Chapter 9

Management of Multiple Myeloma in Developing Countries

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Additional information is available at the end of the chapter

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Abstract

Multiple myeloma (MM) is one of the commonest hematological malignancies of public health importance especially in low-income countries (LICs) of Sub-Saharan Africa. The two major challenges in the management of MM in developing countries are in the diagnosis and treatment. It poses diagnostic dilemma to physicians, especially orthopedic surgeons, because of the skeletal related events (SREs). Lack of modern equipment for diagnosis is a key player in late diagnosis of MM, and the management follows a palliative approach in the region. There is a gross inadequacy in the palliative care of MM in developing countries. The definitive treatment still remains melphalan-prednisone (MP) combination regimen as against the standard bortezomib-lenalidomide-dexamethasone (RVD) triplet regimen used in developed countries. Stem cell transplantation is still a far cry in the treatment of MM in the region due to its high cost and unavailability in the region. About 7.6% of MM patients survive up to 5 years postdiagnosis in LICs. This is below estimated 5 years postdiagnosis overall survival of 44.9% recorded by SEER cancer statistics review of 1975–2007 in the USA. This chapter highlights management and some of the diagnostic and therapeutic challenges encountered by people living with MM in developing countries.

Keywords: multiple myeloma, management, developing countries

1. Introduction

Multiple myeloma (MM), otherwise known as plasma cell myeloma, is a malignant plasma cell disorder characterized by clonal proliferation of terminally differentiated B-lymphocytic cells in the bone marrow. This leads to overproduction of aberrant immunoglobulins in the blood, a condition known as paraproteinemia. It is one of the commonest hematological malignancies

of public health importance in low-income countries of Sub-Saharan Africa. It accounts for 10–15% of all lymphohematopoietic cancers, 1% of all cancer diagnosis, and 0.9–2% of all cancer-related deaths globally [1]. According to 2009 cancer statistics, the cumulative incidence of MM in the United States is 20,580 cases with an estimated number of deaths of 10,580 and a case fatality rate greater than 51% [2]. The prevalence of MM is in the increase in African continent especially in the oil-rich Niger-Delta Nigeria where it accounts for about 8.2% of all hematological malignancies [3, 4]. The management of MM starts with a good history, which brings into limelight the epidemiology, pathogenesis, and the clinical features of the disease. This is followed by a series of investigations to make the diagnosis and to clinically stage the disease before therapeutic interventions. The major challenges in the management of MM in developing countries are in the diagnosis and treatment. The duo are majorly responsible for the complications, poor prognosis, and survival outcome of people living with MM in the region. This chapter highlights the management of multiple myeloma and some of the challenges encountered in the diagnosis and treatment of this disease in developing countries using Nigerian experience as a prototype.

2. Etiopathogenesis of multiple myeloma and its significance in its management

The etiology of multiple myeloma is unknown. However, previous studies have identified factors implicated as "potentially etiologic multiple myeloma risk factors" [5, 6]. These factors include increasing age (>65 years), male gender, black race, and positive family history (first-degree family relatives) of multiple myeloma. Other causes include environmental agents such as cumulative exposure to ionizing radiation and certain chemicals such as dioxin, herbicides, and pesticides. There is a hypothesis that these specific pesticides are causatively linked to myelomatogenesis through the hypothesized precursors of multiple myeloma such as essential monoclonal gammopathy (MGUS) and solitary multiple myeloma (SMM) [7, 8].

Physiologically, a plasma cell is an immunologically activated B-cell that produces antibody. A B-cell goes through series of rearrangement with the immunoglobulin gene to generate functional antibody. It can enter into the circulation to interact directly with antigen to differentiate into a short-lived plasma cell that lives for about 3 days. On the other hand, a myeloma cell is a postgerminal center plasma cell that has undergone immunoglobulin gene recombination, class switching, and somatic hypermutation, and homes to the bone marrow to become long-lived plasma cell (i.e., can live for ≥30 days) [9]. Cytogenetically, MM is divided into two groups based on karyotype gain or loss into hyperdiploid and non-hyperdiploid MM. The hyperdiploid MM, which constitutes about 55–60% of MM primary tumor, is characterized by hyperdiploid karyotype with chromosome range of 48–78 and trisomies of odd number chromosomes, including 15, 9, 5, 19, 3, 11, 7, and 21 (ordered by decreasing frequency). The hyperdiploid variants are typically the IgG kappa-types with bone involvements. The non-hyperdiploid karyotype accounts for the remaining 40–45% of MM primary tumor, and it includes the hypodiploid or near-tetraploid chromosome numbers (i.e., fewer than 48 or more than 74 chromosomes). Chromosomal translocations affect more commonly the non-hyperdiploid karyotypes. In terms of prognosis,

