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Original Research Article

Clinical study of multiple myeloma and treatment responses in a tertiary care centre

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ABSTRACT

Background: Multiple myeloma (MM) evolves from Monoclonal gammopathy of unknown significance (MGUS), a premalignant clinical condition. Second to non-Hodgkin's lymphoma, MM is the most common haematological malignancy. The aim of the study was to review the clinical profile and response of individuals treated for MM from this part of country.
Methods: We evaluated data of patients with MM managed between 2013 and 2019 at a tertiary care cancer hospital in Rajamahenderi, India. Data regarding demographic variables, clinical features, disease characteristics and treatment details were collected and analysed.
Results: Total of 54 patients with MM were managed. Mean age was 59.4 years. Males accounted for 63%. Bone pain (90%) was the most common symptom. Elevated serum creatinine was noted in 16.7% and M band in 42 (77.8%). X-ray of skull showed lytic lesions in 41 (75.9%). Mean haemoglobin value was 8.8±1.9 g/dl and serum calcium was 9.12 mg/dl. Majority of subjects, 44 (81.48%) belong to stage IIIA, 9 (16.67%) to stage IIIB, and 1.85% to stage IIA of Durie Salmon staging system. No response was noted in 17 (31.5%), 4 (7.4%) subjects had a progressive disease even on treatment, and 8 (14.8%) subjects had a very good partial response. Median survival of subjects belonging to DSS stage II was 17 months, IIIA was 11.037 months and stage IIIB was 17.463 months.
Conclusions: MM has an early onset in India. Though MM is an incurable disease, many promising treatment options are there which lead to increase in survival. Early treatment helps in improving mortality rates, better quality of life and decreases disease burden.

Keywords: MGUS, Staging, Survival analysis

INTRODUCTION

Non-communicable diseases (NCDs) are now responsible for the majority of global deaths, and the single most important barrier to increasing life expectancy in every country of the world in the 21st century is cancer, which is expected as the leading cause of death.[1] Of all cancers, Multiple myeloma accounts for 1% and approximately 10% of all hematologic malignancies.[2] Multiple myeloma is slightly more common in men than in women, and is twice as common in African-Americans compared with Caucasians.[3] The median age of patients at the time of diagnosis is about 65 years.

Unlike other malignancies that metastasize to bone, the osteolytic bone lesions in multiple myeloma exhibit no new bone formation.[4] Bone disease is the main cause of morbidity and can be best detected using low-dose Whole body computed tomography (WB-CT), Fluoro-deoxyglucose (FDG), Positron emission

tomography/computed tomographic scans (PET/CT), or Magnetic resonance imaging (MRI).[5] Other major clinical manifestations are anaemia, hypocalcaemia, renal failure, and an increased risk of infections. Extramedullary disease (EMD) as an initial presentation at the time of initial diagnosis accounts for approximately 1% to 2% of patients, while 8% of patients develop EMD later on in the disease course.[6]

Almost all patients with multiple myeloma evolve from an asymptomatic pre-malignant stage termed Monoclonal gammopathy of undetermined significance (MGUS).[7,8] And, MGUS progresses to multiple myeloma or related malignancy at a rate of 1% per year.[9,10] In addition to evidence of either 10% or more clonal plasma cells on bone marrow examination or a biopsy-proven plasmacytoma, the diagnosis of multiple myeloma requires the presence of one or more Myeloma defining events (MDE). MDE consist of established CRAB (hypercalcaemia, renal failure, anemia, or lytic bone lesions) features as well as three specific biomarkers: clonal bone marrow plasma cells ≥60%, serum Free light chain (FLC) ratio ≥100 (provided involved FLC level is ≥100 mg/l), and more than one focal lesion on MRI. Survival in multiple myeloma has improved significantly in the last 15 years.[11] The initial impact came from the introduction of thalidomide, bortezomib, and lenalidomide.[12-15] Using drugs that have shown activity in multiple myeloma, numerous combinations of treatment regimens have been developed.

Specialization especially in oncology has no doubt raised the standards of care of patients with cancer, but it has escalated the cost of cancer care beyond the reach of an average citizen without aid or charity. For a common man, getting right treatment for cancer is a big challenge due to the finances involved in getting cancer care.

