



Review Article

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Haematological Malignancies in Nigeria: Challenges in Diagnosis and Management – A Systematic Review

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ABSTRACT

Haematological malignancies are major cause of mortality and morbidity worldwide. The aim of this review was to summarize some of the challenges that hamper proper diagnosis and management of haematological malignancies in Nigeria and how they affect outcome. MEDLINE Entrez PubMed, Google scholar and African Journals Online (AJOL) search were performed in April 2020 and studies that investigated challenges in diagnosis and management of haematological malignancies from 2005 to 2019 were sought. Search keywords included “haematological malignancies, challenges, Nigeria”. Only studies that provided information on the challenges of diagnosis and management of haematological malignancies in Nigeria were eligible and were selected. Inclusion criteria were original scientific investigations or case reports, not reviews, studies conducted in Nigeria between 2005 and 2019 and studies written in the English language. A total of eight relevant studies that fulfilled the study inclusion criteria were identified out of 4,129 studies found. Challenges of diagnosis and management of haematological malignancies reported by the studies include late presentation of patients in advanced stage of disease, inability to pay for investigations and/or treatment due to financial constraint, wrong/ delayed diagnosis due to poor diagnostic facility such as use of only morphology for histological diagnosis without immunohistochemistry and poorly equipped health facilities to manage haematological malignancies. Poor outcome as a result of those challenges were also reported by the studies. Awareness creation and education on the importance of early presentation to health facility should be encouraged. Health system should be strengthened by including haematological malignancies in National Health Insurance and providing well equipped health facility for proper diagnosis and management of haematological malignancies.

Keywords: Challenges, Diagnosis, Haematological Malignancies, Leukaemia, Lymphoma. .

INTRODUCTION

Cancer is a malignant disease condition resulting from uncontrolled division of cells of the body to form abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change.¹ The cancer cells have the capacity to infiltrate adjacent or surrounding structures or spread to distant sites in the body where they can continue proliferating in an uncontrolled manner, causing damage to the affected structures or organs.² Cancer is a major cause of death and disability in Nigeria and other developing countries, where health systems are poorly equipped to handle the problem.³ Despite the growing burden, cancer is not receiving adequate attention from policy makers. This could be due to either limited resources, the burden of communicable diseases or other pressing public health problems, lack of awareness about the magnitude and burden of the disease or lack of political will.⁴

Hematological malignancies are a group of cancers that arise from a malignant transformation of cells of the bone marrow or lymphatic system.⁵ They can be classified by immunologic, cytogenetic and molecular genetic methods into myeloid or lymphoid, based on their origin and into acute and chronic depending on their clinical course.⁶ These cancers include but not limited to leukaemias, lymphomas and myeloma.⁷

Haematological malignancies has been reported to represent about 6.5% of all cancers worldwide in 2012.⁸ It is the fourth most frequently diagnosed cancer in both men and women in developed countries of the world.⁷ The aetiology of haematological cancers is not known. However, some factors have been identified to increase the risk of their occurrence. Such factors include infections with viruses such as human immunodeficiency virus (HIV), Epstein Barr virus, human T-lymphotrophic virus; chronic bacterial infection like *Helicobacter pylori*; immunosuppression or immunodeficiency states, radiation and chemicals such as benzene.⁹⁻¹⁴ These factors are thought to be involved in a complex interplay of genetic damage in somatic cells as a result of mutations, cytokine dysregulation and chronic antigenic stimulation resulting in development of these malignancies.¹⁵ The incidence of haematologic malignancies has been shown

to vary according to age, gender, geographic region, and histologic subtypes, while cure rates can vary according to region and may be impacted by prompt and accurate diagnosis, treatment availability and access to care.^{16,17}

Haematologic malignancies are major burden to afflicted patients and their families medically, financially and psychologically.^{18,19} The cost of managing these disorders are very expensive. Individuals diagnosed of these diseases receive treatment through out of pocket expenses and are therefore unable to commence, continue or complete treatment as a result of financial constraint. For those who successfully completed the recommended regimen, family income are depleted.²⁰

The outcomes in hematologic malignancies can vary by time of presentation, stage of the disease at presentation, type of the disease, other co-morbidities, availability and quality of diagnostic facilities, availability of qualified manpower, availability and affordability of drugs, availability and access to palliative and supportive medical care.^{21,22}

In Nigeria there is a wide gap between cancer burden and a comprehensive cancer control program, with inadequate provision for accurate diagnosis, chemotherapy, radiotherapy and palliative/ supportive care. This review aimed to summarize some of the challenges that hamper proper diagnosis and management of haematological malignancies in Nigeria and how they affect outcome.

