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CLINICO-IMMUNOLOGICAL PROFILE OF PATIENTS WITH MULTIPLE MYELOMA AND CORRELATION WITH RESPONSE TO FIRST LINE THERAPY AT A TERTIARY CARE CENTRE IN INDIA

Immunohaematology

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ABSTRACT

INTRODUCTION: Multiple myeloma (MM) is a clonal plasma cell neoplasm characterized by end organ damage in the form of renal impairment, lytic bony lesions, hypercalcemia and anemia. Management of MM has improved substantially over the past two decades. This study was undertaken to delineate the clinico-immunological profile of MM patients treated at our hospital and to assess their response to first line chemotherapy.

MATERIALS AND METHODS: In this study, we retrospectively analyzed the medical records of all multiple myeloma patients who were managed at this 1000-bedded tertiary care center from early 2006 to Sep 2018. Myeloma was diagnosed using standard criteria. The conventional chemotherapy used at our center is three drug combination chemotherapy and response assessment was done at 4-6 months of induction therapy.

RESULTS: Out of a total of 82 patients of MM, 62 were males and 20 were females. The median age was 63 years. The most prominent clinical symptom was bone pain. Six patients had plasmacytoma. 27 patients had anaemia (Hb<8 gm%) while 20 had serum creatinine ≥2 mg/dl. The monoclonal serum paraprotein in majority of patients (62 out of 82) was IgG. The overall objective response rate (complete response [CR] + very good partial response [VGPR] + partial response [PR]) was 78.05% with ≥VGPR in 85.94% of them.

CONCLUSION: Multiple myeloma is a disease with a variable clinical presentation involving multiple organ systems. The clinico-immunological profile of our study is comparable to the published data both Indian as well as globally.

KEYWORDS

INTRODUCTION

Multiple myeloma is a clonal plasma cell neoplasm with significant morbidity and mortality that is characterized by end organ damage in the form of renal impairment, lytic bony lesions, hypercalcemia and anemia. With the development of better treatment options, multiple myeloma has changed from an untreatable ailment to one that is still not curable but treatable with mostly outpatient therapy. Management of Multiple myeloma has improved substantially over the past two decades. The first major advance was the development of autologous stem cell transplant in the 1980s and 1990s[1]. The other novel agents were first developed in the late 1990s and early 2000s—Thalidomide and Lenalidomide followed by the proteasome inhibitors (PIs)[2]. More recently, monoclonal antibodies, such as Daratumumab and Elotuzumab, and histone deacetylating agents, such as Panobinostat, have also been approved by the US FDA[2]. Multiple myeloma accounts for 1% of all cancers and approximately 10% of all hematological malignancies[3]. It is slightly more common in men than in women, and is twice as common in African-Americans as compared to Caucasians[4]. The median age of patients at the time of diagnosis is about 65 years[5]. The revised International Myeloma Working Group criteria for the diagnosis of multiple myeloma requires the presence of one or more myeloma defining events in addition to evidence of either 10% or more clonal plasma cells on bone marrow examination or a biopsy-proven plasmacytoma. Myeloma defining events consist of CRAB (hypercalcemia, renal failure, anemia, or lytic bone lesions) features as well as three specific biomarkers: clonal bone marrow plasma cells ≥60%, serum free light chain ratio ≥100 (provided involved FLC level is ≥100 mg/L), and more than one focal lesion on MRI[6]. Standard treatment for multiple myeloma consists of novel agent-based induction chemotherapy usually combining one proteasome inhibitor like bortezomib and immunomodulatory agents like thalidomide, lenalidomide, and steroids followed by high-dose melphalan and autologous stem cell transplantation (ASCT) and maintenance therapy[2]. We carried out this retrospective study to delineate the clinical and immunological profile of Multiple Myeloma patients managed at our hospital and to simultaneously assess their response to first line chemotherapy.

MATERIALS AND METHODS

Study setting

This study was conducted at a 1000-bedded tertiary care, government funded hospital in Pune. The Dept of Hematology of our hospital provides out-patient consultation, day care facilities, in-patient hospitalization, bone marrow transplant and other support services. Patients of multiple myeloma from a wide catchment area including Maharashtra, Gujarat, Karnataka, Rajasthan, Madhya Pradesh and Goa seek treatment in this hospital. The conventional chemotherapy that is used at our center is three drug combination chemotherapy. The various induction regimens used are bortezomib/ Lenalidomide/ dexamethasone (VRD), or bortezomib/ cyclophosphamide/ dexamethasone (VCD) or cyclophosphamide/ thalidomide/ dexamethasone. Frail / elderly patients (>75yrs) are started on two drug induction regime – bortezomib/ dexamethasone or Thalidomide/ dexa, or Lenalidomide/ Dexa. Response assessment is done at 4-6 months of induction therapy, and all patients showing any degree of remission, and if transplant eligible, are taken up for autologous hematopoietic stem cell transplant.

