IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 12 Ser. 7 (December. 2024), PP 24-30
www.iosrjournals.org

Clinical Characteristics And Outcomes In HIV-Associated Diffuse Large B-Cell Lymphoma In Kenya: A Retrospective Single-Centre Study

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Abstract
Background: There are sparse data in patients with human immunodeficiency virus related diffuse large b cell lymphoma from real-world settings, especially where access to newer targeted therapies is limited.
Aim: Therefore, we analysed the characteristics and outcomes of patients with HIV-associated DLBCL from The Kenyatta National Teaching and referral Hospital, Nairobi, Kenya.
Methods: This was a single institution, retrospective cohort study of patients with Diffuse Large B Cell Lymphoma in HIV diagnosed between January 2012 and December 2019 and treated with combination chemotherapy. The main objectives were to characterise the clinical-pathological features and estimate progression-free survival (PFS) and overall survival (OS) from the time of diagnosis.
Results: A total of 82 patients were recruited into the study. Over half 48 (57.8%) were males, while the females were 34 (42.2%) of the study population. Age range, followed with mean. The mean age of the population was 43.9 years (SD = 13.7) interquartile range of 34-56. Median age was 43 with range between 17-71 years. The mean age for the females was 43±11 years while that for the males was 44±12years. The male to female ratio was 1.4:1. Fourt nine 49 (59.8%) were classified as Germinal Center DLBCL while 32(39.0%) were non-germinal center type.
Twenty-seven patients (32.9%) had HIV-associated DLBCL; 18(21.9%) had germinal centre while 9(10.9%) were of the non-germinal centre subtype. Most patients with HIV had extranodal disease (71%) with a significant p=0.01, B-symptoms 78% p=0.003, Bone marrow involvement 63% p=0.01 and poorer ECOG performance status p=0.05. There was also a trend towards higher ki-67 at 79% in HIV associated DLBCL compared to 71 in those who were HIV negative though was not statistically significant p=0.056. In this study, patients who were HIV negative tended to have advanced disease at presentation. There was difference between disease bulk and CNS involvement at presentation between the two groups. The median CD4+ T cell count was 86/µl, and 24 patients were already on combination antiretroviral therapy (cART) treatment at diagnosis of DLBCL.
Local treatment included CHOP and R-CHOP with or without intrathecal methotrexate. The second line treatment included R-ICE, ICE or DHAP.
At a median follow-up of 18 months, of the 34 patients evaluated at the end of treatment, the overall mean survival time was 43.1 (95% CI 20.7 – 65.6) months, while the overall median survival time was 29.0 (95% CI 13.8 – 44.2) months. The mean survival time was 56.7 (95% CI 10.9 – 102.5) months, with the overall median survival time of 48.0 (95% CI 8.2 – 87.8) months for the HIV positive patients while the mean survival time was 30.0 (95% CI 22.9 – 37.1) months, with an overall median survival time of 28.0 (95% CI 24.1 – 31.9) months for the HIV negative patients.
There were no statistical differences in the survival times between the two groups as assessed by the Log Rank test (p=0.384).
Conclusion
In our population, patients with HIV-associated DLBCL presented with aggressive characteristics, even in the modern cART era but exhibited no difference in survival outcomes.

Keywords: *Key words: diffuse large B-cell lymphoma; HIV; outcome*

Date of Submission: 19-12-2024 Date of Acceptance: 29-12-2024

I. Introduction

The development of Human immunodeficiency virus associated malignancies such as diffuse large B cell lymphoma and Burkitt's lymphoma is one of the most devastating consequences of HIV. [1-3]. Other non-Hodgkin's lymphomas (NHLs), also commonly diagnosed in the background of HIV include primary effusion lymphoma (PEL), plasmablastic lymphoma, KSHV-associated multicentric Castleman's disease, primary central nervous system (CNS) lymphoma and classic Hodgkin's lymphoma (cHL) [1]. HIV has been strongly associated with poor outcomes, particularly in acquired immunodeficiency syndrome (AIDS)-defining subtypes [4]. With the introduction of combination antiretroviral therapy (cART), the incidence of HIV-associated lymphoma is expected to decrease, and the survival outcome to improve.

