

Multiple myeloma in Nigeria: An insight to the clinical, laboratory features, and outcomes

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Abstract

Aim: In developing African nations, late presentation and occurrence of complications adversely affects survival. This study aims at identifying initial clinical and basic laboratory features of multiple myeloma (MM), which will aid the physician to entertain a high index of suspicion and therefore target his investigations in order to prevent late presentation and avert complications.

Materials and Methods: A retrospective analysis of 32 patients diagnosed and managed in Nigeria, West Africa was done. Information on the clinical, laboratory, and radiological data as well as response to treatment was obtained at presentation, 3, 6, 12, and 24 months and analyzed.

Results: The median age at diagnosis was 62 years, 17 (53.1%) males and 15 (46.9%) females. The median duration of follow-up was 24 weeks (range, 2-288 weeks). The average percentage of bone marrow plasmacytosis at diagnosis was 38%. Clinical features at presentation were anemia (71.9%) and bone pains (78.1%), while pathological fractures were found in 69%, and nephropathy in 13.8%. The longest duration of survival of 288 and 252 weeks were recorded in patients on melphalan and prednisolone with or without thalidomide.

Conclusion: Presence of bone pain and anemia in elderly patients should alert the clinician to investigate along the lines of MM. Majority of patients have osteolytic lesions on X-ray and pathological fractures, and benefit from melphalan based combinations in situations where facilities for transplant are not available.

Key words: Clinical features, chemotherapy, laboratory features, multiple myeloma, Nigeria, treatment

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Introduction

Multiple myeloma (MM), a clonal malignancy of plasma cells is a common hematological malignancy, currently accounting for 13.4% of all hematological cancers, 19% of all deaths resulting from hematological malignancies, and 2% of all cancer-related mortality.^[1] Studies in Nigeria show that MM represents 8.2% of all hematological malignancies.^[2] It is generally believed that MM starts as a benign monoclonal gammopathy of undetermined significance (MGUS),^[2] which develops further in some cases, to become the asymptomatic Smoldering myeloma (SMM) and eventually leading to the symptomatic myeloma. The probability of progression

from MGUS to symptomatic myeloma is 1% per year. On the other hand between 10 and 20% of patients with SMM progress to symptomatic myeloma per year.^[3] Myeloma has a higher prevalence in blacks as well as people in the older age group, above 60 years.^[4] Prior data from the Statistics, Epidemiology, and End Results (SEER) program and the Multiple Risk Factor Intervention Trial showed consistently higher incidence and mortality among blacks.^[5,6]

Previous single center studies reported poorer survival among African-American MM patients. In contrast, recent data based on MM patients who received autologous

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transplantation in an equal access healthcare system, showed comparable survival between African-Americans and Caucasians, suggesting that the reportedly poorer outcome for African-Americans may be due to inequalities in access to modern care. In fact clinicians have been cautioned to be aware that the excess mortality rates for MM among African-Americans, to a major degree, is a reflection of the fact that MM is two- to three-fold more common among African-Americans.^[7] More recent analysis have shown that disease-specific and relative survival rates were higher in blacks than whites.^[8] In fact, Auner *et al.*, set out directly to compare the characteristics and outcome of autologous stem cell transplantation (ASCT) for white, black, and Asian MM patients.^[9] Their findings were that patients from the three ethnic groups had similar progression free survival (PFS) as well as overall survival (OS), supporting the notion that race should not affect decisions regarding ASCT for MM.

The clinical features of the illness usually include bone pain, which is also a common presentation of other disease conditions in this peculiar age group.^[4] This leads to delay in diagnosis as well as mis-referrals, which usually in the long run affect treatment outcome. A high index of suspicion by the physician is therefore important and may be informed by knowledge of the common presenting clinical symptoms. Evaluation of the common presenting features, especially in a resource poor and predominantly black population will serve as a guide and necessary aid to early diagnosis.

Raised calcium, renal impairment, anemia, and bone lesions (CRAB) symptoms are the currently accepted diagnostic criteria for diagnosis of symptomatic (and therefore treatable) myeloma.^[10,11] Although magnetic resonance imaging (MRI) and computed tomography/positron emission tomography (CT/PET) are very sensitive and may provide more information in certain cases, limited facilities as well as finances have limited the use of these diagnostic tools in resource poor settings where simple X-ray of bone is still considered standard. Prognostic markers such as, β_2 microglobulin may not be easily assayed in some parts of the country or affordable by some patients. However, to the unsuspecting physician, these investigations are not usually regarded as baseline and the diagnosis is usually delayed till complications begin to occur. It may therefore be necessary to examine the proportion of patients that actually have positive results with these laboratory modalities.

