MULTIPLE MYELOMA : THE NATIONAL UNIVERSITY HOSPITAL (NUH) EXPERIENCE

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ABSTRACT

The aim of this retrospective study was to define the characteristics of local patients with multiple myeloma. Twenty-nine de novo cases were accrued from October 1986 to January 1992 at the National University Hospital of Singapore. Features like median age of presentation, sex distribution, the incidence of IgG, IgA and light chain subtypes were similar to published data. However IgD myeloma appeared to be more common here and it tended to be more advanced at presentation. Objective response rate to treatment with the melphalan-prednisolone combination was about 40% with a median survival of 18 months.

Keywords: multiple myeloma, Singapore, characteristics

SINGAPORE MED J 1994; Vol 35: 371-373

INTRODUCTION

The first record of multiple myeloma was contained in a series of publications by John Dalrymple, Henry Bence Jones and William Macintyre in the middle of the last century. A review of these early papers by Clamp emphasised the essential features of this disease which the three authors had meticulously observed and described in their first patient[1]. Today, many clinical and laboratory features of this disease have been recognised as important prognostic factors. These include the haemoglobin level, renal function, serum calcium level, the extent of bone involvement, the type and serum concentration of paraprotein, Bence Jones proteinuria and the percentage of myeloma cells in the bone marrow at diagnosis. In 1975, based on these factors, Salmon and Durie developed the first staging system for multiple myeloma[2]. Since then, many retrospective analysis had confirmed that median survival is closely related to the stage of the disease.

Before the introduction of alkylating agents, the outlook of myeloma patients was poor, with median survival varying from 3.5-11.5 months[3]. With the introduction of melphalan and prednisolone in the early 1960s, median survival had improved significantly. A small proportion of patients could even achieve complete remission but eventually the disease would relapse. Recent therapeutic advances which include biological modifiers like alpha-interferon and highly aggressive chemotherapy with autologous bone marrow transplant have further improved survival.

The decision to initiate treatment, the choice of therapy, the response and the eventual survival clearly depend on the disease stage. All these had been demonstrated in many studies in the West. However, there is no data on the behaviour of our local myeloma patients. The aim of this study is to define the characteristics at presentation, response to therapy and survival of our local patients with myelomatosis.

METHODS AND PATIENTS

This is a retrospective analysis involving 29 patients with multiple myeloma diagnosed at the National University Hospital (NUH) from October 1986 through January 1992. All were de novo cases and had a definite diagnosis of multiple myeloma. Patients who were diagnosed at other centres or had received previous treatment were excluded.

The patients were analysed for their biocharacteristics, prognostic factors, stage of disease, treatment regimes, response to therapy and survival. The usual diagnostic criteria for multiple myeloma were used and they include: more than 20% plasma cells in the marrow, osteolytic bone lesions and serum or urinary M protein. Patients with essential (or benign) monoclonal gammopathy were not included in the analysis. The Salmon and Durie staging method was used for the staging of patients[2].

The cytotoxic regime used for initial treatment was the combination of prednisolone and melphalan (MP) given at four to six weekly interval. MP was stopped when the drop in the plasma M component had reached a plateau, when there was no response after at least four courses, or when the disease progressed while on treatment. Patients refractory to, or progressed while on, MP were given combination chemotherapy.

All patients who received four or more courses of MP were considered evaluable except those who showed a declining M component but had a less than 50% reduction. These patients were considered not evaluable due to inadequate trial of therapy.

Response to therapy was classified as objective response, no response and progressive disease. Objective response to therapy was defined as greater than 50% reduction in the

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plasma paraprotein level. No response was defined as a less than 50% reduction of M protein after at least four courses of MP. A diagnosis of progressive disease was made when there was an increment of M protein, appearance of new bony lesions or development of hypercalcaemia while receiving therapy.

As this was a retrospective study, the clinical data under survey were incomplete in some patients. The data analysis was based on evaluable patients.

RESULTS

Clinical Features

There were 29 patients. Sixteen were males and 13 females. The ratio was 1.2:1. Twenty-three (79.3%) were Chinese, 4 (13.8%) were Malays and 2 (6.9%) were Indians. There was no disease predominance in any race when the distribution was compared to the general population. The median age at presentation was 62 years with a range of 30 to 85 years (Table I). Fourteen out of 27 (52%) patients had a haemoglobin concentration less than 8.5 g/dl at presentation. Hypercalcaemia was seen in 7 (28%) out of 25 evaluable patients either as a presenting feature or during the course of the disease.

Table I – Clinical features of myeloma patients

Characteristics	No.	%
Age		
Median	62	
Range	30-85	
Sex		
Male	16	
Female	13	
Male: Female Ratio	1.2:1	
Racial Distribution		
Chinese	23	79.3 (77.7)*
Malay	4	13.8 (14.1)*
Indian	2	6.9 (7.1)*
Total	29	100 (98.9)*

* Figures in brackets are the percentage racial distribution in the general population obtained from the 1990 population census.

