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Clinical characteristics, treatment outcome and determinants of outcome in patients with multiple myeloma treated at TASH from January 2017 to December 2021.

A five-year retrospective study

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Abbreviations and acronyms

ASCT …… Autologous Stem Cell Transplant

CPT……. cyclophosphamide, prednisolone, thalidomide

CVD ……. Cardio vascular disease

CyBorD……. Cyclophosphamide, Bortezomib, Dexamethasone

FISH…… Fluorescence in situ hybridization

FLC……Free Light Chain

HDT…… High dose chemotherapy

HMIS……Health Management Information System

IMWG……. International Myeloma Working Group

ISS ……. International Staging System

MM……. multiple myeloma

MPT…… Melphalan – Prednisolone – Thalidomide

OS……. Overall Survival

PFS……. Progression-free Survival

PR…… Partial Remission

RD …… Lenalidomide plus Dexamethasone

SPEP……. Serum protein electrophoresis

TASH…… Tikur Anbessa Specialized Hospital

TD…… Thalidomide plus Dexamethasone

UNL……. Upper normal limit

UPEP……. Urine protein electrophoresis

VAD……. Vincristine – Doxorubicin – Dexamethasone

VRD……. Bortezomib, Lenalidomide, Dexamethasone

VTE ……. Venous Thromboembolism

Abstract

Background

Multiple myeloma is a malignant proliferation of plasma cells in the bone marrow, with relatively high prevalence in African populations. Reports from Africa are few and involve small cohorts, but suggest significant epidemiological and clinical differences from Caucasian patients. The outcome of myeloma has significantly improved due to use of chemotherapeutic agents including immunomodulatory agents and proteasome inhibitors.

Methods

A retrospective Cross-sectional study design was used to define the clinical characteristics, outcome and determinants of outcome of multiple myeloma patients treated at TASH from January 1,2017 to December 30,2021.

Result

A total of 85 patients were included in the study. The median age at diagnosis was 53 years, male patients accounted for 64.7 % of the patients. The most common presenting symptoms were bone pain 85.9 % and symptoms of anemia 48.2 %. 41.2 % of patients had hg < 10 g/dl at presentation while 76.5 % had lytic lesions on imaging. In addition, 85.1 % had detectable paraprotein on SPEP. At the end of induction therapy 55.2 % of patients had undetectable paraprotein on SPEP. The median PFS for this cohort was 24 months.

Conclusion

Most patients with multiple myeloma in this cohort were diagnosed at a relatively young age, presented with late stage disease and bone pain, and had a shorter PFS. Factors associated with worse survival were late Durie-Salmon stage disease, high calcium, and presence of pathologic fracture.

Introduction

Background

Multiple myeloma is characterized by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin. It is classified among the paraproteinemias, a spectrum of monoclonal protein secreting disorders that ranges from a pre-malignant condition known as monoclonal gammopathy of undetermined significance to plasma cell leukemia.

Multiple myeloma accounts for approximately 1 to 2 percent of all cancers and slightly more than 17 percent of hematologic malignancies in the United States. [1] The annual incidence in the US is approximately 4 to 5 per 100,000. [2]Incidence is also similar in United Kingdom and in Europe in general. In developed countries the incidence appears to be increasing over time, this more likely reflects the enhanced availability and use of medical facilities, especially by older persons. [5]

The incidence in African Americans and Blacks from Africa is two to three times that in Whites. [3,4] MM is also slightly more frequent in men than in women (approximately 1.4:1). The median age at diagnosis is 66 years; Less than 5% of patients at diagnosis are younger than age 40 years. The established risk factors are age, sex, race, obesity, and family history of hematologic malignancy or MGUS, whereas evidence is less consistent for occupational, environmental or lifestyle factors. [6,7] Familial clustering and recurrent cytogenetic abnormalities also suggest a genetic component.[2]

Patients with MM present with a number of signs and symptoms that are related to either marrow infiltration by plasma cells or manifestations of end-organ damage leading to renal dysfunction, bone lesions, and/or immunoparesis. However, in up to 20% of the patients, MM may present with asymptomatic disease diagnosed on the basis of routine laboratory work. The diagnosis of multiple myeloma is clinico-pathological; the diagnostic criteria were recently updated to require a demonstration of a clonal proliferation of plasma cells comprising 60% of marrow cells, or a smaller clonal proliferation of plasma cells (≥10%) occurring in the setting of characteristic myeloma-related organ or tissue impairment: hypercalcemia, renal impairment, anemia and bone lesions.

The prognosis of patients with myeloma, as in most other cancers, is dependent on Staging, patient factors, disease biology or aggressiveness of the disease and Availability and response to therapy. [29] The International Staging System (ISS) utilizes serum albumin and β-2 macroglobulin to predict three prognostic groups. While the revised international staging system adds serum LDH level and high-risk chromosomal abnormalities. [10 -12]

Autologous stem cell transplant is recommended as the standard of care for patients less than 65 years old with newly diagnosed MM, which should be preceded by induction therapy. Such induction usually comprises approximately four treatment cycles and available data suggest that three-agent induction regimens, containing immunomodulatory drugs and proteosome inhibitors,

result in higher response rates than two-agent combinations. [14-16] Patients' ineligible for SCT may also be treated with combination chemotherapy containing a novel agent. [17,18] Although MM remains largely incurable, the development of new therapies, including proteasome inhibitors and immunomodulatory drugs, has improved overall survival to a median of 5 years. In the United States, 5-year OS rates have increased from 25% in 1975 to 50% in 2014. [20-22]

Statement of the problem

Multiple myeloma as mentioned earlier is one of the most common hematologic malignancies observed worldwide.in addition the prevalence is much higher in African Americans and Africans. Recent advances in diagnosis, prognostication and treatment of patients with multiple myeloma has significantly improved the outcome of disease in developing countries.