MATERIALS AND METHODS

A systematic literature search was carried in PubMed, Google scholar and African Journal Online (AJOL) in April 2020 and studies which investigated challenges of diagnosis and management of haematological malignancies in Nigeria were sought. The authors independently searched the databases and selected studies from Nigeria undertaken from January 2005 to December 2019 which met the inclusion criteria. The following were the search keywords used: "haematological malignancies, challenges, Nigeria," which yielded total of 4,129 publications as at April 2020. The following study inclusion criteria were used: i) studies conducted in Nigeria between 2005 and 2019. ii) Original scientific investigations and case reports, not reviews. iii) Studies conducted which determined the challenges of diagnosis and management of haematological cancers. iv) Studies written in the English language. Studies that did not meet

these criteria were excluded.

Search with PubMed yielded two publications out of which one met the inclusion criteria; AJOL yielded 127 publications out of which only one met the inclusion criteria, Google scholar yielded 4000 publications out of which eight met the inclusion criteria (the one publication each from PubMed and AJOL were also part of the eight publications selected from google scholar) [Figure 1]. Out of the total of 4129 publications found, eight were noted to have met the study inclusion criteria and were selected for review [Figure 1].

Subsequently, the references of all the resulting eight publications were hand-searched for additional studies and information relevant to the review. Publications that did not completely fulfill the study inclusion criteria but adjudged to contain vital information necessary for the narrative aspect of the review were selected and used accordingly. The selected publications were then grouped according to the following: author(s)/year of publication, state where the research took place, study design, evidence generated/outcome from the study, and policy implication of the study including the recommendations.

RESULTS

The eight studies identified to have met the study inclusion criteria were used for this review. The outcomes of the review were presented in this session using table [Table 1]. Challenges of diagnosis and management of haematological malignancies reported by the selected publications²³⁻³⁰ include: late presentation of patients in advanced stage of disease, difficulty in diagnosis / misdiagnosis due to use of only morphology for histological diagnosis without immunohistochemistry, inability to pay for investigations and/or treatment due to high cost of cytotoxic drugs and financial constraint associated with poverty as well as lack of well-equipped facilities to manage haematological malignancies. There were poor outcome such as signing/ withdrawal against medical advice due to financial constraint to continue with treatment with increased morbidity and mortality.