Aarogyasri Scheme is the flagship healthcare program of all health initiatives, introduced in combined Andhra Pradesh (AP) in April 2007, before the AP re-organisation, with a mission to provide quality healthcare for the poor-to achieve 'Health for all'. The Aarogyasri scheme shall provide coverage for the services to the beneficiaries up to Rs. 2.50 lakh per family per annum based on floater basis. For patients diagnosed with cancer, recently in 2020, certain changes have been made to provide entire treatment completely free of cost. We undertook this study to know the profile of colon cancer patients benefited under the Aarogyasri scheme.

METHODS

Study design

An ambi-directional study was conducted in which seven years database of patients with multiple myeloma was undertaken in GSL Trust Cancer Hospital attached to GSL Medical College and General Hospital, Rajahmundry. The records of multiple myeloma patients taken from the Central Record Section in the duration of 1st January 2013 to 31st December 2019. Institutional Ethics Committee (IEC) approval was taken.

The aim of the study was to assess the utilisation of Aarogyasri Community Health Insurance scheme for accessing MM care services and to study the demographic profile, clinical presentation and management of patients with MM. All patients of MM were evaluated by medical oncologists. Data regarding the demography, patient presentation, staging, treatment and follow-up was documented.

Inclusion criteria

All diagnosed patients of MM who had received treatment were included.

Exclusion criteria

Diagnosed MM patients not fit for treatment or who have not given consent for treatment.

Statistical analysis

All statistical analysis was done by using SPSS software version 20.0, MEDCALC software version 14.1 and MS excel 2007. Descriptive data was presented as percentages. Data also tabulated and graphically represented. Keplan Meier test was done to estimate the treatment survival probability and DSS staging survival probability.

RESULTS

A total of 54 patients were diagnosed with multiple myeloma between 2013 and 2019. Mean age was 59.4 years (range 31 years to 89 years). Males accounted for 63%. Out of 54 study subjects, most subjects (49) presented with bone pains followed by loss of appetite (29). Loss of weight accounts for the 3rd most common symptom seen in 28 subjects, followed by fever in 11 subjects. Forty-three subjects presented with other features such as pathological fractures, generalized weakness, low backache, paresthesias (Figure 1).

Out of 54 study subjects, nine subjects had elevated renal function test in the form of elevated blood urea and serum creatinine amounting for 16.7% of the study population. 45 (83.3%) subjects had normal renal function. In the present study, when the subjects are tested for urine Bence Jones proteins, they were present only in 7 (13%) subjects and absent in the remaining 47 (87%) subjects. Out of the study population of 54 subjects, 42 (77.8%) had the presence of M band on serum protein electrophoresis. It is observed that 40.7% (22) of subjects have bony lesions and X-ray of the skull showed lytic lesions in 41 (75.9%) subjects (Figure 2).

Twenty patients (37%) had haemoglobin levels below 8 g/dl. 19 (35.2%) between 8.1 to 10 g/dl, 12 (22.2%)

