PLASMA CELL MYELOMA IN A TERTIARY CENTRE IN NIGER DELTA REGION OF NIGERIA: CLINICOIMMUNOLOGIC ANALYSIS

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ABSTRACT

Objective: To determine the incidence and pattern of presentation of patients with multiple myeloma (MM) in a tertiary health center in Edo state, Niger Delta region of Nigeria noted for its petrochemical industries and gas flare sites.

Design: A retrospective study of 30 cases of MM from 1992 to 2004.

Setting: University of Benin Teaching Hospital, Nigeria.

Main outcome measures: Clinicoimmunologic information in addition to autopsy findings was obtained from case-files. Diagnosis was established according to the standard definition and staged according to the Durie-Salmon clinical staging system.

Results: Advanced stages of the disease (II-III) and performance status scale of 2-4 with pathological fractures were the main form of presentation. Overall median survival was three months (P<0.0001) with 33.3% of the patients surviving at 12 months and 13.3% at 24 months.

Conclusion: Bone pains and anaemia with pathological fractures were the commonest characteristic features with a short three months median survival rate.

KEYWORDS: Multiple myeloma, Incidence, Clinicoimmunologic features.

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INTRODUCTION

Multiple myeloma (MM) is one of the most common haematologic malignacy characterized by proliferation of a clone of plasma cells that manifests by the presence of one or more lytic bone lesions, monoclonal (M) protein in the blood/urine and bone marrow involvement.[1] The occurrence of MM is worldwide and is more commonly seen in Blacks than in the Caucasians.[2] It is the second most prevalent blood cancer after non-Hodgkin's lymphoma, causing 2% of all cancer deaths.[3] MM accounts for approximately 1% of all human cancers and 10% of all haematological malignancies, ranking 13th and 17th among cancer sites in men and women respectively.[4] The current therapeutic approach, especially with the advancement in high-dose chemotherapy and stem cell transplant have improved overall survival and event-free periods, but relapse is inevitable.[5,6] The risk factors responsible for the increasing incidence and characterization of descriptive patterns has been limited. Hence, there are considerable differences in the recorded incidence in different geographic areas. The aim of this study therefore is to determine the incidence and pattern of presentation of patients with MM in Edo state, Niger Delta region of Nigeria noted for its petrochemical industries and gas flare sites.

PATIENTS AND METHODS

Study Design: All cases of MM seen at University of Benin Teaching Hospital (UBTH) and

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the state Central hospital, which are the major referral center serving the South-South geopolitical zone of Nigeria in the Niger Delta region between 1992 and 2004 were reviewed. Clinicoimmunologic and demographic features of 30 patients in addition to autopsy findings were obtained from case-files. These include the age, gender, presenting clinical features and signs at diagnosis including the standard Durie-Salmon (DS) clinical staging system. The Eastern Cooperative Oncology Group (ECOG) scale for measuring performance status (PS) on a scale from 0 to 4 was applied to the patients with age adjustment index. Diagnosis was established according to standard definitions when at least two of the following criteria are met: a) paraprotein detectable in serum or urine together with a subnormal concentration of at least one monoclonal immunoglobulin class, b) ≥30% malignant plasma cells in the bone marrow and c) osteolytic and/or osteoporotic bone lesions compatible with MM.[7] Clinicoimmunologic analysis/diagnosis was done according to the modern serum protein immunoelectrophoretic pattern. Blood samples collected for haematological and biochemical parameters were done using automated coulter counter. The erythrocyte sedimentation rate (ESR) was analyzed by the Westerngren method and reticulocyte count according to Dacie and Lewis.[8] Overall survival (OS) was measured from the date of diagnosis to the moment of death/last follow-up.

