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Review Article

Clinical profile and treatment outcomes of transplant-ineligible multiple myeloma patients from a tertiary centre in Southern India: A Retrospective Review

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ABSTRACT

Background: Multiple myeloma (MM) is the second most common haematological B cell malignancy, resulting from clonal proliferation of plasma cells in the bone marrow. With novel treatment regimens, 5 year survival rates of multiple myeloma have consistently improved from 35% to above 50%. Data on treatment and survival outcomes of multiple myeloma is scarce, especially from developing countries **Methods**: A retrospective review was done in the department of Radiotherapy and Oncology, Government medical college Trivandrum, Southern India. The study aimed to evaluate the clinical profile and treatment outcomes in transplant-ineligible multiple myeloma (TIMM) patients diagnosed and treated between the years 2011 and 2019. **Results**: The review included 173 transplant ineligible patients with a mean age of 61.8 years with a male predominance 1.3:1. Anemia was present in 65.3%(113) patients, hypercalcemia in 11.6%(20) and renal dysfunction in 19.1%(33) patients. Osteolytic bone lesions were identified in 63.6%(110) patients. M spike was noted in 86.1%(149) patients with an elevated IgG in 75.1%(130) and elevated kappa light chain in 66.9%(117) patients. Majority of patients (62.5%) received Bortezomib containing doublet or triplet chemotherapy. After induction chemotherapy, 24.3%(42) patients had complete response, 22.9% (40) had very good partial response, 27.4%(48) had partial response and 4% had progressive disease. After a median follow-up of 25 months, progression free survival rates at 2 year and 5 year was 83.9% and 33.7%, with overall survival rates 54.5% and 44.1% respectively. Age, M spike, raised immunoglobulins, free light chain assay, chemotherapy regimen and treatment response outcomes had showed significant association with survival outcomes. **Conclusion**: Multiple myeloma is a disease with variable clinical presentation and multisystem involvement. Individualised treatment strategies along with novel therapeutic agents have improved the survival and would escalate the outcomes in future.

Keywords: *Multiple myeloma, Treatment outcomes, Transplant ineligible myeloma cases.*

INTRODUCTION

Multiple myeloma is a B-cell lineage malignancy, characterised by aberrant proliferation of clonal plasma cells within the bone marrow(1). Multiple myeloma (MM) is characterized by ≥ 10% clonal plasma cells in the bone marrow or biopsy-proven bony or extramedullary plasmacytoma with a myeloma-defining event: hypercalcemia, renal failure, anemia, or bone lesions; or any biomarker of malignancy such as clonal plasma cells ≥ 60%, a serum-free light chain (FLC) ratio of ≥ 100, or 1 focal lesion on magnetic resonance imaging(2). There are three main stages of plasma cell disorders leading up

to a diagnosis of multiple myeloma; monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM) and symptomatic multiple myeloma(3).

MM accounts for about 1% of human neoplasms, almost 2% of deaths due to cancers, and 12–15% of all cases of hematological malignancy(4). Patients are treated with bortezomib, lenalidomide, and dexamethasone (VRD) followed by autologous stem-cell transplantation and subsequent maintenance with lenalidomide and dexamethasone. Such patients can achieve a median overall survival (OS) of 75 months(5)(6). In transplant-ineligible patients, induction with bortezomib containing regimens and continuous maintenance therapy with bortezomib or lenalidomide containing regimen until disease progression or intolerance, is the mainstay of treatment. But the choice of therapy is individualised according to patient factors(7). Over recent decades, the use of novel therapeutic agents and autologous stem cell transplantation (ASCT) have drastically improved survival rates(8). The identification of new therapeutic target agents such as pomalidomide, carfilzomib, panobinostat, monoclonal antibodies like daratumumab and elotuzumab have brought significant change in the outcomes(9). This study was done to review the clinical profile and treatment outcomes of multiple myeloma in a developing country, to analyse the current status and to recommend priorities for the future.

