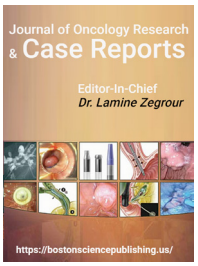
CASE REPORT - OPEN ACCESS

Journal of Oncology Research and Case Reports DOI: http://dx.doi.org/10.51521/ JORCR.2024/1/102

Contents lists available at bostonsciencepublishing.us

Journal of Oncology Research and Case Reports



Outcome of Multiple Myeloma in the Elderly with the use of Bortezomib in Comparison to Old Combination Therapy in UNIMED Teaching Hospital, Southwest Nigeria: 2 Case Reports and Literature Review

Osho P.O*[1], Ojo M.A[2], Okunnuga N.A[3], Oyeneyin A.O[4], Oni O.I[5], Ojo-Rowland M[6], Balogun E.M[7], Ojo-Rowland O.T[8]

[1]*Department of Hematology and Blood transfusion, University of Medical Sciences Teaching Hospital, Ondo City, Ondo State, Nigeria.*

[2]*Department of Hematology, Gurayat General Hospital.Al jouf. Saudi Arabia*

[3]*Department of Radiology, University of Medical Sciences Teaching Hospital, Ondo City, Ondo State, Nigeria.*

[4]*Department of Community Health Science, University of Medical Sciences, Ondo City, Ondo State, Nigeria.*

[5]*Department of Neglected Tropical Diseases, Ondo State Primary Health Care Center, Ondo City, Ondo State, Nigeria*

[6]*Department of Obstetrics and Gynecology, State Specialist Hospital, Ondo City, Ondo State, Nigeria.*

[7]*Department of Nursing Science, University of Medical Sciences, Ondo City, Ondo State, Nigeria*

[8]*Department of Medicine and Surgery, University of Ilorin, Ilorin, Kwara state, Nigeria*

ARTICLE INFO

Article history:
Received 05 August 2024
Revised 16 September 2024
Accepted 09 October 2024
Published 25 October 2024

KEYWORDS:
Multiple Myeloma,
Bortezomib,
Combination Therapy,
Elderly

ABSTRACT

Abstract: Multiple myeloma is a B-cell neoplasm resulting from proliferation of monoclonal plasma cells in the bone marrow characterized by hypercalcemia, bone lesions, renal impairment and anaemia which causes a monoclonal protein secreting disorder call paraproteinemias. Globally, it is known to be a disease of the elderly with a median age incidence of 65 in the western countries and 58 years in Sub-Saharan Africa, it is of rare occurrence in young adults. The significance of this disease in the elderly is being emphasized in this case report showcasing two elderly patients, an 86-year old female and a 79-year old male, both being managed for the past 12 and 5 years respectively. The patients were investigated and diagnosis of multiple myeloma was made using bone marrow aspiration, plasmacytosis >30%, Full blood count, Peripheral blood film, protein electrophoresis, ESR and X-rays findings. The 86-year old woman was placed on old combination therapy; while the 79-year old man was placed eventually on bortezomib-combination therapy, and both of them have shown tremendous improvement in their treatments over the period of time they were being managed. We put forward this case report and literature review for better understanding of this disease in elderly and how different therapies have been introduced to improve their health and survival outcome in our environment.

Introduction

Multiple myeloma (MM) also known as Kahler's disease, is a clonal B cells disorder that affects the plasma cells in the bone marrow. The malignant plasma cells proliferate and secrete abnormal immunoglobulins leading to a monoclonal gammopathy organ damage, osteolytic bone lesions (OBL), hypercalcemia, anemia and renal insufficiency [1].

