Safety, efficacy, and affordability of ABVD for Hodgkin lymphoma in Malawi: a prospective cohort study

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Summary

Background ABVD (doxorubicin, bleomycin, vinblastine, and dexamethasone) is a proven, curative regimen for Hodgkin lymphoma (HL). Prospective data describing HL treatment in sub-Saharan Africa are limited. We aimed to fill this knowledge gap, using data from Malawi.

Methods We report a prospective observational cohort of HL (aged ≥ 15) from a single, tertiary referral centre in Malawi. We enrolled patients with pathologicially confirmed Hodgkin lymphoma between June 1, 2013, and Dec 31, 2021 with follow-up censored on May 31, 2022. Patients were treated with ABVD and concurrent antiretroviral therapy if HIV-positive and were followed up for 5 years. The primary outcome was overall survival; secondary outcomes included progression-free survival, response assessment, and adverse events. Microcosting of HL diagnosis, treatment, and follow-up was embedded.

Findings We enrolled 38 patients with a median age of 27 years (interquartile range 19–46); eleven (28%) were HIV-positive. Of 35 patients treated with ABVD, 24 (71%) had stage III/IV, nine (26%) unfavourable limited stage, and two (6%) favourable limited stage. Among HIV-infected individuals, mean CD4 count at HL diagnosis was 179 cells/uL and ten (91%) had HIV RNA < 400 copies/mL. Grade 3/4 neutropenia occurred in 24 (68%) patients and caused treatment delay in 16 (46%). Of ten deaths, seven were due to HL, two possible treatment-related toxicity, and one uncertain. 2-year overall survival was 82% (95% CI 70–96%) and 2-year progression-free survival was 64% (95% CI 50–83%). PFS appeared better for HIV-positive patients (HR 0.23 (95% CI 0.05–1.02)) after controlling for stage and performance status (p = 0.05). We estimated $2708 (2022 USD) for HL diagnosis, treatment, and follow-up in our cohort.

Interpretation Our findings suggest that treatment with ABVD is safe, efficacious, and affordable for HL in Malawi. Outcomes are worse than in high-income countries due to HL progression. Future studies are needed to understand outcome inequities and to assess efficacy of therapies for patients with relapsed or refractory HL in Malawi.

Funding National Institutes of Health, Lineberger Comprehensive Cancer Center.

Keywords: Hodgkin lymphoma; HIV; ABVD; Sub-Saharan Africa; Cost; Microcosting

Introduction

Hodgkin lymphoma (HL) is a common lymphoma subtype, making up approximately 10% of all lymphomas with an estimated 83,087 new cases globally in 2020 and approximately five times greater risk among patients living with HIV (PLWH).[1–3] Though epidemiological data are sparse, HL incidence may be higher in sub-Saharan Africa (SSA) where the prevalence of human immunodeficiency virus (HIV) and Epstein–Barr virus (EBV) are higher than in other regions of the world.

In high-income countries, HL is highly curable.[4] For example, in the United States 5-year overall survival (OS) for patients with HL is 89%, which is similar to other high-income countries.[5,6] Outcomes are favourable even for advanced HL with 5-year survival rates in the United States for stage III and IV being 86% and 80%,

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Research in context

Evidence before this study

We searched PubMed for studies published in English and Spanish on ABVD (doxorubicin, bleomycin, vinblastine, and dexamethasone) treatment of Hodgkin lymphoma (HL) with a specific focus on studies from low and middle-income countries and sub-Saharan Africa (SSA). Data related to HL treatment and HIV from SSA are limited. A retrospective study in South Africa found that among patients with HL, patients living with HIV (PLWH) were less likely to receive chemotherapy than their HIV-negative counterparts, typically presented with advanced disease, and experienced early death. Another retrospective study in Ethiopia found that patients treated with ABVD had a 4-year overall survival (OS) of 77%. A prospective study in Botswana, where radiation and intensive chemotherapy were widely available, found that PLWH had significantly better 2-year OS (96%) compared with HIV-negative (74%) patients with HL.