Developing countries like ours face multiple problems in treating patients with multiple myeloma. Since TASH is one of the few centers where hematology services are available, patients have to travel long distances to get the services. This leads to delayed disease presentation, multiple interruptions of follow up and treatment and significant economic burden to the patient and the family.

The other problem faced in developing countries is availability of appropriate investigation modalities. Patients with multiple myeloma require extensive tests both to diagnose, prognosticate disease and assess response to therapy. Investigations like SPEP, UPEP, serum and urine immunofixation, FLC assay, and cytogenetic tests are usually not available in the country. Hence patients are expected to pay large sums of money for these investigations to be done at private laboratories or abroad.

In addition to problems faced during investigation, patients also face problems with availability and affordability of therapeutic agents and appropriate supportive care. Treatment of multiple myeloma includes therapeutic agents like bortezomib, lenalidomide and newer targeted agents used in upfront and treatment of relapsed disease. These agents are expensive and not uniformly available in the hospital leading to initiation of suboptimal therapy and multiple interruptions of therapy. In addition, treatment of multiple myeloma also includes ASCT for patients aged less than 65 years, this service is not available in Ethiopia and most patients only receive chemotherapy alone.

Taking the above points into consideration studies like this will assist in identification of gaps in diagnosis, prognostication, response assessment of the disease. The findings from this study will also be used to forward recommendations in order to improve the care of patients with multiple myeloma.

Significance of the study

The clinical features of MM, prognostic factors and treatment out come in Caucasians have been well characterized in large studies. These data may not entirely apply to the African population. Although studies of MM from African facilities tend to involve small cohorts, the reports suggest that at diagnosis, the epidemiological, clinical and laboratory features of Black Africans differ significantly from those of Caucasian patients.

As mentioned earlier the incidence of MM is increasing worldwide, and the disease is associated with high socioeconomic burden. Developing countries like Ethiopia also face challenges multiplied by the low socioeconomic status of the country with associated slowly growing health care system. From practice there seems to be a rising number of multiple myeloma patients coming to TASH both in the inpatient and outpatient departments. Despite this there is only one study done about two decades ago about the clinical characteristics of patients with multiple myeloma.

The value of studies on various health matters is indisputable. Having a national baseline data of any disease is crucial to recognize a change in the incidence, demographic characteristics and treatment outcome of a disease. It will also be used to study outcome predictors. This is crucial in gauging measures, and upgrading interventions at both national and institutional levels. It will also help in health planning, funding of treatment and further research projects on similar disease entities.

Therefore, this study was conducted to describe the clinical characteristics, treatment out come and factors affecting the outcome of patients with multiple myeloma treated at TASH, a tertiary hospital found in Addis Ababa Ethiopia.

Objectives

General Objective

- To study the clinical characteristics, treatment outcome and determinants of outcome of patients diagnosed to have multiple myeloma at TASH from January 1 2017 to December 30, 2021.

Specific Objectives

- To describe the demographic characteristics of patients with multiple myeloma at TASH from January 1,2017 to December 30, 2021.
- To describe the clinical features of patients with multiple myeloma at TASH from January 1, 2017 to December 30, 2021.
- To study treatment outcome of multiple myeloma patients at TASH from Jan 1,2017 to December 30, 2021.
- To identify determinants of outcome among patients with multiple myeloma at TASH from Jan 1,2017 to December 30, 2021.

Methodology

Study Design

A retrospective cross-sectional study design was used to study the clinical characteristics, treatment outcomes and determinants of outcome of newly diagnosed multiple myeloma patients on follow up at outpatient department of hematology unit, TASH from Jan 1,2017 to December 30, 2021.

Study Setting

The study was done at Tikur Anbessa Specialized Hospital which is the largest governmental teaching hospital in Ethiopia located in the capital Addis Ababa. The hospital has served as a medical and health science teaching enter for the country's biggest university, Addis Ababa University, for more than half a century.

It is estimated that the hospital serves 370,000 - 400,000 patients a year and has more than 800 beds. There are 2 hematology wards with bed capacity of and 4 hematology referral clinic days accepting 80 -120 patients a day. It is one of the few institutions where oncology and hematology treatment is given in the country.

Study Period

The study period was from January 1, 2017 to December 30, 2021.

Study Population

Source population

All patients who were on follow up at outpatient department of hematology unit, TASH from Jan 1,2017 to December 30, 2021.

study population

All patients diagnosed to have multiple myeloma based on IMWG 2016 criteria and on follow up at outpatient department of hematology unit, TASH within the five-year period from January 1, 2017 to December 30, 2021will be included in the study.

Sample Size and sampling technique

Since multiple myeloma is a relatively uncommon disease and the study is an institution-based study, all patients diagnosed with multiple myeloma during the study period will be included.

Data Collection

Inclusion Criteria

- All adult patients newly diagnosed to have multiple myeloma based on IMWG criteria and on follow up at outpatient department of hematology unit at TASH from January 1, 2017 to December 30, 2021.

Exclusion criteria

- Patients who didn't receive chemotherapy for multiple myeloma.

Study variables

Independent variables

- Age
- Sex
- Time from symptom onset until presentation
- Stage of the Disease at presentation
- Degree of anemia

- Renal dysfunction
- Skeletal abnormalities at presentation (lytic lesions, pathologic fracture)
- Serum Total calcium, LDH, and ESR level at diagnosis
- Total protein, Albumin and Monoclonal M protein levels at diagnosis
- Treatment modality used
- Stage of disease at presentation
- Therapy related complications – VTE, infections.