hyperdiploid MM is better than non-hyperdiploid karyotype provided the former is not associated with deletion of chromosome 13 (RB1 gene and miRNA-15a/16-1 cluster dysregulation) and 17 (involving the TP53 locus) or amplification of chromosome 1q21 [9, 10]. The critical role of pathogenesis of MM is to give insight into the biology of the disease. Also, the pathways of the pathogenesis of the disease serve as potential sites for therapeutic interventions, especially the target therapies, which can utilize them for their actions.

3. Requirements for standard diagnosis and staging of multiple myeloma

The diagnosis of multiple myeloma is based on a constellation of hematologic, immunologic, histologic, and radiographic features. There are two methods of diagnosis of MM: the old and new methods. In the old method, a minimum of two major criteria, or one major criterion plus one minor criterion, or three minor criteria is used in making diagnosis of MM [11]. The major criteria are plasmacytoma on tissue biopsy, bone marrow infiltration with greater than 30% BMPCs, monoclonal globulin spike on serum electrophoresis, while the minor criteria include bone marrow infiltration with 10–30% BMPCs, paraprotein less than the defined quantity for major criteria, and lytic bone lesion. **Table 1** shows the criteria for diagnosis of MM using the old method. The newer method of diagnosis takes into cognizance of the popularly known criteria which uses the end-organ damage as defined using both the classic as "CRAB" criteria for hypercalcemia, renal failure, anemia, and bone lesions and additional criteria including recurrent bacterial infections (> 2 in 12 months), amyloidosis, or symptomatic hyperviscocity. In the newer method, initiation of therapy is an evidence of organ or tissue damage (end-organ damage) [9]. Diagnosis is made by clonal BMPCs of not less than 10% of biopsy-proven bony or extramedullary plasmacytoma or any evidence of myeloma-defining events. The myeloma-defining events in this context include any evidence of end-organ damage or presence of any one or more biomarkers of malignancy such as clonal BMPCs greater than 60%, serum-free

Major criteria:
I Plasmacytoma on tissue biopsy
II Bone marrow infiltration with >30% BMPCs
III Monoclonal globulin spike (paraprotein) on serum electrophoresis (IgG >35 g/L and IgA >20 g/L) or on concentrated urine electrophoresis (>1 g/24 h or kappa or lambda light chain)
Minor criteria:
A = Bone marrow infiltration with 10–30% plasma cells
B = Paraprotein less than the level defined earlier
C = Lytic bone lesions
D = Normal IgM <0.5 g/L, IgA <1 g/L or IgG <6 g/L

Abbreviations: MM, multiple myeloma; BMPC, bone marrow plasma cell; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M.

Table 1. Criteria for the diagnosis of MM (old method).

1. Clonal BMPCs ≥10% of biopsy-proven bony or extramedullary plasmacytoma
Any one of the following myeloma-defining events:

- Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  - **a.** Hypercalcemia: serum calcium >0.025 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
  - **b.** Renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >177 μmol/L (>2 mg/mg/dL)
  - **c.** Anemia: hemoglobin value of 20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
  - **d.** Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT
- Any one or more of the following biomarkers of malignancy:
  - **a.** Clonal bone marrow plasma cell percentage* ≥ 60%
  - **b.** Involved: uninvolved serum free light chain ratio ≥ 100
  - **c.** >1 focal lesions on MRI studies

*Clonal should be established by showing kappa/lambda-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. BMPC percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
Source: In Table 107-2 [9].

Table 2. Criteria for diagnosis of MM (newer method).

