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RESEARCH ARTICLE

CLINICO-HAEMATOLOGICAL PROFILE OF PATIENTS OF MULTIPLE MYELOMA AND RESPONSE TO BORTEZOMIB BASED INDUCTION

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ABSTRACT

Introduction: Multiple myeloma is characterized by proliferation of a clone of plasma cells that manifest by one or more lytic lesions, monoclonal (M) protein in the blood or urine and bone marrow involvement, (Sirohi and Powles, 2004) having varying presentation and hematological features. Complications such as renal failure, infections, anemia, lytic bone lesions and amyloidosis lead to morbidity as well as mortality (UK myeloma forum, 2001). Though untreated the disease is uniformly fatal, newer advances in treatment like autologous hematopoietic stem cell transplantation, mini–transplants and advances in chemotherapy have improved the quality of life and increased survival (Gupta *et al.,* 2002). The three drug regimens that contain bortezomib (proteasome inhibitor), thalidomide (immunomodulator) and dexamethasone (VTD) is highly effective in newly diagnosed myeloma (Richardson *et al.,* 2010).

Aim and Objectives: To study the clinicohematological profile of patients of multiple myeloma and response to bortezomib based induction.

Material and Methods: This was a cross sectional study conducted at Pt. B.D. Sharma PGIMS, Rohtak on all newly diagnosed multiple myeloma patients attending the haematology department, wards and OPD from Feb 2016 to Nov 2017. All newly diagnosed cases who fulfilled the diagnostic criteria of multiple myeloma by IMWG were included in study. Patient's detailed history, physical examination and hematological parameters and other investigations and response to bortezomib based induction recorded on a study proforma and data was analyzed using standard statistical methods.

Results: The study population consisted of 16 male patients and 14 female patients with male to female ratio 1.14:1. Mean age was 56.43±10.58 years. The common clinical symptom were bone pain seen in 83.33% of patients followed by weakness/fatigue (53.33%), renal failure (20%), polyuria/polydipsia (13.33%), infections/fever (10%), isolated bony swelling (6.67%) and neurological features seen in 3.33% of cases. On examination, 90% patients had pallor. Anemia was normocytic and normochromic in maximum of patients (46.67%) and ESR was raised in all patients and 90% patients had ESR >100 mm in 1st hour. 33.33% patients had hypercalcemia with serum calcium ≥11 mg/dl and 33.33% patients had renal insufficiency with serum creatinine ≥2 mg/dl. M-band was positive in all patients. Bone marrow plasmacytosis >50% was seen in 46.67%. Bence Jones proteinuria was seen in 30 % of patients and on skeletal survey lytic lesions were seen in 66.67 % of patients. ORR to VTD induction was 86.67%.

Conclusion: Overall response rate (ORR) was 86.67%, 56.67 % patients achieved ≥VGPR hence VTD is highly active induction therapy before ASCT.

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INTRODUCTION

Samuel Solley reported the first well-documented case of multiple myeloma in Sarah Newbury in 1844 (Kyle, 2000). Multiple myeloma is a disease of elderly. The median age for multiple myeloma is 55 years in India which is a decade less than the United States (Greenlee *et al.,* 2001). The male to female ratio is 1.4 to 1. In India, the incidence varies from 0.3-1.9 per 100,000 for males and 0.4-1.3 per 100,000 for females (Watermonse *et al.,* 1987).

Multiple myeloma accounts for 1% of all neoplastic disorders, 10% of all haematological malignancies in whites and 20% of all haematological malignancies in African Americans (National cancer Registery programme, 2001). Bone pain is the predominant symptom and is observed in 80% of patients.[8] Anemia occurs in 40-73% of patients at presentation and contributes to the weakness and fatigue observed in as many as 82 % of patients (Kyle *et al.,* 2003). In about 25% of patients recurrent infections are the presenting feature. Renal failure occurs in nearly 25% of patients of multiple myeloma. A hemoglobin value less than 12 g/dl is seen in 40-73% of