MM has a significant connection with age and a mean range of 60 to 70 years with extreme rare cases in younger adults. It accounts for 1% of all cancers and approximately 10% of all hematological malignancies and 2% of all cancer related mortalities, it also accounts for less than 15% of all lymphohematopoietic cancers. However, it is widely accepted that there are certain differences in treatment goals between younger and older patients. When it comes to treating elderly patients, it is crucial to evaluate a subtle balance between effectiveness, safety, and maintaining their quality of life. Moreover, elderly patients represent a heterogeneous population, as depicted by frailty assessments [2]. Its incidence in African descents is twice more than in Caucasians and Asians, and it is slightly more common in men than in women [3]. The male to female ratio is 2-3:1. It is a disease of the elderly with median age incidence of 65 years in western countries and 58 in Sub-Saharan Africa. Higher incidence is seen in black Americans as compared to their counterparts in Africa. A high prevalence rate is also seen in African population with an incidence rate of 12.7% (21 million people) of total population of Nigeria while the male to female ratio in Nigeria is 2-3:1[4].

The precise aetiology of multiple myeloma (MM) remains unknown. However, similar to other cancers, MM arises from genetic mutations that result in uncontrolled cellular proliferation. Specific oncogenic proteins such as KRAS, BRAF, NRAS, and TP53 have been implicated in numerous cases of MM. Additional contributing factors include exposure to ionizing radiation and benzene derivatives, genetic predispositions (notably associated with HLA-Cw5 or HLA-Cw2), chromosomal translocations

* Corresponding author.
Dr. Osho Patrick, Department of Hematology and Blood transfusion, University of Medical Sciences Teaching Hospital, Ondo City, Ondo State, Nigeria, Email: droshopo@gmail.com, droshopo@unimed.edu.nga*

involving the immunoglobulin heavy chain locus on chromosome 14 (observed in 20-40% of cases), and monosomy [5]. At the cellular level, MM induces the secretion of osteoclast-activating factors such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-β (TNF-β). These cytokines are critical in causing the end-organ damage, bone tissue damage and bone resorption seen in MM. This pathological process results in 'holes' or lytic lesion in the bone that weakens the skeletal structure, cause pain, increase the risk of fracture and contribute to other complications such as hypercalcemia. Additionally, the cytokine-rich microenvironment promotes angiogenesis, which in turn supports the growth and survival of malignant plasma cells [6].

MM typically progresses from an asymptomatic premalignant condition called monoclonal gammopathy of undetermined significance (MGUS), which is commonly found in individuals over 50. Smoldering multiple myeloma (SMM) is an intermediate stage between MGUS and active myeloma, characterized by higher levels of monoclonal protein than in MGUS but without symptoms of active disease. MM often presents with symptoms such as bone pain, anemia, fatigue, vertebral collapse, recurrent infections, and renal and neurological complications, frequently leading to end-organ damage. These symptoms align with the CRAB criteria used for diagnosing MM, which includes elevated calcium levels in the blood, renal impairment, anemia, and bone lesions [7].

MM exhibits several distinctive laboratory features. Bone marrow analysis typically reveals hyperplasia, with a smear showing more than 10% plasmacytosis. Patients often present with an elevated erythrocyte sedimentation rate (ESR) exceeding 100 mm/h by the Westergren method, elevated β2-microglobulin levels, hypoalbuminemia, and hypercalcemia. Radiologically, a skeletal X-ray survey frequently identifies osteolytic bone lesions [8].

The new international staging system for MM categorizes the disease into three stages based on laboratory parameters, radiological findings, and immunological features. Stage I is characterized by a median survival of over five years, Stage II by a median survival of approximately three years, and Stage III by a median survival of around two years. Despite its utility in stratifying patients, this staging system does not accurately predict disease-free survival [3,9]. Furthermore, the Durie and Salmon staging system can be used for diagnosis of multiple myeloma based on the extent of the tumor mass, hemoglobin levels, serum calcium levels and presence of bone lesions. Stage I indicates a low tumor burden with normal calcium levels and minimal bone damage. Stage II represents an intermediate level of diseases. Stage III signifies a high tumor burden with significant bone lesions and elevated calcium levels. This helps to predict prognosis and guide treatment decisions [9].

Globally, the treatment outcomes for MM have improved significantly due to novel therapies, stem cell transplantation, comprehensive health insurance coverage, and effective government policies [10]. However, in Nigeria, these advances have not been fully realized due to funding which has been a huge hindrance to purchase these therapies resulting in the heavy reliance on the old therapies. Other factors such as out-of-pocket payments and poor implementation of government policies have also contributed [11].

