Review Article

A Review of Epidemiology and Management of Multiple Myeloma in a Resource Poor Country

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Abstract

Multiple myeloma (MM) is a B-cell malignancy characterized by clonal proliferation of terminally differentiated B lymphocytes. Rational use of proteasome inhibitors, immunomodulators, anti CD38 or CD 138, and tandem autologous stem cell transplant have improved 5-year overall survival beyond 50% in advanced countries. However, the disease prevalence is probably highest in Sub-Saharan Africa where diagnostic and treatment facilities are lacking. The authors have reviewed published articles on epidemiology and outcomes of MM in Nigeria in the light of international recommendations with the aim of suggesting adaptable practices in a resource-poor environment. Publications from Nigeria were obtained from search engines such as Google Scholar and PubMed while recent guidelines were obtained from websites of the National Comprehensive Cancer Network and Medscape Oncology. The mean age at presentation ranged between 54 and 62 years, and there was a higher prevalence among males (ratio 1.1: 1–4.4: 1). A study in Nigeria found an increased incidence in oil-producing areas. In earlier publications between 2005 and 2007 years, about a quarter of patients could not afford treatment and most of the patients presented in advanced stages of the disease. During that period, the mean survival was 7 months and only 13.3% lived beyond 2 years. The treatment then was based on either melphalan ± prednisolone or combination of vincristine, adriamycin, and dexamethasone. By 2012/14, thalidomide, bortezomib, biphosphonates, radiotherapy, and renal dialysis were introduced with a mean survival of 4 years. Optimization of available facilities would, therefore, improve the disease-free survival.

Keywords: Epidemiology, management, multiple myeloma, review

Introduction

Multiple myeloma (MM) is a malignancy of B cells, characterized by clonal proliferation of terminally differentiated post-germinal center B lymphocytes (plasma cells). Clinical presentations include bone pains, osteolytic lesions, immune paresis, clonal gammopathy, hyperviscosity, renal lesion, and anemia. These malignant cells either home to the bone marrow where they are capable of long-term survival or to extramedullary sites on acquiring the capacity of independent long-term survival.[1] This is a narrative review of published articles on MM from Nigeria to highlight the epidemiology and management of the disease with a view of adapting international recommended guidelines to improve clinical practice.

Methodology

Published articles on MM were sought using the terms MM in Nigeria, MM epidemiology, MM pathogenesis, MM diagnostic criteria, and MM management on Google Scholar and PubMed search engines. There were 16 articles sighted and referenced. Recent guidelines were obtained from websites of National Comprehensive Cancer Network version 3.2017, International Myeloma Working Group and MedScape Oncology. Articles from the year 2002 to 2017 on epidemiology, pathogenesis, diagnosis, and management guidelines were reviewed.

Epidemiology

In the United States of America, the annual incidence of MM is 6.6/100,000 with the incidence being twice higher in African–Americans than in Caucasians and lowest among

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Asians.[2-5] In Nigeria, MM accounts for between 5.6% and 12.9% of hematological malignancies being next to chronic myeloid leukemia, nonHodgkin's lymphoma, and chronic lymphocytic leukemia in frequency.[6-10] An average of 9.25% of hematological malignancies is similar to 10% found in other studies.[2] Dapus *et al*. diagnosed MM in 4.1% of bone marrow aspirations done in a center in Nigeria.[11] The male: female ratio ranged widely from 1.1: 1 to 4:1.[7-9,12] The mean age at presentation in Nigeria varied from 54 to 62 years with all centers reporting increased incidence with age while the incidence peaks at the 7th decade in developed countries.[7,8,12] This may be a reflection of the lower average life expectancy.

