Clinicopathological Features and Management of Pakistani Patients with Multiple Myeloma

Pages with reference to book, From 233 To 237

Hina Shaheen,Imran Ghanghroo,lmtiaz Malik (National Cancer Institute and Research Center, Karachi.)

Abstract

Objective: Purpose of the study was to evaluate the clinicopathological features of multiple myeloma in Pakistan and to study the influence of therapeutic management in these cases.
Methods: We retrospectively analyzed 99 newly diagnosed patients with multiple myeloma seen from 1988 to 1996. Diagnostic criteria included bone marrow plasmacytosis, monoclonal gammopathy in serum ot' urine and radiological evidence of skeletal lesions.
Results: There were 57 males and 42 females. Mean age of the patients was 58 years with a range of 23 to 86 years. One-third of the patients were bed ridden at the time of presentation. Common presenting symptoms included bone pain (82%), fatigue (78%) and backache (73%). Physical findings, laboratory features and radiologic assessment revealed pallor (56%), severe anaemia with hemoglobin <8.5 gm/dl (39%), creatinine 2.2 2 mg/dl (57%), serum calcium 2.12 grn/dl (23%), uric acid 2.8 gm/dI (47%) and albumin <3.5 gm/dI (63%). Commonest monoclonal ganimopathy was igG kappa. Majority (71%) of the patients presented with stage Ill disease. Commonest chemotherapeutic regimen utilized was melphalan and prednisolone which was administered to 88% of the patients. Complete remission was observed in 25% and partial remission in 36% of the evaluated patients. Commonest complication during the course of disease was related to skeletal involvement followed by renal failure and bone marrow suppression. Median survival of he patients was 34 months.
Conclusion: Multiple myeloma patients in Pakistan are younger, more frequently have poor performance status and more often present with advanced stage of disease. Response to therapy, however, is adequate and survival is comaparable to Western patients (JPMA 49:233, 1999).

Introduction

Multiple myeloma is a malignant neoplasm of plasma cells arising in the bone marrow. According to the United States surveillance, epidemiology and end results (SEER) program, multiple myeloma accounts for 1% of all malignancies in Whites and 2% of all cancers in Blacks[1,2]. Approximately 14,000 new cases of multiple myeloma are diagnosed in U.S. each year. Age adjusted incidence rates for Whites is 4.7/100,000 in men and 3.2/100,000 in women. Corresponding rates for Blacks are 10.2 in men and 6.7 in women. Median age at diagnosis is 69 years for men and 71 years for women. Incidence of myeloma increases with age. Males are more commonly affected by this disease. Several risk factors have been suggested as etiologically important, including radiation, chemicals such as asbestos, benzene, petroleum products, arsenic, lead, carbon monoxide, etc., farming possibly related to exposure to pesticides, recurrent infections leading to chronic antigenic stimulation in various medical illnesses and genetic fa tors[3]. Association of myeloma with these risk factors, however, has been inconsistent. Myeloma cells release soluble factors which activate the osteoclasts resulting in bone resorption, hypercalcemia, lytic bone lesions, bone pains and pathological fractures[4]. Presence of osteoclast activating factor correlates with the extent of skeletal involvement[5]. Renal involvement (myeloma kidney) occurs in upto 80% of cases and is due to toxic effects of light chains on renal tubular epithelium[6].
Clinical course of multiple myeloma is frequently bi-phasic with an initially chronic stable phase

followed by an accelerated pre-terminal phase. Tumor burden and stage of disease correlate with response to therapy and survival[7,8]. Other important prognostic factors include type of gammopathy, renal impairment, high LDH values and extent of bony involvement[9]. Although institutional variations exist, meiphalan and prednisolone is still regarded as the standard management of an average patient with multiple myeloma[10-12]. Chemotherapy induces renlission in approximately 50% of cases with a median duration of response for two years. Prognosis of these patients with chemotherapy has not changed significantly during the last several decades. Interferon has had a modest effect on the management of multiple myeloma[13-15]. More recently, some encouraging results have been observed with the use of high dose chemotherapy and stem cell transplantation[16-20]. Approximately 5% of patients with multiple myeloma are alive at 10 years after diagnosis[21,22].

