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Research Paper

A Clinical Study of Multiple Myeloma with Special Reference to Clinical Presentation in a Tertiary Care Hospital.

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ABSTRACT: *Multiple Myeloma (MM) is a clonal B-cell tumour of differentiated and usually slowly proliferating plasma cells. It accounts for about 1% of all malignant disorders. It has a strong correlation with age and the risk increases with age, peaking at about 60-70 years. In this study we have set out to determine the various signs and symptoms of the patients of multiple myeloma at the time of presentation. . A total of 52 patients were evaluated from April 2015 to April 2016 in the department of Clinical Haematology, Gauhati Medical College and Hospital. Patients were put on different treatment regimens as per the institutional protocol and followed up for a period of 4 months. As described in literature most of the patients presented with symptoms of bone pain, anaemia, infection and hyercalcaemia. This study also stages the patients according to the Revised International Staging System and assesses the short term outcome of different treatment regimens. A greater number of patients presented with advanced stage disease (stage III – 44.23%). Fluorescent in situ hybridization(FISH)studies were conducted in 19 patients of which 52.93% fall in the low risk group and 21.05% fall in the high risk group. Three drug regimen showed better outcome compared to two drug regimen with increased number of patients demonstrating Stringent complete response(sCR) and Complete response(CR).*

KEYWORDS: *Multiple myeloma, FISH, Hypercalcaemia, clonal B-cell tumour*

I. INTRODUCTION

Multiple myeloma (MM) is the second most common haematological malignancy. [1]. It is a B cell malignancy characterized by clonal proliferation of plasma cells in the bone marrow and is associated with an increased level of monoclonal protein in the blood and/or urine[2]. Although the disease remains incurable, outcomes have improved substantially in recent decades as a result of advances in treatment, including high-dose therapy and the availability of novel agents, as well as improvements in supportive care strategies[3]. 34 percent of Multiple Myeloma patients are asymptomatic at presentation with incidental abnormalities on total protein, creatinine, calcium, or hemoglobin laboratory panels[4]. Rare presentations include soft tissue or solitary bone masses (plasmacytomas), hyperviscosity induced arterial infarctions or venous thrombosis, and concomitant amyloidosis with gastrointestinal symptoms, peripheral neuropathy, or cardiomegaly [5].

The incidence of Multiple Myeloma varies within different geographical ares. Multiple Myeloma occurs at the highest incidence in African Americans and Pacific Islanders; intermediate in Europeans and North Americans whites; and lowest in people from developing countries including Asia. Chinese and Japanese populations have a lower incidence than whites[6] . In India, incidence of Multiple Myeloma varies from 1.2 to 1.8 per 100,000.

Many studies have been published describing various aspects of the disease from Europe and the United States over the past 50 years. However, more data is required from India to study the disease course in

our country. The earlier studies reported from India suggested low incidence of the disease. However, subsequent reports in the late nineties have reported an increased incidence of the disease probably reflecting increased awareness, availability of better facilities for diagnosis or truly increased incidence[7].

There has been very few Indian studies which have evaluated patients with Multiple Myeloma. The present study will assess the magnitude of the disease in a tertiary medical centre in North Eastern India and study its clinical profile.

II. MATERIALS AND METHODS

The clinical and biochemical profile of the multiple myeloma patients are studied in this prospective study. Various presentations of the newly diagnosed multiple myeloma patients were recorded, different prognostic markers were evaluated and patients were staged as per the staging criteria. Wherever feasible risk stratification was done based on different chromosomal translocations which were assessed by fluorescent in situ hybridization (FISH) studies on bone marrow samples. Patients were put on different treatment regimens as per the institutional protocol and followed up for a period of 4 months. A total of 52 patients were evaluated from April 2015 to April 2016 in the department of Clinical Haematology, Gauhati Medical College and Hospital.

III. RESULTS AND OBSERVATION

TABLE 1. AGE DISTRIBUTION

Age (in Years)	Number of Patients(n=52)	Percentage(%)
<30	2	3.84
30-39	6	11.54
40-49	10	19.23
50-59	18	34.61
60-69	12	23.08
70+	4	7.69

The mean age was 61.4 years. The peak frequency was in the 6th (34.61%) and 7th (23.08%) decades. Only 8 patients (15.38%) were less than 40 years of age, while 4 patients (7.69%) were over the age of 70.

TABLE 2. SEX DISTRIBUTION

Sex	Number of patients(n = 35)	Percentage (%)
Male	37	71.15
Female	15	28.85

Of the 52 patients, there were 37 males and 15 females, with a male to female ratio of 2.5 : 1.