Diffuse Large B cell Lymphoma comprises 30-40% of NHL cases without HIV infection and 45% of cases with HIV-related lymphoma [6-8]. A Spanish study compared to HIV-uninfected DLBCL patients with HIV-infected patients,found that even in the era of combined antiretroviral therapy, HIV realted DLBCL still presents wth more aggressive features than HIV unrelated DLBCL with worse overalsurvival.Prevention of HIV-related complications is essential to achieve outcomes comparable with HIV-uninfected patients with DLBCL[5]. In the same study, when treated with the standard of-care regimen rituximab plus cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone (R-CHOP), HIV-infected patients exhibited similar disease-free survival but significantly worse overall survival (OS) compared to those without HIV infection [5]. On the contrary, a study conducted in France demonstrated that HIV-related DLBCL showed survival outcomes similar to those of HIV-negative counterparts. [9]. Infections with other viruses such as Epstein-Barr virus (EBV), hepatitis B virus (HBV), and hepatitis C virus (HCV) have been previously reported in DLBCL with the former two viruses independent predictors of poor prognosis [10-13]. HIV-related DLBCL with elevated EBV load predicts inferior survival outcome; however, few data on HIV and HBV/HCV coinfection in patients with DLBCL have been published [13]

Emerging data suggest that the standard chemoimmunotherapy along with combination antiretroviral therapy, can improve outcomes in patients with HIV associated lymphomas. There is a paucity of data on the outcome of HIV-positive patients with diffuse large cell lymphoma, especially from developing countries with limited access to targeted drugs, which is important to establish a baseline for future analyses. We undertook this retrospective analysis to evaluate the treatment pattern and outcome of patients with HIV associated DLBCL-positive in a real-world clinical setting in a tertiary cancer centre in Kenya. [16, 17].

II. Methods:

Study design: This was a retrospective analysis of a single centre data base conducted after obtaining approval from the Institutional Ethics Committee. Patients consent was also obtained.

Patient Identification: The study population comprised patients with DLBCL diagnosed between January 2012 to December 2019. DLBCL diagnosis was established in accordance with the 2008 WHO classification and was classified using the Hans classification algorithm HIV status was defined as a positive ELISA or rapid test.

Procedure: Patients' records were used to extract data according to the examination findings including physical examination, Eastern Cooperative Oncology Group performance status, Ann Arbor stage at initial diagnosis, tumor characteristics including CD19,20, 45, bcl-6, ki67 status, Serum LDH,B-symptoms, treatment details(, All the patients were treated with CHOP like regimen with or without rituximab (CHOP ± R) and were finally included in the analysis) site of extranodal involvement, radiological reports, disease status at various time points after initiation of chemotherapy and death.

Statistical analysis

The study end point was overall survival (OS) defined as the time interval between date of diagnosis and death due to any cause. Patients who did not experience the events for OS on the data cut-off date on February, 2020, were censored. Patient characteristics were summarized using descriptive statistics. Survival outcomes (OS) was estimated by the Kaplan-Meier method. Median times were estimated with their 95% CI. SPSS software version 22.0 was used for statistical analyses (SPSS Inc, Chicago, IL). Survival curves were plotted using the Kaplan-Meier method, and the log-rank test was used for comparison. A P-value of <0.05 was considered significant.

III. Results

Patient characteristics

A total of 82 patients with a median age of 43 (Interquartile range 17-71) years were included into the study. The male to female ratio was 1.4:1 Table 1 describes the baseline characteristics of patients at diagnosis of DLBCL. More than half 49 (59.8%) were classified as Germinal center DLBCL, while 32 (39.0%) as non-Germinal center DLBCL. There was one patient whose information was missing and was not classified. Twenty-seven patients (32.9%) had HIV-associated DLBCL; 18(21.9%) had germinal centre while 9(10.9%) were of the

non-germinal centre subtype. Most patients with HIV Twenty-seven patients had a trend towards poor performance score p=0.02, extranodal disease (71%) with a significant p=0.01, B-symptoms 78% p=0.003, Bone marrow involvement 63% p=0.01 and poorer ECOG performance status p=0.05. There was also a trend towards higher ki-67 at 79% in HIV associated DLBCL compared to 71 in those who were HIV negative though was not statistically significant p=0.056. In this study, patients who were HIV negative tended to have advanced disease at presentation. There was difference between disease bulk and CNS involvement at presentation between the two groups. The median CD4+ T cell count was 86/µl, and 24 patients were already on combination antiretroviral therapy (cART) treatment at diagnosis of DLBCL.