Dependent variables

- Treatment outcome/response to therapy
- Survival rates - overall survival and progression free survival

Operational Definition

- Disease stage at presentation – clinical stage of myeloma according to the revised Durie salmon staging system
- Anemia – hemoglobin level. < 10 g/dl or >2 gm/dl below the lower limit of the normal range.
- Renal dysfunction – serum creatinine level > 2 m/dl.
- Elevated LDH – above the upper limit of normal of the laboratory.
- Relapse – Either clinical relapse based on the development of one or more of the following attributable to the myeloma: a serum calcium >11.5 mg/dL, decrease in hemoglobin of ≥2 g/dL, rise in serum creatinine ≥2 mg/dL, hyperviscosity related to the serum paraprotein, or 25 percent increase from lowest response value in any of the following: Serum M-protein (absolute increase must be ≥0.5 g/dL), Urine M-protein (absolute increase must be ≥200 mg/24 hours) and difference in the kappa and lambda FLC (absolute increase must be >10 mg/dL).
- Response criteria to induction therapy – since investigative modalities like serum/urine immunofixation, UPEP and FLC assays are not available for most patents, IMWG 2016 consensus criteria for response can't be used. patients with detected M - protein at diagnosis will be classified as those with detected vs undetected M protein at the end of treatment.
- Overall survival – the time from diagnosis to date of death of any cause. All patients including those lost to follow up will be censored at the date of last visit.
- Progression free survival – the time from diagnosis to death due to any cause or disease progression whichever occurs first. All patients including those lost to follow up will be censored at the date of last visit.

Data collection

Data was collected from medical records of patients using a structured questionnaire developed by primary investigator based on prior studies of similar nature.

Patients with the diagnosis of multiple myeloma and on follow up were identified from the HMIS record in the outpatient department of hematology unit.

Data handling and analysis

After data collection was complete, the data was edited and coded for processing and analysis. Data processing and analysis was done manually and using the SPSS statistical software (version 26). Descriptive statistics including percentages, measures of central tendency and dispersion, frequency tables and graphs were used to depict the descriptive aspects of the results. Association between variables was assessed using chi-square test, Pearson correlation, logistic regression and independent sample T test. Survival curves were plotted according to Kaplan-Meier method. Descriptive statistics and odds ratio, with 95% confidence interval were used to show associations between target variables. P-value of less than 0.5 was considered to depict statistically significant association among study variables.

Ethical Consideration

Ethical clearance was obtained from the internal review board of College of Heath Science, Addis Ababa University.

Dissemination of research results

After the completion of the research, results will be presented to hematology unit of the department of internal medicine. The research findings will also be sent to peer reviewed journals for publication.

Results

Demographic characteristics

A five-year hospital based retrospective study was conducted on patients diagnosed with multiple myeloma from January 2017 to December 2021. During the study period a total of 85 patients were identified. Out of these patients 55(64.7 %) were males and 30(35.3 %) were females with male to female ratio of 1.8:1. The median age of presentation was 53 years with range of 30-82 years. In these cohort there was no significant difference in age at presentation between male and female patients. Majority of the patients (30.6 %) were between the ages of 51-60 years followed by ages 41-50 years accounting for 29.4 % of the total. 9.4 % of the patients were 40 years or younger while 38.8 % were 50 years or younger. There was only one patient above the age of 80 years. Most patients were from Addis Ababa (43.5%) followed by Oromia region (27.1%), Amhara region (7.1 %), SNNPR (20%) and Diredawa (2. 4%).During the study period there were no patents seen from the rest of the regions.

Table 1- Baseline demographic and clinical characteristics

Characteristics	Value
Age (years), median	**53**
Sex, n (%)	
Male	**55 (64.7)**
Female	**30 (35.3)**
Region, n (%)	
Addis Ababa	**37 (43.5)**
Oromia	**23 (27.1)**
Amhara	**6 (7.1)**
SNNPR	**17 (20)**
Dire Dawa	**2 (2.4)**
Symptoms at presentation, n (%)	
Bone pain	**73 (85.9)**
Anemia symptoms	**41 (48.2)**
Swelling/plasmacytoma	**23 (27.1)**
Weakness/paralysis	**20 (23.5)**
Weight loss	**19 (22.4)**
Comorbidities, n (%)	
TIIDM	**15 (17.6)**
HTN	**14 (16.5)**
Cardiac disease	**4 (4.7)**
HBV	**1 (1.2)**
Durie salmon stage, n (%)	
Stage I	**12 (14.1)**
Stage II	**33 (38.8)**
Stage IIIA	**34 (40)**
Stage IIIB	**6 (7.1)**

Clinical characteristics

Duration of illness at presentation was ≤ 3 months for 41 (48.2%) of the patients followed by 28 (32.9 %) and 7 (8.2 %) of patients presenting within 3-6 months and > 6 months of presentation. The median duration of illness was 4 months.

The major presenting symptoms at diagnosis were chronic bone pain (85.9 %), anemia (48.2 %), weakness (23.5 %), and weight loss (22.4 %). While 27.1% of patients initially presented with plasmacytoma. Regarding comorbidities at presentation, 40 % of patients had comorbidities. The most common being TIIDM 15(17.6 %) followed by hypertension 14(16.5 %), cardiac illness 4(4.7%) and only one patient had chronic hepatitis B infection.

Laboratory values at presentation

Laboratory values at presentation for the 85 patients diagnosed during the study period were evaluated. Most of the patients had normal white blood cell and platelet counts at presentation with mean value of 6,240/ µLand 240,047/µL respectively. 41.2 % of patients had anemia (<10 g/dl) at presentation. The mean hemoglobin value was 10.5. hemoglobin value of < 8 g/dl was seen in 15.3 %.