Table-I: Plasma cell neoplasm subtypes

Myelomatosis Subtype	*Number (%)*
Multiple myeloma	21 (70)
Solitary Plasmacytoma	5 (16.7)
-2 Solitary plasmacytoma of rib bone	
-1 Left and 1 Right proximal femur plasmacytoma	
-1 Descending colon plasmacytoma	
Extramedullary Plasmacytoma	2 (6.7)
-Nasal lesion plasmacytoma	
-Left maxillary sinus tissue plasmacytoma	
Smoldering myeloma	1 (3.3)
Plasma cell leukaemia	1 (3.3)

Evaluation: The pretreatment evaluation included complete blood count, biochemical tests for renal and liver functions and electrophoresis of serum and urine. Bone marrow aspiration cytology (BMAC) was done to determine the percentage of plasma cells and the morphology. Follow-up studies included the estimation of the monoclonal component in serum or urine by monthly determinations and BMA scheduled for six months after the beginning of treatment.

Statistical analysis: Differences in clinical measurements were evaluated with the Instat Statistical Package software. All the statistical calculations for significance were performed using the one-way analysis of variance (ANOVA) and the Kruskal-Wallis statistic (KW).

RESULTS

A total of 30 patients aged between 34-75 years with a diagnosis of plasma cell neoplasm (PCN) according to standard clinical and laboratory criteria over a period of 12 years were reviewed. These consisted of 20 males (66.7%) and 10 females (33.3%) with a male-to-female ratio of 2:1. The 30 patients of MM variants were identified out of a total of 395 haematological malignancies from the Oncology clinic attendance including autopsy findings within the study period. This gave an incidence of 7.6% of all the haematological cancers. MM constituted the major subtype number of patients (70%), followed by solitary plasmacytoma (16.7%) and extramedullary plasmacytoma (6.7%). Plasma cell leukaemia and Smoldering myeloma comprised 3.3% each (Table-I). All but the two of the 30 residents with myeloma diagnosed between 1992 and 2004 were recognized antemortem. None was known to have a previous monoclonal gammopathy of undetermined significance (MGUS) because tests were not done on them before they transformed to MM. The overall median age at presentation was 54 years with 13.3% of all MM patients less than 40 years. Table-II shows the clinical aspects at

Table-II: Main clinical aspects and baseline characteristics of study patients at the time of diagnosis

Presenting Features	*Number (%)*
Symptoms	
Bone pain	22 (73.3)
Weakness and fatigue	22 (73.3)
Fever	8 (26.7)
Abdominal pain and swelling	6 (20.0)
Paralysis	6 (20.0)
Weight loss	6 (20.0)
Mucosal bleeding	4 (13.3)
Physical findings	
Pathological fractures	14 (46.7)
Pallor	12 (40.0)
Splenomegaly	8 (26.7)
Hepatomegaly	8 (26.7)
Renal mass	4 (13.3)
Performance status	
0-1	2 (6.67)
2-4	28 (93.3)
Clinical staging (Durie & Salmon)	
II	10 (33.3)
III	20 (66.7)

diagnosis. The main presenting symptoms were bone pain (73.3%) and anaemic symptoms (weakness and fatigue) (73.3%). Presence of fever was recorded in 26.7% of the patients while paralysis, weight loss and other symptoms were recorded in 20% each. The least presentation was mucosal bleeding in only four patients (13.3%). Pathological fractures (46.7%) and pallor (40%) formed the commonest physical findings. Baseline characteristics of study patients revealed that PS as assessed according to the ECOG scale that 93.3% of the patients were within the worst scale (2-4). The DS clinical staging system showed that 20 patients (66.7%) presented in the advanced stage III with 13.3% presenting with renal pathology while 10 patients (33.3%) presented in stage II.

The blood findings at the time of diagnosis are shown in Table-III. Majority of the patients (66.7%) presented with severe anaemia with haemoglobin level less than the mean of 7.6g/dl and 93.3% of the patients less than 10g/dl. Presence of an adequate number of leucocytes and platelet counts within the

Table-III: The haematological and biochemical findings of multiple myeloma at diagnosis