Table 1

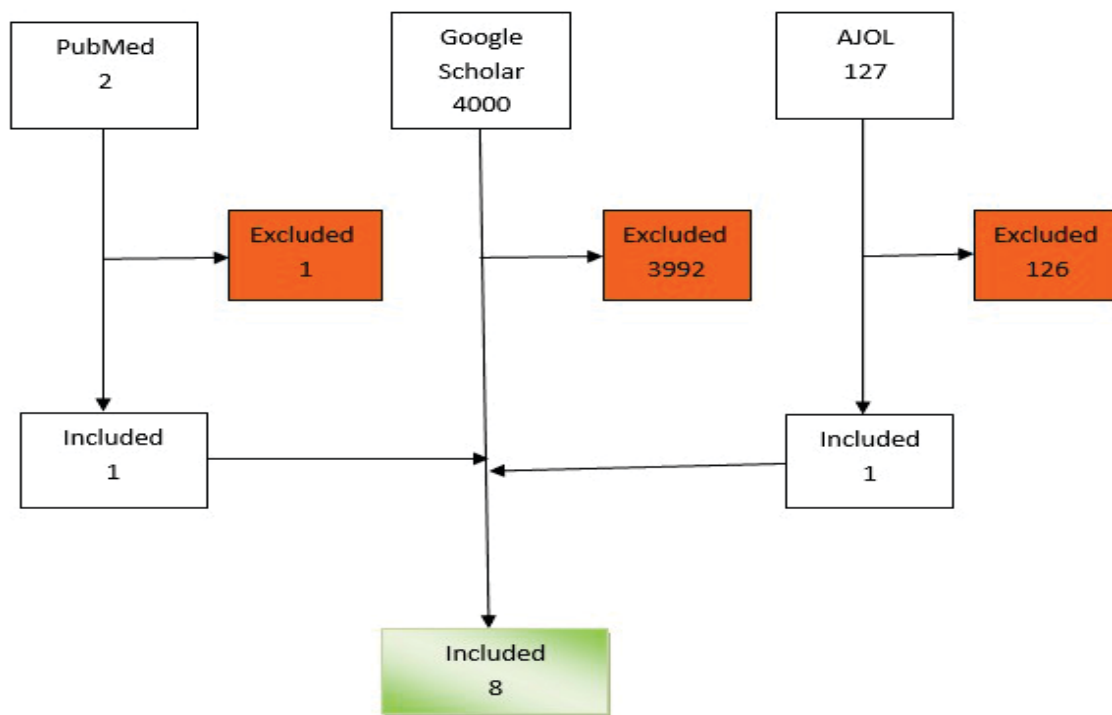


Figure 1: Flow chart of publication identification and selection process

Table 1: Profile and characteristics of scientific publications that assessed the challenges of diagnosis and management of haematological malignancies.

Author/year of publication	Location/ state	Study design	Results of challenges generated/ outcome	Recommendations/ policy implication
Akinde <i>et al</i> , 2016	Lagos/ Lagos State	Cross sectional study	Difficulty in diagnosis and classification lymphomas due to use of only morphology without immunohistochemistry. Out of the 116 cases of lymphomas, only 32 (27.6%) were correctly diagnosed and subtyped by morphology alone, 53 (46%) were diagnosed to be lymphomas but could not be subtyped by morphology, 19 (16.4%) were wrongly subtyped while five cases of reactive lesions were wrongly diagnosed as malignant lymphomas.	Need for additional immunohistochemistry to refine diagnosis and subtyping of lymphomas.
Fasola <i>et al</i> ; 2008	Ibadan/ Oyo State	Retrospective study	The challenges reported were late presentation of patients in advanced stage of multiple myeloma and economic constraint. Out of 64 patients with multiple myeloma, 65% presented at stage 3 Durie and Salmon staging, 72% had basic investigations required for diagnosis and treatment.	Health insurance for multiple myeloma to reduce economic burden of the disease on patients and improve outcome.
Mmeremikwu <i>et al</i> , 2005	Calabar/ Crossriver State	Retrospective Study	Out of the 41 children with Burkitt Lymphoma, half presented in late stage of the disease. A quarter of the children could not afford confirmatory test. A fifth of the patients receive no chemotherapy because of inability of their parents to pay. Thirteen (31.7%) of the parents withdrew their children against medical advice due to financial constraint.	Establishment of a regional Burkitt Lymphoma programme in Africa to help establish a critical mass of resources (human and material) to facilitate the development of an effective and accessible control programme in the region.
Adefehinti <i>et al</i> , 2015	Ile Ife/ Osun State	Case report	A case of 9-year-old girl with primary cardiac lymphoma. Received only two courses of chemotherapy out of the recommended six courses due to inability of her parents to pay for the remaining courses. This resulted to poor prognosis and early fatality.	Health insurance scheme to cover the informal sector and children with cancers.
Amiwero <i>et al</i> , 2011	Bida/ Niger State	Case report	A case of 5-year-old girl with lymphoblastic lymphoma. Some of the challenges identified as constraints leading to inadequate management with poor outcome include socio-cultural, financial (for both investigative and therapeutic interventions), inadequate resources and facilities.	Government and Non-governmental agencies to strengthen and upgrade the existing facilities so as to meet the demand of patients with cancer by providing funding and up-to-date equipment. Implementation of health policy that could benefit cancer patients.