Added value of this study

To our knowledge, this is among the first detailed, prospective cohort studies describing HL treatment from SSA. Understanding the outcomes of patients treated with ABVD and the impact of HIV is paramount and we were uniquely positioned to answer that question in a rigorous manner. We enrolled 38 patients with median age 27 (interquartile range 19–46) and 11 (28%) were HIV-positive. Of 35 patients treated with ABVD, 24 (71%) had stage III/IV HL, 9 (26%) unfavourable limited stage HL, and 2 (6%) favourable limited stage HL. Among HIV-infected individuals, mean CD4 count at HL diagnosis was 179 cells/uL and 10 (91%) had HIV RNA < 400 copies/mL. Grade 3/4 neutropenia occurred in 24 (68%) patients and caused treatment delay in 16 (46%). Of ten deaths, seven were due to HL, two possible treatment-related toxicity, and one uncertain. 2-year overall survival was 82% (95% CI 70–96%) and 2-year progression-free survival (PFS) was 64% (95% CI 50–83%). PFS appeared better for HIV-positive patients (HR 0.23 (95% CI 0.05–1.02)) after controlling for stage and performance status (p = 0.05). We also completed a microcsting study and estimated $2708 (2022 USD) for HL diagnosis, treatment, and follow-up in our cohort.

Implications of all the available evidence

Our findings suggest that treatment with ABVD is safe, efficacious, and affordable for HL in Malawi. Outcomes are worse than in high-income countries due to HL progression; access to more effective therapies is needed. A significant proportion of patients are cured with first-line therapies but advanced therapies like brentuximab, checkpoint inhibitors, and autologous stem cell transplant are not routinely available in low-income countires leading to gross inequities for relapsed and refractory HL. Future studies are needed to better understand the association of HIV with improved outcomes, and, given the relatively high cure rate in a relatively young population and limited total cost, ABVD is likely to be highly cost-effective in this setting and formal cost-effectiveness studies are planned.

respectively.[7] The standard front-line systemic treatment for HL in the United States has historically been adriamycin (i.e., doxorubicin), bleomycin, vincristine and dacarbazine (ABVD).[4] Despite recent approval and incorporation of newer agents, ABVD remains an accepted standard of care for many patients with excellent long-term outcomes.[8,9]

In SSA, data related to HL treatment are limited. A retrospective study in South Africa found that among patients with HL, PLWH were less likely to receive chemotherapy than their HIV-negative counterparts, typically presented with advanced disease, and experienced early death.[10] Another retrospective study in Ethiopia found that patients treated with ABVD had a 4-year OS of 77%.[11] A prospective study in Botswana, where radiation and intensive chemotherapy were widely available found that PLWH had significantly better 2-year OS (96%) compared with HIV-negative (74%) patients with HL.[12]

In addition to safety and efficacy assessments, economic evaluation is also important to inform efforts to increase access to cancer treatment in SSA. Such data for haematologic malignancies among adults in SSA are extremely limited. We have previously shown that the cost of treating diffuse large B-cell lymphoma (DLBCL), the most common subtype of non-Hodgkin lymphoma, is $1776 (2017 United States dollars (USD)) with standard chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]) and $5100 (2017 USD) if rituximab is added to CHOP.[13] In cost-effectiveness modeling, CHOP was extremely cost-effective, and R-CHOP was cost-effective using WHO thresholds.[14]

In this paper, we describe baseline characteristics, treatment details, outcomes, and costs for a prospective cohort of patients with HL treated with ABVD from the Kamuzu Central Hospital (KCH) Lymphoma Study in Lilongwe, Malawi. To our knowledge, this is among the first detailed prospective cohort studies describing HL treatment from SSA.

Methods

Study design and participants

This was a prospective, observational cohort of all patients newly diagnosed with HL (classical or non-classical) at KCH in Lilongwe, Malawi. The study protocol is available in the Supplementary Materials. KCH

is the referral hospital for the Central and Northern regions of Malawi, serving a population of approximately 9 million people. We included participants aged 15 years or older enrolled between July 1, 2013, and Dec 31, 2021. Follow up was censored as of May 31, 2022. All participants had a consensus diagnosis confirmed by immunohistochemistry (IHC) during weekly telepathology conferences including providers and pathologists in Malawi and collaborators at the University of North Carolina at Chapel Hill as previously described.[15] Briefly, primary histologic assessment was conducted by Malawian pathologists. IHC for CD20, CD3, CD30, and PAX5 was available for confirmation in Malawi. EBV expression was assessed by EBV small RNAs (EBER) *in situ* hybridisation (ISH). Ann Arbor stage was assessed by physical examination, chest x-ray, abdominal ultrasound, and bone marrow biopsy.