1. All of the following

   Hemoglobin >10.5 g/dL

   Serum calcium normal

   X-ray showing normal bone structure or solitary bone plasmacytoma only

   Low paraprotein levels

   IgG < 50 g/L

   IgA < 30 g/L

   Urinary light chain <4 g/24 h

2. Fitting neither stage I or stage III

3. One or more of the following:

   Hemoglobin <8.5 g/dL

   Serum calcium >3 mmol/L

   Advanced lytic bone lesions (more than three lytic lesions)

   High paraprotein levels

   IgG >70 g/L

   IgA >50 g/L

Urinary light chain >12 g/24 h

Subclassification

   A. Serum creatinine <170 μmol/L

   B. Serum creatinine ≥170 μmol/L

D-S, Durie-Salmon; IgG, immunoglobulin G; IgA, immunoglobulin A.

Table 3. D-S staging system.

light chain ratio greater than 100, and or greater than one focal lesions on magnetic resonance imagery studies. **Table 2** shows the current criteria of diagnosis of MM.

The staging of MM is another important step after diagnosis. The essence of staging is for decision-making on therapeutic interventions and for prognostication of the disease. There are two clinical staging systems for MM. They include the Durie-Salmon staging system and the international staging system (ISS). The Durie-Salmon (D-S) clinical staging system has been in use for more than 30 years, but it has been remodified to a newer staging system useful for the assessment of myeloma tumor mass [9, 12] The old D-S staging system has three stages (I, II, and III) and two subclassifications (A and B). Here, the staging of MM is based on five parameters viz.: the hemoglobin concentration, the serum calcium level, osteolytic bone lesions, serum, and urinary immunoglobulin quantification. The subclassification A in the staging connotes "normal renal status" (evidenced by normal serum creatinine level), while B connotes "abnormal renal state" (evidenced by deranged serum creatinine level). This is shown in **Table 3**. The modified Salmon-Durie assesses myeloma tumor mass using the old system to stage MM into high tumor mass (stage III), low tumor mass (I), and intermediate tumor mass myelomas (II), which is shown in **Table 4**. The ISS is based on two widely available parameters, serum beta-2 microglobulin and albumin. This staging system recognizes three stages and can be useful for prognostication of survival intervals of MM patients (**Table 5**) [13].

The standard assessment of MM requires a panel of investigations, which are carried out periodically postdiagnosis for prognostication and monitoring of the disease response to treatment. These investigations include complete blood count, blood chemistry, serum and

(I)	High tumor mass (stage III) (>1.2 × 10^{12} myeloma cells/m^2)*
	One of the following abnormalities must be present
	A. Hemoglobin <8.5 g/dL, hematocrit <25%
	B. Serum calcium >12 mg/dL
	C. Very high serum or urine myeloma protein production rates:
	1. IgG peak >7 g/dL
	2. IgA peak >5 g/dL
	3. Urine light chains >12 g/24 h
	D. More than three lytic bone lesions on bone survey (bone scan not acceptable)
(II)	Low tumor mass (stage I) (<0.6 × 10^{12} myeloma cells/m^2)*
	All of the following must be present:
	A. Hemoglobin >10.5 g/dl, or hematocrit >32%
	B. Serum calcium normal
	C. Low serum myeloma protein production rates:
	1. IgG peak <5 g/dl
	2. IgA peak <3 g/dl
	3. Urine light chains <4 g/24 h
	D. No bone lesions or osteoporosis
(III)	Intermediate tumor mass (stage II) (0.6 to 1.2 × 10^{12} myeloma cells/m^2)*
	All patients who do not qualify for high or low tumor mass categories are considered to have intermediate tumor mass
	A. No renal failure (creatinine ≤2 mg/dl)
	B. Renal failure (creatinine >2 mg/dl)

*Estimated number of neoplastic plasma cells.
Data adapted from Durie and Salmon [12]. A remodified D-S staging system.

Table 4. Assessment of myeloma tumor mass (Salmon-Durie).

Stage I	β_2M < 3.5 ALB ≥ 3.5
Stage II	β_2M < 3.5 ALB < 3.5 or β_2M 3.5–5.5
Stage III	β_2M > 5.5

ALB, serum albumin in g/dL; β_2M,serum β_2-microglobulin in mg/L.
Data from Greipp et al. [13].

