Factors influencing the prognosis in myelomatosis

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Summary

One hundred and eighty-eight patients with myelomatosis, 166 of whom had multiple myelomatosis, were studied to assess the prognostic significance of age, sex, mode of clinical presentation, presence of anaemia, azotaemia and abnormal cells in the peripheral blood at the time of diagnosis.

The generalized disease was rapidly fatal in many of these unselected patients. Women survived longer than men and the young slightly longer than the old.

Of the laboratory findings, only a raised blood urea (greater than 60 mg/100 ml) was associated with a statistically poorer prognosis.

Introduction

Multiple myelomatosis is a fatal disease associated with the generalized proliferation of abnormal plasma cells in the bone marrow; it may be preceded by a localized tumour (plasmacytoma). The survival time of myelomatosis (International Statistical Classification of Disease, No. 203) varies widely. We have studied a group of patients with multiple myelomatosis and related some clinical and laboratory features at the time of initial presentation to the survival time.

Methods

The case records of 188 patients with myelomatosis admitted to the Aberdeen General Hospitals between 1954 and 1970 were traced. The diagnosis of myelomatosis was accepted if (a) a marrow aspirate or biopsy of tumour showed an unequivocal excess of abnormal cells of the plasma cell series and, in the case of multiple myelomatosis, either (b) an abnormal protein band was present on serum electrophoresis, or (c) radiological evidence of typical myeloma lesions of bone was detected. Patients in whom the diagnosis of myelomatosis was equivocal were not included in this study.

One hundred and sixty-six patients were regarded as having multiple myelomatosis with multifocal tumours of plasma cells in bones at the time of presentation: twenty-two patients were considered to have a solitary plasmacytoma without evidence of scattered disease.

From the case records were obtained the age, sex, survival time, mode of presentation, blood urea, serum calcium, haematological data and therapy given. For the purpose of analysis survival of under 1 month was taken as 1 month.

Results

Details of the age and sex distribution of the patients with multiple myelomatosis and plasmacytoma are presented in Table 1. The survival times, where known, are shown in Table 2 (the 'alive'

TABLE 1. Age at diagnosis of myelomatosis

Age-group	Plasmacytoma			Multiple myelomatosis		
	Male	Female	Total	Male	Female	Total
30-39	1	—	1	1	—	1
40-49	2	1	3	4	4	8
50-59	3	4	7	25	15	40
60-69	4	2	6	33	19*	52
70-79	3	1	4	24	26	50
80-89	—	1	1	8	7	15
All	13	9	22	95	71	166

* One case plasma-cell leukaemia

TABLE 2. Survival times in plasmacytoma and multiple myelomatosis

Survival time	Plasmacytoma			Multiple myelomatosis		
	Dead	Alive	Total	Dead	Alive	Total
0-3 months	—	—	—	63	—	63
4-12 months	4	—	4	44	1	45
13-24 months	2	1	3	25	5	30
2-5 years	—	—	—	5	2	7
Over 5 years	4	4	8	2	1	3

column refers to patients being treated currently). The mean survival time of the patients who had died before this survey was completed was 8.5 months. The poor prognosis is underlined by the finding that almost one-third of the patients with multiple myelomatosis died within 3 months of diagnosis; this group includes, however, a number who were moribund on admission to hospital. While the prognosis of those with an initial diagnosis of plasmacytoma was better, only four of the fifteen whose survival was known were alive 5 years after presentation. These were all patients with extra-osseous tumours of the upper respiratory tract. Because of the small numbers, the patients presenting with plasmacytoma have not been analysed further.

The age of the patient at the time of diagnosis of multiple myelomatosis influenced the survival time (Table 3), and women, in spite of being slightly older, had a significantly better prognosis than men (Table 4). The mean survival time of the eighty-nine men who had died was 5.9 months compared with 13.2 months for the fifty women: this latter mean survival time for women fell to 8.7 months when three women with an unusually long survival time were excluded.

TABLE 3. Survival time related to age in patients with multiple myelomatosis

Survival time* (months)	Age group			Total
	30-59	60-69	70-89	
0-3	13	23	27	63
4-12	13	10	21	44
Over 12	18	12	10	40
All	44	45	58	147

$$\chi^2=9.58, \text{ d.f.}=4, P<0.05$$

* Includes patients who are alive, and have survived a minimum of 12 months.

TABLE 4. Survival time related to sex in patients with multiple myelomatosis

Survival time* (months)	Sex		Total
	Males	Females	
0-3	45	18	63
4-12	25	19	44
Over 12	18	22	40
All	88	59	147

$$\chi^2=9.05, \text{ d.f.}=2, P<0.02.$$

* Includes patients who are alive, and have survived a minimum of 12 months.

Data on the survival time related to the presenting symptoms of 138 patients are presented in Table 5. There was no significant difference in the length of survival between patients who presented with orthopaedic symptoms, with haematological features, or

TABLE 5. Survival time related to presenting symptoms in patients with multiple myelomatosis

Presenting symptoms	Survival time (months)*			Total
	3	4-12	Over 12	
Orthopaedic presentation	40	30	22	92
Haematological presentation	7	3	5	15
Miscellaneous presentation	11	11	9	31
All	58	44	36	138

$$\chi^2=1.83, \text{ d.f.}=4, P>0.1.$$

* Includes patients who are alive, and have survived a minimum of 12 months.

with miscellaneous symptoms. The orthopaedic symptoms were bone pain, pathological fractures or acute paraparesis; the haematological features comprised either severe anaemia or haemorrhage; the miscellaneous symptoms included those due to uraemia or infection, or those in patients in whom the diagnosis was made by chance.