Table 1: Continued

Asuquo <i>et al</i> , 2014	Calabar/ Crossriver State	Retrospe ctive study	<p>High cost of managing haematological malignancies constitute a major contributing factor to poor compliance and survival.</p> <p>Cost of care ranged from USD192.94 to 846.35 for cytotoxic regimen and USD 12,400.59 to 124,699.41 for targeted regimen. Multiple myeloma USD 916.47 to 3,061.77 for cytotoxics and USD 39,870.59 for targeted drugs. Acute leukaemia patients USD 240.00 to 1,058.20 for Cytotoxics. Chronic leukaemias USD 194.12 to 3,411.77 for cytotoxics and USD 12,400.59 to 12,352.94 for targeted regimen. Diagnostic work up and follow up expenditure ranged from USD 1,110.59 to 1,878.90. Patients will require USD 947.41 to 1,801.48 for supportive care.</p> <p>Average minimum wage is USD105.88/month.</p> <p>The patient's family was the main source of funding for treatment followed by sale of personal and family assets.</p>	Discourage out-of-pocket expenditure for managing haematological malignancies but rather inclusion either whole or partly into national health insurance scheme.
Nwabuko <i>et al</i> , 2015	Umuahia/ Abia State and Port Harcourt/ Rivers State	Retrospe ctive study	<p>Late presentation as 61.5% and 30.8% of 26 patients with multiple myeloma presented in stage III and II Durie and Salmon clinical staging system respectively. Only 7.7% presented in stage I. There was also delayed diagnosis as majority will first present to Orthopaedic clinic due to bone pain which is common as 84.6% of the patients presented with bone pain.</p>	Adoption of measures that will encourage early referral of suspected cases via continuous medical education of health care providers on how to elicit early diagnosis of myeloma.
Korubo <i>et al</i> , 2019	Port Harcourt/ Rivers State	Retrospe ctive study	<p>Limitation on the number of investigations done to aid diagnosis as only 3.1% of 129 patients they studied were able to do immunophenotyping due to high cost. Unavailability and unaffordability of novel drugs. None of the patients received stem cell transplantation as part of treatment due to cost. Mean total monthly cost of cytotoxic drug per patient was N69,321.21 ±84,686.43 (USD189.92 ±232.02). About a third of the patients did not receive any form of chemotherapy due to financial constraints, early mortality or being lost to follow up.</p>	<p>Widespread coverage of healthcare insurance to reduce out-of-pocket expenditure for people who develop hematological cancers.</p> <p>Improved government funding of the health sector, including provision of better diagnostic facilities at affordable rates as well as provision novel drugs for treatment.</p>

DISCUSSION

The findings of this review showed that there was poor outcome of haematological malignancies due to challenges in diagnosis and management. Out of the total of 4,129 publications found from the PubMed, Google scholar and AJOL search related to challenges of diagnosis and management of haematological malignancies in Nigeria, only eight (0.19%) fulfilled the inclusion criteria. This finding suggests that inadequate number of research relevant to haematological malignancies has been undertaken in Nigeria. This may be due to less attention given to haematological cancers in Nigeria.

Challenges of diagnosis and management of haematological malignancies reported by the studies include: late presentation of patients in advanced stage of disease, misdiagnosis due to poor use of only morphology for histological diagnosis without immunohistochemistry, high cost of cytotoxic drugs and inability of the patients to pay for investigations and/or treatment due to financial constraint and lack of well equipped facilities to manage haematological malignancies.

Mmeremikwu *et al*,²⁴ reported that 50% of patients with Burkitt lymphoma presented in late stage of the disease. Some of the patients (26.8%) were reported to have consulted traditional or spiritual healers while 31.7% sought help from unorthodox practitioners and drug sellers before presenting to the hospital. Late presentation was also observed by Fasola *et al*,²⁵ in a study conducted among patients with multiple myeloma and reported that 65% of the patients presented in stage 3 of Durie and Salmon staging. Similarly, Nwabuko *et al*,³⁰ reported that 30.8% and 61.5% of patients with multiple myeloma they studied presented in stage II and III disease respectively. Patients with malignancies in resource-limited settings have been documented to present late with consequent adverse outcome.³¹⁻³³ The reasons for the late presentation in our setting are multi-factorial and include: patient factors such as ignorance and apathy to seek medical attention;³⁴ self-medication with over the counter drugs;³⁵ herbal medication from herbalist which may leave the patients with renal and/or hepatic complications;³⁶ spiritual healers and in extreme cases superstitious belief by laying blames on witches, ancestors or enemies.³⁷ Other reasons include delays in referral, paucity of

