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Molecular Targeted Therapy in Patients with Haematological Malignancies Seen at a Suburban Teaching Hospital in the South-south Region of Nigeria

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Abstract

Background: Targeted therapy refers to agents that block the growth of malignant cells by interfering with specific targeted molecules needed for carcinogenesis and growth of tumors rather than by simply interfering with all rapidly dividing cells. Haematological malignancies (HM) are clonal haemopoietic disorders that arise as a result of varied genetic damages to several key biochemical pathways in cellular differentiation, proliferation and maturation. These pathways have the focus of a new generation of targeted therapy that have revolutionized the management of haematological malignancies. ***Methodology***: The study was a retrospective study carried out at Delta State University Teaching Hospital, Oghara. Participants were recruited consecutively as diagnosis were made. Data obtained were analysed using Statistical Package for the social sciences (SPSS) version 23. ***Results***: A total of 132 patients with haematological malignancies participated in the study. Males were 71 (53.8%) females were 61 (46.2%). 108 (81.8%) of the patients did not use molecular targeted therapeutic agents while 24 (18.2%) used. and 56.8% of the patients with haematological malignancies were dead at the end of follow-up. Financial constraints accounted for the reason 66 patients, (61.1%) did not use molecular targeted therapies while unavailability of the specific therapy within the country accounted for the reason why 42 patients (38.89%) could not access them. Use of targeted therapy was found to have a significant relationship with treatment outcome ($p = 0.035$). Patients who used molecular targeted therapy were more likely to be alive at the end of follow-up. ***Conclusion***: Molecular targeted therapies hold tremendous promise in the treatment of haematological malignancies, with associated improvements in patients quality of life and outcomes. However, challenges such as availability, accessibility and cost remain especially in a developing country such as ours.

Keywords: Molecular Targeted therapy, Haematological Malignancies, Nigeria.

INTRODUCTION

Haematological malignancies (HM) are clonal haemopoietic disorders characterized by the accumulation of malignant haemopoietic cells in various tissues of the body [1]. They are reported as the fifth most common malignancies and the second leading cause of cancer deaths worldwide [2], with a recent study at the center of this study recording a prevalence rate of 17.1% [3], and a mortality rate of 53% [4]. They are classified into myeloid and lymphoid malignancies. The myeloid malignancies include acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), the myeloproliferative neoplasms (polycythemia rubra vera, [PRV], essential thrombocythemia [ET] and primary myelofibrosis [PMF]), myelodysplastic syndrome (MDS) and the myelodysplastic/myeloproliferative Neoplasms (MDS/MPN) while lymphoid malignancies include acute lymphoblastic leukaemia (ALL), chronic lymphoid Leukaemias (CLL), plasma cell dyscrasias (PLD), Hodgkin lymphoma and non – Hodgkin lymphomas [5].

Haematological malignancies arise as a result of varied genetic damages to several key biochemical pathways in cellular differentiation, proliferation and maturation [1]. These damages involve specific genes, molecular proteins and microenvironments involved in regulation of normal haemopoietic activities and have been the focus of a new generation of targeted therapy that have revolutionized the management of haematological malignancies.

Targeted therapy refers to agents that block the growth of malignant cells by interfering with specific targeted molecules (specific genes, molecular proteins, cellular microenvironments) needed for carcinogenesis and growth of tumors rather than by simply interfering with all rapidly dividing cells [6]. They are more effective than cytotoxic chemotherapy and are less harmful to normal cells. Effectiveness of the therapy lies in targeted release of therapeutics at the disease site while minimizing the off-target side effects caused to normal tissues. It is often used in conjunction with chemotherapy and other cancer treatments [7].