MATERIALS AND METHODS

We performed a retrospective chart review of Multiple myeloma patients diagnosed and treated between January 2011 and December 2019 in a tertiary hospital in Southern India. Ethical approval was obtained from the Institutional Research Ethics Committee. Patients who met the diagnostic criteria of active MM according to the International Myeloma Working Group (IMWG) were included(10). Transplant eligible patients were referred to higher centres, hence such patients were not included. Transplant ineligibility was decided by the transplant eligibility criteria along with institutional policies, clinician's selection and patient's choice(11). Medical case records of patients were reviewed and demographic data including age, gender were collected. Presenting symptoms, Eastern Cooperative Oncology Group (ECOG) performance status, laboratory parameters like complete blood count with an erythrocyte sedimentation rate (ESR), renal and liver function tests, lactate dehydrogenase (LDH), urinary bence-jones proteins, β2 microglobulin, serum protein electrophoresis (SPEP) with immunofixation and free light chain assay, skeletal survey, bone marrow plasma cell percentage with immunohistochemistry CD138 were reviewed. Treatment response was assessed with clinical profile, serum electrophoresis with immunofixation assay based on modified IMWG guidelines.

The efficacy outcomes included response rate, Progression free survival (PFS) and overall survival (OS). PFS was defined as the time of treatment initiation to progression, death, or last follow-up. OS was measured from the time of treatment initiation to death or last follow-up. Statistical analysis was carried out using SPSS version 22. Qualitative data was presented in terms of frequencies and percentages. Mean and standard deviation was reported for quantitative variables. Chi-square test was used to determine differences in baseline and outcome variables among categorical variables. Survival curves were constructed according to the Kaplan-Meier method and the impact of covariates of interest was assessed using the log-rank test.

RESULTS

Sociodemographic Characteristics:

A total of 173 TIMM patients were analysed, of which 56.6% (98) were males. Mean age was 61.8 years (range 50 to 85). Majority (89%) belonged to ECOG performance status 1-2. (Baseline characteristics of patients are shown in Table 1).

Baseline characteristics		%(Number) 173
Sex	Male Female	56.6(98) 43.4(75)
Presenting symptoms	Weightloss Fatigue Bone pain Backpain	8.1(14) 45.1(78) 22.6(39) 25.5(44)
Bones	Long bones Spine Pelvis Skull	32.4(56) 46.3(80) 8.7(13) 5.8(19)
ISS	2 3	1.7(3) 98.3(170)
Serum Creatinine	Normal Raised	80.9(140) 19.1(33)
Hemoglobin	Normal Low	34.7(60) 65.3(113)

ESR	Normal Raised	2.9(5) 96.5(167)
Elevated serum lactate dehydrogenase	Raised normal	53.8(93) 46.2(80)
Calcium	Normal High	87.9(152) 11.6(20)
ALP	Normal Raised	73.4(127) 26.6(46)
B2MG	High Normal	56.6(98) 27.2(47)
Qualitative electrophoresis	M band No Band Abnormal band	86.1(149) 11.6(20) 2.2(4)
Quantitative electrophoresis	IGA IGG IGM	9.2(16) 75.1(130) 1.7(3)
Free light chain	Kappa Lamda	66.9(117) 12.6(22)
Kappa Lambda ratio	Normal Increased	44(77) 38.3(67)
Bone marrow positivity	>10 <10	63.6(110) 19.1(33)
Bone lesions	Present Absent	63.6(110) 35.8(62)
RT given	Yes	9.2(16)
Chemotherapy	Doublet Triplet Dexa Bortezomib Lenalidomide Chemo	6.4(11) 38.2(66) 24.3(42) 11.6(20) 5.8(10) 13.9(24)
Completed 6 cycles	Yes No	69.9(121) 21.4(37)
Reassessment	Yes No	61.8(107) 15.6(27)
Remission	Biochemical Clinical Pathological Immunologic	35.9 (62) 9.9 (17) 18.6 (32) 50.9 (88)

Clinical presentation:

Fatigue was the most common presenting symptom (45.1%) followed by bone pain and backpain (22% and 25%) and weightloss (8.1%). Common sites for bone pain were the spine (46.3%), long bones (32.4%) and pelvis (8.7%). Imaging showed osteolytic bone lesions in 63.6% (110) patients and 9.2% (16) of patients received skeletal radiotherapy during their course. None of our patients presented with thrombotic manifestation or hyperviscosity.