STUDY DESIGN

In this study, we retrospectively analyzed the medical records of all multiple myeloma patients who were managed at this center from early 2006 to Sep 2018. All the demographics and disease related parameters were recorded. The details of second line chemotherapy and transplant details were excluded from this study as we just focused on assessing the response to first line chemotherapy. Myeloma was diagnosed using standard criteria. Patients with MGUS / smoldering myeloma were not included. The study protocol was approved by the hospital ethical committee. Newly diagnosed multiple myeloma patients were started on induction chemotherapy as described.

Data collection

Our hospital has a central myeloma registry which is maintained at the Dept of Hematology. As soon as a patient is diagnosed as a case of multiple myeloma, a unique file number is assigned and all the relevant demographic data, clinical presentation, myeloma defining events, investigation results are serially recorded in the file. In this study, we retrospectively compiled all these details of myeloma patients and subsequently analyzed them using appropriate statistical tools.

RESULTS

A total of one hundred patients of Multiple myeloma were managed at our hospital from 2006 to September 2018. Eighteen patients were excluded from the study because of either incomplete data or lost to

follow up before assessment of response to first line chemotherapy.

Out of a total of 82 patients, 62 were males and 20 were females. The male to female ratio was 3.1:1. The median age was 63 years. The most prominent clinical symptom that heralded the onset of multiple myeloma was bone pains and it was seen in 45 out of 82 patients. The other symptoms with which the patients presented were symptomatic anaemia (27 out of 82), fever (06 out of 82) etc. Six patients were detected to have plasmacytoma during the course of their illness. The overall demographic profile of the patients at baseline is as shown in Table-1 and Figure-1

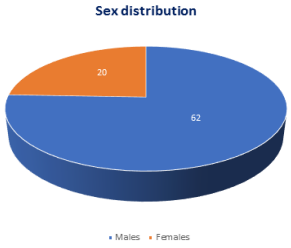

FIGURE-1

TABLE-1

Total no of patients	82
Mean age (years)	63
Hb < 8 gm/dl	27
Hb > 8 gm/dl	55
S. Cr < 2 mg/dl	62
S. Cr > 2 mg/dl	20
S. Calcium < 10 mg/dl	66
S. Calcium > 10 mg/dl	16

A total of 27 patients had hemoglobin level below 8 gm/dl in contrast to 55 who had Hb ≥ 8gm/dl. The mean Hb was 8.2 gm%. Sixty-two patients had baseline S. creatinine < 2 mg/dl while the remaining had creatinine ≥2 mg/dl. Sixteen patients had serum calcium values in excess of 10 mg/dl at baseline. The monoclonal serum paraprotein in majority of patients (62 out of 82) was IgG. There were no IgM paraprotein patients. There were 5 MM patients who did not have any M band on SPEP at diagnosis and had only free light chains. The paraprotein immunoglobulin profile of the patients is shown in Figure-2.

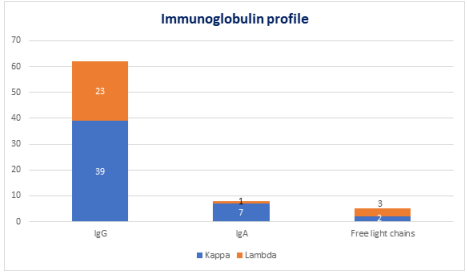

Figure-2

The immunoglobulin profile of the patients as shown above was further subdivided into kappa and lambda type. Out of 62 patients with IgG profile, 39 were kappa predominant and 23 were lambda predominant. Similarly, 7 out of 8 patients with IgA profile and 2 out of 5 patients with light chain disease were kappa predominant.

All the patients were subjected to combination chemotherapy for induction. This included one immunomodulator (either thalidomide or lenalidomide), and / or a proteasome inhibitor (bortezomib) and dexamethasone. The various regimens used were VRd (bortezomib, lenalidomide and dexamethasone), VTd (bortezomib, thalidomide and dexamethasone), VCd (bortezomib, cyclophosphamide and dexamethasone), Thalidomide, Cyclophosphamide Dexa or Lenalidomide, dexa. . The response to first line therapy was assessed at the end of six months using Standard IMWG response criteria.