Of the 34 patients evaluated at the end of treatment, the overall mean survival time was 43.1 (95% CI 20.7 – 65.6) months, while the overall median survival time was 29.0 (95% CI 13.8 – 44.2) months. The mean survival time was 56.7 (95% CI 10.9 – 102.5) months, with the overall median survival time of 48.0 (95% CI 8.2 – 87.8) months for the HIV positive patients while the mean survival time was 30.0 (95% CI 22.9 – 37.1) months, with an overall median survival time of 28.0 (95% CI 24.1 – 31.9) months for the HIV negative patients.

There were no statistical differences in the survival times between the two groups as assessed by the Log Rank test (p=0.384).

Table 1: Clinical Characteristics of HIV patients with DLBCL at the Kenyatta National Hospital

		Frequency *(n=82)*	**Percent**
Diagnosis	Germinal center DLBCL	49	59.8
	Non Germinal center DLBCL	32	39.0
	Missing info	1	1.2

	HIV+	**HIV-**	**p-value**
Diagnosis *(n=81)*			
Germinal center DLBCL	18	31	0.422
Non-Germinal center DLBCL	9	23	
Extranodal involvement *(n=81)*			
Yes	20	22	**0.010**
No	8	31	
BM involvement *(n=50)*			
Yes	14	8	**0.013**
No	8	20	
B-symptoms *(n=82)*			
Yes	22	24	**0.003**
No	6	30	
Bulk disease *(n=82)*			
Present	10	11	0.131
Absent	18	43	
CNS involvement *(n=81)*			
Yes	3	1	0.117
No	25	52	
ECOG Performance			
0	2	1	**0.023**
1	5	11	
2	7	28	
3	8	12	
4	6	2	

Ann Abor Staging	**HIV+**	**HIV-**	**p-value**
Stage I	2	2	**0.018**
Stage II	4	14	
Stage III	0	9	
Stage IV	22	26	
N/A	0	3	

	HIV+	**HIV-**	**p-value**
Ki67%, *Mean (SD)*	79.3 (13.8)	71.5 (15.7)	0.055

Treatment History of the studied population

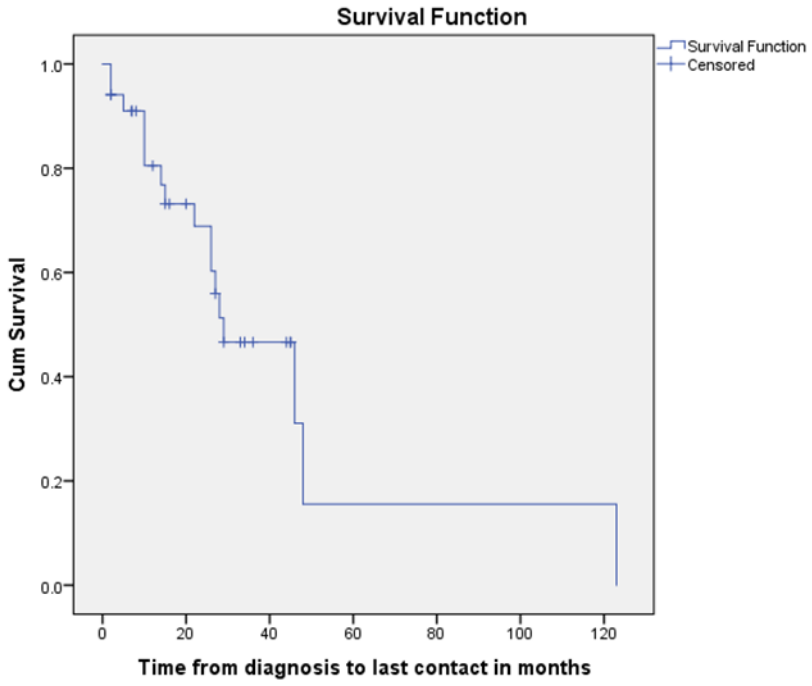
In the studied population, 42(51.2%) received 6 to 8 cycles of CHOP, while 12 (14.6%) received R-CHOP. Only 6(7.3%) received intrathecal treatment. Thirty patients (39.5%) achieved complete remission (CR). At the time of this analysis 18(23.7%) patients were still on treatment. Seventeen (22.4%) had PR. Six (7.9%) had progressive disease while only one patient had stable disease as at the time of this analysis. The most common salvage treatments were ICE in 7(41.2%) and R-ICE in 3(17.6%) patients (**table 2).**