Diagnostic Criteria

There were 28 evaluable marrows and paraprotein levels and 25 skeletal surveys at presentation. All 28 evaluable patients showed paraproteinaemia. Marrow plasmacytosis of more than 20% occurred in 22 (79%) patients. Osteolytic bone lesions, both single or multiple, were present in 17 (68%). Of the 25 evaluable patients for all 3 diagnostic criteria, 12 (48%) patients demonstrated all 3 diagnostic features. Twenty-seven out of 28 (96.7%) had at least 2 out of the 3 diagnostic criteria. Twenty-seven patients were evaluable for their paraprotein subtype. Fourteen (52%) were of the IgG subtype, 7 (26%) IgA, 3 (11%) light chain disease, 2 (7%) IgD and one case of IgM (4%). Twenty-six had their light chain identified, 18 (69%) were kappa and 8 (31%) were lambda (Table II).

Table II – Laboratory features of myeloma patients

Laboratory Test	No. of Evaluable Patients	No. of Patients	% of Patients
Criteria of diagnosis			
Marrow plasmacytosis	28	22	79
Lytic bone lesion	25	17	68
Paraproteinaemia	28	28	100
All 3 of the above	25	12	48
Paraprotein subtype	27		
IgG		14	52
IgA		7	26
Light chain disease		3	11
IgD		2	7
IgM		1	4
Light chain subtype	26		
Lamda		8	31
Kappa		18	69

Staging

Twenty-eight patients were evaluable for staging. Thirteen (46%) patients presented in stage IIIA, 8 (28%) in stage IIIB, 2 (7%) in stage IIA, 3 (11%) in stage IIB and 2 (7%) in stage IA. Seventeen patients (61%) had normal serum creatinine level (subgroup A) and 11 (39%) had a serum creatinine of more than 2.0 mg/dl (subgroup B) (Table III).

Table III – Disease state at presentation

Disease stage	No. of Patients	% of Patients
Stage I	2	7
IA	2	7
Stage II	5	18
IIA	2	7
IIB	3	11
Stage III	21	75
IIIA	13	46
IIIB	8	28
Total number of evaluable patients	28	100%

Response and Survival

Out of 29 cases, 24 patients received MP as initial treatment. Two patients refused any form of chemotherapy. Three had various combination chemotherapy used as first line treatment. Among the 24 who received MP, only 15 could be evaluated for response. The low numbers were due either to inadequate trial of therapy (plateau phase had not been reached), loss of follow-up, or death before adequate courses of MP could be given. Six out of 15 cases (40%) had a greater than 50% decline in the serum paraprotein level.

In 18 evaluable patients the overall median survival was 18 months. Of these 18 patients, 9 had stage IIIA and 5 had stage IIIB disease at diagnosis. The median survival for

patients with stage IIIA and stage IIIB disease were 16 months and 12 months respectively. The number of evaluable patients was too small to derive any meaningful median survival for stage I and II disease.

The outcome of our 29 patients was as follows: 7 are still alive, 8 died from progression of disease, 6 died from treatment-related sepsis and 8 were lost to follow-up.

DISCUSSION

The biological characteristics of our local patients with multiple myeloma are fairly similar to most published data. It manifests mainly in the elderly, median age of 62 years. The sex distribution is approximately equal. Our male to female ratio of 1.2:1 is very similar to that of 1.3:1 in the study by Young[4]. The number of cases at our hospital probably does not reflect the true incidence of myeloma in Singapore because of the system of patient referral to a tertiary referral centre such as ours. Nevertheless there was no racial predilection noted. Diagnosis was not a problem as 48% had the classical triad of criteria and 96.7% had at least 2 of the 3 criteria.

The majority of the paraprotein subtypes in our local patients were IgG (52%) and IgA (26%) and light chain disease (11%). This distribution is very similar to Pruzanski's figures of 52% IgG, 21% IgA and 11% light chain disease[5]. However it is interesting to note that we had 7% of IgD myeloma whereas Pruzanski et al reported only 2%. Whether this reflects a higher incidence of IgD myeloma in the local setting remains to be seen with a larger series of local patients.

At presentation the majority of our patients had rather advanced disease, 75% (21/28) had stage III disease, 18% (5/28) with stage II and only 7% (2/28) had stage I disease. In contrast, Durie and Salmon[2] found 52% with stage III, 31% with stage II and 17% had stage I disease in their study. Whether this is due to a true difference in the biology of the disease here or it merely reflects local patients seeking medical attention later is difficult to distinguish. But it concurs with the general local impression that our patients with myeloma do not do well even with treatment. If the majority of patients present in an advanced stage of the disease, it is inevitable that the overall survival is poor.

The MP combination was most commonly used. In the evaluable patients, this therapy produced an objective response of 40%. Though this figure corresponds to the lower range of response achieved in other series (40-60%)[6], it is encouraging given the more advanced disease seen here. However the overall median survival of 18 months (range of 3-51 months) in the evaluable patients was rather dismal as compared to overall survival varying from 19 to 42 months in published studies[6]. In patients with stage III disease the overall median survival was 16 months for stage IIIA and 12 months for stage IIIB disease. This again is lower than the average of 23 months for stage III disease in the West. The number of patients who were treated with multiple drug combinations was too few to make any reasonable conclusions or comparisons. However with such poor overall survival, one would argue for more aggressive treatment upfront or the use of biological modifiers like alpha-interferon or autologous bone marrow transplantation after achieving an adequate response with MP in order to improve on the current survival.

In summary, many of the clinical features of our local patients with multiple myeloma are similar to those of patients in the West but the disease tends to be in a more advanced stage at presentation with a slightly lower response rate to conventional therapy and a poorer overall survival.

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