To date, targeted therapy has provided enormous benefits for patients with haematological malignancies either as the first-line treatment or in combination with chemotherapy as enumerated by several international studies. Rituximab, the first anti-CD20 monoclonal antibody used in humans, has been shown clinically beneficial in adult B-cell lymphomas including Non-Hodgkin lymphomas and B-CLL [8, 9]. For acute myeloid leukaemia, the introduction of all-trans retinoic acid (ATRA) and Gemtuzumab ozogamicin (Mylotarg) -a selective anti CD33 conjugated with calicheamicin, have had major impacts on therapy regimen [10]. The first generation tyrosine kinase inhibitor (TKI), imatinib, along with the second generation TKIs dasatinib, nilotinib and ponatinib have drastically improved treatment of chronic myeloid leukaemia and when combined with chemotherapy and haemopoietic stem cell transplantation (HSCT), the event-free survival rate of Philadelphia (Ph) chromosome-positive acute lymphoblastic leukaemia patients improved from 20% to 80% [11]. Several agents targeting different biochemical pathways involved in the malignant transformation found in chronic lymphocytic leukemia currently exists. They include ibrutinib, an irreversible burton tyrosine kinase inhibitor (BTK) and idelalisib, an inhibitor of the phosphatidyl inositol 3 kinase pathway. Three proteasome inhibitors, carfilzomib, bortezomib and ixazomib are targeted therapy agents approved for the management of multiple myeloma and they have greatly improved outcome and survival amongst patients [12].

Several other targeted therapy exists for the myriads of haematological malignancies. However, in our clime the availability and the costs of these agents remain daunting challenges to accessibility by patients, where patients are majorly unemployed, pay out of pocket for health care services with lack of health insurance coverage.

This study aims to assess the availability and accessibility of the different categories of molecular targeted therapeutic agents.

The objective of this study is to determine the factors affecting the availability and usage of targeted therapies and attendant outcome by patients with haematological malignancies at the Delta State University Teaching Hospital, Oghara, Delta State.

METHODOLOGY

The study was a cohort cross sectional study carried out at Delta State University Teaching Hospital, Oghara, a tertiary health institution located in Ethiope-West local government area of Delta State, Niger Delta Region of Nigeria. It is a state government-owned teaching hospital with over 300 bed capacity, It is affiliated to Delta State University, Abraka and it has over 20 different medical disciplines.

Study Participants:

The study population comprised patients diagnosed with haematological malignancies who gave voluntary consent to participate in the study and were managed at the hospital.

Study Duration

Participants were recruited consecutively following commencement of treatment. This was done between October 2021 and December 2024, a period of twenty-seven months.

Data Analysis

Data obtained were analysed using Statistical Package for the social sciences (SPSS) version 23. The results were summarised using descriptive statistics (frequencies and percentages) and presented as figures, tables and charts.

RESULTS

Subjects characteristics are shown in table 1. The study population consisted of 123 patients with haematological malignancies. Majority (53.8%) of the patients were males and 31.1% of the patients were between the ages of 46 and 60 years. About two-thirds (65.9%) of the patients were married as at the time of the study. Majority (62.1%) patients were self-employed while only 3.8% were government employed. Most of the patients did not use targeted therapy (81.8%) and 56.8% of the patients with haematological malignancies were dead at the end of follow-up.

Table 1: Demographic characteristics of patients with HM

	Frequency	Percentage
Gender		
Male	71	53.8
Female	61	46.2
Age		
15-30 years	20	15.2

	Frequency	Percentage
31-45 years	21	15.9
46-60 years	41	31.1
61-75 years	39	29.5
76-90 years	11	8.3
Marital status		
Single	26	19.7
Married	87	65.9
Widowed	19	14.5
Occupation		
Student	17	12.9
Self-employed	82	62.1
Civil servant	5	3.8
Retired	28	21.2
Use of targeted therapy		
Yes	24	18.2
No	108	81.8
Status at follow-up		
Dead	75	56.8
Alive	57	43.2