adequate screening, diagnostic and therapeutic facilities.³⁸ Studies have reported that low level of awareness of haematological malignancies among health care providers at all levels of health care and misdiagnosis could be another reason for late presentation.^{39,40} The poor health-seeking behaviour is related to ignorance and concern about cost of care in hospitals. Late presentation has been found to be associated with increased mortality, but early detection and referral has been reported to result in better outcome.^{41,42} The problem of late presentation is not unique to Nigeria but also a challenge in other developing countries. Acquah *et al*, in a study conducted among 169 patients with multiple myeloma in Ghana reported that one third of the patients waited for over one year after onset of symptoms before presenting to the health facility and 51.3% of the patients were diagnosed in stage III of International Staging System (ISS).⁴³ Similarly, Samrawit and Wudeneh in a study conducted among cancer patients in Ethiopia reported that 41.7%, 59% and 42.6% of female patients with cervical, breast and ovarian cancers respectively presented in advanced stage of disease. Among males, 46.7% and 29% of patients with prostate and colorectal cancers respectively presented in advanced stages at the time of diagnosis.⁴⁴ This is contrary to what obtains in developed countries where presentation is mostly at early stage. Howell *et al*, in a study conducted among patients with haematological cancers in England found that only 16% of the patients waited for more than three months after onset of symptoms before seeking medical help.⁴⁵

Another factor reported to be a challenge in management of haematological malignancies is difficulty in diagnosis / misdiagnosis due to inadequate diagnostic facility. Akinde *et al*,²³ in a study conducted in Lagos to determine the challenges of lymphoma diagnosis reported that only 27.6% of lymphomas were correctly diagnosed histologically and subtyped, 46% were correctly diagnosed to be lymphoma but could not be subtyped while 16.4% were wrongly subtyped. They also reported that five cases of reactive/ benign lesions were wrongly diagnosed as malignant lymphomas. This was due to the fact that diagnosis and tumor classification was based purely on morphology alone due to lack of the necessary ancillary diagnostic facilities for specialized techniques such as immunohistochemistry, immunophenotyping and so on. The consequences of wrongly labeling a benign

condition as malignant has some adverse effect ranging from psychological/ emotional trauma to the unnecessary exposure of the patient to cytotoxic drugs, some of which can cause secondary cancers, wastage of the patients' resources in procuring cytotoxic drugs to other unnecessary treatment.^{46,47} Amiwero *et al*, also identified delayed diagnosis, misdiagnosis and proper classification of lymphoma as a challenge in management of haematological cancer due to inadequate resources and diagnostic facilities as their diagnosis and classification of a case of lymphoblastic lymphoma was based purely on morphology.²⁷ This is similar to findings in other developing countries where diagnostic challenges have also been reported. El-Mallawany *et al*, in a study conducted in Malawi among children with lymphoma reported some limitations in diagnosis as histological diagnosis was based only on morphology in addition to limited number of Pathologists available.⁴⁸ In developed countries, availability of modern diagnostic technique and equipment and availability of Pathologists make for easier, quicker, reliable and accurate diagnosis.⁴⁹ It is important to note that effective management of haematological cancers revolves around the availability of modern techniques required for early, accurate and precise diagnosis as well as availability and affordability of cytotoxic drugs.^{50,51} In situation where the diagnosis was eventually made, chemotherapeutic agents/cytotoxic drugs would be required to commence treatment, in addition to supportive care. Unfortunately, these drugs are expensive and are not readily available in the Nigeria.⁵² This unfortunate circumstance is undoubtedly forcing these patients, who might have benefited from these drugs, to seek for alternatives such as traditional healers or spiritualist and of course to early graves.