Table 2: Treatment History of the DLBCL patients at the Kenyatta National Hospital

Treatment	n (%)
CHOP 6-8	49(59.7)
CHOP <6	1(1.2)
CHOP 8+IT	4(4.9)
No chemotherapy	1(1.2)
R-CHOP 6-8	3(3.7)
R-CHOP <6	1(1.2)
R-CHOP 8+IT	1(1.2)
Treatment Intrathecal	
Intrathecal Methotraxate (IT)	6(7.3%)
Salvage treatment	
D-HAP	5(26.3)
ICE	7(36.8)
MACOP-B	1(5.2)
R-DHAP	2(11.5)
R-ICE	4(21.0)

Survival analysis for all the patients
Number of cases that were processed

		Censored	
Total N	**N of Events (Dead)**	**N**	**Percent**
34	17	17	50.0%



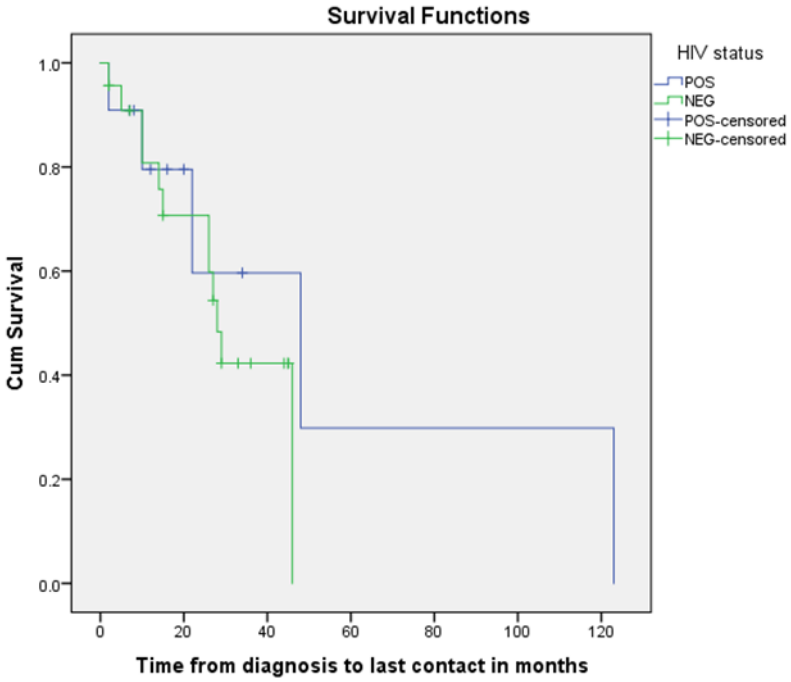
At a median followup time of ????(range…) months, there were 17 deaths on the date of the cut off .The overall mean survival time was 43.1 (95% CI 20.7 – 65.6) months, while the overall median survival time was 29.0 (95% CI 13.8 – 44.2) months.

Mean				**Median**			
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
43.1	11.5	20.7	65.6	29.0	7.7	13.8	44.2

Survival analyis with HIV status of the patients
Number of cases that were processed

			Censored	
HIV Status	**N**	**N of Events (Dead)**	**N**	**Percent**
HIV+	11	5	6	54.5%

HIV-	23	12	11	47.8%
Overall	34	17	17	50.0%



The mean survival time was 56.7 (95% CI 10.9 – 102.5) months, while the overall median survival time was 48.0 (95% CI 8.2 – 87.8) months for the HIV+ patients. The mean survival time was 30.0 (95% CI 22.9 – 37.1) months, while the overall median survival time was 28.0 (95% CI 24.1 – 31.9) months for the HIV- patients.

	Mean				**Median**			
HIV status	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
HIV+	56.7	23.4	10.9	102.5	48.0	20.3	8.2	87.8
HIV-	30.0	3.6	22.9	37.1	28.0	2.0	24.1	31.9

Overall comparison

	Chi-square	**df**	**p-value**
Log Rank (Mantel-Cox)	0.757	1	0.384

There were no statistical differences in the survival times between the two groups as assessed by the Log Rank test (p=0.384).