Although MM remains incurable, both traditional (old therapies) and new therapies have significantly improved disease management. Bortezomib, a novel antineoplastic agent and proteasome inhibitor, has demonstrated superior effectiveness in treating MM, leading to higher response rates, improved patient survival, and longer progression-free periods compared to older regimens. Bortezomib inhibits the growth of MM cell lines, including those resistant to steroids and melphalan. However, it is associated with side effects such as neuropathic pain in the fingertips and toes, sensory and proprioceptive loss, distal muscle weakness, and suppressed deep tendon reflexes while the old therapies e.g Melphalan, steroids, cyclophosphamide, vincristine, and adriamycin, often combined with thalidomide and bisphosphonates (Zoledronic acid) [12]. Melphalan and cyclophosphamide, both alkylating agents, inhibit DNA and protein synthesis, triggering apoptosis in rapidly proliferating tumor cells. However, they can cause bone marrow and gastrointestinal toxicities. Thalidomide is an immune modulator with anti-angiogenic, anti-inflammatory, and anti-proliferative effects. Biphosphonates are bone modifying agents with specific action on the bone tissue rather than directly targeting cancer cells, they work by slowing down bone loss and increasing bone density thereby reducing the risk of fractures and other bone complications such as bone pain and hypercalcemia associated with bone metastases [13].

In recent years, the introduction of more active novel agents like bortezomib, thalidomide or lenalidomide, known for their favorable toxicity profiles, has significantly improved survival rates among elderly patients. This case report highlights our experience with both traditional and modern therapies in treating multiple myeloma in older adults, shedding light on how financial stability impacts survival outcomes in our clinical environment.

CASE REPORTS

Two individuals were presented for the purpose of this study. An 86-year old female and a 79-year old male.

CASE 1

An 86-year old woman from a royal family, queen mother, who was referred to our clinic in 2012 with history of gradual but progressive weight loss, periodic fever, loss of appetite, fatigue, and bone pains of 6-month duration. She is a known hypertensive on amilodipine (10mg/daily) and diabetic on metformin (500mg/BD). There was no associated sphincteric dysfunction, no sensory loss, no leg or face swelling, no nerve dysfunction, or chronic cough and she is stable on her medication. At the time of presentation, significant examination findings were moderate pallor and general bone tenderness. X rays of the skull, thoracolumbar spine, and pelvis showed lytic lesions. Peripheral Blood film showed Rouleaux formation and bone marrow aspiration confirmed hypercellular marrow with >20% plasmacytomatosis marrow. Erythrocyte sedimentation rate (ESR) was 138mmhr^{-1}, serum protein electrophoresis were detected and urinary qualitative bence jones protein was positive. All these confirmed the diagnosis of MM. Laboratory data are summarized in Table 1.

She was initially placed on Malphalan, prednisolone and thalidomide and had three cycles. There was no much improvement observed until later when her drug regimen was changed and she was placed on cyclophosphomides, dexamethasone, thalidomide in combination with zoledronic acid (CTD-Z) and she has done well on her drugs in the last twelve years.

She had a drug-free holiday in year 2020 for one year and three months with a 4 month routine monitoring using the Durie and Salmon with ISI diagnostic criteria together with the full blood count and E,U,Cr. The parameters used for the determination of patient on drug free holiday in management of multiple myeloma includes B2 microglobulin, ESR, Kappa and Lambda light chain and Albumin. In 2022, during her normal routine checkup, it was noticed that the B2 microglobulin (3.8mg/L), ESR (76mmhr^{-1}), albumin, kappa light chain (21.5mg/ml) and Lambda light chain (29.25mg/ml) were elevated which infers disease progression. She was then recommenced back on her previous drugs (CTD-Z) and her present results have returned to the normal reference range. She's currently on her second drug free holiday after receiving 6 cycles of medication since 2022 and she has had her routine check-up with normal laboratory results and her current status shows that she is stable and alive. She's presently only on her anti-hypertensive (Amlodipine), anti-diabetic drugs (Metformin) and some vitamin supplements. See Table 2.