Anemia (<10g/dl) was present in 65.3%(113) patients with mean value of haemoglobin 8.99g/dL, Hypercalcemia was present in 11.6%(20) with mean value of 9.46mmol/L. Renal dysfunction was observed in 19.1%(33) patients while elevated ESR and LDH was seen in 96.5%(167) and 53.8%(93) patients respectively. Alkaline phosphatase was raised in 26.6% (46) patients. Elevated monoclonal protein was seen in 86.1% (149) patients with an elevated IgG in 75.1% (130), and IgA in 9.2% (16) patients. Free light chain assay showed 66.9% (117) and 12.6% (22) as kappa and lambda variant with an increased ratio in 38.3% (67) patients.

Bone marrow plasma cell percentage >10% is seen in 63.6% (110) patients and the percentage of plasma cells ranged from 10% to 92%. Beta2 microglobulin was found to be increased in 56.6% (98) patients. International Staging System was used for staging and 98.3% (170) belonged to ISS stage III.

Treatment:

Out of 173 patients evaluated, 153(87.4%) received six months of induction chemotherapy and 69.1% (121) patients completed the planned cycles. The most prescribed initial chemotherapy regimen was triplet therapy with bortezomib-

lenalidomide-dexamethasone (38.2%) followed by doublet therapy with bortezomib, in 24.3% patients dexamethasone or lenalidomide dexamethasone. Other agents used were single agents (bortezomib/lenalidomide/dexamethasone) or CyBorD, melphalan, endoxan. All patients received adjunctive bisphosphonate treatment, prophylactic therapy for infections and antiplatelets.

On reassessment after induction, 24.3% (42) patients had complete response, 22.9% (40) had very good partial response, 27.4% (48) had partial response and 4% had progressive disease. 35.9% (62) had biochemical remission, 9.9% (17) had clinical remission, 18.6% (32) had pathological remission and 50.9% (88) had immunologic remission.

Outcomes:
On survival analysis, 10 (5.7%) patients were lost to follow-up and 79 died (45.1%). The 2 year and 5-year progression free survival was 83.9% and 33.7% with standard error 3.6 and 6.4 respectively. At a median follow-up of 25 months, the 2 year and 5 year overall survival rates were 54.5% and 44.1% with standard error 4.1 and 4.8 respectively. On variate analysis age, presence of m band, elevation of immunoglobulins, free light chain assay, chemotherapy regimen received and treatment response outcomes showed significant association with survival outcomes. (Kaplan meier curves of disease free survival and overall survival is shown in the figure 1 & 2).

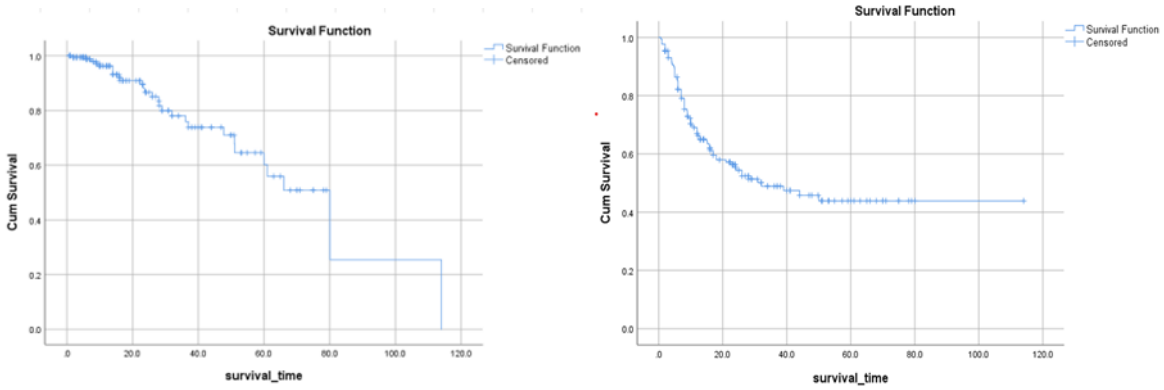

Figure 1 shows disease free survival and figure 2 shows overall survival outcome of multiple myeloma

DISCUSSION
MM usually develops insidiously and is mainly observed in people over the age of 60 years with male predominance(12). The incidence of multiple myeloma is growing over last few decades in developed countries with median age being 69 years, with two-third of the patients being men(25). Data from developing countries had reported 61 years as median age with high male-to-female ratio(13). Our study had also showed similar results with mean age 61.8 years. Patients who are >50 years of age at diagnosis displayed significantly shorter median survival times than younger patients(14).