TABLE 3. SYMPTOMS AT PRESENTATION

SYMPTOMS	YES (Present)	NO (Absent)	Percentage (%)
Bone pain	45	7	86.54
Anaemia(fatigue, malaise, palpitation, dizziness)	41	11	78.85
Fever	25	27	48.08
Symptoms of hypercalcaemia(polyuria, abdominal pain, nausea, vomiting)	14	38	26.92
Bleeding	5	47	9.61
Symptoms of renal disease(oliguria, facial puffiness,shortness of breath)	12	40	23.08
Spinal cord compression	13	39	25
Symptoms of hyperviscosity(visual disturbances, headache, seizures)	9	43	17.31

The most frequent presenting feature was bone pain, occurring in 86.54% of patients. Other common symptoms were those related to anaemia (78.85%), infection (48.08%) and hypercalcaemia (26.92%).

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TABLE 4. SIGNS AT PRESENTATION

SIGNS	YES(Present)	NO(Absent)	Percentage (%)
Lytic bone lesions	40	12	76.92
Pathological fractures	9	43	17.31
Vertebral compression	19	33	36.54
Plasmacytoma	9	43	17.31
Amyloidosis	2	50	3.85
Anaemia	44	8	84.61
Males Hb <13 g/dl	31	6	83.78
Females Hb <12 g/dl	13	2	86.66

Anaemia was the dominant clinical sign occurring in 44/52patients (84.61%). Anaemia was commoner in females (86.66%) compared to males (83.78%). The radiological hallmark of myeloma is the presence of 'punched out' lytic bone lesions, which was present in 76.92% of the patients. The most classical site of involvement was the skull. Vertebral compression fractures were seen in 36.54 % of patients . Pathological fractures were less common (17.31%). The humeri and femurs were the typical sites of involvement. Amyloid occurring in association with myeloma was an unusual finding.

TABLE 5. STAGE OF DISEASE(REVISED INTERNATIONAL STAGING SYSTEM)

R-ISS	NUMBER	Percentage (%)
I	10	19.23
II	19	36.53
III	23	44.23

The majority of patients presented with advanced stage disease (stage III – 44.23%), while early stage disease (stage I) only accounted for 19.23% of the patients.

TABLE 6. RISK STRATIFICATION TESTS

FISH PROBE		NUMBER(n=19)	ISS		
			I	II	III
Del 17p13	POSITIVE	3	0	1	2
	NEGATIVE	16	4	4	8
t(4,14)	POSITIVE	5	1	1	3
	NEGATIVE	14	5	3	6

TABLE 7. RISK STATIFICATION

RISK	NUMBER(n=19)	PERCENTAGE(%)
LOW	10	52.93
INTERMEDIATE	5	26.31
HIGH	4	21.05

FISH studies were conducted in 19 patients of which 52.93% fall in the low risk group and 21.05% fall in the high risk group. Of the 52 patients, 38(73.08%) patients fulfilled transplant eligibility criteria.

TABLE 8. Haemoglobin level:

Haemoglobin	Number of patients (n=52)	Percentage (%)
Hb ≥ 10 g/dl	9	17.31
Hb <10 g/dl	43	82.69
Hb <8.5 g/dl	38	73.08

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TABLE 9. White cell count

White cell count	Number of patients (n=52)	Percentage (%)
<4.0 x 10^9/l	3	5.77
4.0-11 x 10^9/l	13	25
>11 x 10^9/l	19	36.54

TABLE 10. Platelet count

Platelet count	Number of patients (n=52)	Percentage (%)
<150 x 10^9/l	7	13.46
>400 x $l0^9$/l	0	

TABLE 11. ESR

ESR(mm/hr)	Number of patients (n=52)	Percentage (%)
<20	4	7.69
20-100	16	30.77
>100	32	61.54

The mean haemoglobin (Hb) at presentation was 9.38g/dl. In contrast to the low Hb, the white cell count and platelet count was usually normal. Only 5.77 % of patients presented with a leucopenia and 13.46% with thrombocytopenia, compared to 84.61% who manifested with anaemia. The ESR was raised above 20mm/hr in the vast majority of patients (92.30%). The mean ESR was 106mm/hr. A markedly elevated ESR (>100mm/hr) was found in almost two thirds of the patients (61.54%).

