Presentation and survival of multiple myeloma patients in Ghana: a review of 169 cases

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SUMMARY

Background: Africans have an increased risk for multiple myeloma (MM) compared to other races. Reports from Africa are few and involve small cohorts, but suggest significant epidemiological and clinical differences from Caucasian patients.

Objective: This report describes the clinic-pathological features of MM patients in Ghana at diagnosis, and the factors affecting their survival.

Methods: A retrospective review of 169 MM cases diagnosed in a Ghanaian tertiary hospital from 2002-2016.

Results: Median age was 58 years, with 29% ≤50 years. One-third presented >12 months after onset of symptoms, which included bone pain (96%), anaemia (67%), weight loss (55%) and fractures (44%). Myeloma-related tissue impairment included hypercalcaemia (36%), renal impairment (33%), severe anaemia (52%) and osteolytic lesions (76%); 51.3% of patients were diagnosed in ISS Stage III. Median survival was 33 months; 1-year and 5-year overall survival were 51.6% and 15.5%, respectively. Neither the age at diagnosis nor the duration of symptoms prior to diagnosis correlated with prognosis. Median survival improved with early ISS stage, haemoglobin >8g/dL, plasmacytosis <20%, and normal creatinine and calcium levels.

Conclusion: Early onset and late stage presentation are common at diagnosis of MM patients in Ghana, but do not affect survival. Studies into genetic associations are recommended.

Keywords: Multiple Myeloma, Ghana, Africa, survival, presentation

INTRODUCTION

Multiple myeloma (MM), also called plasma cell myeloma, is a haematological malignancy characterised by an accumulation of clonal plasma cells in the bone marrow, often associated with the detection of a monoclonal paraprotein in the blood and/or urine. MM is classified among the paraproteinaemias, a spectrum of monoclonal protein-secreting disorders that ranges from a pre-malignant condition known as monoclonal gammopathy of undetermined significance (MGUS) to plasma cell leukaemia.

MM accounts for 15 to 20% of haematological cancers, and comprised 0.8% of new cancer cases and 1.0% of cancer deaths worldwide in 2012.[1]

The median age at diagnosis is estimated at 71 years.[2] The incidence of MM is two to three times higher in African-Americans compared to Caucasians, while Asians are infrequently affected.[3] However, African-Americans have better survival than Caucasian Americans.[4] The aetiology of MM is not well understood; 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.[5,6] Familial clustering and recurrent cytogenetic abnormalities also suggest a genetic component.[7]

The diagnosis of plasma cell 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: hypercalcaemia, renal impairment, anaemia and bone lesions. A monoclonal paraprotein or abnormal serum free light chain ratio may be present.[8] The International Staging System (ISS) utilises serum albumin and β-2 microglobulin to predict three prognostic groups.[9]

The clinical features of MM in Caucasians have been well characterised in large studies.[2,10] Although studies of MM from African facilities tend to involve small cohorts,[11–16] the reports suggest that at diagnosis, the epidemiological, clinical and laboratory features of Black Africans differ significantly from those of Caucasian patients. Africans have an increased risk for MM compared to other races, but compared to other non-communicable diseases, it is an uncommon disease.

Therefore, an increased understanding of MM in Africans will help improve clinical suspicion and early diagnosis or referral and draw attention to those complications of MM that are associated with prognosis. The goal of this study was to describe the clinical and laboratory features at the initial presentation of a large series of MM patients in a Ghanaian tertiary hospital, the treatment used for these patients and factors associated with survival. We further compare our findings with reports from similar African populations.

METHODS

This retrospective study was conducted in the Haematology Department of the Korle Bu Teaching Hospital (KBTH), in Accra, Ghana. This 2000-bed facility was established in 1923 and is the largest tertiary hospital in the country. Patients are referred from hospitals throughout Ghana, and from some neighbouring countries. We reviewed clinical records and laboratory data available for consecutive patients diagnosed between January 2002 and December 2016 with symptomatic multiple myeloma according to the 2003 International Myeloma Working Group (IMWG) diagnostic criteria.[17] Demographic characteristics, clinical features, laboratory results and treatment records were abstracted and the data analysed for descriptive and inferential statistics using IBM SPSS Statistics software version 20 (IBM Corp, Armonk NY, USA). This study received ethical clearance from the Ethical and Protocol Review Committee of the College of Health Sciences, University of Ghana [CHS-Et/M4-P2.15/2017-2018].