Most of these data are from Western countries. Due to paucity of data from developing countries, we reviewed our experience with management of multiple myeloma in Pakistan. We evaluated clinical characteristics, signs and symptoms, laboratory data, modalities of treatment, response to therapy and survival in order to establish our own data base and make comparisons with the Western data.

Patients and Methods

We performed retrospective analysis of all patients with multiple myeloma seen by the authors between 1988 to 1996. Detailed information was available for 99 patients. This information was obtained from the patients medical records, varified by the patients whenever possible and periodically updated. Diagnosis of multiple myeloma was made in accordance with the criteria established by Chronic Leukemia-Myeloma Task Force[23]. Patients were staged using Salmon and Dune staging system[7]. Chemotherapeutic regimen most commonly employed was melphalan 6 mg/m^2/day for 5 days and predinisolone 60 mg/m^2/day for 5 days. A small number of patients were treated with combination chemotherapy regimens such as cyclophosphamide, vincristine and predinisolone (CVP), cyclophospham ide, vincristine, adriamycin, melphalan and predisolone (C-VAMP), or infusion of vincristine, adriamycin and dexamethasone (VAD).

Response to therapy was assessed clinically, radiologically, biochemically and serologically. More than 75% reduction in tumor mass was labeled as complete remission and 50 to 750/0 reduction as partial remission. Less than 50% reduction in tumor mass was considered as stable disease and increase of 25% or more was considered disease progression[1].

ResuIts

Clinical characteristics of the study patients are provided in Table 1.

Table 1. Clinicopathological features of the study patients.

Characteristics	
Number of patients (%)	99 (100)
Age in years	
Mean	58
Range	23-86
<40	7.0%
40-60	56.6%
>60	36.4%
Sex	
Males	57
Females	42
Ratio	1.35:1
Presenting symptoms and signs	
Bone pain	82%
Fatigue	78%
Backache	73%
Pallor	56%
Weight loss	38%
Neurologic deficit	31%
Fever with infection	21%
Fever without infectious cause	15%
Bleeding diathesis	11%

Mean age of the patients was 58 years. Overall, there was a slight male predominance. Commonest presenting symptom was bone pain which in majority of the cases was backache. Fatigue and pallor were also frequently common. Neurologic deficit was observed in almost one-third of the patients at the time of presentation, half of these cases were due to spinal cord compression related to lytic bone

lesions and para-spinal mass. Anaemia was present in almost all the patients and in 39% it was severe enough to require blood transfusion. Forty percent of the patients presented with significant renal dysfunction. LDH was elevated in half of the patients. Almost one-quarter of the patients had hypercalcernia at the time of presentation. Commonest gammopathy was IgG kappa.

Table 2. Laboratory features and radiologic findings.

Characteristics	Percent
Anaemia of any degree	90
Severe Anaemia (<8.5 g/dl)	39
Leucopenia ($\leq 4x10^9/L$)	11
Thrombocytopenia ($\leq 150x10^9/L$)	28
High ESR (>100)	51
Renal dysfunction (Cr >2 mg/dl)	43
High LDH (>450 IU/L)	48
Hypercalcemia (>12 mg/dl)	23
Hyperuricemia (>8 mg/dl)	47
Hypoalbuminemia (<3.5 gm/dl)	62
Immunoelectrophoretic abnormality	
IgG	74
IgA	23
Free light chains	3
Bence Jones Proteinuria	45
Bone involvement on X-rays	
None	2
Osteoporosis/Solitary lesion	14
Multiple lytic lesions	37
Advanced disease including compression fractures	47

Majority of the patients presented at an advanced stage of disease. Twelve patients underwent surgical intervention primarily related to spinal cord compression or bone fracture. Twenty-five patients

received radiation.
Almost 90% of the patients received chemotherapy which was felt to be adequate in majority. A small number of patients (12) were lost to follow-up and hence were not evaluable for treatment outcome. Complete remission was documented in a quarter of the patients. Partial remission was observed in 36% cases.