The blood urea level at the time of diagnosis was available for 128 patients (seventy-eight men and fifty women) with multiple myelomatosis and was elevated (50 mg/100 ml, or over) in fifty-seven. A raised blood urea level adversely affected prognosis and only twelve of the forty patients (30%) with an initial level over 60 mg/100 ml survived more than 3 months compared with sixty-five of the eighty-eight (74%) with an initial urea of under 60 mg/100 ml. The sex difference in prognosis is not explained by a greater number of men with a raised urea level—twenty-five of the seventy-eight men (32%) had a urea level of 60 mg/100 ml and above, compared to fifteen of the fifty women (30%).

The serum calcium level was raised (5.5 mEq/l and over) in seventeen of the seventy-eight patients in whom it was measured at the time of diagnosis. There was no clear-cut trend in survival time of these patients.

The haemoglobin level at the time of diagnosis was normal (over 13 g/100 ml) in only fourteen of the 138 patients with multiple myelomatosis (10.4%). The initial haemoglobin level, however, bore little relation to the length of survival except that patients with a very low haemoglobin level had a higher immediate mortality: many of these patients were severely uraemic and the poor survival was related to the urea level rather than the haemoglobin level *per se*. Thus, of the twenty patients with a haemoglobin level of 7.0 g/100 ml or below, the twelve with a urea of 50 mg/100 ml and over had a mean survival time of 3.8 months compared with 8.0 months for the eight patients with a urea level of under 50 mg/100 ml.

Thirty-one of the 147 patients with multiple myelomatosis whose blood film was examined had an abnormal blood picture at the time of presentation—either plasma cells were present or there was a leuco-erythroblastic blood picture. The survival time in these patients did not differ significantly from that of the remaining patients ($\chi^2=2.33$, d.f.=2, $P>0.1$).

The patients with multiple myelomatosis received a wide range of therapy. For convenience of presentation this has been divided into four groups—radiotherapy alone, radiotherapy with chemotherapy, chemotherapy alone, and either adrenocorticosteroid alone or no specific therapy. The dosage of radiotherapy varied considerably within the palliative dose range. Chemotherapeutic drugs used included melphalan and cyclophosphamide and, occasionally, uracil mustard. Some earlier patients received urethane. Some of the patients receiving radiotherapy or chemotherapy also received steroid therapy. It should be emphasized that many of the patients who did not get specific therapy were admitted moribund or severely uraemic and died before appropriate therapy could be commenced. Table 6 shows that combined radiotherapy with chemotherapy was associated with the longest survival time.

TABLE 6. Survival time related to therapy in patients with multiple myelomatosis

Treatment	Survival time (months)*			Total
	0-3	4-12	Over 12	
Radiotherapy	18	22	13	53
Radiotherapy and chemotherapy	1	8	16	25
Chemotherapy	15	8	9	32
Steroids or no treatment	31	7	10	48
All	65	45	48	158

* Includes patients who are alive, and have survived a minimum of 12 months.

Discussion

This survey points again to the poor overall survival in multiple myelomatosis. Our survival times are shorter than in most previously reported series (Martin, 1961; Innes & Newall, 1961; Alexanian *et al.*, 1969; Hobbs, 1969); it is likely that this difference is due, at least in part, to the strict diagnostic criteria used in this survey and to the inclusion of *all* patients admitted to hospital with multiple myelomatosis. The survival time did not differ markedly from the unselected series reported by Feinleib & McMahon (1960).

The patients with plasmacytoma survived, on average, considerably longer than the patients with

multiple myelomatosis. Indeed, all those with extra-osseous tumours survived many years, some in spite of the development of several distant recurrent tumours. Prolonged survival in extra-osseous plasmacytoma has been noted previously (Hellwig, 1943). The better prognosis in plasmacytoma may merely represent diagnosis at an earlier stage in the disease; Bergsagel and his associates (1967) have stressed that patients with plasmacytoma almost always progress to multiple myelomatosis.

Both the age and the sex of the patients were found to influence prognosis significantly. There is general agreement that survival times become less as age at diagnosis increases (Feinleib & McMahon, 1960; Galton & Peto, 1968). The longer survival times of female patients with multiple myelomatosis has been noted by Videbaek & Johansen (1956), Feinleib & McMahon (1960) and Waldenström (1968), but women were reported to have a poorer prognosis by Galton & Peto (1968).

There is general agreement that a raised blood urea at the time of presentation of multiple myelomatosis is associated with a poor prognosis (Bergsagel *et al.*, 1967; Broad *et al.*, 1968; Galton & Peto, 1968; Report of the Medical Research Council Trial of Melphalan and Cyclophosphamide Therapy, 1971). In the present series an initial blood urea of 60 mg/100 ml was found to be a critical level as an indicator of probable short survival.

In contrast to the experience of Innes & Newall (1961), Broad *et al.* (1968) and Galton & Peto (1968), we have no evidence that a low haemoglobin *per se*, in the presence of a normal blood urea level, affects prognosis adversely; this was also the conclusion of Rivers & Patno (1969) but only when they considered patients who survived more than 6 weeks. Similarly, the presence of peripheral blood film abnormalities, due to marrow involvement by plasma cells, did not significantly affect prognosis.

This survey was not planned to assess the effect of therapy on prognosis in myelomatosis and a wide variety of therapeutic regimens was used. Patients who received both chemotherapy and radiotherapy during the course of their illness had the longest survival, but this may merely reflect the time available to employ such therapy. Indeed, the high death-rate in the first 3 months after presentation in an unselected series of patients indicates the artificiality of survival times calculated from series where these patients are excluded as in trials of therapeutic agents (Alexanian *et al.*, 1969; Hobbs, 1969).

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