Table 2 – Laboratory values at presentation and distribution by sex

Laboratory parameter	N, (%)	Median	Distribution by sex	
			Male, n (%)	Female, n (%)
Hemoglobin <10 (g/dl)	35 (41.2)	10	22 (40)	13 (43.3)
Plasma cell % ≥ 20 % <20 %	 59 (81.9) 13 (18.1)	36	 20 (74.1) 7 (25.9)	 39 (86.7) 6 (13.3)
LDH (IU/L) >ULN	 28 (32.9)	237	 17 (30.9)	 11 (36.7)
Creatinine >2 mg/dl	 6 (7.1)	1.0	 5 (9.1)	 1 (3.3)
Calcium (mg/dl) >11 ≤11	 13 (15.5) 71 (84.5)	8.9	 10 (18.5) 44 (81.5)	 3 (10) 27 (90)
Total protein (g/dl) >8 ≤8	 43 (79.6) 11 (20.4)	9.15	 25 (71.4) 10 (28.6)	 18 (94.7) 1(5.3)
Albumin (g/dl) < 3.5 ≥ 3.5	 33(64.7) 18 (35.3)	3.3	 12 (40) 18(60)	 6 (28.6) 15 (71.4)
Paraprotein (g/dl) ≥3 <3	 40 (54.1) 34 (45.9)	3.34	 10 (38.5) 24 (50)	 16 (61.5) 24 (50)
Lytic lesion	65 (76.5)		45 (81.8)	20 (66.7)

Among other common presentations hypercalcemia (> 11mg/dl) was seen in 15.5 % of patients. The median calcium level at presentation was 8.9. Renal failure defined as serum creatinine level of >2 mg/dl was seen in 6 % of the patients but 24 (28.2 %) of patients were diagnosed as having AKI at presentation. The median creatinine levels in this cohort was 1.0, in addition male patients were more likely to present with higher creatinine levels than the female patients (p-value = 0.018)

Lytic bone lesions (mostly identified using x-ray) were seen in 76.5 % of patients. Common sites of lytic lesions included vertebra (42.9 %), ribs (36.9 %), skull (33.3 %), pelvis (22.6 %), appendages (15.5 %), sternum (13.1 %) and scapula (11.9 %). pathologic fracture and vertebral compression fracture were seen in 8.2 % and 41.2 % of patients respectively. Plasma cell percentage was determined using BMA/BMB and the median plasma cell percentage was 36 % and 81.9 % of patients had plasma cell percentages ≥20%. No immunophenotyping, flow cytometry or chromosomal studies were done on marrow samples.

Serum total protein was increased (>8 g/dl) in 79.6 % of patients and serum albumin level was decreased in 64.7 % of patients. Of the total patients evaluated 87.1 % had SPEP done. Of these patients 85.1 % had detectable paraprotein on serum electrophoresis with median of 3.3 g/dl, inadditon 54.1 % patients had serum paraprotein levels ≥3 g/dl. Light chain myeloma was confirmed in 54.5 % of patients without paraprotein on SPEP.while 2 patients had no detectable paraprotein with either SPEP of FLC assay. Of 76 patients evaluated, 14.1 % presented Durie salmon Stage I disease, 38.8 % with stage II disease, 40 % with stage IIIA while 7.1 % presented with Stage IIIB disease. There was no significant relationship between patients' age groups or duration of symptoms prior to presentation, and any of the hematological and biochemical parameters measured other than creatinine.

Treatment and Complications

All patients were managed with chemotherapy and supportive care such as pain management, blood transfusions, infection treatment and correction of electrolytes. Induction chemotherapy regimens included CyBorD (cyclophosphamide, bortezomib, dexamethasone), CPT (cyclophosphamide, prednisolone and thalidomide), MPT (melphalan, prednisolone and thalidomide), Rd (lenalidomide and dexamethasone), VRd (bortezomib, lenalidomide and dexamethasone), VMP (bortezomib, melaphalan and prednisolone), and CP (cyclophosphamide and prednisolone).Most patients received CyBorD (41.2 %) followed by CPT(31.8 %), CP (11.8 %), and MPT (5.9 %). Other regimens were given only for one patient each. The number of cycles of induction chemotherapy varied between patients with median number of cycles given being 9. consolidation chemotherapy was not used while 2 patients received ASCT abroad. Maintenance chemotherapy was given to 61.2 % of patents. Of the patients who received maintenance therapy Thalidomide was given to 75 % and lenalidomide was given to 23.1 % of

the patients while one patient was put on indefinite therapy with Rd. All patients received zolendronic acid. Chemotherapeutic regimens used during relapse included CyBorD (41.7 %), CPT (8.3 %), CP (8.3 %), MPT (8.3 %), Rd (4.2 %), VTD (8.3 %) and VRd (20.8 %).

Treatment interruption was seen in 29.4 % of patients the most common reasons attributed to interruption were treatment side effect (72 %), patients lost to follow up (20 %) and drug unavailability (8 %).36.5 % of patients reported complications since the start of therapy. The most common complications observed included peripheral neuropathy (36.8 %), infection (31.6), VTE (26.3 %) and severe cytopenia (5.3 %). 6 patients had more than one complication. Association between the development of VTE and chemotherapy regimen was evaluated and there was no signification association seen.

Treatment outcome and determinants

Of the total 85 patients, determination of end of treatment SPEP was available for 78.8 % of patients. of these patients where SPEP was determined serum paraprotein was not detected 45.1 % of patients ,19 (23.2%) had ≥ 50 reduction, 8(9.8%) had stable M- protein level and 1 patient had increase in M- protein. There were no determinations of other parameters of response assessment like free light chain assay at the end of therapy.