Table 3. Stage of disease, response to therapy and surgical.

Stage of disease	Number of patient
I	8
II	21
III	70
Treatment with chemotherapy	89
Adequate	77
Inadequate (lost to follow-up)	12
Response to therapy	Percent
Complete remission	24.6
Partial remission	36.4
Stable disease	20.8
Progressive disease	18.2

Median servival of adequately treated patients 34 months.

Some of the common complications observed during therapy included worsening of bone disease (68%), renal failure(59%), need for blood transfusion (57%), hypercalcemia (57%), infections (57%), neurologic problems (38%) and hyperviscosity (9%).
Median survival of the patients was 34 months in adequately treated patients.

Discussion

There are no incidence figures of multiple myeloma available in Pakistan. Similarly, there is paucity of data from other developing countries. It is not clear if myeloma is more common in the developing countries. Infections, which may be etiologically important, are more common in the Third world countries. However, myeloma is a disease of old age. In the United States, <2% of patients are younger than 40 years of age[22,24]. Reduced life expectancy in the Median servival of adequately treated patients 34 months.
developing countries may result in lower than expected incidence of multiple myeloma. Relative frequency of multiple myeloma as a fraction of the total patient population seen during the study period was 2.4% of all malignancies. This may reflect referral bias. In general, myeloma is expected to be under-diagnosed in this country. This is primarily due to lack of awareness as well as inadequacy of laboratory facilities related to serum protein electrophores is, immuno-electrophoresis and quantitative immuno-globulin level testing.

Bone pain is the commonest presenting symptom in myeloma patients[1,22]. We observed similar presentation in our patients. Bone lesions in myeloma are caused by proliferation of abnormal cells as

well as activation of osteoclasts by the OAF[15]. The bone lesions are almost lytic in nature and are rarely associated with osteoblastic new bone formation. This results in associated abnormalities such as bone pain, frequent fractures and hypercalcemia. Frequency of bone involvement in our patients appears higher than what has been observed in the Western countries[22]. In general, our patients presented at a more advanced stage of disease with more frequent spinal cord compression, anaemia, hypercalcemia and renal dysfunction[25,26]. Similarly, higher percentage of our patients presented with stage 111 disease and had poor performance status.

Type of gammopathy observed in our patients is similar to their Western counterparts[1,22]. lgG was the commonest nionoclonal gammopathy on immunoelectrophoresis. Predominant light chains associated with gamma heavy chains were kappa (60%). IgA was the second commonest monoclonal protein Despite more advanced stage of disease, poor performance status and more frequent presence of poor prognostic factors, response to therapy was achieved in almost 60% of the patients. This is similar to what has been reported from Western countries[1,22]. Although many corn plex corn bination chemotherapeutic regimens are in Vogue, they have not been demonstrated to be consistently superior to meiphalan and prednisolone. Some of our patients received interferon, however, none underwent high dose therapy with stem cell infusion. More widespread use of these modalities may improve upon the results achieved in patients with myeloma.

Certain characteristics of this study require emphasis. Most importantly, it is a retrospective analysis and hence suffers from all inherent inadequacies of such an analysis. Several factors of interest could not be properly evaluated such as beta 2 microglobulin levels. Results of this test Were available in only a small number of patients and hence no meaningful information could be obtained. Furthermore, influence of certain treatment modalities such as interferon or other measures of proven benefit such as use of bisphosphonates and erythropoietin could not be properly assessed[12,27,28]. We are presently prospectively evaluating influence of these therapeutic interventions.

In conclusion, multiple myeloma is not an infrequent disorder in Pakistan. Lack of laboratory facilities may be responsible for under-reporting of this disease. Younger age of onset, more advanced stage of disease at presentation and more frequent presence of poor prognostic factors are some interesting features of myeloma in Pakistan. Biologically, however, multiple myeloma appears to be similar to the disease observed in the Western countries. This is primarily reflected by the type of gammopathy, response to therapy and survival.

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