between 10.1 to 12 g/dl and 3 (5.6%) had their haemoglobin level above 12 g/dl. The mean haemoglobin value was 8.8±1.9 gm/dl (Figure 3). In the present study with 54 subjects, 41 (75.9%) had serum calcium levels below 10.1 g/dl, 5 (9.3%) between 10.2 to 10.9 g/dl, 12 (22.2%) and 8 (14.8%) had their serum calcium level above 11 g/dl. The mean value was 9.12±1.5 g/dl (Figure 4). Durie Salmon system of staging was used to stage the study subjects and, out of 54 study subjects, none of the patients belong to DSS stage I or DSS stage IIB. Majority of subjects i.e.; 44 (81.48%) belong to stage IIIA, 9 (16.67%) belong to stage III B, and 1 (1.85%) belonged to stage IIA. Out of 54 subjects in the study group, 2 (3.7%) subjects lost to follow up, 17 (31.5%) subjects had no response, 4 (7.4%) subjects had a progressive disease even on treatment, 12 (22.2%) subjects had stable disease, 11 (20.4%) subjects had a partial response and finally 8 (14.8%) subjects had a very good partial response. From the survival analysis, it is proclaimed that the median survival of study subjects is seven months with 95% CI between 4 to 47 months. The Kaplan Meier survival analysis shows that the median survival of subjects belonging to DSS stage II is 17 months, and that of DSS stage III A is 11.037 months. The median survival of subjects with DSS stage III B is 17.463 months (Figure 5). Median survival of 14 (25.9 %) subjects treated with Thalidomide and dexamethasone (TD) was 10.571±3.162 years, and for 37 (68.5%) subjects who were treated with Lenalidomide and dexamethasone (RD) was 12.387±2.089 years. Remaining 3 (5.6%) subjects treated with other regimens had a median survival of 15.333±12.347. Hazards ratio between the groups receiving different treatment regimens showed 0.8378 for lenalidomide over thalidomide, showing there is approximately 17% risk reduction or superiority of lenalidomide over thalidomide (Figure 6).

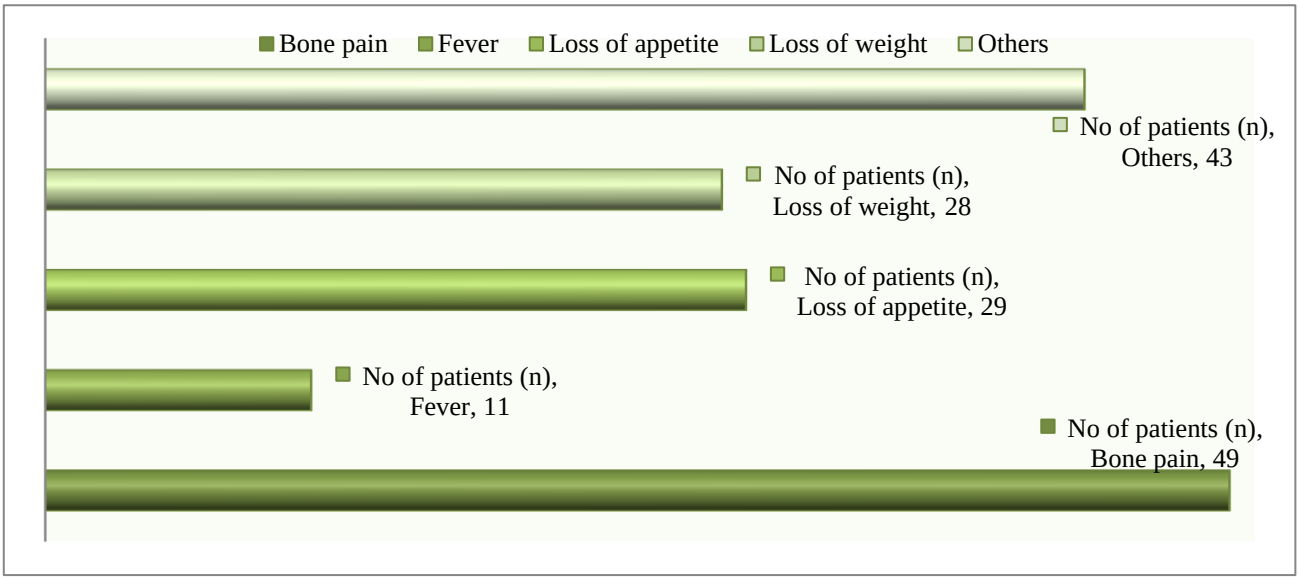

Figure 1: Distribution of study subjects based on clinical features.