Etiology

MM, being a malignancy of terminally differentiated B lymphocytes, is probably provoked by chronic antigenic stimulation of immune system but association with autoimmune disorders and handling of organic solvents, herbicides, or insecticides have not been conclusive.[3,13-16] However, familial predisposition, male sex, HIV, hepatitis C virus, shingles, and obesity have significant association.[3,14-17] In addition, there is increased incidence of MM 15–20 years after exposure to ionizing radiation.[18] A study in Nigeria found an increased incidence in oil-producing areas.[6]

Tumor Heterogeneity

Studies have revealed that MM is a multi-stage disease as all monoclonal gammopathy of undetermined significance (MGUS) and MM have chromosomal translocations to the heavy-chain immunoglobulin gene region or/and multiple trisomy. Progression to MM or extramedullary MM is associated with dysregulation of the cellular oncogenes such as N-RAS, K-RAS, MYC, phosphatase, and tensin homolog, retinoblastoma genes or p53 as a result of further translocations, mutations or changes in epigenetic events.[19,20]

The common translocation partners to the heavy chain immunoglobulin gene on chromosome 14 are 4p16, 6p21, 11q13, 12p13,16q23, and 20q11 causing dysregulation of the fibroblast growth factor receptor 3 and MM SET domain protein (FGFR 3/MMSET), cyclin D3, D1, D2, and transcription factors-MAF and MAFB genes, respectively. Among these, translocations involving chromosomes 4p and 16q have a poor prognosis. The trisomies, which involve chromosomes 3, 5, 7, 9, 11, 15, 19, and 21, tend to have a good prognosis, while deletions involving chromosomes 13 and in 1p or gain in 1q have a poor prognosis.[19,20]

Apart from these complex cytogenetic abnormalities noted in MM, dysregulation of noncoding microRNAs (miR), which through complementary base pairing with mRNAs, can inhibit or degrade mRNAs essential in proliferation, survival, or apoptosis of plasma cells. Chief among these are miR-19a and b, which downregulates, by methylation, the SOCS-1 induction of IL-6, and JAK/STAT pathways; miR-17-92 cluster, which regulates the proapoptotic BIM gene and the group of miR-181a/b, 106b-25, 32 which control p53 activities through p-300CBP (PCAF), a histone acetyltransferase.[21-23] These tests are presently not readily available in Nigeria. However, cytogenetic studies, which may identify patients with poor prognosis and who would benefit from tandem autologous stem cell transplant or bortezomib (BOR) treatment, are feasible but unaffordable in most cases.

Stromal Cell Crosstalk

The expansion of MM cells which crowds the bone marrow and cytokines produced as a result of their interaction with bone marrow stromal cells, result in anemia but less frequently pancytopenia because IL-6 has thrombopoietic effect.[19] This is corroborated by studies in Nigeria which showed that at presentation, 63%–78.9% of patients had anemia while 42.3% had thrombocytopenia.[13,24-26]

The adherence of MM cells to the bone marrow stromal cells activates the nuclear factor kappa β (NF-kB) via stimulation by B-cell activating factor and a proliferation-inducing ligand produced by stromal cells.[27] Constitutive signaling of NF-kB via the transcription factor X-box binding protein 1 or by cytokines produced by stromal cells enhances the production of IL-6 which in turn enhances the survival of MM cells.[27,28] The MM cells produce dickkopf-1 (DKK-1) and macrophage inflammatory protein-1 alpha (MIP-1α). DKK-1 inhibits Wnt-mediated osteoblastic maturation and hence a reduction in the production of osteoprotegerin by osteoblasts. Osteoprotegerin is a decoy for RANKL on osteoblasts [Figure 1]. Therefore, its reduction promotes binding of