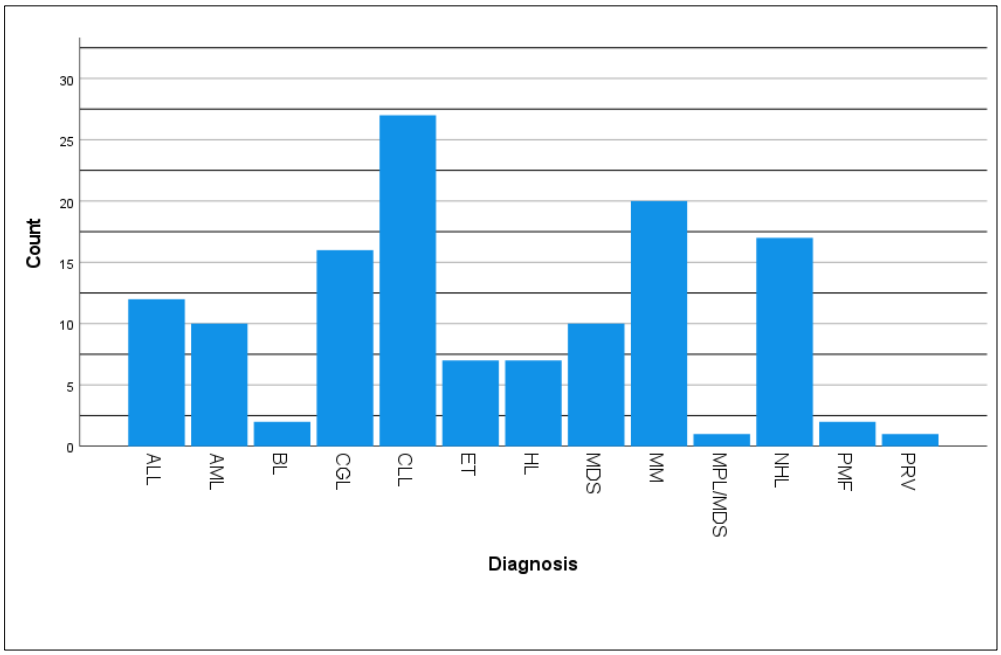

Figure 1: Types of Haematological Malignancies

Figure 1 above shows the different types of haematological malignancies. Twenty -seven (20.5%) of the subjects had CLL. Twenty representing 15.2% had MM while 18 (12.9%) had NHL.

Table 2: Relationship between use of targeted therapy and haematological malignancies

Haematological Malignancies	Did not use targeted therapy (n = 108)	Used targeted therapy (n = 24)
ALL	12 (100%)	0 (0.0%)
AML	10 (100%)	0 (0.0%)
BL	2 (100%)	0 (0.0%)
CGL	13 (81.25%)	3 (18.75%)
CLL	26 (96.3%)	1 (3.7%)
ET	7 (100%)	0 (0.0%)
HL	7 (100%)	0 (0.0%)
MDS	10 (100%)	0 (0.0%)

Haematological Malignancies	Did not use targeted therapy (n = 108)	Used targeted therapy (n = 24)
MM	0 (0.0%)	20 (100%)
MPL/MDS	1 (100%)	0 (0.0%)
NHL	17 (100%)	0 (0.0%)
PMF	2 (100%)	0 (0.0%)
PRV	1 (100%)	0 (0.0%)

The use of molecular targeted therapy in individual hematological malignancy is shown in table 2 above. From the table, it can be deduced that targeted therapy was mostly used by patients with MM (100%) at the centre of the study. This was distantly followed by CGL (18.75%) and CLL (3.7%) while use of molecular targeted therapies was not used for any of the other haematological malignancy.

Figure 2 depicts the reasons patients with haematological malignancies did not use molecular targeted therapies. Financial constraints was the overriding reason for which sixty-six patients, representing 61.1% did not use molecular targeted therapies while unavailability of the specific therapy within the country accounted for the reason why forty-two patients (38.89%) could not access them.