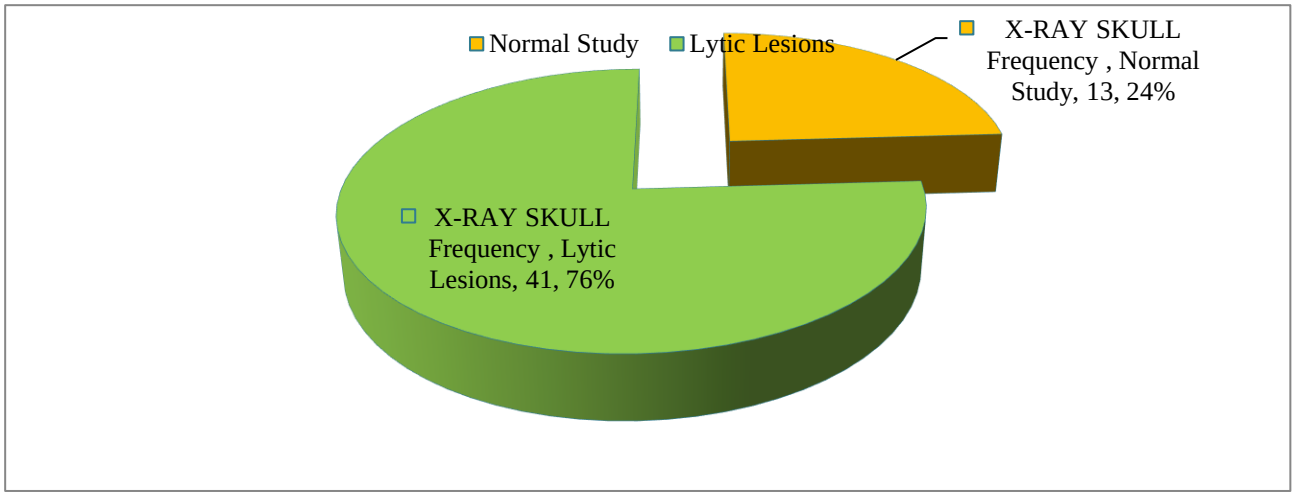

Figure 2: Distribution of study subjects according to X-ray skull.