RESULTS

Demographic characteristics

Medical records were available for 169 patients diagnosed within the study period. Half of the cases were diagnosed between 2012-2016. All patients were indigenous Ghanaians, from all regions of the country. The patients were 51.5% male, and age at diagnosis ranged from 27 to 90 years, with a median age of 58 years. However, men were significantly younger at diagnosis than women, 56.1 vs. 61.2 years (p=0.008) [Figure 1].

Patients who were 50 years or younger at diagnosis made up 29% of the study population, with those 40 years or younger comprising 7.1%. Altogether, these 'younger' patients were three times more likely to be male than female (p=0.005).
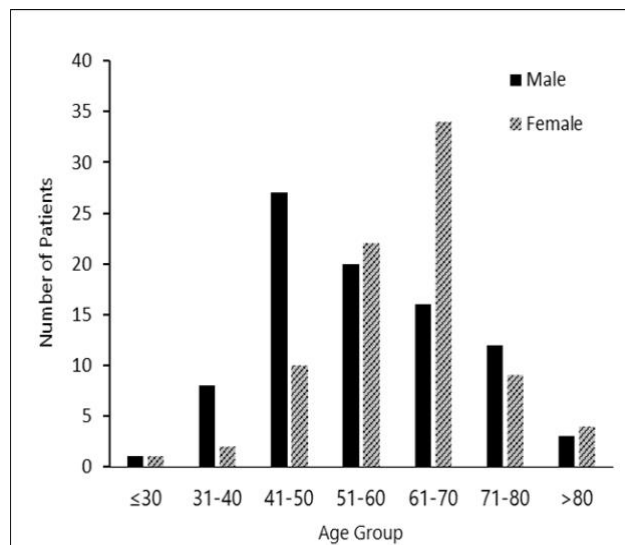
Figure 1 Distribution of patients by age and sex

Symptoms at presentation

None of the patients had been previously screened for MGUS. Three patients were diagnosed after they had been referred for an apparent solitary plasmacytoma. Most patients were diagnosed within 6 months of onset of symptoms (57.7%), but 31.5% presented after 12 months of illness. Over half of the patients (55.6%) reported more than two symptoms. The most common clinical features at presentation were bone pain, anaemia, weight loss, and limb fracture or paralysis [Figure 2].
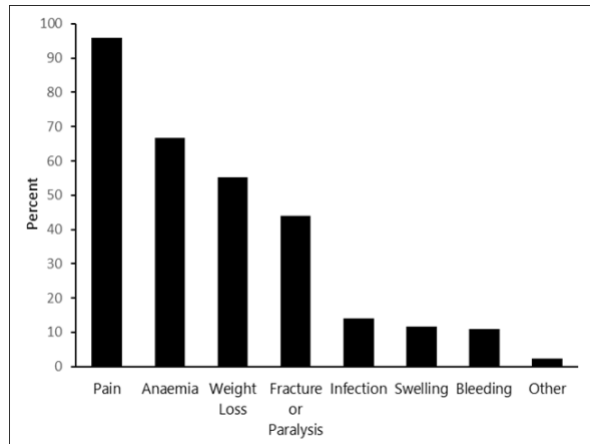
Figure 2 Symptoms at presentation

For those with pain at presentation, 73.4% had pain localised to the waist and/or the back. Overall, infection rates at presentation were similar in women and men. However, women were more likely to present with urinary tract infection, and men with pneumonia (p=0.003). The duration of symptoms prior to diagnosis was not associated with the number or type of clinical features at presentation.

Laboratory Values at Diagnosis

The laboratory data are presented in Table 1. The median plasma cell count on marrow aspiration was 28%. No immunophenotyping, flow cytometry or chromosomal studies were done on marrow samples.

Of the 125 patients evaluated, 77% had a detectable paraprotein on serum protein electrophoresis, with a median of 32 g/L. Generally, immunofixation was not done. Light-chain myeloma was confirmed in 94% of patients without a serum paraprotein.

The λ light chains were three times more likely to be elevated than κ chains. The total serum protein was elevated (>80g/L) in 69.7% of evaluable patients, and in 94% of these cases, the increased total protein was found to correlate with a paraprotein level above 5g/L.

Anaemia (Hb < 10g/dL) was present in three-quarters of the patients. Most patients had a normal WBC (84%) and platelet count (74%). Bleeding was more frequently observed in patients with thrombocytopenia (p=0.003), although only one patient with a history of haemorrhage had a platelet count below 30×10^9/L. One-third of patients presented with renal impairment (defined by the IMWG as serum creatinine >177µmol/L).