patients.[8]Anemia is usually normocytic normochromic. The combination of anemia and hyperproteinemia leads to a marked increase of the erythrocyte sedimentation rate in more than 90 % of cases. About 10% of patients have a platelet count <1 lac per cmm at the time of presentation**.** 15-25% have a creatinine value above 2 mg/dl (Kyle *et al.,* 2003). Hypercalcemia is present in 18-30% of patients (Kyle *et al.,* 2003). Total serum M-proteins are increased, albumin is decreased but globulins are increased with reversal of A: G ratio. M component is found in the serum or urine of 99% patients (Roodman, 1997). About 70 % have a monoclonal protein or fragment detected in the urine. Approximately 75% of patients have punched out lytic lesions, osteoporosis or fractures on conventional radiography (MRC working party on leukemia in adults, 1984). The therapy of myeloma includes an initial induction regimen followed by consolidation and/or maintenance therapy and, on subsequent progression, management of relapsed disease. The three drugs combination of Bortezomib (proteasome inhibitor), Thalidomide and Dexamethasone achieve more than 90% response rate (Braunwald *et al.,* 2015). Studies have been carried out in various regions on clinico-hematological profiles of patients of multiple myeloma, however, we conducted this study; because by this study we shall get the clinico-hematological profile of patients of multiple myeloma and their response to bortezomib based induction therapy in the area catered by our institute. Moreover, no such study including response to bortezomib based induction have been conducted at P.G.I.M.S. Rohtak in the past.

MATERIALS AND METHODS

This was a cross-sectional study conducted at Pt. B.D. Sharma PGIMS, Rohtak on all newly diagnosed multiple myeloma patients attending the haematology department, wards and OPD from Feb 2016 to Nov 2017.

Inclusion criteria: All newly diagnosed cases who fulfilled the diagnostic criteria of multiple myeloma by IMWG as mentioned below after taking the informed consent

For diagnosis of multiple myeloma all three must be met (The International Myeloma Working Group, 2003).

1. Clonal bone marrow plasma cells more than or equal to 10% or biopsy proven plasmacytoma.
2. Presence of serum M band or urinary monoclonal protein (except in patients with true non secretory multiple myeloma) and
3. Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically

    a. Hypercalcemia: Serum calcium more than or equal to 11.5 mg/dl or
    b. Renal insufficiency: Serum creatinine more than 2 mg/dl
    c. Anemia: normocytic normochromic with a hemoglobin value of more than 2 g/dl below the lower limit of normal or a haemoglobin less than 10 g/dl.
    d. Bone lesions: lytic lesions, severe osteopenia, or pathologic fractures.

Exclusion criteria: Patients of multiple myeloma already on treatment.

Method of study: A detailed history was taken for fever bone pains, back pain, easy fatiguability, abnormal bleeding or bruising, shortness of breath, decreased urine output, nausea, vomiting, swelling all over the body, polyuria, polydipsia, history of recurrent infections and multiple fractures. Detailed General Physical examination especially for pallor, fever and Systemic Examination of the patient was carried out in all patients. Routine hematological and biochemical investigations, urine for bence jones proteins, skeletal survey, serum protein electrophoresis (SPEP), Immunofixation, bone marrow aspiration and biopsy were carried out in each and every case of multiple myeloma. All newly diagnosed patients of multiple myeloma were given standard VTD chemotherapy regimen for induction in following dose schedule after taking consent in following doses

a. Bortezomib: 1.3 mg/m^2 subcutaneous or intravenous on days 1, 8, 15 and 22.
b. Thalidomide: 100-200 mg oral on days 1-21.
c. Dexamethasone: 40 mg on days 1, 8, 15 and 22

All patients were given 4-6 monthly cycles of VTD to achieve VGPR

All patients received aspirin 75 mg od for deep vein thrombosis prophylaxis and concomitant treatment with antiviral medication i.e. acyclovir 400 mg b.d. The efficacy of treatment was evaluated according to the International Uniform Response Criteria for MM (Durie *et al,* 2006). Assessment of response to bortezomib based induction was assessed by serum protein electrophoresis after induction therapy to quantify the reduction of M band.

Statistical analysis: At the end of the study, the data was collected and statistically evaluated using SPSS 20.0 version software. All quantitative variables were described as Mean (SD). For determining the statistical significance, Chi-square test was used. A p value of <0.05 was considered as significant.

RESULTS

Clinico-haematological profile: Study population consisted of 30 patients with a mean age of 56.43±10.58 years. The age range was 32-80 years. Out of 30 cases, 2 cases (6.67%) belong to age group <40 years, 10 cases (33.33%) are in age group 41-50 years, 6 cases (20%) in age group 51-60 years, 10 cases (33.33%) in 61-70 years and two cases (6.67%) in >70 years age group. There were 16 males (53.33%) and 14 females (46.67%) in the study group with a male to female ratio (M:F) of 1.14:1.