Treatment options in MM have not only been determined to be age-dependent, but current views indicate individualized treatment, involving assessment of the genetic mutation peculiar to each patient.^[12] The non-availability of facilities and specialized personnel for stem cell transplant, contributes to the lack of this treatment option to majority of patients. The standard of care in myeloma is induction chemotherapy with immunomodulatory drugs and proteasome inhibitors

followed by stem cell transplant. However, in resource constrained centers such as ours, most patients still receive melphalan based chemotherapy regimen.

This study therefore aims to describe the frequent clinical and laboratory features associated with MM at presentation in this environment, as well as describe the response to various chemotherapeutic combinations commonly used.

Materials and Methods

A retrospective study of 32 patients who were diagnosed with MM and managed at the University of Nigeria Teaching Hospital, Enugu, Nigeria over a period of 10 years, January 2002-2012, were reviewed. Permission was obtained from the University of Nigeria Teaching Hospital Cancer Registry and Data Collation Institute. Clinical presentation and laboratory and radiographic data were extracted from patients' medical records, at 3 monthly intervals for 2 years post-diagnosis; poor data filing and documentation was a major setback in this study. The various chemotherapeutic regimen used and survival patterns were analyzed. Only patients who had received two or more cycles of chemotherapy or whose duration of follow-up was more than 3 months were included in the study. Lack of adequate record keeping and patients being lost to follow-up resulted in small numbers for analysis.

Statistics

Patients' parameters were analyzed using Statistical Package for Social Sciences (SPSS) 10.0 to obtain Spearman's rho correlation coefficient (two-tailed) between patient survival and serum albumin, β_2 microglobulin, absolute neutrophil count, and platelet count at diagnosis. Demographic data were explored as expressed in figures.

Results

Thirty-two patients were assessed; their ages ranged from 35 to 87 years, with a median age of 62 years. There were 17 (53.9%) males and 15 (46.1%) females. The median duration of follow-up was 24 weeks (range, 2-288 weeks). The average percentage of bone marrow plasmacytosis at diagnosis was 38%, in this patient group.

Table 1 shows some important clinical factors which may affect patient survival. The known clinical prognostic indicators of poor outcome, such as presence of nephropathy and pathological fractures were found more in males at presentation. In our study, duration of follow-up was defined as the duration between the day of diagnosis and the last day the patient was seen alive. Only about 20% of the patients were officially known to have died as at the time of review; however these were those who had either died in the facility or those whose death had been reported to

the hospital. The pitfalls include patients who were lost to follow-up who probably may have died at home without formally informing the hospital or caregivers.

The clinical features at presentation were anemia (71.9%) and bone pains (78.1%), while complications of myeloma such as pathological fractures were found in 69% and nephropathy in 13.8% of the patients. Laboratory abnormalities were observed at diagnosis. The median hemoglobin concentration (Hb) at diagnosis was 8.5 g/dL, total white blood cell (WBC) count $5.85 \times 10^9/L$, platelet count $192.5 \times 10^9/L$, and absolute neutrophil count $3.1 \times 10^9/L$. The median values of other results at diagnosis were: Serum globulin 4.95 g/L (range 2.1-11.9), albumin 3.8 g/L (range 1.9-5.2), β_2 microglobulin 4.0 $\mu\text{g/mL}$ (range 2-11), and calcium 2.5 mmol/L (range 2.1-9.6), and phosphate 1.35 mmol/L (range 0.8-8.6). The median values of other results at diagnosis were immunoglobulin (Ig) G 0.88 $\mu\text{g/mL}$ (range 0.32-0.89), IgA 0.4 $\mu\text{g/mL}$ (range 0.12-0.64), IgM 0.37 $\mu\text{g/mL}$ (range 0.04-0.78).

With regards to the chemotherapeutic regimen used, 22.2% of the patients were placed on melphalan/prednisolone (MP), 29.6% on melphalan/prednisolone/thalidomide (MPT), 14.8% on cyclophosphamide/vincristine/adriamycin/prednisolone (CVAP), 14.8% on melphalan alone, 7.4% on bortezomib based combinations, while 11.1% received no anticancer agents. Higher mortality rates were recorded in patients on MP and MPT, though this regimen was used for majority of the patients. Some of the patients were not placed on any regimen as at the last visit. These were patients who were lost to follow-up or who due to several co-morbidities could not be commenced on cytotoxic chemotherapy.