Haematological features	*Mean±SEM*
Haemoglobin (g/dl)	
Mean	7.6±0.4
Median	7.4
Range	5-13.3
Reticulocyte count (%)	
Mean	2.1±0.2
Median	2.0
Range	0.2-4.0
Total leucocyte count (x 10^9/l)	
Mean	6.5±0.6
Median	2.0
Range	2.6-15.5
Platelet count (x10^9/l)	
Mean	211±24.5
Median	210
Range	35-460
Erythrocyte sedimentation rate (x10^9/l)	
Mean	112.5±8.7
Median	137.0
Range	24-150.0
Tumor bulk (marrow plasmacytosis)	
<30%	8
≥30%	22
Biochemical indices	
M-component type	
IgG	16
IgA	6
IgD	1
Light chain (LC)	4
Nonsecretory	3
Creatinine (mg/dl)	
Mean	2.4±0.3
Median	1.9
Range	0.6-5.2
Calcium (mmol/l)	
Mean	2.3±0.08
Median	2.2
Range	1.8-3.7
Albumin (g/l)	
Mean	30.7±1.7
Median	32.0
Range	19.0-44.0
Globulin (g/l)	
Mean	39.5±2.8
Median	35.0

normal limits was recorded, as granulocytopenia and thrombocytopenia are rare. The ESR was markedly elevated (≥100mm/hr) in 73.3% of cases. Increased plasma cells (≥30%) with abnormal morphology of flaming/mott myeloma cells in the bone marrow were seen in 73.3% of cases.

The serum protein immunoelectrophoretic pattern showed M-band in 53.3% with IgG, 20% IgA, 3.3% IgD, 13.3% Light chain (two kappa and 2 lambda type) while 10% of the cases were nonsecretory. Of note is that Bence Jones protein (BJP) and raised immunoglobulin were found mainly in the cases of MM. Renal function impairment (serum creatinine ≥1.3mg/dl) was observed only in 26.7% of cases. Remarkable serum calcium levels (≥3.0mmol/l) were found in 6.7% of cases. High peak of abnormal globulin (≥40g/l) was found in 33.3% of cases while marked hypoalbuminaemia (<30.0g/l) was also found in 33.3% of cases. The haematological and biochemical indices estimated by the one-way analysis of variance (ANOVA) for association was found to be statistically significant; P<0.0001 and P= 0.0193 respectively.

Therapy and survival: The most commonly used chemotherapeutic regimen were MP (melphalan 10mg/m^2 po Days 1-4 and prednisolone 1mg/kg/day po Days 1-4) for the elderly patients while VAD (Vincristine 0.4mg/day iv Days 1-4, Doxorubicin 10mg/m^2/d iv Days 1-4 and 4-day pulses of high dose Dexamethasone 40mg/d) was used for the younger patients providing control of symptoms and/or tumor mass reduction. The median period of survival was three months (P<0.0001). Eight patients were seen up to six months and only six patients beyond one year while the remaining patients either died before three months or were lost to follow-up or voluntary cessation of clinic attendance. At two month of diagnosis, 53.3% of the patients had died from the disease related complications and were unable to purchase their cytotoxic drugs due to financial constraints. Overall survival (OS) was estimated to be only 33.3% at 12 months and 13.3% at 24 months.

DISCUSSION

Multiple myeloma (MM) B cell malignancies of plasma cells with controversy about the origin of the plasma cells still remains incurable. Advances in high-dose chemotherapy and stem cell transplantation have improved overall survival and event-free disease, but relapses are inevitable.[5] Therapeutic novel agents are therefore being considered with a focus on immunomodulatory drugs, proteasome inhibitors and arsenic compounds.[5]

MM accounted for approximately 7.6% of all haematological malignancies which is quite close to the 10% recorded in United States and is regarded as the second most frequently occurring haematological malignancy.[3] The higher incidence in some other geographic regions probably reflects the better and earlier detection of the disease. MM, which is the proto type of monoclonal malignant proliferation of plasma cells was the most frequent (70%). This was similar to the study in Ile-Ife, another major center in the South-Western rain forest area of Nigeria.[9] Other studies in the diaspora[10] have reported similar findings with the average specific incidence rates increasing sharply with age, independent of gender or race with a slightly lower rate being reported in UK, Eastern Europe, South America, India and Japan.[11]

The median age of 54 years at presentation (age range 34-75years) was similar to the findings in the Western world including the Myeloma Research Group in Melbourne; Australia.[12] It is uncommon in persons younger than 40 years as the incidence increases with age.[13] This was the observation in this study as less than 15% of our cases were 40 years and below which was similar to the studies of Salawu et al[9] and Nossent et al.[14] The male predominance found in this study is at variance with other studies that reported a male-to-female ratio of 1:1[15,16] but similar to the study of Salawu et al.[9] This difference may be due to the poor economic empowerment of women in our environment which made it difficult to attend the hospital and also not being exposed to environmental pollution.