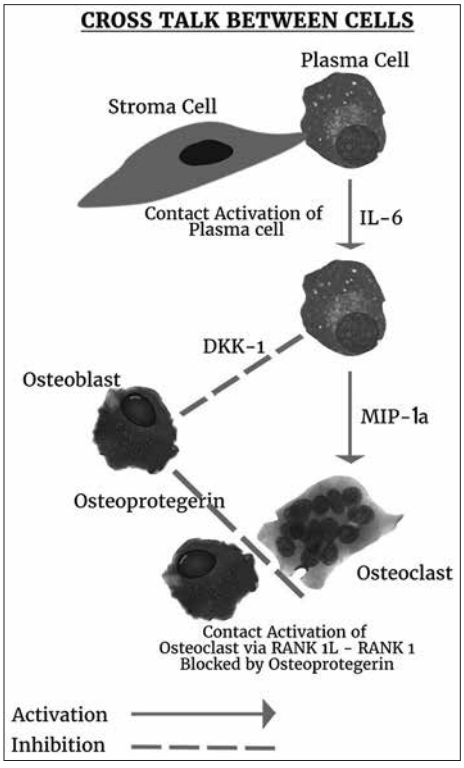

Figure 1: Legend is Cross talk between cells

RANKL to RANK l on developing osteoclasts with an increase in osteoclastic activities.[29-33] MM cells, via production of MIP-1α, also stimulate osteoclastic activities. In addition, IL-7, IL-3, and Runx-2 produced by stromal cells have a dual role in osteoblastic and osteoclastic balance in MM.[32,33] These, eventually cause the osteolytic bone lesions and hypercalcemia seen in MM. These were revealed by Nigerian studies where 53.3% to 78.1% of patients presented with bone pains with 44% to 69% presenting with X-ray evidence of fractures.[13,24,25] The cost-effectiveness of magnetic resonance imaging in the diagnosis of MM will require further studies in Nigeria.

Paraprotein

MM cells, arising from activated B cells that have undergone immunoglobulin class switch, secrete immunoglobulin G and A mainly, although about 3% neither present with monoclonal gammopathy in serum nor in urine, i.e., nonsecretary or oligo-secretary MM. In Nwabuko *et al*. study, immunoglobulin G (IgG) formed 75% of immunoglobulins and 25% were immunoglobulin A (IgA) whereas 2 case reports of nonsecretary MM were sited.[26,34,35] The immunoglobulins are monoclonal with a reduction in normal polyclonal antibodies resulting in immune paresis.[36] Hyperviscosity and increased plasma volume may also develop if the immunoglobulins are IgA or IgG 3 subclass.[37] The abnormal immunoglobulin may damage the vascular wall, coat the platelets and interfere with fibrin aggregation or coagulation factors such as factor X and protein C, thus promoting bleeding or thrombus formation.[38] Amyloid deposits and MM infiltration of the cranial and spinal nerves may cause pain and polyneuropathy.[39]

The light chain immunoglobulins, which are usually, produced in excess of the heavy chain, account for the amyloidosis, and light chain deposits in the renal glomeruli and tubules. These, together with hypercalcemia, infections, use of anti-inflammatory drugs, and hyperuricemia seen in MM cause a renal failure that is reversible if treated early before interstitial fibrosis occurs.[40-42] Published work in Nigeria has shown that 26.7% of patients presented with fever and that sepsis accounted for 54% of MM deaths in 2007. Few patients (13.3%) presented with bleeding disorders whereas 39%–66.7% presented in renal failure, but 19% had dialysis.[24,25,43] Future determination of common agents of infection and more access to dialysis in Nigeria is desirable [Table 1].

Tumor Adaptation

The progression of MM is assured by neoangiogenesis promoted by upregulation of vascular endothelial growth factor alpha, hypoxia inducing factors, hepatocyte growth factor, and syndecan 1.[44-47] Cancer immune surveillance is also reduced by a combination of immune-paresis, upregulation of IL-17, and expression of cytotoxic inhibitor PD-1 on MM cells [Table 2].[47-49]

Diagnosis and Staging

MM can progress from a benign disorder identified as MGUS through an asymptomatic smoldering MM. MGUS could progress to MM, amyloidosis or lymphoma at a rate of 1% per year while smoldering myeloma progresses to MM at a rate of 10% per year in the first 5 years and reduces gradually thereafter.[50,51] The risk of progression increases in the presence of Immunoglobulin M or IgA, immunoglobulin level >1.5 g/dl, abnormal free light chain ratio or a high-risk cytogenetic lesion.[50,51] A Nigerian study showed that 65% of patients presented in Stage III of disease, but there is no established factor for progression.[24,52]

