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Pharmacovigilance in Multiple Myeloma Care in Sub-Saharan Africa: A Review of Immunomodulatory Anti-myeloma Guidelines Using Kenyan AMPATH Framework

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Pharmacovigilance is a science that deals on the impact of therapeutic interventions (i.e., benefits and adverse effects) on the target body. In multiple myeloma treatment, it deals with the impact of anti-myeloma drugs on target patients through their risk assessment and risk management. This framework ensures safety and surveillance of anti-myeloma drugs administered to prospective multiple myeloma patients. Pharmacovigilance of anti-myeloma therapy is rarely instituted in the health institutions in sub-Saharan Africa due to late diagnosis and poor palliative care system in the region. The hallmarks are increased disability adjusted life-years, reduced quality adjusted life-years and average survival interval of people living with multiple myeloma in the region.
Aim: This study highlighted the safety measures undertaken by the healthcare professionals and multiple myeloma patients who are on immunomodulatory (Thalidomide and Lenalidomide) anti myeloma drugs to prevent or minimize adverse drug reactions.
Methodology: This study was a review of the guidelines for Pharmacovigilance using Kenyan AMPATH anti-myeloma pharmacovigilance brochures and other research database as literature sources. The paper was analysed and grouped according to the following categories namely the

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adverse drug reactions encountered with the use of anti-myeloma drugs and pharmacovigilance risk management programme (RMP) for immunomodulatory drugs (thalidomide and lenalidomide).
Results: The three major identified safety tools for effective pharmacovigilance of the anti-myeloma patient population were the healthcare professional workforce, safety guidelines brochures and safety forms for registration and documentation of impact of therapeutic interventions. The healthcare professionals are key players in the formulation of pharmacovigilance risk management protocols. The risk management starts with education of the healthcare providers and myeloma patients using guidelines brochures designated for the respective groups. The prescriber registration-, pharmacy registration-, treatment initiation-, prescription authentication-, and adverse drug reaction forms are the essential safety working documents that are needed to be completed by the patient and healthcare professionals for effective monitoring and evaluation. Both the healthcare provider and the myeloma patient are expected to adhere strictly to the safety measures enshrined in the pharmacovigilance guideline brochures. The patient's anti-myeloma safety measures are stratified into female of child bearing age, women above the child-bearing age and the male sub-population.
Conclusion: In setting up a comprehensive multiple myeloma care centre, an effective pharmacovigilance program is paramount. This requires healthcare professional workforce, safety guidelines brochures and safety forms for registration and documentation of impact of therapeutic interventions. Policy formulation, sustainable drug availability and collaboration with support groups are vital tools to drive this operative framework in underserved settings of sub-Saharan Africa.

Keywords: Multiple myeloma; pharmacovigilance; risk assessment; risk management programme; thalidomide; lenalidomide (revlimid).

ABBREVIATIONS

ADRs: Adverse Drug Reactions; AEs: Adverse Effects; AJOL: African Journal Online; AMPATH: Academic Model Providing Access to Healthcare; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CNS: Central Nervous System; DALY: Disability Adjusted Life-Years; HCPs: Healthcare Providers; HIC: High-income country; IMiDs: Immunomodulatory Drugs; LIC: Low-Income Country; MeSH: Medical Subject Heading; MM: Multiple Myeloma; PLWMM: People Living With Multiple Myeloma; PV: Pharmacovigilance; PIDM: Program for International Drug Monitoring; QALY: Quality Adjusted Life-Years; RMP: Risk Management Program; REMS: Risk Evaluation Management Strategy; SSA: Sub-Saharan Africa; USA: United States of America; WHO: World Health Organization.

1. INTRODUCTION

MM is a plasma cell malignancy in which monoclonal plasma cells proliferate in bone marrow, resulting in an overabundance of monoclonal paraprotein (M-protein), destruction of bone, and displacement of other hematopoietic cell lines [1].