Men were significantly more likely to present with renal impairment (p=0.016). Hypercalcaemia was found in 54.7% of patients.

Table 1 Laboratory and Radiological Parameters at Diagnosis

Laboratory Parameter	N	Median (Range)	Distribution of Patients by Parameters	
Haemoglobin (g/dL)	161	7.9 (3.0-16.0)	3-6 g/dL 7-9 g/dL $\geq$ 10g/dL	37.3% 38.5% 24.2%
WBC (x10⁹/L)	157	6.6 (2.1-37.3)		
Platelet (x10⁹/L)	157	231 (4-696)	< 100 150 - 400 > 400	10.2% 73.7% 4.8%
Rouleaux	117		Present	82.1%
ESR (mm fall/hr)	77	125 (2-150)	$\geq$ 20 $\geq$ 100	6.5% 64.9%
Marrow Plasma Cells (%)	122	28 (0-97)	< 10% $\geq$ 10%	17.2% 82.8%
Paraprotein (g/L)	125	32 (0-113)	Absent 1 – 5 > 5	22.4% 3.2% 74.4%
Urine Bence Jones protein	66		Absent Present	53.0% 47.0%
Serum Free Light Chain Ratio	36		Normal κ:λ Excess κ Excess λ	11.1% 22.2% 66.7%
Total Protein (g/L)	142	91.9 (54.0-180.0)	< 60 60 – 80 > 80	4.9% 25.4% 69.7%
Albumin (g/L)	155	32 (14-50)	< 35 35 – 50	60.6% 39.4%
Creatinine (µmol/L)	147	114 (44 – 1281)	< 60 60-120 > 177	5.4% 47.6% 32.7%
LDH (IU/L)	16	455 (81-2250)	< 400 $\geq$ 400	31.2% 68.8%
b2-microglobulin (mg/L)	76	5.5 (1.1-54.0)	< 2.5 > 2.5	17.1% 82.9%
Calcium (mmol/L)	137	2.59 (1.85-4.58)	< 2.15 2.15-2.55 > 2.75	8.0% 37.2% 35.8%
Lytic bone lesions	134		Present Skull	76.1% 41.8%
Fractures	140		Present Verterbrae	44.3% 25.6%
ISS	76		ISS I ISS II ISS III	22.4% 26.3% 51.3%

Those with elevated creatinine were more likely to have coexisting hypercalcaemia (p=0.038). Few patients had had lactate dehydrogenase measured at presentation.

The most common sites for lytic lesions were the skull (40.2%) and vertebrae (11.5%). The presence of lytic lesions on imaging corresponded significantly with a presentation of bone pain (p=0.002). Bone fractures were

present in 44.3% of patients, half of which involved the vertebral column. Neither age nor sex was associated with the presence of fractures.

Of 76 patients evaluated, half presented with ISS Stage III disease, while 22.4% presented in Stage I. Late ISS stage was associated with severe anaemia (p<0.05), hypercalcaemia (p=0.027), elevated serum creatinine (p<0.05), and bone marrow plasmacytosis >20% (p=0.021). However, the ISS stage at diagnosis was not associated with the level of a monoclonal paraprotein.

There was no significant relationship between patients' age groups or duration of symptoms prior to presentation, and any of the haematological and biochemical parameters measured. Apart from the aforementioned higher frequency of renal function in men, men and women had similar laboratory parameters.

Treatment and Complications

With the exception of three patients who declined specific treatment, all patients were managed with chemotherapy and supportive care such as pain management, blood transfusions, infection treatment and correction of electrolytes. For most patients at the facility, first-line chemotherapy was a non-infusional modified VAD (vincristine-doxorubicin-dexamethasone) regimen consisting of six 21-day cycles of bolus intravenous vincristine and doxorubicin with a four-day pulse of oral dexamethasone, and three-quarters of patients received this treatment. In nearly all cases, patients continued on maintenance therapy, usually melphalan-prednisolone (MP), until plateau. Elderly patients were started on MP, or cyclophosphamide with prednisolone or dexamethasone. Thalidomide-based therapies used included VAD-T, MPT (VAD or MP with thalidomide), Thal-Dex (thalidomide with dexamethasone) or CTD (cyclophosphamide-thalidomide-dexamethasone).

Combinations involving novel agents—specifically, lenalidomide or bortezomib with MP or dexamethasone—were generally offered for relapsed or refractory disease. Zoledronic acid was the bisphosphonate of choice (85%) for managing hypercalcaemia and bone disease. Radiation-therapy was primarily indicated for pain control and compression fractures. Stem cell transplants were not standard of care in the hospital during the study period, due to limited resources, and were thus not offered to any of the patients.