TABLE 12. ROUTINE BIOCHEMICAL TEST

- **BLOOD UREA**

Blood Urea(mg/dl)	Number of patients (n=52)	Percentage (%)
<22	5	9.61
≥22	47	90.38

- **SERUM CREATININE LEVEL**

Serum creatinine (mg/dl)	Number of patients (n=52)	Percentage (%)
<1.2	15	28.85
1.2-2	14	26.92
>2	23	44.23

- **SERUM CALCIUM(CORRECTED)**

SERUM CALCIUM(CORRECTED) (mg/dl)	Number of patients (n=52)	Percentage (%)
<8.5	3	5.77
8.5-11	32	61.54
>11	17	32.70

- **SERUM URIC ACID**

SERUM URIC ACID (mg/dl)	Number of patients (n=52)	Percentage (%)
≤7.2	22	42.31
>7.2	30	57.69

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- **SERUM ALKALINE PHOSPHATASE**

ALKALINE PHOSPHATASE (U/L)	Number of patients (n=52)	Percentage (%)
<150	42	80.77
≥150	10	19.23

Hypercalcaemia (>11mg/dl) occurred in 32.70% of patients. Hyperuricaemia was common, being present in almost 2/3 (57.69%) of our patients. An elevated urea of >22mg/dl and creatinine of >1.2mg/dl (after rehydration) was evident in 90.38% and 71.15% respectively. Levels of beta 2 microglobulin >5.5mg/l were found in 61.53% at presentation. In keeping with the non-osteoblastic nature of myelomatous bone disease, the alkaline phosphatase was usually normal (<150U/l) in 80.77%. The LDH level was elevated in 48.08% of the patients The mean bone marrow plasma cell representation was 26.7%. 34.61% of the patients had more than 10% plasma cells, while in 38.46 % a level of >30% was present.

TABLE 13. TRANSPLANT ELIGIBILITY AND TREATMENT GIVEN

TRANSPLANT ELIGIBILITY	THERAPY STARTED		
	BORTEZOMIB+ DEXAMETHASONE	BORTEZOMIB+DEXAMETHASONE+ THALIDOMIDE/LENALIDOMIDE	BORTEZOMIB+ DEXAMETHASONE+ CYCLOPHOSPHAMIDE
TRANSPLANT ELIGIBLE	6	22	10
TRANSPLANT INELIGIBLE	4	4	6

TABLE 14. BEST RESPONSE TO THERAPY AT THE END OF FOLLOW UP PERIOD (3MONTHS)

THERAPY STARTED	Stringent complete response (sCR)	COMPLETE RESPONSE (CR)	VERY GOOD PARTIAL RESPONSE(VGPR)	PARTIAL RESPONSE (PR)	STABLE DISEASE(SD)
BORTEZOMIB+ DEXAMETHASONE	0	1	3	5	1
BORTEZOMIB+DEXAMETHASONE+ THALIDOMIDE/LENALIDOMIDE	4	6	13	2	1
BORTEZOMIB+ DEXAMETHASONE+ CYCLOPHOSPHAMIDE	2	5	8	1	

Accordingly, 10(19.23%) patients were subjected to two drug regime, VD(BORTEZOMIB+DEXAMETHASONE), 42(80.77%) patients received three drug regime, of which 26(50%) received VTD(BORTEZOMIB+DEXAMETHASONE+THALIDOMIDE/LENALIDOMIDE) and 16(30.77%) received VCD(BORTEZOMIB+DEXAMETHASONE+CYCLOPHOSPHAMIDE). Short term response was assessed at 4 months. 40% patients of two drug regime,VD showed CR(10%)and VGPR(30%) where as 88.46% of VTD regime demonstrated sCR(15.38%), CR(23.07%) and VGPR(50%). 93.75% of the patients who received VCD regime showed sCR(12.5%), CR(31.25%) and VGPR(50%). Of the 38 transplant eligible patients, 16(30.77%) patients subsequently, underwent successful autologous stem cell transplantation(ASCT).

IV. DISCUSSION

In the present study among patients with Multiple Myeloma, majority of patients were in the age group 50- 59 years at the time of diagnosis of their illness constituting 34.61% of total. . Advani et al(1978) also reported majority of patients to be in the age group 50 – 59 years of age [8].

In the present study among Multiple Myeloma patients 71.15% were male and 28.85% were female. The M:F ratio was 2.47: 1. Similar male predominance was reported by Advani et al(1978), National Cancer Registry Programme Statistics, P. Kaur et al(2004)[8,9,10].

