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Outcome of stage III-B IgA-Kappa FLC MM with t(4:14) karyotype: A Nigerian jehovah witness nine-year experience

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SUMMARY

Multiple myeloma (MM) is the second commonest hematologic malignancy of public health importance after non-Hodgkins lymphoma. It has been found to occur commonly among the Blacks. Unfortunately, there is poor case ascertainment of the disease in Low-Income Countries (LICs) such as those in sub-Saharan Africa. The few newly diagnosed MM do not have access to a complete assessment tests making it difficult to stratify them and decide appropriate target therapy for their treatment. In this report, a 54-year old female who was diagnosed MM in Nigeria underwent risk stratification 9 years after. A complete assessment test showed a Stage III-A IgA-kappa FLC myeloma with 4;14 translocations and chromosome 13 deletion. She was on thalidomide-dexamethasone; melphalan-prednisolone and bortezomib-dexamethasone combination regimens at different cycles. She went into progression (cord compression fracture) 7 years after diagnosis She subsequently underwent laminectomy, but was lost to follow-up 3 years after.

Key words: multiple myeloma, risk stratification, outcome, IgA-kappa

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INTRODUCTION

Multiple Myeloma (MM) is a malignant proliferation of terminally differentiated B-lymphoid cells in the bone marrow [1]. It is classified under aggressive (intermediate-risk) Non-Hodgkins lymphoproliferative disorder [2]. It accounts for 10%-15% of all lymphoproliferative disorders and about 1-2% of all cancer diagnosis [2-4]. Hence, it is a hematological malignancy of public health importance, especially among the blacks due to its epidemiological causal-relationship with the race. Based on the descriptive epidemiology of MM, it is assumed that its prevalence is high in Low- and Middle-Income Countries (LMICs) of sub-Saharan African regions. However, this has not translated in the case ascertainment of the disease due to the peculiar challenges in its diagnosis and treatment in this part of the world [5-8].

The diagnosis of MM is based on a constellation of hematologic, immunologic, histologic and radiographic features [9]. Unfortunately, most developing countries in sub-Saharan Africa are yet to meet the minimum assessment tests for diagnosis, staging, and prognostication of the disease outcome [5-9]. This has made it difficult for this part of the world to catch-up with the current trend in the management of MM, as seen in most high-income countries [10]. The standard assessment tests for MM requires a panel of investigations, some which include Beta-2 Microglobulin (B2M), labeling index (PCLI) which are rarely available in the region [11].

The implication is that most of the MM patients diagnosed in LICs are not cytogenetically and immunologically categorized, and so they do not meet the criteria for an international staging system. Therefore, they do not benefit from accurate risk stratification, prognostication and personalized risk-adapted therapies offered to their counterparts in most high-income countries [12-14]. These disparities contribute to poor survival interval of people living with MM in LICs such as those found in sub-Saharan Africa [15].

Cytogenetically, MM is classified based on karyotype into hyperdiploid (chromosomes range of 48-78 and odd-numbered trisomies) and non-hyperdiploid (hypodiploid or near

tetraploid chromosomes <48 or >74 chromosomes) variants [16, 17]. While the hyperdiploid karyotypes (constitutes 55-60% primary MM tumors) are predominantly IgG kappa-types with skeletal-related events, the non-hyperdiploid (40%-45% primary MM tumors) karyotypes are usually associated with chromosomal translocation [11]. In terms of prognosis, the hyperdiploid karyotypes offer better prognosis provided they are not associated with deletion of chromosomes 13 and 17 or 1q amplification [18-20]. The cytogenetic study of MM has proffered a significant contribution in decision-making on the choice of therapy. The karyotypes and immunologic markers of MM currently serve as potential sites for modern target therapeutic interventions. These new innovations have made individualization of novel therapies and evaluation of their subsequent responses possible in MM disease trajectory.

MM has been described as a disease with marked cytogenetic, molecular and proliferative heterogeneity. The Mayo Stratification for Myeloma and Risk-adapted Therapy (mSMART) is a new consensus opinion which takes into cognizance genetically determined risk status of MM and the varieties of therapeutic strategies currently available [12-14]. The "risk-dependent therapy" in this context does not depend solely on cytogenetic stratification, but also on the host factors, disease stage and a variety of other prognostic factors.