Table 5. International staging system (ISS).

Complete Blood Count and differential count; examination of blood film
Chemistry screen, including calcium, creatinine, lactate dehydrogenase, BNP, proBNP
β_2-microglobulin; C-reactive protein
Serum protein electrophoresis, immunofixation, quantification of immunoglobulin, serum-free light chains
24-hour urine collection for protein electrophoresis, immunofixation, quantification of immunoglobulins, including light chains
Marrow aspirate and trephine biopsy with metaphase cytogenetics, FISH, immunophenotyping; gene array, and plasma labeling index (if available)
Bone survey and MRI; PET-CT
Echocardiogram with assessment of diastolic function and measurement of interventricular septal thickness; EKG (if amyloidosis suspected)

BNP, brain natriuretic peptide, CT, computed tomography; EKG, electrocardiogram; FISH, fluorescence in situ hybridization, MRI, Magnetic resonance imaging; PET, positron emission tomography; proBNP, prohormone B-type natriuretic peptide.
Source: In Table 107-4 [9].

Table 6. Assessment of myeloma.

urine monoclonal protein assay, C-reactive protein, beta-2 microglobulin test, marrow study, skeletal survey, echocardiogram, immunophenotyping, cytogenetic tests, etc. (**Table 6**).

4. Challenges in diagnosis of multiple myeloma

The prevalence of MM is on the increase in developing countries such as those found in Sub-Saharan Africa [3, 14]. The oil-rich regions are worse hit probably due to a wide range of environmental pollution, flaring of gases, water pollution, oil spillage, and lack of effective environmental policies [6]. This is understandable based on the hypothesis that occupation studies of chemical, petroleum, and radiation industry workers have provided inconsistent evidence of causal association with MM [5]. Another potential etiologic factor that could be a key player in the increasing prevalence is the median age of diagnosis. Studies in Nigeria, Africa's most populous black nation, have shown that the median age of diagnosis of multiple

myeloma is 59.9 years (45–78 years) [14–17]. This age is less than the 65 years median age of diagnosis recorded by SEER cancer statistics review of 1975–2007 in the USA [18]. The implication of this early age of diagnosis is that more people may likely be diagnosed with MM by the time they attend the age of 65, hence increasing the burden of the disease. The male to female ratio of about 2:1 recorded by most of the studies shows a gender disparity of the disease. However, the later may not have much role to play on the increased prevalence of MM in developing countries.

There is a dearth of data on the diagnosis or prevalence of premalignant plasma cell disease in low- and some middle-income countries. The two known hypothesized precursors of MM are MGUS and smoldering MM. Based on retrospective data from Mayo clinic, MGUS is associated with 1% annual risk of progression to MM, while SMM has 10% annual risk of progression to MM. However, due to lack of resources for making diagnosis at this early stage, these premalignant diagnoses are missed. This ultimately leaves the attending physicians with MM patients who present at advanced stages of the disease.

The diagnosis of MM is made late, usually between Durie-Salmon stages II-A (intermediate myeloma mass) and III-B (high myeloma mass) in developing countries [14–17]. The mean duration from onset of symptoms to diagnosis in a study was 13.12 months (95% CI, 6.65–19.58) [6, 17]. In some geographic regions, the onset of symptoms to diagnosis can last as long as 10 years [17]. The lack of modern equipments for diagnosis and staging of the disease are the key players in the late diagnosis of MM in most developing countries including Nigeria [14]. Most health institutions in developing countries (especially the low-income) do not have the infrastructural and medical capacities to handle comprehensive assessment investigations for MM patients. In a recent study in Nigeria, it was found that only 72% of patients with a preliminary diagnosis of MM could afford basic assessment tests required for confirmation and staging of the disease. Out of this number, 43 and 55.7% could do immunoglobulin quantification and Bence Jones Protein tests, respectively.