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In the present study among Multiple Myeloma patients, most common clinical features were bone pain (86.54%) and symptoms related to anaemia (generalized weakness and increased fatigability) (78.85%). In studies by Gupta et al (1995) and Kyle et al(2003), 79% and 58% patients respectively had bone pains at diagnosis[11,12].

In the present study the mean corrected calcium level is 11.08 mg/dl. 32.70% of the Multiple Myeloma patients has corrected serum calcium level >11mg/dl. Makkar et al(2014) reported serum calcium level of >11mg/dl in 41.66% of Multiple Myeloma patients[13].

In the present study a feature common to the Multiple Myeloma patients seen is late stage presentation, with advanced stage disease. Based on the International Staging System(ISS) the majority of patients with Multiple myeloma presented with stage III disease(44.23%) whereas patients with stage l and stage ll constitute 19.23% and 36.53% of the patients. Similar observation was made by P. Kaur et al2004) who reported higher incidence of stage lll disease(64.3%) as compared to stage ll(28.5%) and stage l(7.2%) disease. Greipp et al(2005) also reported 28%, 33% and 39% of patients presenting with stage l, ll, and lll disease respectively[14].

In the present study Fluorescent in situ hybridization (FISH) to detect adverse translocation t(4,14) and del17p13 was done in 19 patients with Multiple Myeloma and risk stratification was done using combination of ISS and FISH. t(4,14) was found in 5/19 (26.31%) patients and del17p13 was found in 3/19(15.79%) patients with Multiple Myeloma. Accordingly, majority (42.10%) of Multiple Myeloma patients were having low risk at presentation. Intermediate risk was present in 36.84% of patients and high risk in 21.05% of the patients. Similar observations were made in various other studies. In the study done by Avet-Loiseau H et al(2013) patients with low, intermediate and high risk disease constituted 51%, 29% and 20% of total respectively[15]. Boyd KD et al(2012) reported high, intermediate and low risk in 38%, 48% and 14% of their patients respectively[16]. Neben K et al(2010) observed 42%, 44% and 14% of their patients had low, intermediate and high risk disease[17].

In the present study response to therapy was assessed after 4 cycles of induction chemotherapy. In the patients receiving VD, 10% patients achieved CR, 30% patients achieved VGPR and 50% patients achieved PR. In the three drug regime, patients receiving VTD achieved sCR/CR, VGPR and PR in 30.77%, 46.15% and 15.38% of the Multiple Myeloma patients. Patients receiving VCD achieved sCR/CR, VGPR and PR in 18.75%, 31.25% and 31.25% of the Multiple Myeloma patients. Moreau P et al(2011) observed that patients receiving 4 cycles of VD or VTD , the complete response (CR) rate was the same in both groups (13% in the VTDD arm, 12% in the VD arm)[18]. However, the CR plus very good partial response (VGPR) rate was significantly higher in the VTD arm as compared to VD group. (49% vs 36%). Rosinol et al (2012) reported that in patients receiving VTD regime, 35%, 60% and 25% of patients achieved sCR/CR, VGPR and PR respectively[19]. In the study done by Moreau et al (2011) patients on VTD regime, 31%, 49% and 39% patients achieved sCR/CR, VGPR and PR respectively[20].

V. CONCLUSION

In the present study an attempt has been made to study the clinical spectrum and response to treatment with short term follow up in patients diagnosed to have Multiple Myeloma. Among a total of 52 patients, the peak incidence was seen in the 5^{th} and the 6^{th} decades of life. A slight male predominance was seen. Presenting complaints in majority of Multiple Myeloma patients were bone pain, increased fatigability, fever, polyuria, lower limb paresthesias and oliguria. Nearly all patients were anaemic and lytic bone lesions were evident in three fourth of the patients. Majority of the Multiple Myeloma patients presented with advanced disease and nearly half of the patients had renal impairment at the time of presentation. In those patients in whom Fluorescent in situ hybridization was done, half were having low risk at presentation. Majority of the patients were transplant eligible at the time of presentation. All the patients were managed with bortezomib based regimen. Most patients were treated with three drug regimen consisting of bortezomib, dexamethasone and either thalidomide or cyclophophamide while 11.54% of the patients received two drug regimen containing bortezomib and dexamethasone. Stringent complete response(sCR), Complete Response(CR) and Very Good Partial Response(VGPR) was better achieved with three drug regimen as compared to two drug regimen and that too in those receiving bortezomib, dexamethasone and thalidomide.

Since this was a hospital based study with a small sample size, a larger study recruiting more patients with a longer duration of follow up is necessary for a better understanding of the disease and to arrive at a definite conclusion.

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