Treatment of the disease consists of chemotherapy, antiangiogenic agents, IMiDs, and autologous stem cell transplants [2]. The AEs of anti-myeloma therapies are sometimes grave challenges to patients with consequent impact on the QALYs and DALYs. Many of these effects go unnoticed, ignored or simply accepted as divinity in the disease course.

PV is the science and activities relating to the detection, assessment, understanding and prevention of AEs of medicine/vaccine-related problem [3]. The aims of PV are to enhance patient care and patient safety in relation to the use of medicinal products; and to support public health programmes by providing reliable, balanced information to assess the risk-benefit profile of medicines [4-5].

Monitoring the safety of drugs is particularly important in oncology, due to the intrinsic biologic toxicity of antineoplastic agents, their narrow therapeutic windows, and the high doses and rigid timing of treatment regimens [3-5].

Every chemotherapeutic agent deployed for MM care expectedly undergoes safety and efficacy assessment (clinical trial) before being deployed for clinical usage. This regulatory mechanism of monitoring ensures that drugs safety outweighs their AEs. Improving identification of ADRs is critical in the care of MM as this helps to improve the survival outcome. Therefore, PV is imperative in MM care in the developing Africa as it is world over.

The WHO PIDM has enshrined PV as a global best practice with collaborative advances advocated worldwide that may promote timely identification of suspected problems in medicinal products. As at the year 2021, about 170 countries were enlisted members of the WHO PIDM [5-6].

The importance of PV in oncology generally is highlighted with every effort, to improve safety and offer cancer patients every possible help to improve their quality of life during such a critical period of their lives [3,7]. Starting from the tragedy of thalidomide in the 1960s, the field of PV has developed into an international superstructure that promotes the surveillance of drugs for human use [3]. PV is today structured in complex communication systems, registries and databases. It is the fundamental approach for the early detection of new signals of risk for patients taking drugs. PV involves the detection and spontaneous reporting of ADRs occurring during drug therapy. It can achieve its goal—the safety of drugs—only if its methods are carefully and continuously applied. For this reason, the complete involvement of all HCPs is required, and patient education and involvement are also necessary. The contribution of PV has been, and continues to be, of paramount importance in recognizing the risks associated with treatments and being able to intervene promptly [3-6].

Studies suggest that haematological malignancies constitute significant cancer mortality and morbidity and impacting on the health and economy of many developing countries of Africa. Amongst these, MM is remarkable with a projected mortality of 91% by 2030 [7-9]. In spite of these indicting reports in Africa, cancer has been given low priority in the research field and health care services and only few countries have incorporated PV in the care of MM patients [10]. There is a need to deploy strategies to improve the care of patients in the developing Africa especially from internationally developed programs that have proven to be effective in similar countries in the region.

1.1 Study Aims

This study aimed: To highlight the safety measures undertaken by the HCPs and MM patients who are on IMiDs (Thalidomide and Lenalidomide) to prevent or minimize their ADRs.

To educate the public health providers on how to set up a RMP for IMiDs (Revlimid and Thalidomide) using the Kenyan AMPATH framework.

2. METHODOLOGY

The articles on PV in relation to chemotherapies, radiotherapy and targeted therapies were searched in PubMed, using MeSH terms and text words. The Scopus, AJOL, CINAHL, Embase, Micromedex, the Cochrane Library and the gray literature for articles related to the topic were also searched.

The Kenyan AMPATH RMPs for IMiDs (Thalidomide and Lenalidomide) were identified, studied and stratified into safety pamphlets (brochures), risk management safety forms and ADRs forms.

There was a narrative review of the PV REMS, under Kenyan AMPATH for MM patients, as a core component for establishment of comprehensive MM care centre in underserved setting.

The results section was analysed and grouped into the PV HCPs workforce, the safety pamphlets, the safety forms, the ADRs checklists, (encountered with the use of anti-myeloma drugs) and PV RMP (for IMiDs such as thalidomide and lenalidomide).