Table 2 contains the correlation coefficient (Spearman rho and Kendall tau_b) and P values for the various clinical and laboratory parameters in the patients reviewed. This shows no significant correlation between treatment outcome with regards to duration of follow-up and any of the clinical and laboratory parameters. The number of cases recorded for β_2 microglobulin was too low to be analyzed with the Spearman correlation. International staging system (ISS) for myeloma for few of the patients (eight people) in this group revealed that 37.5% of the patients were in the high and intermediate risk group each, while 25% were in the low risk group. Majority of the patients (24 people) were staged using the Durie and Salmon staging and revealed; 53.6% in stage III, 17.9% stage II, and 28.6% stage I.

The median follow-up time was 24 weeks (6 months), range 2-288 weeks. The longest duration of follow-up of 288 and 252 weeks were recorded in patients on MP and had died while on admission, and another who had asymptomatic myeloma and was not on treatment up until the time of this write up. There was no significant correlation between

Table 1: Frequency of occurrence of some important clinical and laboratory factors

Features	Presence of this feature (%)	
	Yes	No
Presence of co-morbidities (n=26)	16 (61.5)	10 (38.5)
Bone pain at diagnosis (n=29)	25 (86.2)	4 (13.8)
Pathological fracture at diagnosis (n=28)	17 (69)	11 (31)
Anemia at diagnosis (n=26)	22 (78.9)	4 (21.1)
Nephropathy at diagnosis (n=27)	4 (13.8)	25 (86.2)
Bence Jones proteinuria (n=12)	9 (47.4)	10 (52.6)
Serum β_2 microglobulin at diagnosis > 3.5 mg/dL	5 (71.4)	2 (28.6)
Serum albumin at diagnosis > 3.5 g/dL (n=23)	14 (60.9)	9 (39.1)
Immunoglobulin (m protein) type	IgA 5 (45.5)	Others (54.5)
Thickened gamma band on electrophoresis (n=18)	17 (89.5)	2 (10.5)
Osteolytic lesions on X-ray (n=15)	11 (73.3)	4 (26.7)
“Punched out” lesions on skull X-ray (n=14)	7 (50)	7 (50)
Presence of amyloidosis (n=15)	0 (0)	15 (100)
Clinical evidence of hyperviscosity (n=13)	3 (23.1)	10 (76.9)

Table 2: Patient survival and correlation with clinical and laboratory factors

	P value	Spearman rho (2-tailed)	P value	Kendall tau_b (2-tailed)
Serum albumin	0.557	-0.153	0.443	0.139
Serum β_2 microglobulin	NA	NA	0.871	-0.040
Serum calcium	NA	NA	0.178	0.289
Absolute neutrophil count at diagnosis	0.474	0.186	0.456	0.157
White blood cell count at diagnosis	0.626	0.102	0.616	0.085
Platelet count at diagnosis	0.302	-0.225	0.291	-0.188
Presence of pathological fracture	0.887	0.029	0.884	0.029
Presence of nephropathy	0.357	-0.184	0.347	-0.184
Chemotherapeutic regimen used	0.162	-0.325	0.156	-0.291
Age at diagnosis	NA	NA	0.774	-0.045
Durie and Salmon Staging	NA	NA	0.864	0.032

NA=Not available (could not be analyzed)

patient survival and chemotherapeutic regimen used, serum albumin, β_2 microglobulin, calcium, presence of pathological fractures, or nephropathy. However, these values were obtained at diagnosis and subsequent values post diagnosis