In current Mayo's stratification algorithm, three cytogenetic risk levels of MM based on a widely varied outcome to therapy include the standard-, intermediate- and high-risk karyotypes MM. The standard-risk karyotypes are t(6;14), t(11;14) and trisomies; the intermediate-risk include t(4;14), 1q amplification and a high plasma cell at S-phase, while the high-risk include t(14;16), t(14;20), Del 17p and high-risk signature GEP (Table 1). Sometimes, a sub-set of patients with standard- and intermediate-risk will be classified as a high-risk signature by GEP, especially while considering other prognostic factors (i.e., age, high LDH, beta-2M>5.5 alone and/or with anemia) that can worsen the outcome [21]. The standard-risk translocation, t(11,14) may sometimes be associated with plasma cell leukemia while trisomies may ameliorate disease prognosis [12]. The risk stratification of MM has given birth to new target therapeutic interventions which can be individualized based on the risk status of the patient.

The mSMART algorithm is ideally the strategic definitive anti-myeloma intervention available in a setting where cytogenetic stratification of MM and other prognostic factors that can influence the outcome is offered. These robust lines of management, together with other supportive (palliative) interventions, have the potential to improve the overall response rate (ORR) and survival intervals (OS and PFS) of people living with MM. Unfortunately, this is a far cry from what is obtainable in resource-constrained settings, such as those found in sub-Saharan Africa and other LMICs, where assessment tests for MM are grossly inadequate. The case report is the outcome of a stage III-B MM patient (a Jehovah's witness) who was diagnosed in Nigeria and had the privilege to do complete assessment tests for MM in the United States of America.

Clinical presentation

Mrs. NA, a 54-year-old woman and Jehovah witness, reported in 2008 with chronic backache, chest pain and features of anemia. It was discovered in the course of history that she had been with orthopedic surgeons on account of Skeletal-Related Events (SREs) three months prior to presentation. On clinical examination, she had severe grade anemia (3+pallor), confirmed by a hemoglobin concentration of 5 g/dL (PCV< 15%). However, every attempt to transfuse her was declined on religious ground.

A preliminary MM assessment tests such as Cite tables in chronological orderCite tables in chronological orderaspiration, skeletal radiograph, Serum Protein Electrophoresis (SPE), Serum Electrolyte Urea Creatinine (SEUC), Serum Calcium, Total Protein (TPR) and Liver function tests were done to establish the initial diagnosis of stage III-B Multiple myelomas. This was evidenced by Bone Marrow Plasma Cells (BMPC) of about 45%, paraproteinemia (Monoclonal spike on SPE), more than three focal lesions (osteolytic lesions, fracture of the posterior border of right 7th rib), a serum creatinine level>120 μMol/L, and erythrocyte sedimentation rate (ESR) greater 150/mm^3 (a minimum of one major and one minor criterion is required to make a diagnosis of MM). However, the international staging system could not be ascertained because she was not able to do B2M, immunophenotyping, immunofixation, Immunoglobulin quantification, cytogenetic analysis at this stage due to their inaccessibility in the region. She was placed majorly on old

Tab. 1. Risk classification of active MM

Standard-risk karyotype	Intermediate-risk karyotype	High-risk karyotype
All others including • Trisomies • t(11;14)(q13;q32) • t(6;14)	**FISH** • t(4;14)(p16.3;q32) • 1q gain • High PC S-phase	**FISH** • Del 17p • t(14;16)(q32;q23) • t(14;20) **GEP** • High risk signature

Tab. 2. Results of myeloma assessment test

Test	Value	Remarks
Hematological		
CBC (4/27/17)		
WBC	4.99	Normal
RBC	2.99	Low (Anemia)
HGB	8.8	Low
HCT	28.4	Low
PLT	128	Low (Thrombocytopenia)