Ethics

Written informed consent was obtained from all participants. If a participant was age 18 years or younger, guardian consent and child assent were obtained. This study was approved by the UNC Institutional Review Board (#12–2255, initial approval 11/5/2012) and Malawi National Health Sciences Research Committee (#1107, initial approval 3/10/2013) in accordance with the Declaration of Helsinki.

Treatment

Regardless of initial staging, participants were treated with doxorubicin (25 mg/m^2), bleomycin (10 units/m^2, maximum 15 units), vinblastine (6 mg/m^2, maximum 10 mg), and dacarbazine (375 mg/m^2). Treatment was for up to six cycles (twelve doses) of chemotherapy; chemotherapy was delivered every two weeks unless adverse events (AEs) dictated a delay in treatment at the discretion of the provider. Consolidation radiotherapy was not available for limited stage disease or residual disease after ABVD therapy and computed tomography (CT) and positron emission tomography computed tomography (PET-CT) were not available to choose on escalation or deescalation of therapy. These treatment recommendations are in line with the NCCN Harmonized Guidelines for sub-Saharan Africa. At each chemotherapy visit, patients underwent clinical assessment and laboratory assessment. Though the general recommendation was not to delay therapy for neutropenia alone, this was left to the treating providers discretion. Unfortunately, treatments for relapsed/refractory Hodgkin are quite limited in Malawi. At the time or relapse or refractory disease, patients were typically treated with platinum-based chemotherapy regimens and attempts were then made to petition the Malawi governemnt to support the patient to travel outside the country for access to autologous stem cell transplant or alternative therapies such as brentuximab vedotin or immune checkpoint inhibitors.

For HIV-positive patients, antiretroviral therapy (ART) was given concurrently with ABVD. All patients received infectious prophylaxis with trimethoprim-sulfamethoxazole 80 mg/400 mg once daily. Patients with an absolute neutrophil count (ANC) < 800/uL at the time of treatment or history of febrile neutropenia were given ciprofloxacin 500 mg twice daily and those with ANC < 800/uL or HIV-infection were given fluconazole 300 mg once daily.

Outcomes

The primary outcome for the survival analysis was OS from the date of enrollment and secondary outcome was progression-free survival (PFS). All participants were followed until death, lost to follow-up, or administrative censoring on 31 May 2022. Any patients lost to follow-up were censored at the date of last contact. Secondary outcomes included adverse events and response assessment. Adverse events (AEs) were graded by National Cancer Institute Common Terminology Criteria for AEs version 5.0.[16] Response assessment was assessed according to the Lugano criteria using the same methods available on initial assessment including physical exam, abdominal ultrasound, and chest xray. We were unable to assess residual lymph nodes for activity as positron emission tomography (PET) scan was not available and repeat biopsies were not done if the patient was asymptomatic as consolidative radiotherapy was not available. Finally, bone marrow biopsies were not routinely repeated to confirm resolution of bone marrow disease if patients were asymptomatic with normal complete blood count at the end of treatment.

Statistical analysis

We measured differences in baseline characteristics by HIV status using chi-square test for categorical variables, t-test for normally distributed continuous variables, and Wilcoxon Rank–Sum test for non-normally distributed continuous variables. For all continuous variables, mean and standard deviation were reported if normally distributed whereas median and interquartile range were shown if non-normally distributed. Kaplan Meier curves were used to estimate OS and PFS. We assessed the differences in survival estimates between groups using log-rank test. An unadjusted and adjusted cox proportional hazard regression model were used to assess the association between baseline characteristics and survival. We began with an adjusted Cox proportional hazard regression model of age, stage, Eastern Cooperative Oncology Group (ECOG) performance status, and HIV status. These variables were chosen based on associations with survival in previous studies of HL.[14] We added other variables of interest to the model if they yielded significant results ($p < 0.05$) on univariate analysis. We then excluded age from our multivariate analysis as our cohort was particularly young (median age 27) and only three patients were age ≥ 45, which is

the age group designated as a negative prognostic factor in the International Prognostic Score. All statistical analyses were done using R version 4.21 software (Vienna, Austria).