Sixty-eight percent (68%) of patients reported complications during their management. The most frequent of these were infections (44.9%), particularly pneumonia and gastroenteritis. Twelve percent (12%) of patients had a venous thromboembolism, but this did not

appear to be associated with any particular type of chemotherapy regimen. About one-fifth of patients developed new limb or spinal fractures, peripheral neuropathies, or acute/chronic renal failure at some point during their management.

Prognostic Features

Median overall survival was 33 months [95% CI 21.4, 44.6]. The 1-year and 5-year overall survival rates were 51.6% and 15.5%, respectively. Median survival was significantly improved for patients with haemoglobin >8g/dL, marrow plasmacytosis <20%, normal creatinine and calcium levels at diagnosis [Table 2]. Hypoalbuminaemia and normal platelet count were not associated with a significant survival advantage. Neither age at diagnosis nor duration of illness prior to diagnosis correlated with survival outcomes.
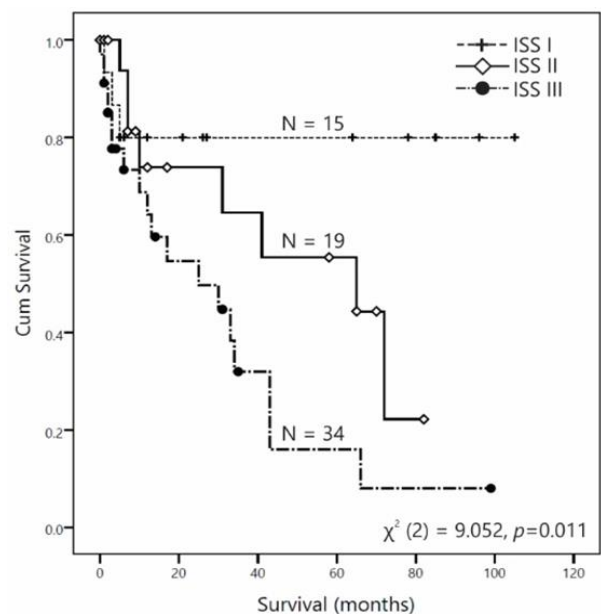
Figure 3 Survival by ISS Stage. Median Survival for ISS II and ISS III were 65 and 25 months, respectively

There was no difference in the 6-month survival between patients diagnosed before and after 2012. However, patient survival varied significantly by ISS Stage at diagnosis with median survival for ISS II and III being 65 and 25 months, respectively (p=0.011); median survival for patients diagnosed with ISS Stage I disease had not yet been reached at the close of the study period (Figure 3).

Table 2 Median Survival of Patient Groups

		Median survival (months)	Log Rank test
Sex	Male	36	0.766
	Female	32	
Age Category	<50 years	36	0.170
	51-65 years	43	
	>65 years	22	
Duration before Diagnosis	<6 months	22	0.083
	6-12 months	66	
	> 12 months	41	
Haemoglobin	<8g/dL	22	0.004
	≥8g/dL	65	
Platelet	<150x10⁹/L	23	0.138
	≥150x10⁹/L	34	
Marrow Plasma Cells	<20%	65	0.023
	≥20%	26	
Paraprotein	<30g/L	44	0.327
	≥30g/L	27	
Albumin	<35g/L	27	0.114
	≥35g/L	44	
Creatinine	<120µmol/L	41	0.002
	≥120µmol/L	23	
Calcium	<2.75mmol/L	41	0.004
	≥2.75mmol/L	17	
Fracture	Present	32	0.770
	Absent	36	

DISCUSSION

This study corroborates previous findings that the median age at diagnosis of MM in Africans lies in the sixth decade of life.[11–13,15,16,18] In contrast, Caucasian patients are typically a decade older at diagnosis.[2,10] Nearly one-third of patients were 50 years of age or younger, an observation that has also been noted by Odunukwe *et al* in Nigeria.[16] Seven percent of patients were 40 years or younger, which is consistent with other reports from elsewhere in Africa,[14,16,19] but twice as many as reported for Caucasians. Since this observation could be biased by the lower life expectancy in Africans, adjusting the incidence for age would allow for more reliable comparison.

Men are slightly more likely to be diagnosed with MM than women, regardless of race.[10,19,20] However studies from Cameroon[15] and Sudan[21] have reported wide variations in male-female distribution. Our study found nearly equal numbers of males and females; younger patients were more likely to be male, and older patients, female. Risk factors such as chronic inflammation, exposure to chemicals and radiation, and obesity were not universally assessed in the medical records.