Table 1. Clinical profile of study patients (n = 30)

Symptoms	No. of cases	Percentage
Bone pains	25	83.33
Weakness andfatigue	16	53.33
Renal failure	6	20
Polyuria, polydipsia	4	13.33
Infections/fevers	3	10
Isolated swelling	2	6.67
Neurological symptoms	1	3.33

Table 1 shows that the most common symptom was bone pains seen in 25 cases (83.33%) followed by anemia, weakness, fatigue seen in 16 cases (53.33%). 6 cases (20%) presented

with renal failure, 4 cases (13.33%) presented with polyuria, polydipsia, 3 cases (10%) presented with infections/fever, 2 cases (6.67%) presented with isolated bony swelling, 1 case (3.33%) presented with neurological symptom of neuropathy. Anemia was seen in all (100%) of cases. Median hemoglobin concentration observed was 7.95 g/dl. mean haemoglobin observed was 8.14±1.87 g/dl. Range was 4.8-12.00 g/dl. Platelet count <1.5lacs cells/cmm was seen in 6 patients (20%). Most common morphology of anemia observed was normocytic normochromic seen in 14 patients (46.67%). ESR was increased in all patients. ESR above over 100 mm in the first hour were seen in 27 patients (90%). Out of total 30 cases, 15 patients (50%) had normocalcemia, 5 patients (16.67%) had calcium in range 10.3-10..9 mg/dl and 10 patients (33.33%) had serum calcium above >11. Serum creatinine was normal in 19 patients (63.33%), 1.5-1.9 mg/dl in 1 patient (3.33%) and renal insufficiency with serum creatinine ≥2 mg/dl was seen in 10 patients (33.33%). All showed M-band on serum-protein electrophoresis i.e. an M-band on serum electrophoresis was detectable in 100 % of patient. Mean serum albumin was 3.38±0.93 g/dl. Mean A:G ratio was 0.56±0.27. Only 9 patients (30%) had urinary Bence Jones protein. Out of total 30 patients, 20 patients (66.67%) had osteolytic lesions. Bone marrow examination was done in all of study patients for plasma cell percentage (plasmacytosis). Mean plasma cell percentage was 45.3±23.77. Range of plasmacytosis was 12-84%. Plasma cell burden was <20% in 7 patients (23.33%), 20-50% in 9 patients (30%) and >50% in 14 patients (46.67%) Bone marrow biopsy showed plasma cells >10% in all of patients.

Response to induction: Mean M-protein before induction was 4.42±1.88 g/dl with range of 1.15-8.5 g/dl and median M-protein was 4.32 g/dl. All 30 cases were given induction chemotherapy with 4-6 cycles of VTD regimen and M-protein level was reassessed. After induction mean protein was 0.74±0.86 g/dl with range of 0.00-2.8 g/dl. Mean of difference of M-protein before and after induction was 3.67±1.92. Paired test was applied for the difference of mean and it was found to be statistically significant with p-value of .000.

Table 2. Response to bortezomib Based Induction

Response	No. of Patients	Percentage
ORR	26	86.67
≥VGPR	17	56.67
PR	9	30
MR	4	13.33
TOTAL	30	100

All of study patients i.e. a total of 30 patients received VTD based induction. The median duration of VTD therapy was 4 cycles (range 4-6 cycles). 17 patients (56.67%) achieved ≥VGPR and 9 patients (30%) achieved partial response (PR). The overall response rate (ORR) to VTD induction 86.67%.