Median progression free survival was 24 months [95% CI 16.4, 31.6]. Median progression free survival was significantly improved for patients for patients with normal calcium levels (p value- 0.013) at diagnosis and patients with bone marrow plasma cell percentage of ≤ 50 % (p value – 0.015) and patients without pathologic fracture at presentation (p-value = 0.038). other laboratory features had no significant effect on PFS. In addition, neither age at diagnosis nor duration of illness prior to diagnosis correlated with survival outcomes.

Table 3 –Median progression free survival of patient groups

		Median progression free survival (months)	Log – rank test
Sex	**Male** **Female**	**24** **24**	**0.54**
Age category (years)	**≤ 40** **>40**	**24** **24**	**0.317**
Hemoglobin	**<8** **≥8**	**16** **27**	**0.091**
LDH	**>ULN** **<ULN**	**24** **24**	**0.354**
Stage	**Stage II** **Stage IIIA** **Stage IIIB**	**27** **24** **8**	**0.047**

Paraprotien	**≥ 3** **<3**	**24** **27**	**0.055**
Pathologic fracture	**Present** **Absent**	**7.2** **24**	**0.038**
Calcium	**>11 mg/dl** **≤11 mg/dl**	**7.2** **27**	**0.013**
Paraprotein level post induction	**Undetected** **Detected**	**35** **11**	**0.001**
Maintenance treatment	**Received** **Not received**	**35** **11**	**0.028**

patient survival varied significantly by Durie salmon Stage at diagnosis with median survival for D-S II, IIIA and stage IIIB being 27 months [95% CI 9.4, 44.6], 24 months [95% CI 10.5, 37.5] 8 months [95% CI 1.0,23.7]; median survival for patients diagnosed with D-S Stage I disease had not yet been reached at the close of the study period.

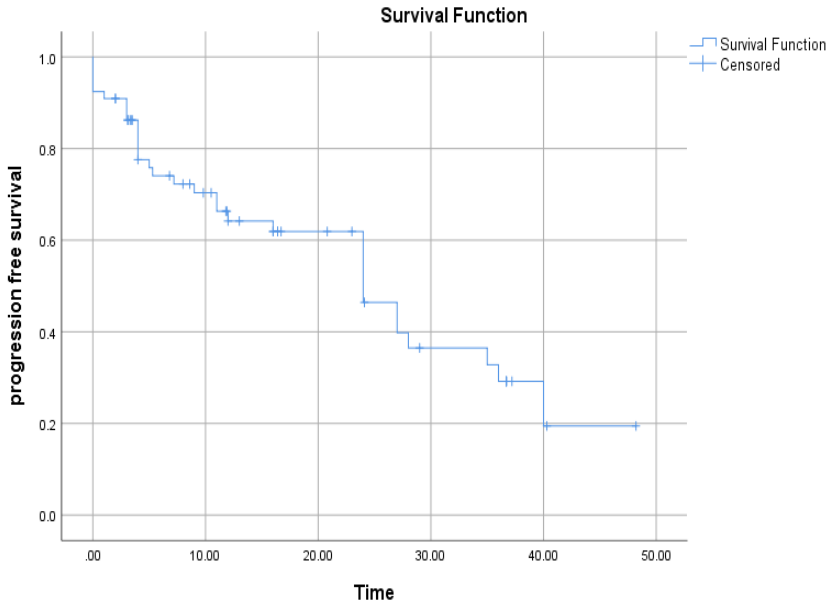

Figure 1 - Kaplan Meier survival curve for PFS of newly diagnosed patients on first-line therapy for multiple Myeloma.

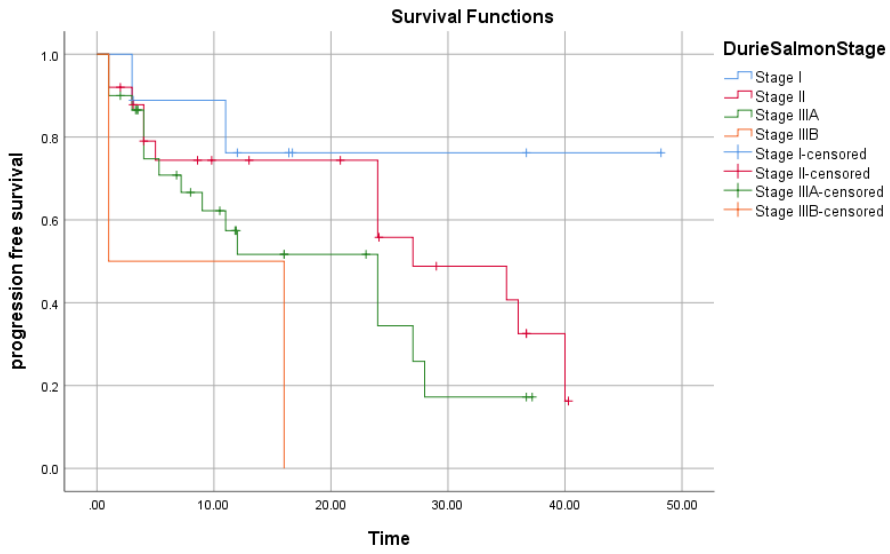

Figure 2 – Kaplan Meier survival curve for PFS of patients with Myeloma compared with the D-S stage at diagnosis.

The median overall survival for this cohort was not reached. But median overall survival patients with pathological fractures and hypercalcemia was 40.5 months [95% CI 38.3, 54.2] and 40.5 months [95% CI 26.2, 43.4]. In addition, patients who achieved only ≥ 50 % reduction of M-protein post induction therapy was 37.7 months [95% CI 24.8, 50.6].