The commonest assessment tests done by the patients are hematocrit, erythrocyte sedimentation rate, skeletal x-ray, bone marrow aspiration, and trephine biopsy in centers where there are hematologists [14–17]. About 56–60% of MM patients could afford serum electrolyte urea and creatinine assessment tests required for staging the disease [**Table 2**], while less than 50% of the patients could do serum protein, globulin, and albumin level estimation. The serum albumin is one of the analytes essential for international prognostic staging of MM. The β_2M, serum immunofixation test, marrow aspirate and trephine biopsy with metaphase cytogenetic, FISH, immunophenotyping, gene expression profiling (GEP), and plasma cell labeling index (PCLI) are myeloma assessment tests, which are not readily available in developing countries due to the cost and prevailing poverty in the countries. The implication of this is that most MM diagnosed in these regions are cytogenetically unknown and are not internationally staged. Hence, MM patients do not benefit from accurate risk stratification and prognostic assessments as offered to their counterparts in developed countries [19].

These challenges in diagnoses and disease staging contribute to the poor survival outcome of people living with MM in these regions. In a 10-year retrospective study of 26 MM patients in Niger-delta region of Nigeria, only one (3.8%) of the patients could do a marrow metaphase

cytogenetic (FISH) test and this happened to be a high risk category (t(4,14) immunoglobulin A)multiple myeloma [3, 20]. In the study, only four subjects could afford immunofixation test, which showed IgA:IgG-type myeloma ratio of 1:3 and this was in keeping with previous study by Salawu and Durosimi [16].

5. Challenges due to skeletal related events (SREs) and other complications

MM poses a diagnostic dilemma for the orthopedic surgeons because of the frequent skeletal manifestations." It is usually misdiagnosed as an orthopedic disease when in the real sense it is a hematologic disease with orthopedic complications. At advanced stage, it causes multiple lytic bone lesions with severe osteoporosis and pathological fracture. A recent observational study in Nigeria [14] found that about 84.6% of newly diagnosed multiple myeloma patients in Nigeria presented with multiple bone lesions. Pathological fracture constitutes about 42.3% of SREs in the MM patients in the region. It is surprising to note that 84.6% of all newly diagnosed MM are referrals from orthopedic wards [3, 14]. The key players of the bone lesions in multiple myeloma are cytokines namely IL-6 (Interleukin-6), TNF-alpha (tumor necrosis factor), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and insulin-like growth factor (IGF). These cytokines, especially VEGF and PDGF, have angiogenic effect on the bone marrow microenvironment and this effect favors the growth of myeloma cells in the bone. IL-6, an important osteoclast-activating cytokine, plays an important role in the pathogenesis of osteoporosis in MM [21]. Annibali et al. [22], in their pilot study, described the roles of these cytokines in bone tissue destruction and the effect of zoledronic acid (a bisphosphonate) on their chemical behaviors in MM patients. Other complications such as anemia, hemiplegia, nephropathy, and constipation accounted for 61.5%, 35%, 23%, and 19% of newly diagnosed MM patients in same study. Anemia in MM results from bone marrow invasion by abnormal plasma cells that secret erythropoiesis-suppressive cytokines, and this anemia is usually anemia of chronic disorder [23].

6. Challenges of multiple myeloma treatment

The last step in the management of multiple myeloma is the therapeutic intervention. The current standard treatment for MM is palliative care. This is a holistic treatment that offers supportive, definitive, and psychosocial care for people living with MM [24]. There is a gross inadequacy in the palliative care of MM in developing countries, hence the call to scale-up the care of people living with MM. This is because of the life-threatening nature and the suffering associated with the disease. A recent study has shown that inadequate palliative care accounts significantly for the low survival interval of MM patients [3]. The overall survival interval of MM patients in various studies in a developing country such as Nigeria showed a range of 3 months to 39.7 months [3, 15–17]. In one of the studies, it was found that only about 7.6% of MM patients survive up to 5 years postdiagnosis. This was far below the estimated 5-year period survival of 32 and 44.9% recorded by Ries et al. [25] and Altekruse et al. [26] in

Surveillance, Epidemiology, and End Results (SEER) cancer statistics review of 1975–2002 and 1975–2007, respectively, in the USA. The implication is that many LMICs are more than 40 years backward in terms of management of MM compared to high-income countries such as the USA. The two major challenges in the treatment of MM in developing countries are anchored on the supportive and definitive treatment of MM.