3. RESULTS

The three major identified safety tools for effective pharmacovigilance of the anti-myeloma-patient population were the HCPs workforce (Table 1), safety guidelines brochures (Table 2) and safety forms for registration and documentation of impact of therapeutic interventions (Table 3).

The REMS for MM patient on IMiD is a safety measure developed by AMPATH in collaboration with a drug company in the USA to prevent these patients from the teratogenic (embryofoetal) ADRs of IMiDs.

The safety guidelines brochures: These provide guidelines on safety measures. These are the first instruction pamphlets given to the HCPs (Prescriber, Physician, Nurse, Pharmacist, Pharmacist assistant) and the MM patient to study as soon as they register in the PV unit. The HCP brochure guides the practitioner on the basic safety measures required to teach the

patient who is on anti-myeloma therapy (''the do and don't'' acronyms) while the patient brochure teaches the patient the ADRs of the IMiDs and how they can be prevented. The risk evaluation starts with both HCPs and the patient target group adhering strictly to the guidelines in these pamphlets. The patient's anti-myeloma safety measures are stratified into female of child bearing age, female above the child-bearing age and male gender. The essential safety requirements include signing treatment initiation form and avoidance of blood donation during treatment. Other requirements stipulate that the female must be birth control compliant, pregnancy negative and must not breastfeed during treatment with thalidomide or lenalidomide, while the male must use condom during sexual activities while on treatment. The HCP brochure guides the HCPs on safety measures required while prescribing or dispensing the IMiDs. The requirements from the HCPs include a) Provision of appropriate contraception throughout IMiD therapy, b) Retrieval of residual supplies of drugs from close contacts of deceased to avoid accidental poisoning, c) ADRs monitoring, d) Enforcement of adherence, e) Look out for teratogenicity/embryofoetal malformation, f) Periodic awareness creation on the risks of IMiD agents for the old and new HCPs, g) Documentation into the five safety forms (Table 3).

Table 1. PV HCPs workforce

1. Oncology Director (Hemato-Oncologist)
2. Physician (Prescriber)
3. Clinical Pathologist
4. Pharmacist (Dispenser)
5. Nurse
6. Social Worker
7. Palliative Care team

Table 2. Safety guidelines brochures for HCPs and MM patient target population

1. Patient
• Pre-menopausal Female Patient
• Post-Menopausal Female Patient
• Male Patient
2. HCPs
• All HCPs workforce registered with PV unit

The safety forms: Five essential forms in REMS useful in RMP are prescriber registration form, pharmacy registration form, treatment initiation form, prescription authentication form, and adverse drug reaction forms. These are the essential safety working documents that are needed to be completed by the patient and HCPs for effective monitoring and evaluation of the drug safety and ADRs on MM patients (Table 3).

Table 3. The 5 safety forms used in PV REMS for IMiDs

1. Prescriber registration form
2. Pharmacy registration form
3. Treatment initiation form
4. Prescription authentication form
5. Adverse drug reaction form

4. DISCUSSION

PV is a health protective and quality preserving measure for PLWMM who are on cancer chemotherapeutic interventions. It impacts strategically on the predictive markers (DALYs and QALYs) of ALE of cancer survivors).

Effective PV system depends on human capacity development, strong capacity of health facilities, strong laboratory capacity, REMS, active survivorship support group, active collaborators, social insurance advocacy group, periodic education and awareness campaign, operational frameworks for researching and diffusion of innovation (Fig. 1).

The AMPATH for MM care in Kenya was developed to improve the survival outcome of MM patients in SSA countries [11]. It was established in 2012 through the support of Celgene and Kenya was one of the first countries in SSA to introduce a comprehensive PV REMS for the care of MM patients [11]. PV as a safety measure has the capacity to address the disparity in survival intervals (5-years post diagnosis survival intervals) of PLWMM in LIC (7.6% -15%) and HIC (50.7%) [12].

