research was indicated for many others.

In this study all patients seen with multiple myeloma at this hospital were analysed for prognosis and response to therapy over a period of 9 years. Data at presentation, serial laboratory results and treatment group were analysed with non-parametric multivariate statistical techniques to investigate their relationship to patient survival.

Patients and methods

All the patients with multiple myeloma seen at Tygerberg Hospital from 1 January 1975 to 31 December 1983 were included. Patients' referral and hospital records before this time were too incomplete for inclusion. In this study of 144 patients the date of the deaths of 72% of the patients were known, 22% were alive on 31 December 1983 and only 6% had to be excluded for incomplete follow-up.

The diagnostic criteria followed at Tygerberg Hospital are those recognized by the Eastern Cooperative Oncology Group of the USA.[15]

For every patient in the study the following details were recorded:

Data recorded at initial presentation

Race and sex, date of birth, age at presentation, number of lytic lesions on skeletal radiography and the number of fractures, the place of the monoclonal peak on protein electrophoresis, the presence of light-chain proteinuria and the immunoglobulin class were recorded. Bone marrow trephine biopsy was introduced as a routine investigation only during the latter part of the 9-year course of this study, so that the percentage of plasma cells were evaluated in some of the earlier patients only on their bone marrow aspirate. The aspirate report provided a convenient percentage figure in contrast with the trephine biopsy results which frequently reported 'patchy infiltration'. In a few of the recent patients, where the aspirate resulted in a 'dry tap', the percentage of plasma cells was re-evaluated from the trephine biopsy specimen.

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Serial data

The following serial results were recorded at subsequent visits: haemoglobin, total white cell count and platelet count (Coulter model S plus, Coulter model S or Coulter model F). The following serial tests were performed on an SMAC 20-channel system: serum calcium (mmol/l),[16,17] lactate dehydrogenase (LD),[18] alkaline phosphatase (AP),[19] alanine transaminase (ALT),[18,19] aspartate transaminase (AST)[20] and gamma-glutamyl transaminase (GGT) (U/l at 37°C),[21] total serum bilirubin (TSB) (μmol/l),[22] serum urea (mmol/l),[23] serum uric acid (mmol/l),[24] serum creatinine (μmol/l) and total serum protein (g/l). For the serum albumin level and the monoclonal peak height (g/l) a Beckman microsone cellulose acetate electrophoresis system was used.

For light-chain proteinuria (qualitative) a fresh urine specimen preserved with sodium oxide was used. If the protein electrophoresis on concentrated urine showed globulin, the presence of free kappa or lambda chains was investigated by immuno-electrophoresis.

Therapeutic programmes

Various therapeutic programmes have been used at Tygerberg Hospital since 1975. The first was standard oral therapy using melphalan and prednisone (treatment 1). The second had cyclophosphamide added (treatment 2). Treatment 3 also contained vincristine and treatment 4 consisted of melphalan/prednisone/carmustine (BCNU)/cyclophosphamide and vincristine. The therapy was changed depending on drug toxicity or patient non-response. The longest or most important regimen was selected for the purpose of the analysis. Treatment 1 was given to 66 patients, 37 received treatment 2, 15 received treatment 3, 15 received treatment 4 and 11 patients were not treated for multiple myeloma.

Statistical analysis

An exploratory investigation of the serial data was undertaken by plotting all the observations during the course of the disease to evaluate whether any of the variables showed consistent trends. The relationship between pairs of variables at the time of diagnosis was investigated using the Spearman rank correlation coefficient in the case of continuous variables and the Student *t*-test or one-way analysis of variance in the case of a continuous variable being compared with a categorized one. The generalized Wilcoxon test and the Savage test were used to compare the survival of groups of patients (for example males v. females). These are non-parametric tests which can accommodate censored observations, and which differ by the weighting given to the survival over time. Cox's proportional hazard regression model was used with the presentation data as covariates for prediction of the survival times to investigate which factors could be used to predict a patient's prognosis.

The proportional hazard model is given by

$$h(t;\underline{z}) = H_o(t) \exp(\underline{\beta}'\underline{z})$$

in terms of $((h(t;\underline{z}))$ the hazard rate ('instantaneous death rate' at time t) for a person with covariate $\underline{z}$ (t represents the time in days), $\underline{\beta}$ is a vector with the unknown regression coefficients and $h_o(t)$ is the hazard rate for a person with $\underline{z} = \underline{o}$.

Estimates of the regression coefficient were made with an iterative technique similar to the maximum likelihood ratio test.

To evaluate the effect of all the variables (prognostic factors) on the hazard rate, the variables were introduced stepwise into the regression, and with each step the statistical significance was evaluated. The covariates were all tested at a significance level of 5%. This analysis was undertaken on the IBM 4341 computer using the BMDP2L program.