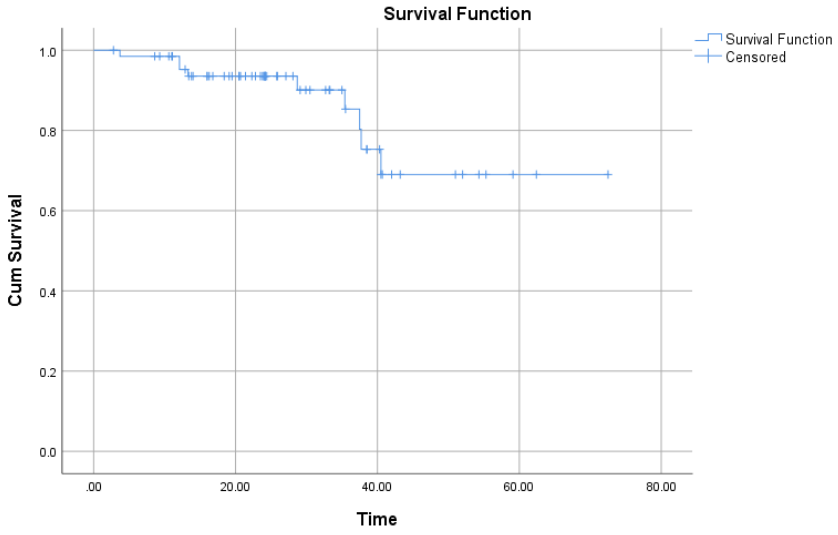

Figure 3 – Kaplan Meier survival curve for OS of patients with newly diagnosed Myeloma on first line therapy

Discussion

The prevalence of multiple myeloma in male patients in this study is 64.7% with male to female ratio of 1.8:1. which is consistent with the observation that the multiple myeloma is more prevalent in male patients. A UK cancer research statistic in 2013 showed higher prevalence of multiple myeloma in male patients with male to female ratio of 1.3:1.[27] Men are more likely to be diagnosed with MM than women in studies done in Ghana, Uganda and Nigeria with male patients accounting for 51.5 %, 55 % and 53.9 % of the study population.[28-30] However, compared to global statistics reports were the median age at diagnosis of multiple myeloma is 66 years. This study shows younger median age of diagnosis of 53 years. This is already corroborated with past studies showing younger age at presentation for Africans and African Americans. In a series of 123 patients (including white and black patients) observed over 5 years in south Africa.[31.] The median age of black patients at presentation was 52 years, 10 years younger than white patients. A report from Kenya on retrospective analysis of 75 patients diagnosed with multiple myeloma showed median age at diagnosis of 51 years.[32] Okello et al., in the largest retrospective study done in sub-Saharan Africa including 217 patients, the reported median age at diagnosis was 59 years.[29]

Regarding presenting symptoms, the most common presenting symptoms were bone pain (85.9 %) and symptoms of anemia (48.2 %). This finding is similar to that reported by Kyle et al.[33] where the leading presenting symptoms were bone pain and anemia. similar findings were also seen in other African countries.[28-30]

The prevalence of anemia was 41.2 % which was lower to that reported in a Caucasian population by Kyle et al.,[33] which showed a prevalence of 73 %, similarly reports from other African countries also show higher prevalence of anemia. in contrast to higher percentage of severe anemia reported in other African countries, percentage reported ranging from 52 – 78.9 %.[28,29]This study only showed 15.3 % of patients with severe anemia. This presentation might be due to patients receiving repeated blood transfusion from local health institutions where they are referred from or other cofounding factors such as higher prevalence of nephropathy in the studies showing higher prevalence of severe anemia. Severe anemia was seen only 7% in Kyle's report.

Majority of the patients in this study had lytic lesion detected by plain X-ray which is a common practice where either whole body CT scan, PET-CT or MRI are expensive and not readily available. in addition, 8.2 % of patients had pathologic fracture at presentation. This is another preventable consequence of late presentation of multiple myeloma and is associated with increased morbidity and poorer prognosis.

In this cohort creatinine level >2 was seen in 6 % patients. This value is significantly lower than those reported by kyle et al., that showed 19 % of patients in the study having creatinine level > 2 mg/dl, Higher percentage of patients with nephropathy was also reported in report from Ghana, Nigeria were patients affected were 30% and 13.8 % respectively.[28,30] This might be explained by lower number of patients with hypercalcemia in this study (15.5 %), compared to 30 % in the studies mentioned above. As also mentioned in the study from Ghana, diclofenac and other

NSAIDs are frequently prescribed analgesics to patients with bone pain. This finding needs to be verified by further studies.

Albumin level was decreased in majority of the patients 64.7 %. Albumin is one of the parameters included in staging of patents and it was found to be a significant prognostic factor for assessing disease severity in various studies. In this study low albumin level was not found to affect survival. This might be explained by the fact that only 65 % of patients had determinations of serum albumin level at presentation. In the majority of patients (85.1 %) paraprotein was detected with 54.5 % of patients without paraprotein on SPEP having abnormal FLC assay. Further characterization by immunofixation was frequently not done. Kyle et al., from a mayo clinic report, 82 % of patients has thick band on SPEP.

Most (47.1%) of our patients presented with D-S stage III (stage IIIA and stage IIIB) disease at diagnosis, Unlike in developed countries where diagnosis is usually made during evaluation of anemia detected during routine evaluation. The finding might be due to lack of easy access to healthcare facilities and prolonged time from referral of the patient to being seen at our center and longer. Advanced stage at presentation might also be indicative of aggressive disease. Other studies done in Africa also corroborate this, in a study done in Ghana most patients (50 %) present with late stage disease. Similar finding was also seen Nigeria (53.6 %).[28-29]

41.2 % patients in this study received CyBorD, while the remaining patients received therapies that lack combinations including bortezomib, which is now current standard of therapy showing improved efficacy and outcome. In addition, there is no ASCT service in the country and only 2 patients went abroad for the service during the study period which is expensive. Even though evidence in use of maintenance chemotherapy without ASCT not as strong as its use post ASCT, there are studies showing its use being associated with improved outcome. In this study 61.2 % patients received maintenance therapy with either thalidomide 75 % or lenalidomide 23.1 %.