PBF (3/28/17)		Normochromic normocytic anemia. Marked rouleaux formation. Leukoerythroblastic reaction. Mild leukocytosis. Left-shifted neutrophil series. Moderate absolute eosinophilia. Marked thrombocytopenia.
BMA findings	≥ 45% BMPCs	Plasmacytosis
Coagulation profile		
PT	18.8	High
APTT	33.3	Normal
INR	1.8	High
ESR	>150 mm/hour	High
Blood Chemistry		
Immunofixation, Ig Quantification, BUN and CR		
M-protein estimation	9	High
B2M	11.6	High
Albumin	2.7	Low
IgA	9307	High
IgG	306	Low
IgM	10	Low
KAPFLC	4.7	High
LAMFLC	0.74	Low
KLFLCRATIO	6.35	High
TPRO	15	High
BUN	9	Normal
CR	0.44	Low
Liver function test		
TBILI	0.3	Normal
AST	28	Normal
ALT	38	High
ALP	53	Normal
Fish	t(4;14) (p16.3;q32)	Intermediate-Risk MM (mSMART) High-Risk MM (IMWG Risk Stratification)
Immunophenotype	CD45- CD56+ CD38+ CD138+	
Others		
Vitamin D	Reduced	Vitamin D deficiency
Serum iron	Reduced	Iron deficiency anemia
Serum ferritin	Raised	Chronic inflammation (APP)
RBC folate	Reduced	Background Megaloblastosis

conventional anti-myeloma regimen (melphalan-prednisolone) after reacting to thalidomide-dexamethasone double-only combination regimen at the second cycle. There were challenges accessing the target therapies especially the proteasome inhibitor-based regimens. However, 7 years after diagnosis she relapsed with severe skeletal complication (cord compression). In 2016, she was referred to India where she underwent a laminectomy and other corrective surgery. She was transiently relieved only to relapse with more severe bone pain. In 2017, she traveled to the United States of America on the invitation, where complete myeloma assessment tests were conducted. The complete blood count findings revealed marked rouleaux formation, marked normochromic normocytic anemia, leukoerythroblastic reaction, mild leukocytosis, moderate absolute eosinophilia, left-shifted neutrophil series, and marked thrombocytopenia. The SPE together with immunofixation and immunoglobulin quantification tests revealed a monoclonal gammopathy with characterized IgA-Kappa Free Light Chain (FLC). Monoclonal estimation was 6.5 g/dL with moderate hypoalbuminemia and hypogammaglobinemia. BM biopsy confirmed 95% involvement by myeloma cells. Metaphase cytogenetics showed 4;14 translocations and deletion of chromosome 13. The bone marrow aspirate flow cytometry revealed abnormal plasma cell population (Figure 1) that were CD45 negative (about 19% of nucleated cells) but showed expression of CD56, CD38, and CD138 (Table 2). In addition to the above tests, she was found to have vitamin D, folate and iron deficiencies, but ferritin assay showed iron overload.

Case management

She was initially commenced on thalidomide-dexamethasone (TD) for the first three cycles. She responded favorably initially

to the regimen but later developed some side effects such as psychiatric complications and chronic constipation. The regimens were replaced with melphalan plus prednisolone-double-only regimen (melphalan was given per oral at 6 mg daily × 7 days; prednisolone 80 mg daily × 5 days in a 28-day cycle). She could achieve a Very Good Partial Remission (VGPR) with this regimen after about 15 months (15 cycles) of commencing anti-myeloma chemotherapy. She was on mephalan-based maintenance for about 2 years after an effort to get bortezomib failed. The bortezomib was added 6 years after not clearly for progression, but due to finally being able to obtain the drug. She was managed on other palliatives such as opiate analgesics (DF118 one tablet by mouth 8 hourly) erythropoietin (4000 IU twice weekly), bisphosphonate (Zoledronic acid 4 mg in 100 ml 0.9% NaCl intravenous drip over 20 minutes) and G-CSF (Filgrastim 300 μg 72 hourly per week PRN). A periodic bone marrow aspiration and blood film were conducted 6-monthly to monitor response to anti-myeloma therapy.

In 2016, the patient went into relapsed with evidence of disease progression (i.e., >60% BMPC and osteolytic bone lesions). She had spinal compression fractures (T4-L1 vertebral body compression) with the inability to walk without aid. She was later referred to India where she had laminectomy and fusion between T4 and T11. However, she was transiently relieved for only 5 months and later developed severe anemia with an inability to walk. She was referred to the USA by invitation in March 2017 where complete myeloma assessment tests were conducted. A diagnosis of stage III-A IgA-Kappa FLC MM with t(4;14) translocation and deletion of chromosome 13 was finally made. She was found to have cord compression and was subsequently hospitalized, treated with palliative radiation therapy, bortezomib-dexamethasone double-only regimen, EPO (Darbepoetin) and other palliative interventions.