Results

Fifty-nine white males, 36 white females, 23 coloured males, 13 coloured females, 10 black males and 3 black females were included in the study. Ninety-two patients were IgG, 23 were IgA, 8 had light-chain proteinuria and 1 patient had the non-secretory class of multiple myeloma. In 13 patients no final decision about the class was available from the records. In 7 patients no documentation about the immunoglobulin class was available. On skeletal radiography of 138 patients, 40 demonstrated no lytic lesions, 10 patients had a solitary lytic lesion, 5 had 2 lesions, 17 had between 3 and 5 lesions and 66 had 6 or more lytic lesions. Table I shows the means, standard deviations and the number of observations for some of the data at presentation.

TABLE I. MEAN, SD AND THE NUMBER OF OBSERVATIONS FOR SOME OF THE PROGNOSTIC FACTORS AT PRESENTATION

	Mean	SD
% plasma cells	**46,03**	**27,04**
Haemoglobin	**10,55**	**2,77**
Serum urea	**11,60**	**11,77**
Serum creatinine	**231,06**	**336,70**
Serum protein	**91,58**	**22,48**
Serum albumin	**31,84**	**7,08**
Serum monoclonal peak size	**34,61**	**23,83**
Serum IgG	**40,09**	**34,80**
Serum IgM	**0,58**	**0,52**
Serum IgA	**5,38**	**13,54**

Relationship between factors

The non-parametric Spearman rank-order correlation method was used and the correlations have been based on all available information. The following statistically significant correlations were found:

(*i*) Haemoglobin with percentage of plasma cells ($P = 0,0009$), serum IgM ($P = 0,0032$), serum creatinine ($P = 0,0001$), serum albumin ($P = 0,001$) and monoclonal peak size ($P = 0,0085$).

(*ii*) Percentage of plasma cells with lytic lesions ($P = 0,0092$).

(*iii*) Serum IgM with lytic lesions ($P = 0,014$), serum protein ($P = 0,0008$) and IgG ($P = 0,0001$).

(*iv*) Serum creatinine with serum calcium ($P = 0,0054$), serum urea ($P = 0,0001$) and uric acid ($P = 0,0001$).

(*v*) Serum albumin with serum calcium ($P = 0,0116$), LD ($P = 0,0061$), AST ($P = 0,0001$) and serum AP ($P = 0,0236$).

(*vi*) Monoclonal peak size with serum creatinine ($P = 0,0084$), serum protein ($P = 0,0001$) and serum albumin ($P = 0,0001$).

Significant correlations were found in 38 other pairs of prognostic factors but have been omitted from this article to assist clarity. The large number of highly significant correlations increased the difficulty of the final interpretation of the statistics, and necessitated the use of Cox's regression analysis.

The following differences were found between the race groups based on the one-way ANOVA and Student's *t* test: serum albumin was significantly higher in whites than in blacks, and levels in blacks were significantly higher than in coloureds ($P = 0,0009$). The abnormal serum monoclonal peak was significantly higher in coloureds than in blacks, and significantly higher in blacks than in whites ($P = 0,0033$). Haemoglobin values were significantly higher in blacks than in whites ($P = 0,0272$) but those of coloureds and whites were not significantly different.

Haemoglobin values were significantly higher in males than in females ($P = 0,001$), the percentage of plasma cells on the bone marrow was higher in the females than in the males ($P = 0,003$) and the extent of the drop of the abnormal serum monoclonal peak values after presentation was significantly higher for females than for males ($P = 0,0362$).

Serial information

Very few consistent trends were observed in the serial data. Representative samples of patients were selected with stratified random methods and all the serial variables of these patients were plotted. Only the haemoglobin, the monoclonal peak size and the

LD appeared to follow general trends during the course of the disease. The serial data relating to all the subjects were then plotted for these variables. The haemoglobin increased slowly after diagnosis, and dropped slightly before the death of the patient; however, this tendency was not completely consistent. The peak appeared to drop rapidly within the first month and was then followed by a gradual increase. No consistent trend was observed in the LD when all the subjects were considered.

Relationship between factors and survival

The total group of 144 patients had a median survival time of 390 days, i.e. 50% of the patients died within 13 months of diagnosis. Several factors were found to be significantly associated with survival time.

On the basis of the Savage test, white males experienced a better survival than white females ($P = 0{,}0303$). The survival times of the two groups are illustrated in Fig. 1. It can be seen that although the initial survival is poorer in females, both groups have long-term survivors. Fig. 2 shows that the survival of patients on treatment 1 was worse than that of patients on other treatments ($P = 0{,}029$). Cox's regression analysis was used to consider the relationship between continuous variables and survival allowing for adjustment for the treatment group (1 or others), the race, group and sex by including them as factors in the model. Longer survival time was associated with increased haemoglobin ($P = 0{,}011$), serum albumin ($P = 0{,}015$) and the extent of the monoclonal peak drop during the first 40 days ($P = 0{,}04$). Shorter survival was associated with an increased number of lytic lesions ($P = 0{,}007$), percentage of plasma cells ($P = 0{,}003$), total white cell count ($P = 0{,}005$), serum creatinine ($P = 0{,}001$), serum urea ($P = 0{,}002$), serum AP ($P = 0{,}003$) and serum IgM ($P = 0{,}002$).