The AMPATH model involves globalization of ideas, human capacity development in diagnosis and care of patients including the prompt provision of advanced technological diagnostic infrastructures, new and target anti-myeloma agents. It also includes the development of PV protocols, health insurances and peer pressure support groups for MM target population in collaboration with HICs like the United States of America (USA) and other North American

countries [11-14]. This collaboration is lacking in most African union member countries. This collaboration came up with a strategic leadership approach of identifying and preventing ADRs including embryofoetal malformations associated with IMiD anti-myeloma agents in MM patients, otherwise known as REMS [15].

Table 4. ADRs checklist showing the systemic adverse effects of IMiDs

The ADRs of IMiD anti-myeloma agents are systematically categorized under:

1. Gastrointestinal AE: abdominal pain, mouth sores, metallic taste, anorexia, nausea, vomiting, constipation, diarrhoea, heart burn, haemetemesis, haematochezia
2. CNS AE: headache, hearing loss, dizziness, numbness, peripheral neuropathy, photosensitivity, etcetera.
3. Respiratory AE: dyspnea, cough, chest pain, etcetera.
4. Cutaneous AE: skin rash, alopecia, etcetera.
5. Haematological AE: anaemia, neutropenia, thrombocytopenia, bleeding diathesis.
6. Renal: Deranged renal function test
7. Cardiovascular:
8. Dyslipidaemias: Deranged Fasting lipid profile
9. Liver dysfunctions: Deranged Liver transaminases or serum bilirubin levels.

However, the main adverse effects of thalidomide and bortezomib are peripheral neuropathy and neutropenia while diarrhoea and constipation are commoner with bortezomib and thalidomide respectively [6]. The clinical indicators of these adverse effects are shown in the adverse drug reaction form of the risk management protocol (RMP) PV form.

Table 5. RMP Checklists for IMiDs Anti-myeloma

The REMS of IMiD Anti-Myeloma Agents (Lenalidomide (Revlimid)^{R} and Thalidomide) are summarized in the RMP checklist, and this contains all the vital information in the safety forms

1. The ‘’AMPATH treatment initiation form for patients starting with lenalidomide’’ is given to him for completion before handing him over to the prescriber or physician.
2. The physician completes the ‘’lenalidomide prescriber registration form’’ to enrol in the lenalidomide RMP.
3. The physician completes a ‘’lenalidomide treatment initiation form’’ to register the patient in the lenalidomide RMP and obtain a Unique Patient Identification Number (UPIN).
4. The physician communicates the benefits and risks of lenalidomide therapy to the patient.
5. The physician councils the patient on the risk of exposing an unborn baby to lenalidomide and what the patient must do to minimize the risk.
6. The physician provides the patient with a ‘’lenalidomide RMP patient brochure’’ and issue the patient with a ‘’Lenalidomide Prescription Authorization Form’’ including the UPIN on the form with each lenalidomide script.
7. The physician should perform a pregnancy test (if appropriate) prior to each prescription.
8. The physician should remind the patient on the safe use of lenalidomide.
9. Once the patient is done with the prescriber or physician, he is handed over to the pharmacist or pharmacy assistant).
10. The pharmacist completes the ‘’lenalidomide pharmacy registration form’’ to enrol in the ‘’lenalidomide RMP.’’
11. The pharmacist checks and validates the lenalidomide script and the ‘’Lenalidomide Prescription Authentication Form’’ and send it to AMPATH Oncology Director.
12. The pharmacist dispenses a patient’s lenalidomide only after obtaining AMPATH Oncology Director Approval.
13. The pharmacy should dispense no more than a 4-week (28 days) supply of lenalidomide for women of child-bearing age or a 12-week (84 days) for all other patients.
14. The pharmacist should dispense further prescriptions only if fewer than 7 days of therapy remain on the previous prescription.