Management

Studies published between 2005 and 2007 indicated a mean survival of 7 months with only 13.3% surviving beyond 2 years in Nigeria.[8,9] Most of the patients presented in advanced stage of disease and 23.3% of them could not afford treatment. The main treatment options were either melphalan (mel) ± prednisolone (PRED) (MP) or a combination of vincristine, adriamycin (DOX), and dexamethasone (VAD) while cyclophosphamide (CYC) was reserved for those who could not tolerate melphalan [Figure 2].[8,9,24] By 2012/2014, studies found that though patients were still presenting late and 11.1% could not afford treatment, the mean survival had improved to 4 years due to the introduction of thalidomide (THAL), BOR, and biphosphonates coupled with increased use of renal dialysis and radiotherapy.[13,26,43,52] Independent prognostic factors from these studies were raised

Table 1: Criteria for diagnosis[50-57]

Parameters	Essential monoclonal gammopathy	MGUS	SM	MM
Marrowplasma cells (CD19, 45 negative; CD 56, CD38, CD138, CD 319 positive)	<10%	<10%	>10% but <60%	10% or 60% or plasmacytoma
Paraprotein	<2.5 g/dl	<3 g/dl	3 g/dl but <7 g/dl if IgG or <5 g/dl if IgA	3 g/dl
Free light chain ratio				100
Osteolytic lesion	Nil	Nil	Nil	On X-ray or >1 on MRI
Normal immune globuline			Low	Low
CRAB	Negative	Negative	Negative	Positive

CRAB: Hypercalcemia >11 mg/dl, renal failure with creatinine >177 mmol/l or clearance <40 ml, anemia with HB <11 g/dl, osteolyic lesion.
MGUS: Monoclonal gammopathy of undetermined significance, MM: Multiple myeloma, MRI: Magnetic resonance imaging, SM: Smoldering myeloma

Table 2: Validated staging methods[53-57]

Stage	Reviced international staging system (using β_2M, a component of HLA class 1, as a surrogate for tumor mass and serum albumin as a surrogate for IL-6 level)[41]	Durie-salmon
I MS=62 months	Serum beta-2 microglobulin <3.5 mg/L and serum albumin ≥3.5 g/dl	Hb >10.5 g/dl Normal calcium No bone lesion IgG <5 gm/dl; IgA <3 g/dl; bence jones protein <4 g in 24 h urine
II MS=44 months	Serum beta-2-Microglobulin <3.5 mg/l and serum albumin <3.5 g/l	Intermediate between I and III
III MS=29 months	Serum beta-2 microglobulin ≥5.5 mg/L, high LDH and high-risk cytogenetic lesion (del 17p, t(4;14), t(14;16))	Hb <8.5 g/dl Calcium>12 mg/dl >3 lytic bone lesions on skeletalsurvey IgG >7 g/dl; IgA >5 g/dl; Bence Jones protein >12 g in 24 h urine

Sub Group A if renal failure absent and B if present. MS is median survival. LDH: Lactate dehydrogenase, Hb: Hemoglobin, HLA: Human leukocyte antigen, IL: Interleukin