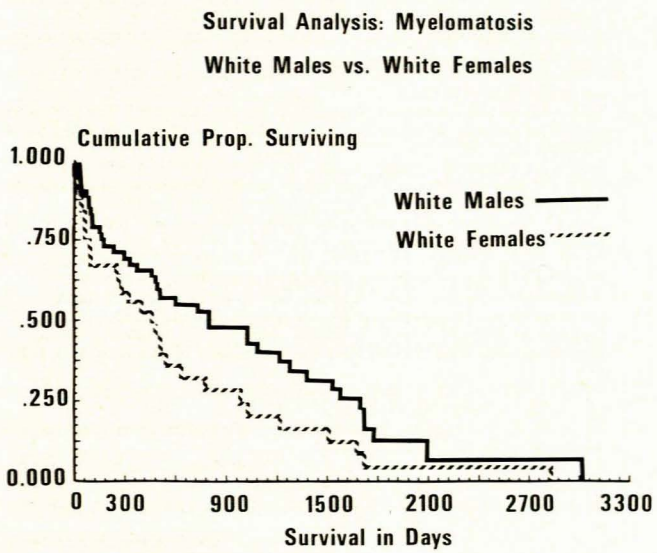

Fig. 1. Survival curves for white males and females.

When the 54 patients with a positive serum monoclonal peak size were divided into two equal groups on the basis of being above or below the median drop within the first 40 days, it was found that those patients with a larger fall in monoclonal peak size were associated with a longer survival than those with a smaller drop ($P = 0{,}0432$). Fig. 3 illustrates the survival of the two groups of patients.

When only those variables significantly associated with survival on their own were included in the stepwise procedure, in combination with TSB and the monoclonal peak size (two additional variables which were selected in the stepwise procedure when all the variables had been included), the analyses were conducted on 92 cases. These results are given in Table II. Treatment 1, higher plasma cells in the bone marrow aspirate, serum IgM and serum

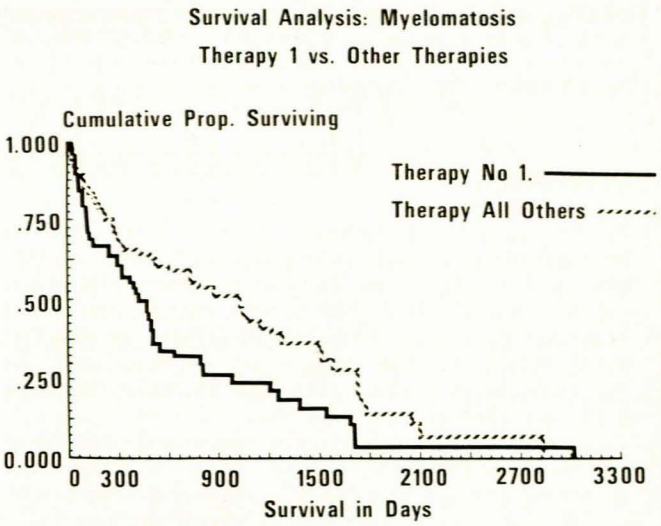

Fig. 2. Survival curves for treatment 1 v. other therapies.

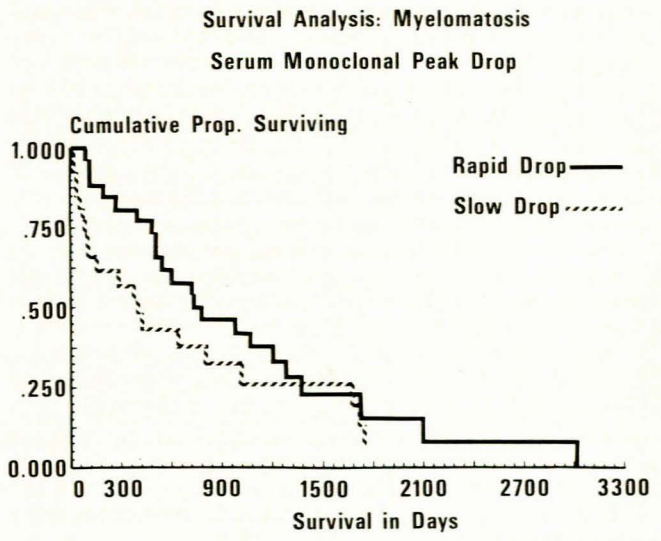

Fig. 3. Survival curves for serum monoclonal peak drop (rapid and slow).