Although MGUS has been reported to be twice as prevalent in Ghanaian men as in Caucasians,[22] none of the patients in this study had been screened prior to diagnosis. In Ghana, screening for paraproteinaemia is not included in routine health checks, possibly due in part to a low awareness of paraproteinaemias in primary health facilities, coupled with inadequate testing facilities nationwide.

Bone pain was the most common presenting complaint, consistent with other reports in African patients.[11,15,16] Half of the patients in this study presented with weight loss, which represents a significantly higher prevalence than reported for patients in Kenya[11] and the United States.[10] One-third of the patients were diagnosed more than 12 months after onset of symptoms, similar to observations from Nigeria by Fasola *et al*.[14] However, the clinical features and results of investigations including ISS stage, as well as the overall survival in these later-diagnosed patients were similar to patients who were diagnosed within 6 months of symptom onset.

In the majority of patients (77.6%) a paraprotein was detected; however, further characterization by immunofixation was frequently not done. The prevalence of paraproteinaemia varied between 45-87% in other African studies.[12,13,16] With the introduction of assays for serum free light chains, many cases previously assigned as non-secretory myeloma were found to be of the light chain variant. Of note was the three-fold increased prevalence of λ-chain restriction compared to κ, although this difference was not associated with prognosis.

The prevalence of anaemia was similar to that reported in a Caucasian population by Kyle *et al*;[10] however, 52% of the patients in this series presented with severe anaemia (Hb <8g/dL), in contrast to only 7% in Kyle's report. Severe anaemia was likely due to advanced MM disease and renal impairment, both of which were prevalent in this cohort. Significantly elevated serum creatinine was seen in one-third of patients. This is similar to reports from Nigeria[16] and Burkina Faso,[13] but less than reported from Kenya[11] (52%), and twice that reported from Cameroon[15] (17%). In Ghana, diclofenac and other NSAIDs are frequently prescribed analgesics.

With a high prevalence of bone pain in the study population, it is likely that many of the patients in Ghana would have been prescribed NSAIDs by the time of referral, which could contribute to the development of renal impairment. One third of patients had hypercalcaemia, similar to a report from Kenya,[11] however there is a wide variation (6.8-69%)in the prevalence of hypercalcaemia in Africans at diagnosis.[12,13,19] Lytic lesions were more often detected on skull imaging, a reflection of the local protocol for investigating suspected myeloma. Plain x-rays were most often used to evaluate bone pain, instead of MRI or CT scan, due to cost.

The prevalence of fractures was higher than reported by Kiraka *et al* from Nairobi,[11] but similar to studies from Zambia[18] and West Africa.[12,15,16] Fifty percent of patients who were evaluated presented with ISS Stage III disease, compared to 19% in a study of African-American patients,[23] which possibly reflects the barriers to accessing healthcare in sub-Saharan Africa.

More than half of patients in this study received whole blood or packed cell transfusion, due to the prevalence of severe anaemia, and to permit the administration of a moderately myelosuppressive regimen. Until recently, the mainstay of treatment at our facility for younger patients and those in renal failure was the modified VAD regimen, with MP reserved for elderly patients and for maintenance therapy. In the last 10 years of the study period, thalidomide was frequently added to treatment regimens.

Bortezomib and lenalidomide were the two other novel agents available in Ghana, but few patients were able to afford them. The overall median survival of 33 months (range, 0 - 138 months) in this study compares favourably with centres where MP was the predominant treatment.[16,19,24] The utility of the ISS staging criteria method in a wholly African patient population is supported by the inverse association of stage with survival in the stage-specific survival curves. This is in contrast to findings from a large cohort from Egypt, in which ISS stage did not significantly affect prognosis.[25] The impact of treatment regimens on various prognostic factors that have been identified in this cohort (such as severe anaemia and renal impairment) could not be evaluated with the study design. The absence of an influence of early versus late presentation on outcomes suggests the presence of individual patient modifiers, which likely include genetic factors, for which further study is recommended. Other important limitations of this study include the retrospective design, limited laboratory investigations for some patients, and dependence on archival records, some of which were incomplete.

CONCLUSION

The current study shows that MM patients in Ghana are about a decade younger than Caucasians at diagnosis, with about half presenting with late stage disease. The absence of an influence of early versus late presentation on outcomes suggests the presence of individual patient modifiers and underscores the need for further study on genetic factors associated with African MM patients.

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