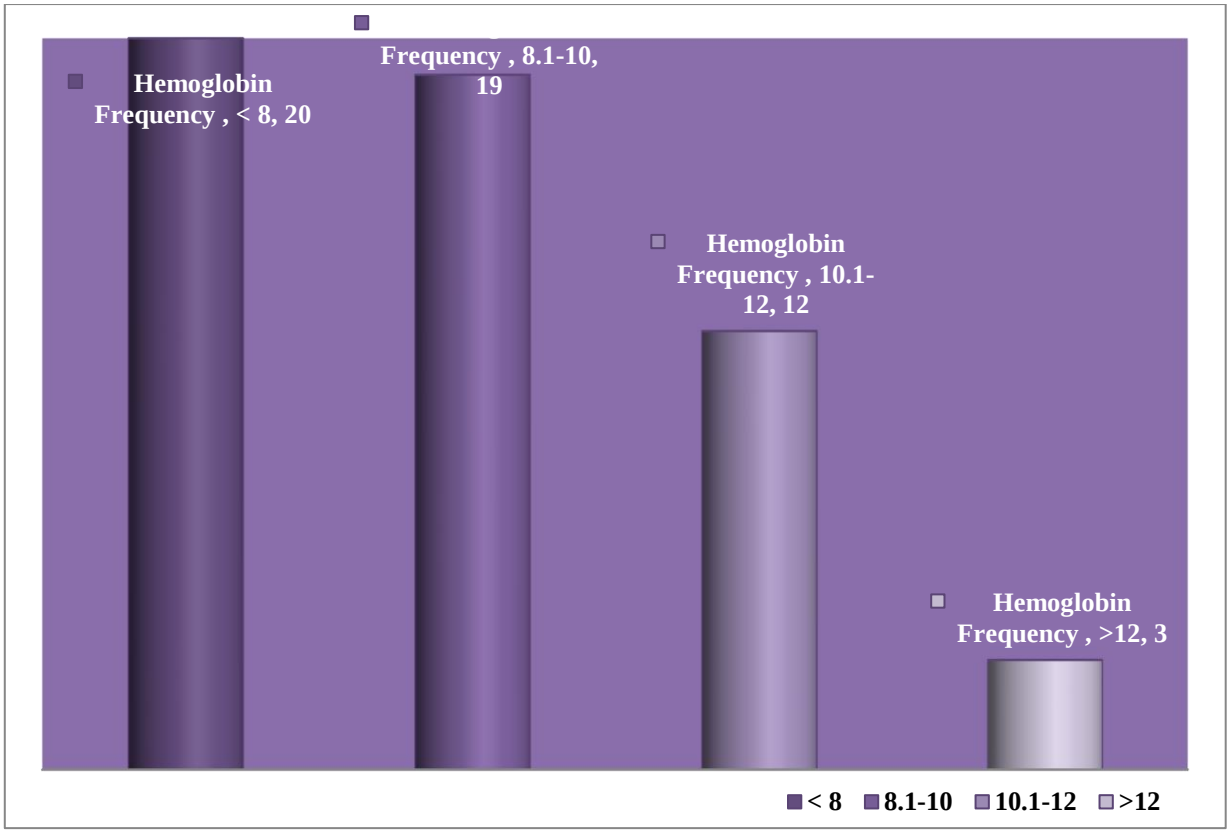

Figure 3: Distribution of study subjects according to Haemoglobin.

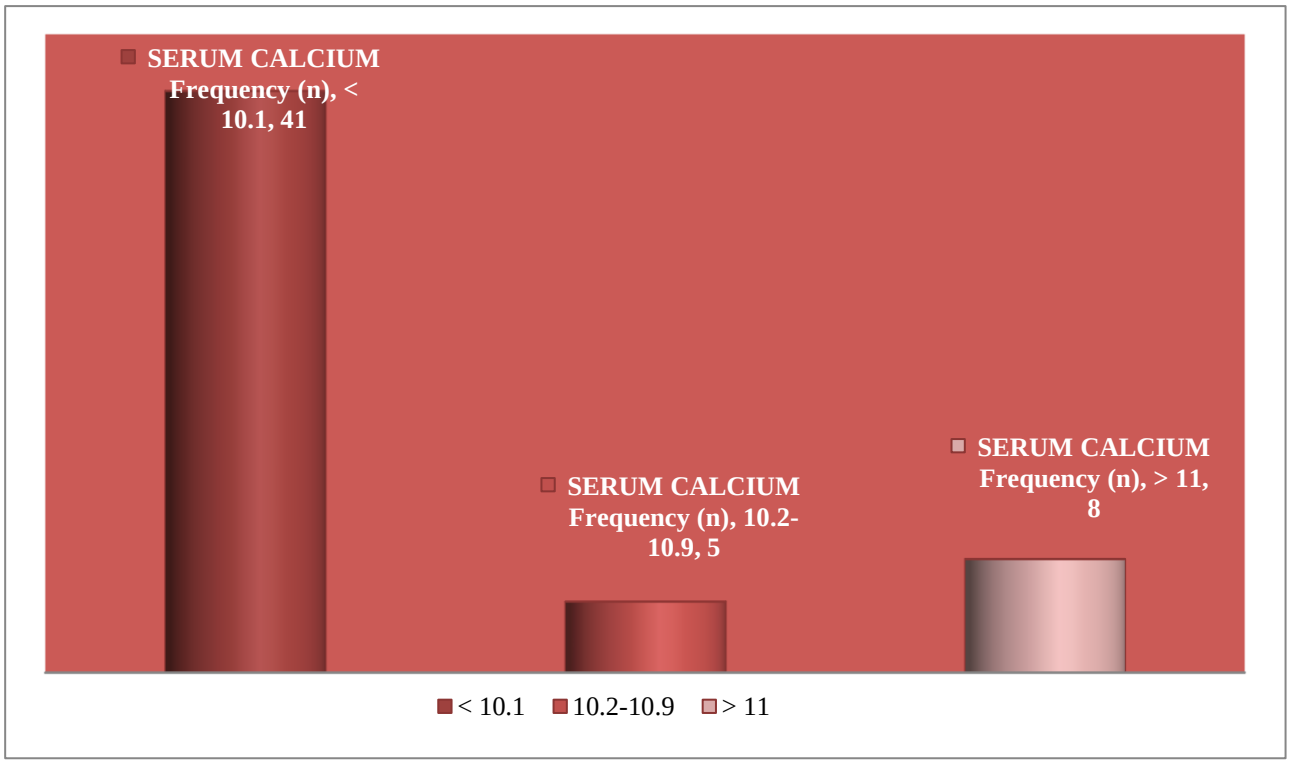

Figure 4: Distribution of study subjects according to Serum Calcium.