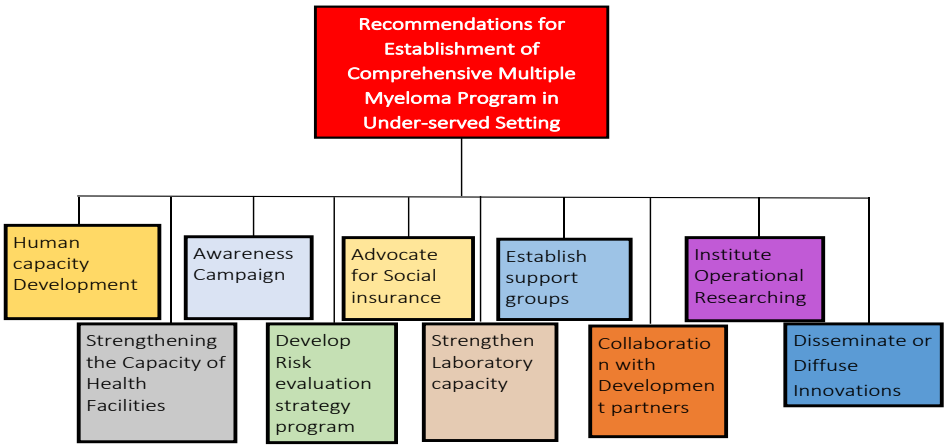

Fig. 1. The component units of a MM comprehensive care centre in underserved setting

The anti-myeloma agents registered under the AMPATH program include melphalan, thalidomide, lenalidomide, bortezomib, cyclophosphamide, dexamethasone, prednisolone and zoledronic acid [16]. These drugs are strictly under the care of the PV pharmacist (or assistants and nurses).

The PV team has a guideline on the line of anti-myeloma regimen administered to MM patients. Drug costs, income status of the patients, disease stage and previous anti-myeloma therapeutic regimen are considered in decision-making on choice of therapy [11,17]. Given this consideration, the standard lenalidomide-bortezomib-dexamethasone which is the first-line anti-myeloma therapy in HICs remains a second-line in many underserved SSA. The weak social insurance system in SSA has worsen the access to cancer chemotherapy in the target population. However, this is partially captured by the Kenyan AMPATH program and very few SSA countries [18].

In order to avoid non-compliance or drug abandonment by the MM patients, a survivorship support initiative could be a strategic leadership approach. The survivorship support initiative together with prevention of risk factors contributing to drug abandonment such as drug AEs, lack of family support, lack of funding to access the medication and flare for alternative (herbal) medication are the elements of good compliance to cancer chemotherapy [16,19-21].

5. CONCLUSION

An effective PV program is paramount in setting up a comprehensive MM care centre in SSA. This requires HCPs workforce, safety guidelines and safety documents for registration and recording the impact of therapeutic interventions. Policy formulation, sustainable drug availability, effective RMP and collaboration with support groups are vital tools to drive this operative framework in underserved settings of SSA. This form of cancer care is given low priority in research fields and health care services and only few countries have incorporated it in the care of MM patients in SSA. We strongly recommend that the Kenyan AMPATH framework could provide a useful template of quality improvement in other African Union member countries.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Dimopoulos M, Kyle R, Fermand JP, Rajkumar SV, San Miguel J, et al. Consensus recommendations for standard investigative workup: Report of the international myeloma workshop consensus panel 3. Blood. 2011;117(18): 4701-5.

2. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008; 111:2516–2520.
   DOI: 10.1182/blood-2007-10-116129
3. Paolo Baldo, Giulia Fornasier, Laura Ciolfi, Ivana Sartor, Sara Francescon. Pharmacovigilance in oncology International Journal of Clinical Pharmacy. 2018;40: 832–841.
4. Pharmacovigilance – World Health Organization (WHO).
   Available:https://www.who.int/teams/regulation-prequalification/regulation-and safety/pharmacovigilance
   (Accessed date: 25th September, 2022).
5. Programme for international drug monitoring- World Health Organization (WHO).
   Available:https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info/pidm
   (Accessed Date 24th September, 2022)
6. Castro TBM, Hallack Netro AE, Atalla A, et al. Pharmacovigillance of patients with MM being treated with bortezomib and/or thalidomide. Braz J Med Biol Res. 2016; 49(6).
   Available:https://doi.org/10.1590/1414-431X20165128
7. Satish G, William AW, Stephanie JL, Thomas CS, Kikkeri NN, Peter NK, Corey C, Peter BH, Ronald TM. Meeting the challenge of hematologic malignancies in sub-Saharan Africa. Blood. 2012;119(22): 5078–5087.
   DOI: 10.1182/blood-2012-02-387092
8. Ugwu NI, Okoye AE, Ugwu CN, Iyare FE, Edegbe FO, Ugwu GC, et al. Distribution pattern and prevalence of haematological cancers among adults in abakaliki, south-eastern Nigeria. Niger Postgrad Med J. 2021; 28:266-72.
9. Leak SA, Mmbaga LG, Mkwizu EW, Mapendo PJ, Henke O. Hematological malignancies in east Africa—Which cancers to expect and how to provide services. PLoS ONE. 2000;15(5): e0232848.
   Available:https://doi.org/10.1371/journal.pone.0232848
10. Hamdi Y, Abdeljaoued-Tej I, Zatchi AA, Abdelhak S, Boubaker S, Brown JS, Benkahla A. Cancers in Africa: The untold story. Front. Oncol; 2021.
    Available:https://doi.org/10.3389/fonc.202.650117
11. Oduor MA, Lotodo TC, Vik TA, Manyega KM, Loehrer P, Omondi AA, Oguda JO, Asirwa FC. Building a sustainable comprehensive multiple myeloma program in western Kenya. JCO Global Oncology. 2021;7(1):40-7.
12. Nwabuko OC. Chikezie JA, Ejele OA. Public health. approach on multiple myeloma prevention in Nigeria. J blood Lymph. 2018;8:229.
    DOI: 10.4172/2165-7831.1000229
13. Ministry of Health: Kenya national cancer treatment protocols. Nairobi, Kenya, Government of Kenya; 2019.
14. Strother RM, Asirwa FC, Busakhala NB, et al. The evolution of comprehensive cancer care in western Kenya. J Cancer Policy. 2013;1:25-30.
15. Topazian H, Cira M, Dawsey S, et al. Joining forces to overcome cancer research and control stakeholder program. J Cancer Policy. 2016;7:36-41.
16. Kugo L, Oduor M, Chite F. A pharmacy-led pharmacovigilance program for multiple myeloma patients at the moi teaching and referral hospital: A five-year experience. J Oncol Pharm Pract. 2019; 25(suppl 039).
17. Nwabuko OC. Management of MM in developing countries. Intechopen Available:https://dx.doi.org/10.5772/intechopen.76500
18. Barasa E, Rogo K, Mwaura N, Chuma J. Kenya national hospital insurance fund reforms: Implications and lessons for universal health coverage. Health System & Reform. 2018;4(4):346-361.
    DOI: 10.1080/23288604.2018.1513267
19. Fairley TL, Pollack LA, Moore AR, Smith JL. Addressing cancer survivorship through public health: An update from the center for disease control and prevention. J Women Health. 2009;18(10):1525-1531.
    DOI: 10.1089/jwh.2009.1666
20. Moore AR, Buchanan ND, Fairley TL, Smith JL. Public health action model for cancer survivorship. American J Prev Medicine. 2015;49(6):470-476.
    Available:https://doi.org/10.1016/j.amepre.2015.09.001

21. Underwood JM, Townsend JS, Stewart SL, et al. Surveillance of demographic characteristics and health behaviours among adult cancer survivors- Behavioural Risk Factor Surveillance System, United States, 2009. MMWR Surveill Summ. 2012;61(1):23.

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