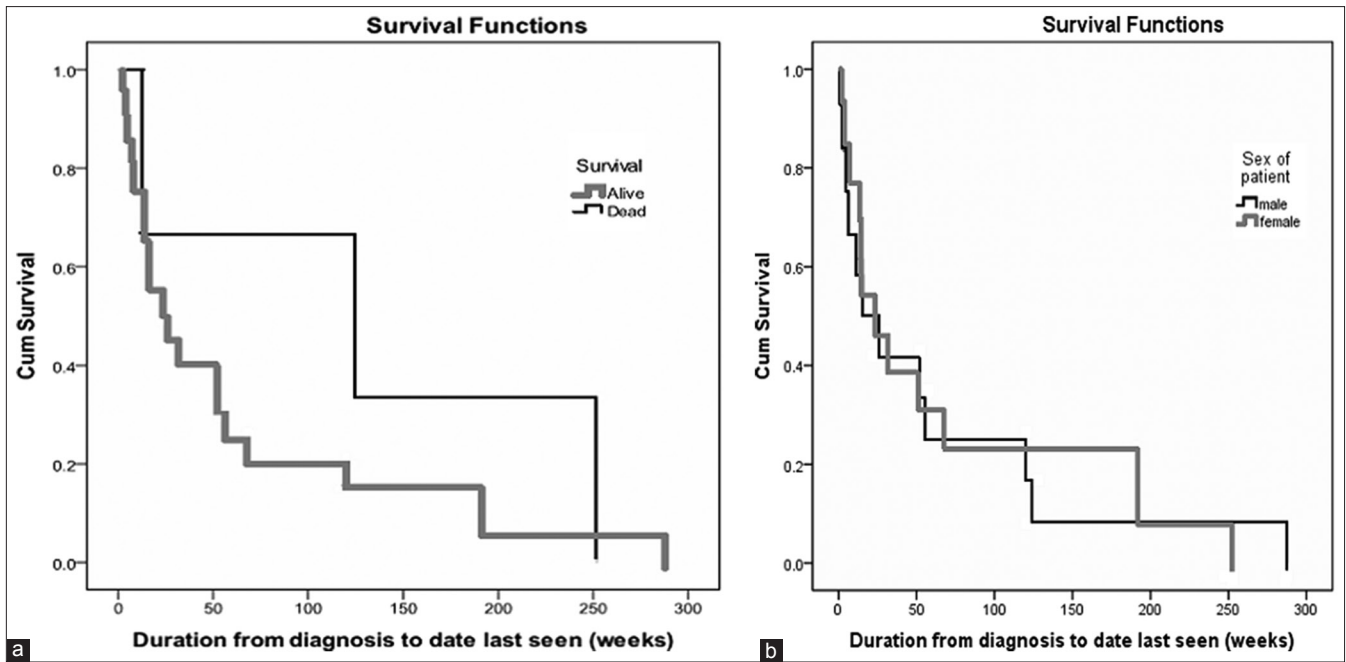


Figure 1: (a) Kaplan-Meier survival curve for all myeloma patients, (b) Kaplan-Meier survival curve for the different sexes

which may show a positive relationship, were not accessible. Figure 1a is the Kaplan-Meier survival curve for all the patients, and indicates that the fatalities were encountered as from the around the 10th week of management. Figure 1b shows the survival curve of males versus females and indicates that mortality in males seems to be more between the weeks 120 and 180 (2.5-3.5 years). Figure 2 illustrates the various chemotherapeutic combinations given the patients. Most of the patients received combinations containing melphalan.

Discussion

The median age at diagnosis of myeloma in this patient group was 62 years. This is similar to studies done in other Nigerian centers. In Ile-Ife, western Nigeria where a median age of 60 years was obtained, while Omoti and Omuemu, in Benin City south western Nigeria, got a slightly lower age of 54 years.^[13,14] Initial complaints in MM consist mainly of bone pains, which is also a common presenting feature of several diseases of old age. Majority of the patients in this study had bone pains and this is similar to the findings of previous studies.^[4,10] However, in the older age group this will need to be further evaluated to rule out myeloma as well as other diseases of the elderly. Physicians should bear this in mind as a leading cause of delayed presentation or referrals.

Anemia occurring also in this background of bone pains is another frequent presenting feature. This finding is similar to that reported by Fasola *et al.*, Omoti *et al.*, and Riccardi *et al.*, who noted in their various reports that the presenting features of low hemoglobin concentration such