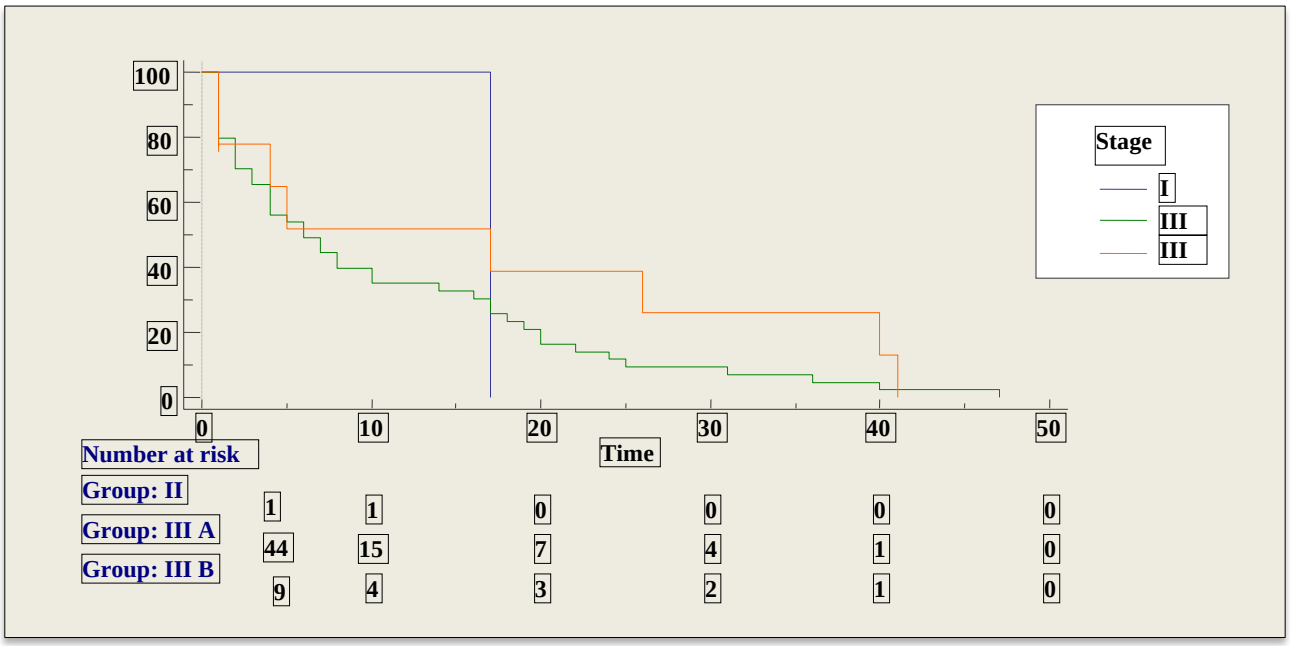

Figure 5: Comparison of survival analysis among subjects with DSS stage.