DISCUSSION

The ages of patients included in the study group ranged from 32 to 80 years, with a median age of 60 years. This is in accordance with the median age of 55 years reported in National Cancer Registry Programme statistics[7] (Indian council of medical research). The mean age was 56.43±10.58 in the present study. Wadhwa *et al.* and Advani *et al.* 1978 have reported mean ages of 55.4 and 51 years respectively. Out of these 30 cases, maximum number of cases (33.33%) belong to age group of 61-70 years. In our study 6.67% of patients were 40 years or younger than 40 years This is comparable with observations of Kyle *et al.* 2003 and Diwan, *et al.* 2014 reporting 2 % and 5 % patients younger than 40 years respectively. There were 16 males (53.33%) and 14 females (46.67%) in the study group with a male to female ratio (M:F) of 1.14:1 with slight male preponderance. Study conducted by Diwan, *et al.* 2014 showed M:F ratio of 1:1. P. Kaur *et al.* 2014 reported male preponderance with M:F ratio of 1.1:1. Other studies also reported male preponderance. Male to female ratio was found 2:1 by Advani *et al.* 1978 study and in National Cancer Registry Programme statistics (National cancer Registery programme, 2001). The most common symptom in our study was bone pains noted in 83.33% of cases followed by generalized weakness and easy fatiguability in 53.33% of cases followed by renal failure in 20% of cases, polyuria/polydipsia in 13.33% of cases, fever in10%, isolated bony swelling in 6.67% of cases and neurological features in 3.33% of cases. No bleeding manifestation were noted (Table 1). These findings were comparable with study by Diwan *et al.* 2014 in which most common presentation was bone pains in 85% of cases, generalized weakness and fatigue in 55% followed by renal failure in 30% of cases, infections/fever in 35% of cases, neurological symptoms (motor weakness) in 11 % of cases. In studies conducted by Gupta et al[4], bone pains was complaint in 79% of patients. Hemoglobin values in our patients ranged from 4.8 g/dl to 12.0 g/dl with a mean Hb 8.14±1.87 g/dl. A haemoglobin value of <10 was seen in 83.3% of our patients compared with 92.8% in the study by Kaur *et al.* 2014. Similarly significant anemia (Hb<8.5 g/dl) was seen in 60% of our patients compared with 75% in the study by Kaur *et al.* 2014. and 71% in the study conducted at the PGIMER Pondicherry (Subramanian *et al.,* 2009). Gupta *et al.* 1995 have, however reported a 40% incidence of severe anemia in their subset of patients. The anemia was normocytic normochromic in maximum of our patients, as has been reported in literature by Kaur *et al.* 2014. The percentage of our patients having hypercalcemia was 33.33% while Sagale *et al.* 2017 observed hypercalcemia in 23%. Raised serum creatinine more than 2 mg/dl were found in 33.33% of the patients, and study by Diwan *et al.* 2014 showed renal insufficiency with serum creatinine more than 2 mg/dl in 30 percent of patients and the results are comparable between the two studies. An M-band was detectable in 100% of patients. An M-band was detectable in 92.8% patients in the study by Kaur *et al.* 2014 and in 100% of patients in the study by Diwan *et al.* 2014. Urine was positive for Bence Jones protein in 30 % of patients as was reported in study by Diwan *et al.* 2014 in 30% of patients. Among skeletal involvement, lytic lesions were seen in 66.67% of patients compared with Prakash *et al.* 2009 reporting lytic lesions in 62% of patients and 80% in study by Kaur *et al.* 2014 and 85% in study by Diwan *et al.* 2014. The plasma cell burden in our bone marrow biopsies was >50% in 46.67% cases compared with 64.3% in the study by P. Kaur et al[15], 45% in the study by Diwan *et al.* 2014.

Response of VTD regimen in patients of multiple myeloma (bortezomib based induction): The study demonstrate that VTD is highly effective as induction therapy, with 56.67 % achieving a ≥VGPR. It is noteworthy that VTD induction therapy resulted in very high overall response rates (ORR) in previously untreated patients with multiple myeloma of 86.67%, ≥VGPR rate of 56.67% and partial response rate (PRR) of 30%. However, 13.33% patients showed minimal response with MR rate of 13.33%. It is noteworthy that our

results are very similar to interim data from a phase 3 study by the Italian Group For Adult Hematologic Diseases (GIMEMA), where VTD produced 94% overall response rate and ≥VGPR rate of 62% (Cavo *et al.,* 2008). In a study by Kaufman *et al.* 2010 VTD produced 91 % overall response rate and 57 % of greater than or equal to very good partial response rate (≥VGPR) and partial response in 34%. In a study by M. Leiba *et al.* 2014 VTD produced 93 % overall response rate and 62% of greater than or equal to very good partial response rate (≥VGPR) and partial response rate 31%. Before induction mean M-protein was 4.42±1.88g/dl and post induction mean M-protein was 0.74±0.86g/dl. The difference of mean before and after induction was 3.67±1.92g/dl. This difference of mean was statistically significant with p-value of .0001.

Conclusion

A cross-sectional study of 30 patients of multiple myeloma demonstrated that the median age of incidence was 60 years, minimum age of patient with multiple myeloma was 32 years and maximum age was 80 years. Male to female ratio was 1.14:1. Patients most 0commonly presented with bone pain seen in 83.33% of patients, followed by weakness and fatigue seen in 53.33% of patients. Moderate to severe anemia was seen in 83.33% of patients. Most common type of anemia was normocytic normochromic. ESR was raised in all patients. Hypercalcemia and renal insufficiency were seen in 33.33% of patients. M band was positive in 100 % of patients. All patients had bone marrow involvement with plasma cells >10%. 30% patients had Bence Jones proteinuria and 66.67 percentage of patients showed lytic lesions. All above results as regards to age of onset, male to female ratio, clinical presentation, Hb level, type of anaemia, ESR percentage of M-band positivity, serum creatinine, serum calcium level, bone marrow plasmacytosis were comparable with the Indian studies. There was statistically significant fall in mean M-protein after induction. Overall response rate (ORR) was 86.67%, 56.67 % patients achieved ≥VGPR, 30% patients achieved partial response (PR) and 13.33% patient had only minimal response (MR). These response rates are comparable with other studies. Hence VTD is highly active induction therapy before ASCT in patients with multiple myeloma. However it was a smaller study and larger studies are required.

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