CASE 2

A 79-year-old man, a merchant cocoa farmer with very good family support, presented with unresolving bone pains that was persistent and radiating throughout his entire body particularly the joints and back. He showed symptoms of fever, weight loss and fatigue which he had constantly experienced for 2 years before visiting our hematology clinic in 2019. He was initially being treated for chronic anemia of unknown origin and had received several blood transfusions. Not a known diabetic or hypertensive. His laboratory results from our hospital showed haemogram of 5.8g/dl, peripheral blood film showed Rouleaux formation, there was elevated creatinine levels and ESR of 193.60µmol/L and 126mm/hr respectively which were above the normal range. Albumin level was 37g/dl, and the beta-2-microglobulin level was 1.3 mg/L. The X-ray results shows positive lytic lesions (Chest/Hip region), bone marrow aspirate (BMA) showed suppressed erythropoesis with megaloblastoid change, and hypercellular marrow >20% plasmacytosis, serum protein electrophoresis were detected and urinary qualitative bence jones protein was positive which led to the diagnosis of MM. See Table 1

He began treatment with Thalidomide, Dexamethasone, and Cyclophosphamide (CTD) along with zoledronic acid which he continued till the 5th cycle without improvement of his anemic status despite several blood transfusions. Later, prednisolone replaced dexamethasone in his routine

therapy but there was no noticeable improvement in his health. The body pains were still persistent, and he also presented with scrotal swelling, ankle swelling along with abdominal pain. Following his lack of improvement, the CTZ regimen was then replaced with lenalidomide, dexamethasone and zoledronic acid (LDZ) regimen alongside IV Lasix. After several cycles with no appreciable development, bortezomib and thalidomide along with IV zoledronic acid regimen were introduced in 2022. It was observed that his haemogram improved upon the introduction of the novel drug to his regimen and by the 3rd cycle of bortezomib and regular health check-ups, his health had improved tremendously till date i.e. no more blood transfusion. See Table 2b.

Despite his regular clinic visits for chemotherapy, he was unable to afford finances for essential investigations (Quantitative Bence jones protein, Protein electrophoresis and Beta 2 microglobulins) due to the nature of his job and the economic situation of the country. So he was monitored based on Full blood count, ESR, EUCR and Fasting blood sugar.

Parameter	Reference range	Case 1	Case 2
Hemoglobin	12.0-18.0g/dL	8.0	5.8
ESR	0.0-20.0mm/hr	110	126
Calcium	2.02-2.60mmol/L	2.07	2.76
Urea	1.70-9.10mmol/L	4.51	13.03
Creatinine	50.0-110.0µmol/L	107.8	193.60
Albumin	33-57g/L	59	37
Bone marrow aspiration	Plasmacytosis >20%	Present	Present
Bence Jones protein (qualitative)		Present	Present
Total protein	3.2-4.6g/dL	7.2	9.02
Alpha 1 globulin	1.0-4.0g/L	0.16	0.89
Alpha 2 globulin	3.0-9.0g/dL	0.72	10.92
Beta 1 globulin	4.9-9.9g/dL	1.9	10.61
Beta 2 globulin	0.74-1.06g/dL	0.49	21.82
Beta 2 microglobulin	0.6-2.4mg/ml	2.4	2.13
Gamma globulin	5-14g/L	20.5	29.44
Fasting Blood Sugar (FBS)	3.90-6.10mmol/L	5.80	4.69
Skeletal bone x-ray survey	Bone lytic lesion	Present	Present

Table 1: Laboratory results of patients at presentation/diagnosis.