IV. Discussion

There has been an improvement in the outcomes of patients with DLBCL because of newer CD20-targeted agents, but the presence of HIV continues to be associated with mixed outcomes. Our analysis of the real-world outcome in these patients suggests a substantial clinical benefit of multimodality treatment in some of them, with a 2-year OS of 50%. Notably, only 9 (10.9%) patients received rituximab-based therapy. The majority of patients (60%) in our cohort had received at least six cycles of CHPO which suggests poor compliance to standard practice guidelines. We did not compare those who received rituximab with those who didn't due to the few numbers. Some previous studies have suggested better overall survival benefit with rituximab-based therapies. Our study was limited, and the results are likely due to the heterogeneous timing of prior CD20-targeted therapy, and the majority numbers of patients (n = 73) who did not receive any prior CD20-targeted therapy, leading to an imprecise estimate. The lower use of CD20-targeted therapy in our population is due to high cost of drugs and lack of reimbursement facilities for all patients.

In addition to clinical heterogeneity demonstrated by the IPI, recent publications have described molecular entities within DLBCL that influences prognosis (1,12). These prognostic factors have, however, not been reported previously among patients diagnosed and managed for lymphomas in our setting (20, 16).

This study demonstrated that majority of DLBCL were of germinal center origin, a finding that is consistent with other studies, mostly in the developed countries. A study by Choi *et al* involving 74 cases of DLBCL, for instance, reported 47(56%) as GCB DLBCL (13,14). Other studies have also applied IHC algorithms as a valuable tool in the risk stratification of diffuse large B cell lymphomas (33). However, some studies have shown contrary findings on the prevalence of DLBCL subtypes. A study by Hans *et al* that employed the Hans' algorithm, which include markers such as CD10, BCL-6 and MUM-1, in a cohort of 152 DLBCL cases reported 88(58%) of the cases to be of the non-GCB subtype. In addition, they also found that the GCB subtype was associated with better prognosis (7, 24, 25).

Currently, subtyping of DLBCL into GCB and non-GCB can be achieved with significant accuracy by immunohistochemical (IHC) algorithms such as the Han's method (7,15, 16). In our study, however, complete remission did not correlate with differences between the germinal center and non-GCB subtypes, p=0.91. Besides, we did not get any significant association between the two subtypes and the clinical or demographic parameters such as sex, stage at diagnosis, IPI score, nodal or extra nodal involvement or HIV status. In our opinion, this lack of significant association between the DLBCL subtypes and the other clinical characteristics including disease outcome may, in part, be related to retrospective analysis of samples and management that incorporated different treatments protocols.

Age and ECOG performance status were the only clinical characteristics significantly associated with cell of origin. Older age was significantly associated with the development of GCB subtype of DLBCL, using both univariate, OR 1.45(1.03-2.04) p=0.032 and multivariate analysis, OR 1.67(1.07-2.52) p=0.023. Other studies have also demonstrated strong association between age, performance status and outcome with various chemotherapy regimens. The value of age and performance status in risk stratification of NHL including DLBCL was first demonstrated in the international NHL prognostic factor Index study in 1993. This was a project, involving 2031 patients, was designed to develop a model of predicting outcomes of patients with aggressive NHL on the basis of clinical characteristics before treatment (17, 22, 23). Several other studies have since re-evaluated this model with age adjustment in the advent of newer treatment modalities most notably with the addition of Rituximab with similar outcomes (18,19,21)

The finding that approximately 54% of the study population had extra nodal sites presentation could be of therapeutic significance and comparable with the 30-40% extra nodal presentation observed among DLBCLs in other studies (26, 27). Thus it seems that nodal and extra nodal DLBCL, as well as DLBCL from different primary sites, are heterogeneous with regard to different biologic characteristics and prognostic implications (28, 29).

Prospective studies of HIV associated DLBCL, have demonstrated that IHC analysis of DLBCL subtype predicts both lymphoma-specific and overall survival (30). In our study, sub-classification of HIV/AIDS related DLBCL into GCB or non-GCB type using the Hans' methods did not predict CR and was neither associated with significant clinical or demographic parameters. Various studies have, however, reported higher incidence of lymphomas expressing markers such as CD10 and BCL-6 in HIV positive patients (31,32,33). The observations of the present study thus showed that the majority of DLBCL are of the germinal center origin, and older patients with poor ECOG performance status are more likely to be of GCB subtype. There was impact of HIV in the development of either subtype of DLBCL, but HIV associated DLBCL had higher proliferative index.

In conclusion, the findings of our study underscore the need for determination of cell of origin, which may predict the disease outcome for patients with non-Hodgkin B cell lymphomas managed at Kenyatta National Hospital.

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