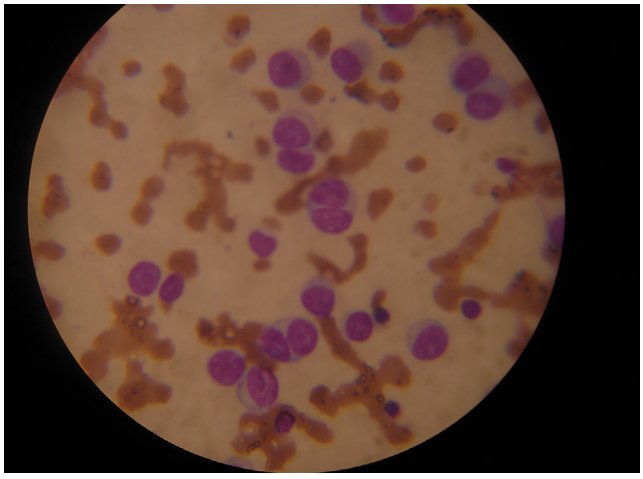

Fig. 1. BMA slide picture of the patient showing bi-nucleated plasma cells

She responded favorably to this line of management but opted to go back to Nigeria after receiving only 2 cycles of the regimens. She lived for about 6 months before she was lost in follow-up.

Clinical outcome

The patient took about 2 years to attain VGPR despite that risk stratification and access to standard anti-myeloma target therapy were six years after diagnosis. She was evaluated 6-monthly using BMA and Complete blood count. Three years after commencement of anti-myeloma regimen, she attained complete remission but went into progression 3 years after CR. This was evidenced by cord compression fracture, inability to walk and anemia. She re-started a new cycle of anti-myeloma regimen in the USA which she took for two cycles before opting to come back to Nigeria. She lived for about 11 years after diagnosis before she was lost to follow-up.

DISCUSSION

The management of MM has been quite challenging in Low-income and Some Middle-income Countries (LMICs). This is because of lack of insurance coverage for people living with cancer, unavailability of cancer drugs, the high cost of procurement when available, and lack of collaborations in cancer research and management between the LICs and HICs of the world. The index case had the highest survival outcome of all 30 MM patients seen over the past 10 years, but still, there were so many things that could have been done to improve the survival interval which was not done.

The treatment of MM based on mSMART classification varies based on age, risk level and eligibility of patients to Autologous

Stem Cell Transplantation (ASCT). Basically, the treatment options are divided into two major categories namely the Transplant Ineligible MM and Transplant Eligible MM. There are subtle variations in the choice of therapy in these two groups of patients based on their cytogenetic risk stratifications and prognostic factors.

1. In transplant-ineligible MM with standard-risk karyotype, bortezomib-lenalidomide-dexamethasone (VRd) combination regimen is the standard therapeutic option for a duration of 12 months. However, if the patient is >75 years and frail, Rd may be considered if there is a favorable response with low toxicities. After an induction period of 12 months, Rd is maintained for a period of 1 year. Thereafter, dexamethasone is discontinued.

In transplant-ineligible MM with intermediate-risk karyotype, the same VRd combination regimen as with standard-risk karyotype applies over the same period of induction while

Tab. 3. Stratified risk-dependent therapy for transplant-ineligible MM

Standard-risk	Intermediate-risk	High-risk
Karyotype	**Karyotype**	**Karyotype**
t(6;14), t(11;14), trisomies	t(4;14), 1q gain	t(14;16), t(14;20), 17p
Induction	**Induction**	**Induction**
VRd approx. 12 months (Rd >75 years or frail	VRd approx. 12 months	VRd for approx. 12 months
Maintenance	**Maintenance**	**Maintenance**
Rd × 1 year	Bortezomib-based regimen for a minimum of 1 year	Bortezomib-based for a minimum of 1 year