6.1. Challenges in supportive treatment of MM

The standard supportive care for MM patients at advanced stage of the disease, which include the use of analgesics, bisphosphonates (BPs), component blood therapy, antibiotics therapy, renal dialysis viz-a-viz renal transplant, radiotherapy, orthopedic care, is grossly inadequate. Chronic bone pain appears to be one of the commonest clinical features of MM, and analgesic drug is the first supportive therapy offered to patients with the disease. However, in the assessment and treatment of pain in MM patients in some low-income countries such as Nigeria, the WHO analgesic ladder for cancer pain control is not usually adhered to, as only few centers can access oral morphine and other opiate analgesics [27]. This leads to analgesic abuse (self-medication), most of which are nephrotoxic, hence, worsening the prognosis of the disease. A study showed that less than 40% of MM patients could afford BPs. BPs are useful in preventing, reducing, and delaying MM SREs such as bone pain, osteoporosis, and other lytic bone lesions. They can also help to control the growth of extramedullary tumors, hence the need to scale-up their usage in MM [22, 28].

There is a gross inadequate access to radiation therapy in LICs including Nigeria. Studies have shown that only about 3.8–20% (average 12%) of MM patients who need radiotherapy at one point or the other of the disease could access it [3, 17]. The major reason is that the megavoltage radiotherapy machine per population size is grossly inadequate (1-MV machine per 24 million population as against the International Atomic Energy Agency (IAEA) requirement of 1-MV machine per 250,000 population or per 350–400 new cancer patients in centers with excellent cancer registry) [29].

About 60% of MM patients seen in LICs such as Nigeria present with severe grade of anemia (hemoglobin <7 g/dL). The implication is that they will rely on blood transfusion therapy in order to improve the quality of their life. Unfortunately, many of the LICs do not practice safe blood transfusion. They depend majorly on commercial (paid) blood donation as against voluntary non-remunerated blood donation (VNRBD), thereby predisposing the patients to transfusion transmissible infectious diseases (TTIs) including HIV [30]. The facilities for component blood therapy (i.e., apheresis machines) are not available in most health centers. For instance, there was no documented beneficiary from component blood therapy in previous studies in Nigeria. All severely anemic patients that require blood transfusion benefited from either allogeneic whole blood transfusion (50%) or the use of erythroid growth factor such as human recombinant erythropoietin (38%) [3, 14].

Infection is one of the major killers in MM in LICs, especially when immune paresis has set in. About 11.1% of MM patients present with neutropenic sepsis in this region. Infection control is by the use of antibiotic therapy/prophylaxis and colony forming unit-granulocyte-monocyte

agents (CFU-GM) such as filgrastim or neupogen. However, the later is usually expensive and only very few patients can afford it, hence worsening the survival outcome of the disease [3].

There is an increase in the incidence of nephropathy in MM in LICs. A range of 16–36% was recorded in previous studies in Nigeria [3, 17, 31] as against 20% in the USA [32]. A striking finding about the nephropathies in MM patients in LICs is their severity at presentation, which qualifies most of them for renal dialysis (or renal transplant). However, this is an expensive palliative intervention as only very few patients can comply with the courses of dialysis, which may not be available in some centers.

In African continent, the major complications that bring MM patients to the hospital for the first time are operable (surgical) complications. A recent study revealed that 56.7% of patients diagnosed with MM received different forms of surgery ranging from craniotomy (plasmacytoma of the skull), partial cystectomy (solitary plasmacytoma of bladder), to internal fixation of orthopedic pins due to SREs complications arising from myeloma cells. Surprisingly, these complications have set in long before diagnoses were made. The presence of extramedullary plasmacytoma indicates poor prognosis, and this is worsened further in the absence of involved field radiotherapy (IFR) [33].