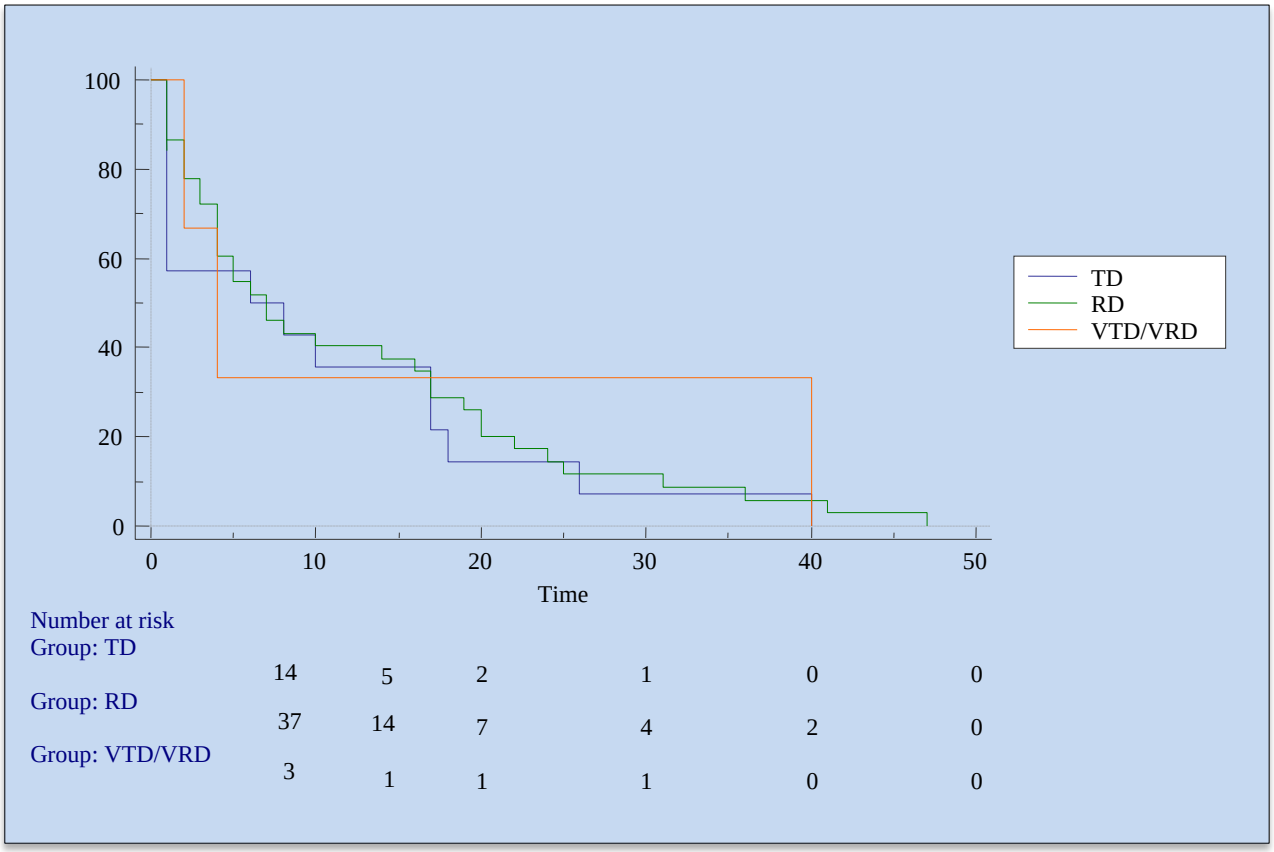

Figure 6: Comparison of survival analysis among treatment regimen.

DISCUSSION

The main emphasis of this study was on the clinical profile of MM and its response to various modalities of treatment instituted. The observations of the current study were compared with other studies across the world.

Comparison of age distribution

In the current study, the age of the study population ranges from as low as 31 years to 89 years. The mean age of the study population was 59.4±12.1 years. The majority of the study population (50%) was above the age of 60 years. In

a study involving 302 patients in NIMS institute, Hyderabad by Konatam et al the mean age was 54 years.[16] Similarly, in another study by Jacob et al at Kidwai cancer institute in Bangalore had a mean age of 54 years.[17] In Kerala, the average age of presentation was 64±10.77 years, as mentioned in a study by Fousad et al.[18]

Comparison of clinical features

In the present study carried out among 54 subjects, the various clinical manifestations are as follows: bone pain is the most common clinical feature, which was manifested in about 90.7% study population. 53.7% of the study population complained of loss of appetite, while 51.9% had weight loss. In an Indigenous study by Jacob et al, in Kidwai cancer institute Bangalore, 71% of patients had bone pains, 72% had anaemia, and 72% had fatigue.[17] Another study based in Kerala India by Fousad et al published results with bone pains, loss of weight, fever, anaemia, and fatigue comprising 96.9%, 84.5%, 56.3%, 90.6% and 100% respectively.[18] Another indigenous study by Sridhar et al in JIPMER Pondicherry had shown that bone pain is the most common presenting symptom comprising 24% of study subjects, other symptoms being fatigue in 3% and 20% with other symptoms such as pathological fractures, etc.[19]