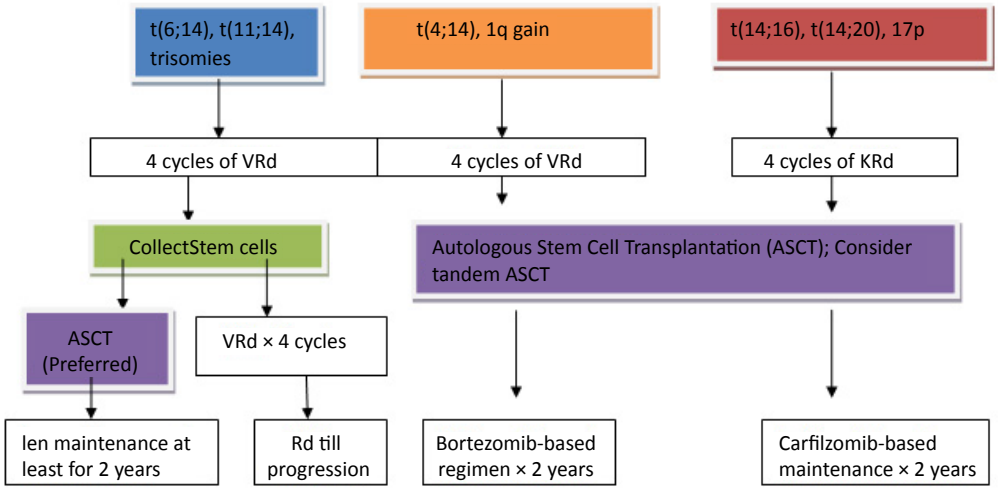

Fig. 2. Flow Chart showing stratified risk-dependent therapy for transplant eligible MM

bortezomib-based maintenance (i.e., Vd) is given for at least 1 year. This same therapeutic option is available for transplant-ineligible MM with high-risk karyotype. However, a clinical trial is a strongly recommended first option [12-14] (Table 3).

2. In transplant eligible MM, a 4-cycle of VRd is the standard choice of therapy for all risk karyotypes except the high-risk karyotype where bortezomib is replaced by carfilzomib (kRd). After the first-4 cycles of

VRd in transplant eligible MM with standard-risk karyotype, the stem cells are harvested by mobilization with G-CSF plus Cytoxan or Plerixafor. Thereafter, the patient is left with two options: either to undergo ASCT or another 4-cycle combination therapy. For the patients who undergo ASCT, lenalidomide is maintained for a minimum of 2 years based on tolerance, risk, and benefits. For the categories of patients who do not undergo ASCT, they are maintained on Rd until progression. Those who respond to Rd with minimal toxicities continue with the regimen. Both the intermediate-and high-risk karyotypes transplant eligible MM patients undergo ASCT (i.e., tandem ASCT) after the initial 4-cycle duration and thereafter maintained on bortezomib-based and carfilzomib-based regimens respectively for another duration of 2 years based on tolerance [12-14] (Figure 2).

The index patient gave insight into many newly diagnosed MM patients who could not undergo risk stratification in this part of the world. The 4:14 translocation with deletion of chromosome 13 is associated with high-risk myeloma using International Myeloma Working Group diagnostic criteria [21] and with intermediate-risk myeloma utilizing mSMART diagnostic criteria [14]. The implication was that the patient would have benefited from high-risk karyotype MM standard definitive anti-myeloma regimens for transplant eligible patients such as carfilzomib-based regimen (i.e, KRd). Unfortunately, this was discovered after progression had set in.

The patient's religion (believe) was another major drawback. She could potentially receive many treatments, but given her significant anemia and her refusal to receive blood product, it was agreed to avoid immunomodulators or monoclonal antibodies such as daratumumab upfront.

The supportive (palliative) intervention drugs which helped to improve her quality of life included Darbepoetin, radiotherapy, bisphosphonate, laminectomy, analgesics (i.e., oxycodone), ergocalciferol, acyclovir, and a multivitamin. Darbepoetin is a hyperglycosylated form of Erythropoietin. Its advantage over EPO alfa and beta is that it can be administered less frequently than the others in order to achieve a comparable increment in hemoglobin levels. These palliative care contributed to the improved average life expectancy of the patient.

CONCLUSION

The management of MM in LICs is still rudimentary. The survival outcome depends on a robust assessment test for MM. There is a need to adopt the risk stratification strategy in this part of the world so as to decide the appropriate target therapy of choice. This is a call for collaboration with HICs.

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