6.2. Challenges in definitive treatment of MM

The standard definitive interventions for people living with MM are antimyeloma chemotherapy regimens and stem cell transplantation (autologous stem-cell transplantation (ASCT)). The antimyeloma chemotherapeutic regimens have undergone series of transformation and evolution over the years. The current antimyeloma therapeutic agents have changed the paradigm in the management of the disease. These agents have the best effect in improving the quality of life and overall survival intervals of MM patients. They have positively changed the course of the disease especially in high-income countries where they are relatively more available. This has been due in large part to a better understanding of the biology of the disease and the development of several highly effective therapies. They include proteasome inhibitors [PI] (bortezomib, carfilzomib, ixazomib, marizomib, and oprozomib), immunomodulatory [IMiD] agents (thalidomide, lenalidomide, and pomalidomide), monoclonal antibody therapies (elotuzumab, daratumumab, and siltuximab), Bcl inhibitor (navitoclax), FGFR3 inhibitor (dovitinib), and histone deacetylase (HDAC) inhibitors (panobinostat, romidepsin, vorinostat, and rocilinostat). These agents include those that target the myeloma itself, some that target the bone marrow microenvironment, and those that target both [34].Unfortunately, these agents are not readily available in low- and some middle-income countries (LMICs) including Nigeria. The huge disparity in income, health-care infrastructure, and access to novel drugs in LMICs hinders the delivery of optimum care to every patient with MM in the region [35] due to limitation in purchasing power.

There may be no "standard therapy" for MM treatment, based on the many novel therapies, which have emerged for the treatment of the disease. The treatment approaches that are often referred to as standard are usually those with strong evidence of clinical efficacy. Although a recent clinical trial has shown that a combination of PI and IMiD will make for a standard regimen when added with dexamethasone [36], the current opinion is in favor of individualized treatment options,

which is based not only on cytogenetic risk classification, but also on host factors, disease stage, and a variety of other prognostic factors.

According to the National Comprehensive Cancer Network (NCCN) guidelines, the consensus standard of care in newly diagnosed MM who have no intention for ASCT is RVD (lenalidomide, bortezomib, and dexamethasone) [36]. This is because RVD has improved median overall survival (OS) compared to conventional RD (75 months versus 64 months; HR 0.709; two-sided p = 0.025), improved overall response rate [ORR] (82 versus 72%), and improved progressive-free survival (PFS) (43 months versus 30 months, HR 0.712; one-sided p = 0.0018) [37, 38].

This consensus standard of treatment of MM is yet to be achieved in many developing countries. Unlike in developed countries where treatment is beginning to be customized based on mapping of patient's genome, most low-income countries are yet to offer their patients such opportunities. In Nigeria, the major antimyeloma chemotherapy drug is the old conventional alkylating agent known as melphalan (M), which is usually combined with a steroid (i.e., prednisolone, P) as a double or triple-only combination regimen. MP is still the most accessible commonly used regimen for treating MM patients because of the cost and availability, long after it has been phased out for treating MM patients in developed countries. About 84% of newly diagnosed MM patients in some LICs still depend on MP doublet combination regimen [3].This is contrary to the standard RVD triplet regimen accepted worldwide as the current treatment of choice for MM. About 28% of MM patients from the group of patients already on MP could afford a "partial-standard" triplet regimen made up of either one PI (i.e., bortezomib-melphalan-prednisolone VMP (7.7%)) or one IMiD agent (i.e., thalidomide-melphalan-prednisolone TMP (19.7%). "Partial" in this context connotes combination of a target (novel) therapy with old conventional regimen (i.e., MP in this case). However, a recent study in Nigeria has shown that up to 16.7% of MM patients use bortezomib-thalidomide-dexamethasone (BTD) as their first-line regimen [39]. Although RVD has a better median overall survival (OS), progressive free survival (PFS) and overall response rate (ORR) compared to BTD, this is a move toward the right direction as the latter regimen is close to the standard regimen (RVD) in terms of the benefits derived from a PI and IMiD combination regimens [36]. But, again, this is a bad news for many developing countries as less than 20% of MM patients in the region could access close-to-standard (partial) antimyeloma regimen [40]. The remaining 16% constitute the MM patients who are either on unclassified (i.e., neither known old conventional nor new novel therapy) antimyeloma regimens (such as vincristine adriamycin dexamethasone VAD, CVP, and CVAP) or not on any cytotoxic chemotherapy [3].