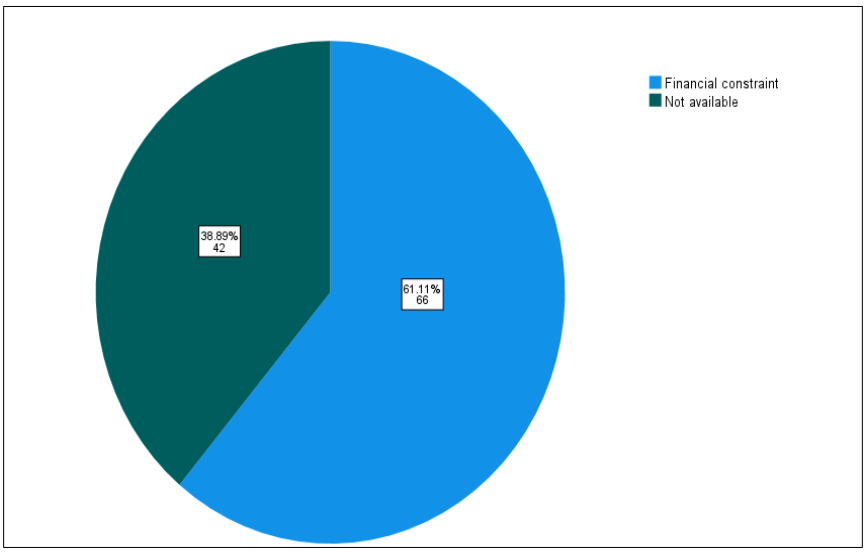

Figure 2: Pie chart showing reasons why molecular targeted therapy was not used

Table 3: Relationship between use of targeted therapy and treatment outcome

Clinical outcome	Did not use targeted therapy (n = 108)	Used targeted therapy (n = 24)
Dead (n = 75)	66 (61.1)	9 (37.5)
Alive (n = 57)	42 (38.9)	15 (62.5)
	$\chi^2 = 4.462$	df = 1 $p = .035$

Table 3 above shows the relationship between the use of molecular targeted therapy and treatment outcomes. It can be deduced that the use of molecular targeted therapy was found to have a significant relationship with treatment outcome ($p = 0.035$). Patients who used molecular targeted therapy were more likely to be alive at the end of follow-up.

DISCUSSION

The advent of targeted therapies represents a paradigm shift in the management of haematological malignancies, offering new avenues to address treatment resistance and improve the outcome of patients. This study was carried out to determine the availability, accessibility and usage of molecular targeted therapeutic agents by patients with haematological malignancies at the Delta State University Teaching Hospital. A total of 132 patients with haematological malignancies were seen during the period of the study. Of these, a mere twenty-one patients representing 18.2% used a form of targeted therapeutic agent. This study seems to be a pioneer study viz a viz availability, accessibility and usage of molecular targeted therapies in malignancies as literature review yielded no comparative study.

This study showed that targeted therapy was used by all patients with MM (100%). This is due to the availability, accessibility and affordability of the first generation immunomodulatory agent bortezomib to the patients.

Three (18.75%) out of a total number of sixteen patients with CGL used the tyrosine kinase inhibitor Imatinib mesylate despite being provided free of charge by a foundation. The reason for the low usage was attributed to lack of finances to travel as the foundation is located in a teaching hospital in Southwestern part of the country.

The anti-CD20 monoclonal antibody is commonly used by patients with NHL and CLL. It is readily available and accessible for patients who can afford it as it comes at a high price. None of our NHL or CLL used it because of financial constraints. Of note was that one patient with refractory CLL, representing 3.7% of patients was able to afford ibrutinib, a Bruton kinase inhibitor.

Our study showed that financial constraints accounted for 61.1% why targeted therapies could not be used by patients with haematological malignancies. Financial burden is saddled by patients who have to pay out of pocket for medical services rendered at the hospital. This is especially so in a country where the multidimensional poverty index is greater than 60%, especially in a suburban area such as ours [13]. The poor financial risk protection remains a major barrier to universal health coverage and the provision of quality healthcare in Nigeria as well as a significant reason why patients could not afford targeted therapeutic agents.

The use of these agents by patients with haematological malignancies has been shown in this study to have a significant effect on the outcome of the patients as patients who used them. This is consistent with several studies carried out on malignancies of the haemopoietic systems [8-16].

CONCLUSION

In conclusion, molecular targeted therapies hold tremendous promise in the treatment of haematological malignancies, offering novel strategies to overcome resistance and improve outcomes for patients. By integrating targeted agents, overall survival rate, quality of life, and prognosis are improved for patients with haematological malignancies.

While these therapeutic agents show significant potentials, challenges such as availability, accessibility and cost remain especially in a developing country such as ours. Hospital management, governments at all levels need to do more to ensure the availability and accessibility of these agents. Also, the costs of these agents can be mitigated either by way of subsidy or insurance coverage.

Conflict of Interest: None declared

AUTHORS CONTRIBUTIONS

Dirisu Ishau Muhammad; Ohwotake Ezekiel Iphierooghene: **Conception and design of research.**

Dirisu Ishau Muhammad, Okuonghae Mobolaji Efe, Ohwotake Ezekiel Iphierooghene: **Drafting of manuscript.**

Dirisu Ishau Muhammad, Ohwotake Ezekiel Iphierooghene, Okuonghae Mobolaji Efe, Nwajei Ifeanyichukwu; **Revision of drafts**

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