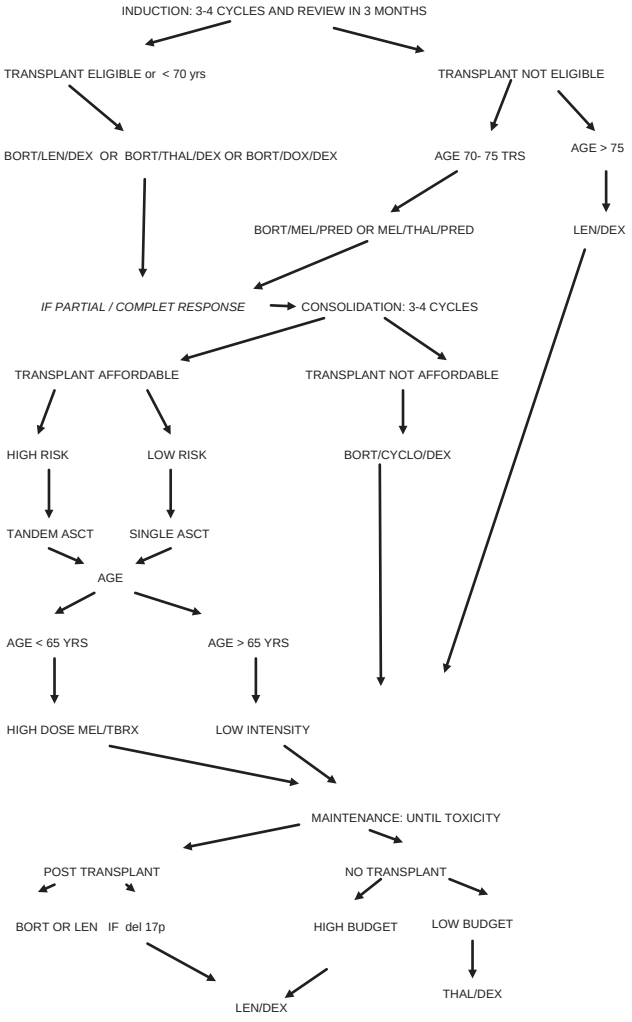

Figure 2: Treatment algorithm.[52-62] Use DEX for a maximum of 1 year and biphosphonate for a maximum of 2 years

ESR, anemia, thrombocytopenia, percentage of plasma cells, and the presence of kidney disease while infection was a significant cause of death.

Internationally, the overall survival without treatment is 6–7 months, but this increases with conventional treatment to 3 years while the event-free survival is >2 years.[53-55] However, with stem cell transplant, the 5-year survival is 82% in RISS Stage I, 62% in Stage II, and 40% in Stage III.[53-57] Bone marrow transplant for hematological malignancies is not readily available in Nigeria, and very few patients can afford to travel to developed countries. This choice of treatment should, however, be discussed at the initial counseling of all patients.

MM is a slow-growing tumor with sub-clones that are resistant to apoptosis therefore resistance to chemotherapy and multiple relapses should be expected. Specific treatment is therefore done in stages: induction, consolidation, and maintenance. This was evident in a study by Omoti CE *et al*. where patients that had sequential treatment with MP and later VAD had better survival.[9] The choice of drugs depends on affordability, age, comorbid conditions, and presence of high-risk cytogenetic lesions. Experience in Nigeria has revealed that VAD was better tolerated in young patients and the response was better.[9] Figure 2 is a treatment algorithm adaptable in a resource-poor center or in community practice. Therapy based on BOR gives the best outcome but for increased incidence of viral infection and neuropathy.[54] Only 48% of hematologists in Nigeria prescribe BOR in 2017.[58] Some centers (oral communication), use weekly subcutaneous BOR (2 mg) to reduce adverse event with good outcome. Induction therapy with BOR in combination with an immunomodulating drug and dexamethasone for a period of 3–4 months is preferable. Otherwise, the combination of melphalan, THAL and prednisolone is a convenient alternative. Immunomodulating drugs in the market are THAL and lenalidomide (LEN). Both are associated with marrow suppression, fatigue, and thromboembolism. LEN is given in pulses of 3 out of 4 weeks and it is better avoided in patients with renal impairment while fatigue may be managed with dose adjustment.[54] In the absence of ASCT, CYC, doxorubicin, or melphalan may replace immunomodulatory drug in combination with BOR and dexamethasone in a 3–4 months consolidation therapy.[9] Maintenance therapy is recommended using an affordable immunomodulatory drug or BOR until evidence of toxicity or relapse occur.[54] Where stem cell transplant is possible, patients ≤65 year old will benefit