Out of a total of 82 patients, 50 achieved complete remission (CR) at the end of completion of first line chemotherapy. 5 patients had very good partial response (VGPR), 9 had partial response (PR), 7 had minimal response (MR), 3 had stable disease (SD) while 8 patients had progressive disease. These values are also depicted in Figure-3 below.

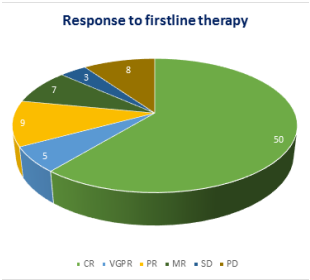

FIGURE-3

The overall objective response rate (complete response [CR] + very good partial response [VGPR] + partial response [PR]) was 78.05% with ≥VGPR in 85.94% of them.

DISCUSSION

MM is one of the plasma cell dyscrasias which is characterized by bone marrow infiltration with clonal plasma cells, production of paraproteins and is associated with end-organ damage including lytic lesions in the bones, renal impairment, hypercalcemia, and anemia. In our study, we analyzed the medical records of one hundred multiple myeloma patients managed at our center over the last twelve years.

In an Indian study by Jacob LA et al published recently, the median age at diagnosis was 54 years (range: 39–85 years)[7]. The median age of our study group was 64.5 years (range: 32-85 years). Multiple myeloma is a disease of the elderly and only about 5-10% patients are below 40 years of age. 3.66% of patients in our study were less than 40 years of age. The male to female ratio in our study was 3.1:1. In a large pooled analysis of multiple myeloma patients done in Scandinavian countries over a six year period by Bringhen S et al, the male to female ratio was approximately 1:1[8]. In an Indian study by Jacob LA et al, the male to female ratio was 2.1:1. Our study has a higher male to female ratio and this can be partly explained by the fact that majority of our dependent population are serving soldiers, thereby, skewing the sex ratio. About 70% of patients with multiple myeloma present with bone pain of varying intensity especially in the ribs or lower back[9]. In our study 55% patients had bone pain. In recent years, the incidence of hypercalcemia in newly diagnosed multiple myeloma patients has been found to be 10-15%[9]. In our study, 19.51% patients had hypercalcemia (S. calcium. 10 mg/dl). The mean Hb in our study was 9.2gm/dl and 56.09% patients were found to have anaemia (Hb<10gm/dl). In a large retrospective analysis of 345 Multiple Myeloma cases done in Iran recently, the mean Hb was 9.70 gm% and 58% patients had Hb< 10 gm%[10]. This is consistent with the findings of our study. In a large study conducted at All India Institute of Medical Sciences, New Delhi, 5.6% of 1129 patients with plasma cell dyscrasias treated over a 10-year period had plasmacytoma. Our study also had a similar number of patients with plasmacytoma i.e. 7.32%[11]. According to Mayo Clinic data regarding the immunoglobulin isotype distribution in patients with multiple myeloma, IgG accounts for 52%, IgA for 21% and only light chain secretion for 16%; IgD and IgM phenotypes are rare (2% and 0.5% respectively)[12]. In a study involving a large number of Multiple myeloma patients conducted in Southern India, the number of patients with IgG type of myeloma was 72%[7]. Our study is in line with the Indian study as we had 75.61% patients with IgG myeloma.

Monoclonal gammopathies are characterized by secretion of monoclonal protein by the clonal plasma cells, which in the majority of patients is in the form of intact immunoglobulins. In addition, normal as well as clonal plasma cells also secrete kappa and lambda light chains unbound to a heavy chain. In a study by M A Moustafa et al, the percentage of kappa free light chain isotype was 68% while that of lambda isotype was 32%[14]. In our study, kappa free light chain isotype was seen in 58.54 % while the remaining were lambda FLC isotype.

The most common first-line therapy in our patients was Bortezomib based regimen. Among our 82 patients, 61% achieved CR, 6% had VGPR, 11% had PR, 8.5% had MR, 3.5% had SD, 10% had progressive disease at the end of completion of first line chemotherapy. These figures are comparable to a study from Mayo clinic Rochester in which a partial response or better was seen among 81% of patients including 32% with a VGPR and 49% with a PR[14]. We used Indian generic Bortezomib (costing Rs 900/- per 2 mg dose) and lenalidomide

(costing Rs 100/- per 25 mg dose). Our outcomes are comparable to the data using originator molecules in western studies.

CONCLUSION

Multiple myeloma is a disease with a variable clinical presentation involving multiple organ systems. The clinico-immunological profile of our study is comparable to the published data both Indian as well as globally. Bone pain is the commonest presentation. MM should be considered as a differential in the workup of anemia in patients above 60 years age.

Conflicts of interest: The authors have none to declare

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