Parameter	1st Drug free Holiday at 2020	Disease progression at 2022	2nd Drug free Holiday at 2023	Current status at June, 2024	Reference Range
Hemoglobin	10.8	9.3	11.3	11.2	12.0-18.0g/dL
ESR	46	76	49	60	0.0-20.0mm/hr
Urea	3.2	5.4	4.76	4.91	1.70-9.10mmol/L
Creatinine	92	86	77.74	65.10	50.0-110.0µmol/L
Albumin	38	61	37	33	33-57g/L
Total Protein	78	81	75		60-80g/L
Alpha 1 Globulin	1.9	1.6	1.8		1-4g/L
Alpha 2 Globulin	6.1	5.8	6.0		3-9g/L
Beta 1 Globulin	14	11	12		7-15g/L
Beta 2 Globulin	10	8	10		7-15g/L
Gamma globulin	7.0	19	7.4		5-14g/L
Beta-2 microglobulins	2.22	3.8	2.1	0.80	0.6-2.4mg/ml
Kappa light chains	5.70	21.5	5.25	6.40	3.3-19.4mg/ml
Lambda light chains	5.54	29.25	5.10	6.62	5.71-26.30mg/ml
Fasting blood sugar	5.5	5.8	5.6	5.7	3.90-6.10mmol/L

Table 2a (Case 1:): Laboratory results for patient at Drug free holidays and disease progression.

Parameter	Reference Range	Status in 2023	Status in 2024
Hemoglobin	12.0-18.0g/Dl	9.2	10.8
ESR	0.0-20.0mm/hr	88	44
Urea	1.70-9.10mmol/L	6.3	4.2
Creatinine	50.0-110.0µmol/L	84	89
Albumin	33-57g/L	41	35
Total Protein	60-80g/L	N/A	N/A
Alpha 1 Globulin	1-4g/L	N/A	N/A
Alpha 2 Globulin	3-9g/L	N/A	N/A
Beta 1 Globulin	7-15g/L	N/A	N/A
Beta 2 Globulin	7-15g/L	N/A	N/A
Gamma globulin	5-14g/L	N/A	N/A
Beta 2 microglobulins	0.6-2.4mg/ml	N/A	N/A
Kappa light chains	3.3-19.4mg/ml	2.6	N/A
Lambda light chains	5.71-26.30mg/ml	27.1	N/A
Fasting blood sugar	3.90-6.10mmol/L	5.5	5.8

Table 2b (Case 2): Laboratory result following bortezomib introduction.

DISCUSSION

This report of two extremely unique clinical presentation of Multiple Myeloma seen in the elderly in Sub-Saharan Africa compared to what is common globally. MM is known to be a disease of the elder with a median age of 65 and approximately one third of patients are over 75 years of age at diagnosis. However, the presenting clinical features and response to therapy have been shown to be similar to those of patients of all ages [14]. Studies have shown that cases of MM in the elderly is more common in males and they have a more prolonged survival but this case study shows a reversal with an 85-year-old female on multidrug combination for 12 years and is currently on drug free holiday as compared to the male, 79 managed for 5 years and still on drugs (Bortezomib Regimen). In a multi-center retrospective study of 52 patients diagnosed with MM at the age 60 and above, the median overall survival was approximately 5-8 years and it varies by region with developed regions around 55-60% and developing regions often below 40% [15]. The prognosis of multiple myeloma in the elderly according to our experience have shown to be as good as what is seen in developed regions possibly because of tolerance to therapeutic regimen, novel agents, financial and family support, stage at diagnosis [16].

At the time these patients were being managed, the anti-myeloma agents available in Nigeria include; cyclophosphamide, dexamethasone, thalidomide, zoledronic acid and bortezomib. Although, hemopoietic bone marrow transplantation is available but it was not considered a treatment option since they responded to treatment. Common challenges in the management of MM noticed in this environment are affordability of treatment, access to drugs and patients compliance with treatment. However, these challenges were not seen in both patients due to a good financial and family support. The case 2 patient on Bortezomib regimen was placed on the generic type due to cost consideration. The intent of therapy in elderly patients is usually for them to have a better symptom control, prolonged treatment-free intervals, and good quality of life over prolonged survival.

Despite the realization of novel therapies, the outcomes in the treatment of MM still vary significantly across different regions globally. However, our patients have shown sustained response to treatment and follow up at 12 and 5 years respectively.

CONCLUSION

In conclusion, MM remains incurable, the landscape of its treatment is rapidly evolving providing hope for longer remissions and better quality of life for patients. The continuous development of novel therapies, treatment strategies and financial stability is crucial in managing this complex disease in our environment.