TABLE II. VARIABLES SELECTED IN STEPWISE COX'S PROPORTIONAL HAZARD MODEL (92 CASES), THE ESTIMATED PROPORTIONALITY FACTOR ($e^{\beta i}$) OF THE VARIABLE ON THE HAZARD RATE AND THE CONTRIBUTION OF THE VARIABLE TO THE FIT OF THE MODEL (X^2 AUDITS ASSOCIATED *P* VALUE)

	Improvement		
	$e^{\beta i}$	X^2	*P* value
Plasma cells in BM aspirate	1,0220	11,688	0,001
Serum IgM	1,0249	4,354	0,037
Serum creatinine	1,0014	5,116	0,024
Serum albumin	0,8979	5,519	0,019
Monoclonal peak size	0,9785	7,736	0,005
Treatment group (1 or other)	0,5865	3,397	0,065

creatinine were associated with shorter survival (the proportionality factor $e^{\beta i}$ is greater than 1), while higher serum albumin and monoclonal peak size were associated with longer survival (the proportionality factor $e^{\beta i}$ is less than 1).

Discussion

The presence of certain factors at the time the disease manifests has already been associated with prognosis; this was substantiated in our study. These factors are: higher haemoglobin and/or serum albumin, which indicate longer survival; and higher number of lytic lesions on radiography, percentage of plasma cells in the bone marrow aspirate, total white cell count, and serum urea, creatinine and AP, which indicate a shorter survival time.

In our series: (*i*) a higher serum monoclonal peak size at presentation of the disease; and (*ii*) a larger fall in the serum monoclonal peak size than the median drop within the first 40 days after presentation were both associated with longer survival. This is contrary to the findings of Alexanian *et al.*[12] and Salmon and Smith[7] based on the experimental work by Hobbs.[5] It should be noted that peak size and peak drop are significantly associated ($P = 0{,}001$), and it is also logical to expect that a higher peak at presentation can lead to a faster fall. A low peak is also associated with treatment 1 and this could be a confounding factor. It is, however, interesting that when the total number of 144 patients was divided into three equal groups on the basis of the size of the serum monoclonal peak at the time of presentation of the disease, the median survival for the patients with a low (or absent) peak was 435 days, the middle peak was 510 days and the high peak was 875 days. Although the groups did not differ significantly, a trend was apparent.

Our study demonstrated a significant difference in the survival rate of the earlier patients, who were treated with only melphalan and prednisone, in contrast with the rate in later patients on various other combinations.

White males survived significantly longer than white females. Females probably presented at a later stage of the disease, or had possibly been misdiagnosed in the earlier stages. It is significant that: (*i*) the percentage of plasma cells was higher in females than in males (therefore shorter survival); (*ii*) the peak drop was higher for females (therefore longer survival); and (*iii*) the haemoglobin values were lower for females (therefore shorter survival).

All these contradictory facts complicate or mask the role of gender in survival. When the role of gender was evaluated in the multivariate statistical methodology it was not selected as a significant prognostic variable.

Our study did not substantiate the following factors as being of prognostic importance in the survival rate — serum uric acid, presence of light-chain proteinuria, age at presentation of the disease, and the IgG rather than the IgA class.

No ethnic differences were found in the survival rates but few black patients were included and they did not survive for long. This could be because the diagnosis was made at a later stage of the disease.

The stepwise Cox's proportional hazard model fitted to the data indicated that for any patient a value above the average for percentage of plasma cells, serum IgM and/or serum creatinine meant an increased hazard or a poorer prognosis. Values above average levels for serum albumin and/or monoclonal peak size indicate a decreased hazard or a better prognosis.

This formula has been calculated on retrospective data for patients seen at Tygerberg Hospital, and it is not necessarily applicable to patients seen at other hospitals investigated at other laboratories. Serum IgM was selected as an important prognostic variable and it was significantly associated with serum IgG and protein, haemoglobin and the number of lytic lesions. At the moment there is no satisfactory explanation for the selection of serum IgM.

In addition to the data being collected retrospectively from hospital records, the stage of the disease at presentation has been assumed to be consistent for all the patients. The consequent inherent degree of unreliability in these data could well mask any true correlation. It is therefore not surprising to find discrepancies with other studies and even within this study. Despite the inadequacies of the design of these types of studies, it is felt that they are useful in indicating possible associations which can be used in formulating hypotheses which can be further investigated.

This study once again demonstrates the use of retrospective statistical analysis of routine hospital data. Presentation data of 144 patients with multiple myeloma, as well as the individual serial laboratory results of the follow-up years were included in the survival analysis. The prediction model that emerged can now be used with advantage in ensuring comparability of patients in future prospective studies. For example, the predictive survival can help in meaningful formation of comparable groups for stratified randomizations in future chemotherapeutic trials.

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