from high dose melphalan plus total body radiation followed by autologous stem cell transplant (MEL + TBRx + ASCT). Patients between the age of 65 and 70 years without comorbidity can have low-intensity conditioning before stem cell transplant while patients above the age of 70 years can have triple drug combination in place of ASCT. Above the age of 75 years, two-drug combination treatment (e.g., tolerable dosage of LEN and low dose dexamethasone (DEX) is recommended.[53-62] Response to treatment is monitored with monthly erythrocyte sedimentation rate and 3 monthly serum protein electrophoresis or free light chain ratio. Regular screening for marrow suppression, liver toxicity, kidney injury, and metabolic derangement is necessary. Monitoring with minimal residual disease test is not feasible presently in Nigerian clinical practice unless there is an affordable collaboration with a foreign center that has capacity for genomic studies.

Success achieved so far in Nigeria may be attributed to improved supportive care and better understanding of the tumor biology, which therefore requires emphasis. Since patients are elderly and may be on prolonged steroids, it is desirable to screen for comorbid conditions such as diabetes mellitus, tuberculosis, viral hepatitis, HIV, hypertension, cardiac lesions, and benign prostatic hypertrophy so that these can be treated simultaneously if present. Patients with moderate anemia may benefit from high dose erythropoietin for 6–8 weeks while red cell transfusion is indicated in the presence of severe anemia. Erythropoietin is better avoided in patients with high risk of thromboembolism. Prophylactic use of paludrine, cotrimoxazole, vaccination against encapsulated bacteria, immunoglobulin, and antiviral drugs will require randomized, controlled clinical trials to determine their appropriate use in Nigeria. Judicious use of growth factor in patients presenting with severe neutropenia and fever should be considered. Patients with renal impairment will require good hydration and nephrologist consultation for possible renal dialysis in accordance with the hospital protocols. Bone pains are better managed with mild opioids in place of nonsteroidal anti-inflammatory drugs to avoid kidney injury while radiotherapy, kyphoplasty, or vertebroplasty if available are indicated in cord compression. Use of low dose aspirin, warfarin, or low molecular weight heparin in the first 3 months of treatment, especially while on immune modulators, immobilization, or erythropoietin is recommended to prevent pulmonary embolism. Bisphosphonates are recommended to reduce osteoclastic activities and bone pains. Usage should be limited to 2 years and requires attention to dental care to prevent osteonecrosis of the jaw bones. The presence of microalbuminuria is an indication to suspend bisphosphonate or to replace zolendronate with pamidronate which is less nephrotoxic. Use of weekly oral clodronic acid (70 mg of alendronic acid) is convenient but probably less effective.[53,54]

Relapse or Refractory Disease

If there is significant adverse drug event, disease progression during treatment or within a short time (60 days) of stopping treatment, carfilzomib or ixazomib or elotuzumab (an anti SLAMF-7 IgG1) may replace BOR while pomalidomide may replace LEN or THAL. Other drugs are panobinostat a histone deacetylase inhibitor, anti CD38 antibody (Daratumumab) or pembrolizumab, a checkpoint inhibitor, in combination with LEN and dexamethasone.[63-66]

Conclusions

The prevalence of MM is probably highest in sub-Saharan Africa though the exact disease burden and possible association with major histocompatibility complex require further studies. Lack of cytogenetic studies, transplant technology, and funds are impediments to best practices. Prophylactic use of paludrine, antibiotics, antivirals, vaccinations, and immunoglobulin require controlled clinical trials. Similarly, THAL as against LEN in maintenance therapy deserves a clinical trial in resource-poor centers. The authors, therefore, suggest the establishment in Nigeria, of a nonprofit, non-Governmental driven center for hematological malignancies with facilities for autologous stem cell transplant in collaboration with hospitals with appropriate experience outside the country.

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Conflicts of interest

There are no conflicts of interest.

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