Due to financial constraints parameters like FLC assay were not done to assess response to therapy. Hence it was not possible to strictly adhere with the uniform response criteria suggested by IMWG. However, in this study patients were reassessed using disappearance of M-band by SPEP.The follow up assessment showed 55.2 % patients with undetectable paraprotein, 23.2 % had partial reduction while 9.8 % had stable disease not responding to therapy. A similar study showed that 56 % patients had complete response and 44 % had partial response. In a study done in south India published in 2018 where similar parameters were used, majority (64%) showed partial response to treatment and 7 (23%) showed complete response while Four (13%) of the patients had stable disease not responding to treatment.[20,21]

The median PFS of patients with multiple myeloma is approximately 29-66 months with survival varying depending on host factors, tumor burden (stage), biology (cytogenetics abnormalities) and response to therapy.[12] in contrast the median progression free survival of patients in this study was 24 months which is shorter than observed elsewhere. This might be related to late stage at presentation, due to treatment availability, in general this cohort received treatments that are suboptimal compared to the currently recommended treatments for MM by international guidelines.

In this study it was not possible to stage patients by currently acceptable method using R-ISS, since cytogenetics determinations are available only for samples sent abroad which most of our patients can't afford. Despite that other parameters that are known to affect outcome of patients with multiple myeloma were evaluated. Of these parameters late D-S stage, presence of pathological fracture, high serum calcium levels and bone marrow plasma cell percentage > 50 % were associated with significantly shorter median PFS. The results this study are consistent with the observation that advanced disease and manifestation of late presentations confers an adverse prognosis in patients with MM. In addition, disappearance of M protein on SPEP after completion of induction chemotherapy and receiving maintenance therapy were associated with prolonged progression free survival. However, this study didn't show that high LDH and advanced age as predictors of survival. this might be due to the general younger age of patents in the study and other cofounding factors affecting the outcome of patients with MM.

Strength and limitations

Strength

This study is the largest study done on multiple myeloma patients in Ethiopia. It provides valuable information about demographic, clinical characteristics, outcomes and factors affecting outcome in patients treated in the largest tertiary referral hospitals in Ethiopia. it also provides baseline data to perform further studies.

Limitations

It was difficult to obtain medical records of patients especially 2017 and 2018 since most of the charts were lost. In addition, some of laboratory parameters were not available for some patients. In most patients, it was difficult to determine the outcome of treatment and causes of mortality as most of the patients died outside of the hospital. There was also no tracking system for others who are lost to follow up after completion of their induction treatment coarse.

Conclusion

In conclusion, patients with MM in the present study had a male preponderance with most patients diagnosed with MM at a relatively young age compared to global statistics. The patients in this cohort predominantly presented with late stage disease with bone pain being the most common presenting symptom. The patients in this study had a relatively shorter progression survival. Factors associated with worse survival were late stage disease at presentation, presence of pathologic fracture and hypercalcemia at presentation. In addition, patients who had undetectable M- protein at the end of induction chemotherapy and patients who received maintenance therapy had longer median progression free survivals. A reasonable clinical outcome can be achieved by availing proper MM care to our patients and this will provide a platform for the design of future studies and clinical trials involving African MM patients.

References

1. RL, Miller KD, Jemal A. Cancer statstics, 2018. CA cancer J Clin 2018; 66:7.
2. Kyle RA, Therneau TM, Rajkumar SV, et al. Incidence of multiple myeloma in Olmsted County, Mennesota: Trend over 6 decades. Cancer 2004: 101:2667.
3. Waxman AJ, Mink PJ, Devesa SS, et al. Racial disparities in incidence and outcome of multiple myeloma: a population-based study. Blood 2010; 116:5501.
4. Shirley MH, Sayeed S, Barnes I, et al. Incidence of hematological malignancies by ethnic group in England, 2001-7. Br J Hematol 2013: 163:465.
5. Huang SY, Yao M, Tang JL, et al. Epidemiology of multiple myeloma in Taiwan: increasing incidence for the past 25 years and higher prevalence of extramedullary myeloma in patients younger than 55 years. Cancer 2007; 110:896.
6. Becker N. Epidemiology of Multiple Myeloma. In: Moehler T, Goldschmidt H, editors. Multiple Myeloma. Springer Berlin Heidelberg; 2011. p. 25–35.
7. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body Fatness and Cancer — Viewpoint of the IARC Working Group. *N Engl J Med*. 2016;375(8):794–8.
8. Rajan AM, Rajkumar SV. Interpretation of cytogenetic results in multiple myeloma for clinical practice. *Blood Cancer J*. 2015;5(10):e365.
9. Kariyawasan CC, Hughes DA, Jayatillake MM, Mehta A. Multiple myeloma: causes and consequences of delay in diagnosis. QJM 2007; 100:635.
10. Fonseca R, Bergsagel PL, Drach J, et al. International myeloma working group molecular classification of multiple myeloma: spotlight review. Leukemia 2009; 23:2210.
11. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. J Clin Oncol 2005; 23:3412.
12. Palumbo A, Avet-Loiseau H, Olivia S, et al. Revised international staging system for multiple myeloma: Report from International Myeloma Working Group. J Clin Oncol 2015; 33:2863.
13. Durie BG, Salmon SE. A clinical staging system for multiple myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975; 36:842.
14. J.-L.Harousseau,M. Attal, H. Avet-Loiseau et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. Journal of Clinical Oncology 2010; 30:4621–4629.
15. H. Einsele, P. Liebisch, and C. Langer. Intravenous cyclophosphamide and dexamethasone (VCD) induction for previously untreated multiple myeloma (GermanDSMMXIa trial). *Blood 2009*;114-59.
16. H. Ludwig, M. Beksac, J. Blade et al. Multiple Myeloma Treatment Strategies with Novel Agents in 2011: A European Perspective. *The Oncologist* 2011; 16:388–403.