Stem cell transplantation (i.e., ASCT) is not a common option of treatment of MM in most developing countries. The only patient (3.8%) who benefited from this intervention from a previous study was outside Nigeria and the patient died two years posttransplantation. There is paucity of data regarding stem cell transplantation in most LICs especially those from Sub-Saharan African region. For instance, no center offers ASCT in Nigeria presently. Although few successful attempts on allogeneic stem-cell transplantation have been made in a center in Southern Nigeria (on sickle cell disease), but it has not been sustainable due to technological inequalities, brain drain of health workers, lack of funding, and political-will from the government. The public health system does not guarantee health insurance coverage

for oncology treatment and stem-cell transplantation. Transplant-eligible patients who require stem-cell transplantation usually pay out from their pockets, and this could add to another burden to the patients [41–43]. However, in high-income countries, the reverse is the case and the survival outcome is usually better.

7. Other challenges

7.1. National Cancer (MM) Registry

There is no standard National cancer (MM) registry or Surveillance Epidemiology End-Result (SEER) cancer statistics review center in most developing countries including Nigeria. This has hindered getting accurate statistics of the disease in most developing countries.

7.2. National Guideline for management of MM

There are no standard guidelines for the treatment of MM in many developing countries including Nigeria. This is responsible for the disparities in some of the outcomes. A lot of confounding issues have arisen as a result of disharmony in the management of the disease in many developing countries. There is a need to control all confounding issues that may arise as a result of heterogeneous management of the MM in developing countries. Each country is expected to design its own consensus guidelines that will best serve the patients putting international best practices in mind.

7.3. Psychosocial input

One of the components of a good palliative care of people living with terminal diseases such as MM is the psychosocial care. In developed countries, the social workers and the spiritualists have their roles to play in order to improve the quality of life of the patients. For instance, some patients who have financial challenges in procuring their treatment may not access social workers either because they are not there or they might be there but they are not functioning. This may create more health burden or even cause death of the patients in some cases.

8. Conclusion and recommendations

Late diagnosis and inadequate palliative care are the hallmarks of poor prognosis and overall survival outcome of MM in developing countries [3]. There is a need to educate the physicians, especially orthopedic surgeons, renal physicians, and gastroenterologists to exercise higher index of suspicion, as they are usually the first to see such patients [44].

The government, stakeholders in health institutions, and donor agencies who are passionate for MM have a role to play in its management toward improving the quality of life of people living with the disease. This is achievable by improved funding of MM research and treatment in

developing countries. The public health system should as a matter of urgency provide health insurance coverage for the management of MM patients especially in LICs such as Nigeria where the over 62% of population lives on extreme poverty of less than two dollars per day [41].

There is also a need to build special centers designated for the treatment of MM where all relevant modern health-care facilities/equipments for diagnosis, risk assessments, and treatment of MM should be available, while taking into cognizance international best practices for the management of the disease.

Adequate access to radiation therapy is a crucial component of modern multidisciplinary cancer care including MM. There must be a strict adherence to the IAEA recommendation of one megavoltage machine per 400 new cancer patients in areas with excellent cancer registry or one per 250,000 population size in areas without excellent cancer registry. The implication is that in countries like Nigeria where there are barely five functioning radiotherapy machine, the number has to be scaled up between 260 and 840 megavoltage units taking into cognizance a population size of 210 million people (based on 2006 population census and average annual growth rate of 3.1%) [29].

Supportive care of people living with MM must take into cognizance psychosocial health of the individuals and their families. This is the only way forward in ensuring a holistic care and improved quality of life of these patients. Every component of palliative workforce including the social workers must be involved in realizing this goal.

There is a need to scale-up definitive treatment of MM in developing countries using stem-cell transplantation. Autologous non-cryopreserved stem-cell transplantation avoids the cost of establishing and maintaining a cryopreservation facility, and this can be feasible in transplant centers in economic-constrained regions [45, 46]. Studies have shown that high-dose melphalan with autologous stem-cell support improves the survival rate for patients with myeloma. Also, when they are carefully selected for treatment with ASCT, they can be managed with a brief initial hospitalization and outpatient follow-up, with low morbidity and mortality [47–50].

Also, efforts should be intensified to set up excellent cancer (MM) registries in developing countries so as to improve on the statistics and epidemiology of MM and other cancer diseases. Each country is expected to formulate its own consensus guidelines that will best serve the patients using international best practices.

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