Clinical presentation of MM patients generally results from tumor mass effects and from the proteins or cytokines secreted by tumor cells or normal accessory cells under the influence of tumor cell products. The severity of MM depends on the tumor load. The preponderance of lytic bone pain and anaemic symptoms in over 70% of the myeloma patients confers a less favorable prognosis and probably reflects the advanced stage of the disease. This lytic bone lesions are due to excessive osteoclast activating factor (OAF) activity exerted by cytokines.[11,17] Fever was the second biggest problem encountered. In a review by Nossent et al[14] infection was found to be the immediate cause of death in 54% of cases. This was ascribed to granulocytopenia, immunoparesis and suppression of CD4+ cells.[18] In addition, 20% of our patients also presented with neurological complications that may have resulted from wedge compression fracture of the vertebrae, mucosal bleeding (13.3%) that could result from platelet coating by the M-protein,[19] though thrombocytopenia is rare. Detection of pathological fracture was the most common physical finding (46.7%).

Majority of the patient population had advanced-stage disease. Twenty patients (66.7%) were in stage III while 10 patients (33.3%) were in stage II according to the DS clinical staging system. This system is actually a functional system which serves to evaluate the prognosis using various types of clinical and laboratory tests. Hence, it differs from the anatomic staging systems for solid tumors. However, the system is not optimal as the two recently studied systems of Kyle and Greipp, and the British Columbia Cancer Agency turned out to be the shortest and easiest of the systems.[20] The disease was usually disseminated at presentation and therefore majority of the patients were treated with systemic chemotherapy. This could be the reason why none of the patients was diagnosed as having MGUS. Also, lack of polymerase chain reaction (PCR) along with allele-specific-oligonucleotide (ASO) designed to detect the CDR3 sequence of the tumor in early stage/monitoring minimal residual disease may also be responsible.[21,22] This was also reflected in the poor PS where 93.3% of the patients presented with the worst scale (2-4). Over 80% presented with some degree of anaemia but not all were symptomatic at the time of presentation. This has also being documented in other series.[9,14] The key factors in the pathogenesis of anaemia is usually due to destruction of the bone marrow with invasion by MM cells, inhibitor of erythropoiesis by tumor factors, renal failure and plasma volume expansion secondary to M-protein.[11]

The mean survival of 6.0 months (median; 3.0) obtained in this series is unacceptably low when compared with the 24 months of the population study on MM survival in a National Health Service in UK[23] and the 60 months of Blade et al study.[24] The short survival of patients in this study is however not surprising in view of the unfavorable laboratory and clinical indices at presentation and lack of therapeutic novel agents present in developed countries. At the time of analysis only four patients (13.3%) survived beyond two years while the longest and only known survivor (a hospital matron) is still alive after six years. An important observation from this study was the high default rate which was due mainly to financial constraints and this is generally a problem in cancer management in Nigeria.[25] This could be traced to the general poverty level in the society with very high cost of medical facilities despite being an oil producing country, religious beliefs and other strong limiting factors.

In conclusion, of 30 patients of PCN studied in Edo state, Niger Delta region of Nigeria MM was the commonest subtype. Bone pains and anaemia with pathological fractures were the commonest characteristic features with a short three months median survival rate. If survival is to be improved, we advocate early referrals of patients with abnormal clinical features and laboratory tests (especially ESR) to the Haematologists for further follow-up. National Health Insurance Schemes and Health care planning with a view to better therapeutic drug availability is also emphasized.

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