17. P. M. Fayers, A. Palumbo, C. Hulin et al. Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials. *Blood 2011*; 118:1239–1247.
18. L. Benboubker, M. A. Dimopoulos, A. Dispenzieri et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *The New England Journal Of Medicine* 2014; 10:906–917.
19. B. G. M. Durie, A. Hoering, M. H. Abidi et al.. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomized, open-label, phase 3 trial. *The Lancet* 2017; vol. 38:519–527.
20. S. El Mahou, M. Attal, B. Jamard et al. Do new therapeutic approaches (autotransplants, thalidomide, dexamethasone) improve the survival of patients with multiple myeloma followed in a rheumatology department. *Clinical Rheumatology 2006;* 25:175–182.
21. L. Kumar, J.Ghosh, P. Ganessan, A. Gupta, R. Hariprasad, and V.Kochupillai. High-dose chemotherapy with autologous stem cell transplantation for multiple myeloma: What predicts the outcome? Experience froma developing country. *BoneMarrow Transplantation 2009*; 43:481–489.
22. National Cancer Institute, "Surveillance, Epidemiology and End Results Program: Cancer Stat Facts, Myeloma," 2019, https://seer.cancer.gov/statfacts/html/mulmy.html.
23. Onyemelukwe G, Kulkarni A. Immunoglobulin types and features of multiple myeloma in northern Nigeria. *East African Medical Journal*. 1988;65(1):33-8.
24. Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv52-iv61.
25. Morgan GJ, Davies FE, Gregory WM, Bell SE, Szubert AJ, Coy NN, et al. Articles and Brief Reports Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation: MRC Myeloma IX randomized trial results. 2012;97(3):442–50.
26. Shamebo M, Tekle-Haimanot R. Multiple myeloma in Ethiopians: analysis of 22 cases. Ethiop Med J. 1992 Jul;30(3):143-9. PMID: 1396616.
27. Cancer Statistics, Cancer Research UK; 2013. Available from: http:// www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma. [Last accessed on 2014].
28. Acquah ME, Hsing AW, McGuire V, Wang S, Birmann B, Dei-Adomakoh Y. Presentation and survival of multiple myeloma patients in Ghana: a review of 169 cases. Ghana Med J. 2019 Mar;53(1):52-58.
29. Okello CD, Mulumba Y, Omoding A, Ddungu H, Welch K, Thompson CL, Cowan AJ, Cooney MM, Orem J. Characteristics and outcomes of patients with multiple myeloma at the Uganda Cancer Institute. Afr Health Sci. 2021 Mar;21(1):67-74.
30. Madu A, Ocheni S, Nwagha T, Ibegbulam O, Anike U. Multiple myeloma in Nigeria: an insight to the clinical, laboratory features, and outcomes. *Nigerian Journal of Clinical Practice*. 2014;17(2):212-7.
31. Blattner W, Jacobson R, Shulman G. Multiple myeloma in South African blacks. *The Lancet*. 1979;313(8122):928-9.

32. Mukiibi J, Karimi M, Kyobe J. Multiple myeloma in Kenyan Africans-a prospective study. *East African Medical Journal*. 1981;58(3):171-80.
33. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003; 78:21.

Annex 1

stage	Criteria	Tumor mass
Stage I	Hgb >10 g/dL Serum IgG <5 g/dL Serum IgA <3 g/dL Normal serum calcium Urine monoclonal protein excretion <4 g/day No generalized lytic bone lesions	Low cell mass: <0.6 x 10^{12} cells/m^2
Stage II	Neither stage I or II	Intermediate tumor mass
Stage II	Hgb <8.5 g/dL Serum IgG >7 g/dL Serum IgA >5 g/dL Serum calcium >12 mg/dL (3 µmol/L) Urine monoclonal protein excretion >12 g/day Advanced lytic bone lesions	High cell mass: >1.2 x 10^{12} cells/m^2
Stage III is subclassified as IIIA or IIIB based on serum creatinine	A. Serum creatinine <2 mg/dL (177 µmol/L) B. Serum creatinine ≥2 mg/dL	

Annex 2

R-ISS staging system of multiple myeloma

Prognostic Factor	Criteria
ISS stage	
I	Serum β2m <3.5 mg/l, serum albumin ≥3.5 g/dl
II	Not ISS stage I or III
III	Serum β2m ≥5.5 mg/l
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

Annex 3

IMWG diagnostic criteria for multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following myeloma-defining events:

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  - Hypercalcemia: serum calcium >0.25 mmol/l (>1 mg/dl) higher than the upper limit of normal of >2.75 mmol/L (>11 mg/dl)
  - Renal insufficiency: creatinine clearance <40 ml per min or serum creatinine >177 μmol/l (>2 mg/dl)
  - Anemia: hemoglobin value of >20 g/l below the lower limit of normal, or a hemoglobin value <100 g/l
  - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT or PET-CT

-Any one or more of the following biomarkers of malignancy:

- ≥60% clonal bone marrow plasma cells
- Involved/uninvolved serum-free light chain ratio ≥100
- ≥1 focal lesion on MRI studies (each focal lesion must be 5 mm or more in size)