The cost of treatment was reported as a challenge to proper management of haematological cancers. Diagnosis and management of haematological malignancies results in significant socioeconomic burden for the patient and their family. Mmeremikwu *et al*,²⁴ reported that the cost of treatment is more than twice the minimum monthly wage for some of their patient who were state employees. Additionally, the income of subsistence farmers who constituted the majority of their patients was far less than the minimum wage of state employees. Korubo *et al*,²⁸ also reported high cost of care for patients with haematologic malignancies and majority were not able to receive

standard treatment due to cost. They also reported that none of their patients had health insurance and so all their expenditure was out-of-pocket and constituted a huge economic burden. In addition, Asuquo *et al*,²⁹ reported that patients and their families were the main source of funding for treatment. They also reported that high cost of managing hematologic malignancies constitute a major contributing factor to poor compliance and survival. Other studies outside Nigeria have also given similar reports.^{53,54} The cost of anti-cancer drugs is enormous and challenging in resource limited setting like Nigeria. Out of the total cost of managing haematological cancer, cytotoxic drugs have been noted to make up two-thirds of the cost of treatment.⁵⁵ Availability of necessary chemotherapeutic agents at affordable cost are vital for effective management of haematological cancers. World Health Organization has recommended universal health coverage with the aim making healthcare accessible to individuals irrespective of their financial status.⁵⁶ This can be achieved via health insurance. Presently only about 4%–5% of Nigerians have some form of government funded or private insurance.⁵⁷ Similar report has also been given by other developing countries. Martijn *et al*, in a study conducted in Kenya among children with Non-Hodgkins lymphoma reported that 73% of the patients had no health insurance at diagnosis.⁵⁸ In addition, the outcome of children with and without health insurance differ significantly as majority (58%) of children with health insurance had event-free survival while 44% of children without health insurance abandoned their treatment.⁵⁸ The situation is different in developed countries where availability of health insurance with more universal health coverage makes treatment of haematological malignancies less burden for the patients and their families with better outcome.⁵⁹

Following diagnosis, adequate treatment with cytotoxic drugs and supportive care leads to better outcome. However, this review found poor health outcomes among majority of patients with haematological cancers in Nigeria. Mmeremikwu *et al*,²⁴ reported that among the patients with Burkitt lymphoma they studied, 31.7% of the children did not receive chemotherapy because of inability of their parents to pay and were subsequently withdrawn against medical advice, presumably to die at home or to seek for help from traditional healers. They also noted that 18% of the children died while in the hospital and some

discharged survivors did not keep any follow up appointments. Poor prognosis and early fatality were also reported by Adefehinti *et al.*,²⁶ in a child with primary intracardiac lymphoma who received only two courses of chemotherapy out of the six courses recommended due to inability of her parents to pay for the remaining courses of chemotherapy. Amiwero *et al.*,²⁷ also reported poor outcome in a girl child with lymphoblastic lymphoma whose treatment was abandoned after receiving only one course of chemotherapy to which she responded well but did not represent in the hospital for completion of the remaining courses. Outcome of treatment in many parts of Nigeria remains sub-optimal for reasons ranging from poor health-seeking behaviour to poor economic status. Studies from other resource poor settings have also reported poor outcome.^{60,61} Financial difficulties associated with poverty and non-availability of health insurance, lack of awareness, belief for spiritual causes of illness by patients, lack of/ difficulty in accessing appropriate treatment and supportive care services such as cytotoxic drugs, blood and blood products are some of the challenges that could explain the outcomes obtained in this review. By meeting these challenges, the suffering of millions afflicted by haematological cancers will be mitigated and many of the patients will be transformed into long-term survivors.

CONCLUSION

Management Outcome of haematological malignancies in Nigeria is poor. This is due to challenges of diagnosis and management of haematological malignancies including late presentation of patients in advanced disease stage, inability to afford chemotherapy and supportive care due to poor economic status, high cost of treatment, difficulty/delay in diagnosis and classification of haematological cancers due to lack of adequate diagnostic facilities. There should be public awareness and education to enlighten the public on the need to adopt positive health seeking behavior and to seek medical care from good hospitals whenever they are sick. Government should subsidize the cost of diagnosis and management of haematological cancers, expand health insurance scheme to involve self employed individuals, provide up-to-date diagnostic equipment and ensure implementation of health policy that could benefit patients with

haematological malignancies.

Study limitation

Although we employed an extensive search strategy encompassing three of the most prominent databases it is possible that relevant publications were missed.

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