ETHICAL APPROVAL & CONSENT

Written ethical approval was obtained from the ethical committee of the University of Medical Science Teaching Hospital.

AUTHOR'S CONTRIBUTION

Osho P.O conceived the study, participated in its design and coordination, as well as drafting of the manuscript. Ojo M.A, Oyeneyin A.O, Oni O.I, Ojo-Rowland M. and Okunnuga A.N participated in the study design as well as drafting of the manuscript. Ojo-Rowland O.T and Balogun E.M participated in the manuscript preparation and reviewing it critically.

ACKNOWLEDGEMENTS

We want to appreciate our research assistant, Obaloluwa for typing and collation of data

COMPETING INTERESTS

We hereby declare that there is no conflict of interest in this report.

FUNDING

There was no funding provided for this study.

REFERENCES

1. Kaushansky K, *et al.,* eds. Myeloma. In: Williams Hematology. 9th ed. McGraw Hill; 2016. https://accessmedicine.mhmedical.com. Accessed Sept. 1, 2020.
2. Muhlbacher, A.C.; Nubling, M. Analysis of physicians' perspectives versus patients' preferences: Direct assessment and discrete choice experiments in the therapy of multiple myeloma. Eur. J. Health Econ. **20ss11**, 12, 193-203.
3. Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification and management. Am J hematol. 2022;97(8):1086-1107.doi:10.1002/ajh.26590
4. Durosinmi MA. A design Handbook of Haemato-oncology Chemotherapy for Medical Students and Doctors
5. Walker, B. A., *et al.* (2020). The genetic architecture of multiple myeloma. *Nature Reviews Cancer*, 20(3), 222-238.
6. Delforge, M., *et al.* (2021). Health-Related Quality of Life in Multiple Myeloma: Recommendations for Future Studies. *Hematological Oncology*, 39(2), 220-230.
7. Mateos, M. V., & Landgren, O. (2021). MGUS and Smoldering Multiple Myeloma: Diagnosis and Epidemiology. *Cancer Treatment and Research*, 183, 1-13. [Link](https://link.springer.com/chapter/10.1007/978-3-030-63759-0_1)
8. Rajkumar, S. V. (2020). Multiple myeloma: 2020 update on diagnosis, risk-stratification, and management. *American Journal of Hematology*, 95(5), 548-567. (https://onlinelibrary.wiley.com/doi/full/10.1002/ajh.25791)
9. Andgren O, Kyle RA, Pfeiffer RM, *et al.* Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study .Blood. 2009;113:5412-5417.

10. Odeyemi I.A.O., *et al.* National Health insurance Scheme in Nigeria: challenges, benefits, and risk mitigation strategies.'' Health Policy and Planning 38.2 (2023): 177-184

11. Uzochukwu, B.S.C., *et al.* ''Healthcare financing in Nigeria: implications for achieving universal health coverage.'' Nigerian Journal of Clinical Practice 24.5 (2023): 569-574.

12. Richardson, P.G., *et al.* ''Bortezomib or High dose dexamethasone for relapsed multiple myeloma.'' New England Journal of Medicine 352.24(2022): 2487-2498.

13. Searle, E., *et al.* (2022). ''Promising results in Newly Diagnosed and Relapsed/Refractory Multiple Myeloma.'' Cancer Therapy Advisor.

14. S. Mainier., *et al* (2024). Elderly patient with newly diagnosed multiple myeloma: Continuous or fixed duration treatment.'' Hemato 2, 5(2), 115-118; https://doi.org/10.3390/hemato5020010

15. https://www.cancer.org/cancer/types/multiple-myeloma/about/key-statistics.html#:~:text=The%20American%20Cancer%20Society's%20estimates%men%20and%205%2C520%20in%20women).

16. Cowan AJ, Allen C., *et al.* ''Global Burden of Multiple Myeloma'': A Systematic Analysis for the Global Burden of Disease Study 2016. JAMA Oncol. 2018 Sep 1;4(9):1221-1227. doi: 10.1001/jamaoncol.2018.2128. PMID: 29800065; PMCID: PMC6143021.