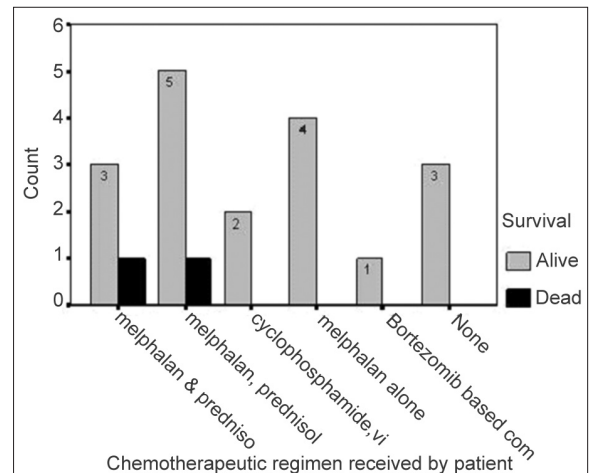


Figure 2: Patient survival on the different chemotherapeutic regimen

as weakness, dizziness, and fainting feeling in the elderly are common presenting features.^[13,15] This presentation is of more importance in resource-poor settings where the clinical acumen rather than diagnostic facilities are relied upon. Most of our patients have with stage II or III disease at diagnosis, indicative of late presentation or aggressive disease. Unlike in developed countries where diagnosis is usually made during evaluation of anemia detected during routine evaluation, in Nigeria, there are no routine healthy adult yearly evaluation and hence patients present with symptomatic and with more advanced disease. This may partly explain the poor outcome.

There was a high incidence of pathological fracture amongst this patient group. Majority of these fractures were clinically discernable, while the others were diagnosed on plain

radiograph. This is similar to the findings by Salawu *et al.*, who observed pathological fractures in 44% of their myeloma patients in Ile-Ife, western Nigeria. This is another preventable consequence of late presentation and majority of the patients were initially seen and referred from the Orthopedic Unit. Bone pain usually precedes fracture in myeloma and early diagnosis may prevent this debilitating complication if a high index of suspicion is maintained. Fracture in myeloma is associated with increased morbidity and poorer prognosis.^[10] Therefore, efforts to avert this complication will definitely improve treatment outcome. MM therefore should be ruled out in any adult or elderly patient with a history of chronic bone pain. Majority of the patients did not have renal impairment at presentation. This has been known to adversely affect treatment outcome. This is similar to figures obtained in other studies on nephropathy in myeloma done in Nigeria, where 36% had renal impairment compared to 16% in this study. However, in the Ibadan study the serum electrolytes, urea, and creatinine were used to estimate glomerular filtration rate and renal impairment; while in this study only those patients with clinical diagnosis renal failure (chronic kidney disease) were recorded.^[16] Causes of nephropathy in myeloma such as hypercalcemia, amyloidosis, severe hyperproteinemia, and hyperviscosity were also noted to be absent in majority of the patients at diagnosis.

Laboratory investigations as well as radiological tests are the mainstay of diagnosis of MM. However, in a resource poor setting with limited funds and access to facility for in-depth investigation, physicians should be aware of the most frequently positive diagnostic tests. Presence of Bence Jones proteinuria was found to occur infrequently (47.4%) in this patient group, though gammopathy on serum protein electrophoresis was quite rife (89.5%). Similar figures were also observed by Salawu *et al.* Anemia was also another common presenting feature as well as osteolytic bone lesions on plain radiograph. These represent simple and affordable diagnostic tools which may further inform the choice of early referral. However, "punched out" skull lesions were observed in only half of the patients. Reversal of the albumin/globulin ratio was another commonly observed presenting feature in this patient group and had previously described in other studies. However, some disease features such as amyloidosis and symptoms of hyperviscosity has been found to be quite rare and may not be easily found at presentation.

The relationship between patient survival and serum albumin, β_2 -microglobulin, platelet count, absolute neutrophil, and WBC count did not reveal any significant correlation. Also presence of pathological fracture or nephropathy did not significantly affect survival as had been previously suggested by Talamo *et al.*

The median follow-up time in this group of patients was 24 weeks (6 months). However, majority of the patients in this group were still alive as at the time of analysis and

repeat assessment after several years may eventually show a relationship. There was also no significant difference in duration of treatment and the type of chemotherapeutic combination used. Most of the patients were placed on melphalan and prednisolone based regimen. The choice of chemotherapy was not randomized, but was based on patients' performance score and presence of co-morbidities. Although being a retrospective study, analysis of response to treatment may not be optimal, however some insight can be obtained as with regards to the effectiveness of chemotherapeutic combinations.

Therefore, in a resource poor setting investigations should be targeted at those parameters with a high frequency of positivity and greater diagnostic power in order to avert debilitating complications and improve survival. Larger studies in resource poor settings may be necessary with the aim of generating a need based diagnostic and treatment algorithm, peculiar to these environments.

Conclusion

Bone pain and anemia in the elderly patients are important clinical signs which should alert the clinician in a resource poor setting to investigate along the lines of MM. Majority of the patients will present with osteolytic lesions on X-ray and pathological fractures, though skull radiograph may not show the typical lesions. Gammopathy on serum protein electrophoresis is more likely to turn out positive than Bence Jones proteinuria.

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