Comparison of mean plasma cells on bone marrow examination of multiple myeloma with other studies

The mean plasma cell percentage of the study population was 42% with values ranging between a minimum of 3% to a maximum of 90%. In a study by Fousad et al based in Kerala, the mean plasma cell percentage was 31.26%.[18] In another indigenous study by Sridhar et al in JIPMER Pondicherry, the mean plasma cell percentage was 56%.[19] A study by Kyle et al at Mayo clinic the mean plasma cells on bone marrow examination was 50%.[20] In comparison, the mean plasma cell percentage in our study is similar to other studies.

In the present study, the serum calcium levels were elevated to levels greater than 11 g/dl in 14.8% of the study subjects. In an indigenous study by Sridhar et al serum calcium levels were elevated to levels greater than 11 g/dl in 20%.[19] In a Kerala based study by Fousad et al serum calcium levels were elevated to levels greater than 11g/dl in 18.8%.[18] 23% of study subjects had elevated serum calcium levels greater than 11 g/dl in a study by Jacob et al in India.[17]

In the present study, out of 54 subjects of multiple myeloma, 42 (77.8%) subjects had M band on serum protein electrophoresis, absent in the remaining 12 (22.2%) subjects. In a US-based study by Singhal et al serum protein electrophoresis showed a monoclonal band in 61% of the subjects.[21] In an indigenous study by Fousad et al the monoclonal band was present in 94% of the study subjects.[18]

In the present study with 54 subjects, it had been revealed that 9 (16.7%) subjects of multiple myeloma had renal impairment. In a study by Fousad et al in Kerala, there was the presence of renal impairment in 21% of study subjects.[18] In another study by Kyle et al at Mayo clinic, 55% of the study population were presenting with renal failure.[20]

Another study in India by Jacob et al revealed results showing that 27% of subjects had renal failure at the time of the presentation.[17] In the present study, out of 54 study subjects, none of the subjects belong to stage I, 85% of the study subjects belong to DSS stage II while the majority of the study population i.e.; 81.48% belong to stage IIIA. Stage IIIB constitutes 16.67% of the study subjects. In an Indigenous study by Jacob et al, stage I, II, and III comprised 31%, 30%, and 39%, respectively.[17] In another indigenous study by Sridhar et al in JIPMER Pondicherry, 80% of the subjects belonged to stage III.[19] Study done by Singhal et al, in Massachusetts had 61% of study subjects belonging to stage III.[21]

In the present study with 54 subjects, 3.7% were lost to follow-up. 31.5% have died even before assessing the response hence labelled as no response. 14.8% of study subjects had a very good partial response. 22.2% of the study population had partial response. The disease had a stable course in 20.4% of the study subjects, and 7.4% of study subjects had progressive disease. In the present study among 54 subjects with multiple myeloma, the overall survival was found out to be 12,109 months.

The median survival of subjects in a study by Greipp et al was 30 months.[22] A study by Oken et al had subjects with a median survival of 43 months.[23] Another study by Salmon et al had subjects with a median survival of 30 months.[24] The median survival of subjects in a study by Lennan et al was 28 months.[25] Blade et al conducted a study in 1993 in which the median survival was found out to be 29 months.[26] Another study by Blade et al in 1996, the median survival was 54 months.[27] The median survival of subjects in a study by Kyle et al among 869 subjects was 20 months.[28] The median survival of subjects in another study by Kyle et al was 33 months.[20] A study by Weil et al in Israel had study subjects with a median survival of 63 months.[29] A study by Xu et al in China, the median survival was 29 months.[30]

CONCLUSION

MM has an early onset in India compared to western literature. Though multiple myeloma is an incurable disease, lenalidomide is one of the promising treatment options. Early detection of asymptomatic disease and early treatment, helps in improving the mortality rates, providing better quality of life and decreases the disease burden.

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