Most of our patients presented with fatigue, bone pain and backpain. Sadia sultan et al reported that majority of their patients presented with fatigue (81.9%) and backaches (80.3%). Other studies from India also reported similar symptoms(17). Around 75% of MM patients had reported bone lesions such as punched-out lytic lesions, osteoporosis or fractures on conventional radiography(15). Spinal cord compression was detected in a considerable proportion of myeloma patients (11-25%)(16). Bone lesions was found in 63.6% of our patients and 9.2% of them had received skeletal radiotherapy.

The common clinical manifestations of multiple myeloma are anemia, infections, lytic or osteopenic bone disease, or renal failure. Studies have shown that low hemoglobin, hypercalcemia and renal dysfunction have negative prognostic value for the survival of multiple myeloma(16)(17)(18). Anemia was observed in 65.3% of our patients but hypercalcemia(11.6%) and impaired renal function(19.1%) was present in low proportion of patients. This might be due to the proposed upper range of calcium and creatinine as 11mg/dl and 2mg/dl. The most common immunoglobulin reported in the studies about multiple myeloma was IgG followed by IgA which was similar to our results(20).

Biswal et al reported 83.82% of patients demonstrated satisfactory response to therapy (either complete response or VGPR) as compared to 70% by the ICMR consensus document(22). In our study only 47.2% achieved complete to very good partial response, this might be because our study had included only transplant in eligible patients. Tandon et al reported rates of VGPR or better were as follows: 29% after 2 cycles, 42% after 4 cycles, and 66% as overall best response(23). Qian et al reported the first year overall survival rate of multiple myeloma as 85.8%, third year as 64.0%, and fifth year as 42%(20). Our survival results showed 54.5% survival at 2 years and 44.1% at 5 years. This reflects though the disease responds to initial chemotherapy regimens, it could not be translated to long term survival. This requires further attention for better survival outcomes.

Our study had observed a significant association between the factors such as age, myeloma spike, raised immunoglobulins, light chains and survival outcomes. Qian et al had also reported age as an independent prognostic factor(20). Similar studies on multiple myeloma had reported other factors influencing the survival such as gender, thrombocytopenia, hypoalbuminemia and bone marrow percentage of plasma cells(16)(20). High LDH, and ISS 3 were reported as worse prognostic factors for MM patients(8)(10)(17)(19)(24). According to Qian et al, two hundred and fourteen MM patients out of 548 have high levels of β2-MG and shorter OS. Snozek et al had reported FLC ratio also as an important prognosticator of the disease(21).

The limitations of this study include retrospective nature of analysis, small sample size and short time of followup. Cytogenetic detection and MRD status are not routinely done at our institution during the study period. Our study findings might not be generalizable to the overall population of MM patients.

CONCLUSION

Our study observed multiple myeloma as a disease of the middle aged, with a median age of 60 years and male preponderance. About half of the patients had complete or very good partial response to induction chemotherapy. The survival rates showed an improvement initially but declined over years. The main challenge further will be to identify the most efficient therapeutic strategies in induction and maintenance regimens tailored according to the risk stratification and patient characteristics. Future research efforts should be directed toward multicentre cohorts for prospectively determining the depth of response to treatment and prognostication of the disease.

Ethics approval

Ethics approval was given by the Hospital Ethics committee HEC No 01/20/2021/MCT, Government medical college Trivandrum where the study was conducted

Competing interests

No conflicts or competing interests

Authors' contributions

First author collected data and prepared manuscript. Second author helped in preparing, proofreading and editing the manuscript. Third author did the statistical analysis of the study. Fourth author was the motivation and reason behind this study

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