Micro-costing analysis

We conducted a micro-costing of analysis first-line therapy of HL in Malawi with ABVD chemotherapy. We also estimated costs for palliative care in the setting of relapse or for patients who did not wish to pursue cytotoxic chemotherapy treatment. Cost analysis was conducted from a health systems perspective. Micro-costing was completed as described previously[13,14] and summarised below.

Cost inputs

Data were taken the Malawi Ministry of Health Patient Tariffs at KCH, an itemised list of estimated costs per patient. Variable costs included medications, laboratory tests, transportation reimbursement, clinical and laboratory supplies, radiology testing, and hospitalisation costs.

Costs were calculated on a per patient basis for the following discrete care elements: tissue biopsy, bone marrow biopsy, initial assessment, chemotherapy administration, palliative care, treatment completion, hospitalisations, neutropenic fever, and follow-up. Follow-up was assumed to occur every three months after treatment completion for 2 years. In assigning visit frequencies, we used the average number of events over the entire cohort to calculate a per patient frequency (e.g., chemotherapy cycles, hospitalisations, laboratory, and radiologic tests). All costs were collected in Malawian Kwacha (MWK) in 2022 values and converted to USD using the average exchange rate for 2022.

Budget impact analysis

To estimate HL burden in Malawi, we used data from the 2020 Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) publication.[6] The source data are from the Malawi National Cancer Registry.[17] By these estimates, there were 117 incident annual cases of Hodgkin lymphoma in Malawi. We then calculated the annual budget impact by multiplying the per patient costs by the anticipated annual number of incident HL cases.

Role of the funding source

The funder no role in the study design, data collection, data analysis, data interpretation, writing of the manuscript, or in the decision to submit the manuscript for publication.

Results

Between Jan 1, 2013, and Dec 31, 2022, we enrolled 38 patients with HL, 37 (97%) of whom had classical HL and one (3%) had nodular lymphocyte predominant HL. Of these patients, 21 (55%) were men and the median age was 27 years (range 15–59) (Table 1). Eleven patients (29%) were HIV infected. Twenty-five patients (66%) presented with stage III or IV disease, nine (24%) had limited stage, unfavourable risk and two (5%) had limited stage, favourable risk disease. Furthermore, 13 (35%) had an ECOG performance status ≥2, and 24 (65%) had a high-risk International Prognostic Score (IPS) of ≥3. Bone marrow was involved in seven out of 24 (29%) patients tested. Of patients with measurable tumours, nine (24%) had bulky disease, defined as tumours with maximal dimension ≥10 cm.

Of the PLWH, eight (73%) were aware of their HIV-positive status prior to HL diagnosis. For PLWH, the time between diagnosis of HIV and diagnosis of HL was a median of 1.6 years. All PLWH previously aware of their status were receiving antiretroviral therapy (ART) at time of diagnosis. Median duration of ART use prior to HL diagnosis was 1.2 years. Mean CD4 count was 179 cells/uL (range 102–298 cells/uL).

Compared with HIV-negative patients, PLWH were older and had a lower white blood cell count. There was also a trend toward them being more commonly female and with less bulky disease. Of biopsy specimens tested for EBV, 14/17 (83%) were EBER positive. Among PLWH, 6/6 (100%) were positive and among HIV-negative participants 8/11 (73%) were positive.

Among all patients, 35 (92%) patients were treated with ABVD as first-line therapy. The median number of chemotherapy cycles patients received was twelve. There were seven (20%) patients who were treated with <12 cycles of chemotherapy. Two of the seven died after only one cycle of ABVD. One patient received six cycles before death likely due to disease progression, complicated by treatment delays related to transportation barriers. One patient died of neutropenic sepsis after eight cycles of chemotherapy. Finally, two patients achieved complete remission after nine and ten cycles of ABVD, respectively, and the provider opted to stop chemotherapy.

There was a total of 37 grade 3/4 AEs, which resulted in 18 (51%) patients who had at least one treatment delay ranging from 1 to 2 weeks. Most AEs associated with treatment delays were grade 3/4 neutropenia, which occurred in 16 patients. However, other grade 3/4 AEs occurred in three patients who had neutropenic fever, two who had anaemia, and one who had thrombocytopenia. Of other AEs of interest, there were three episodes of grade 1 neuropathy and no episodes of pulmonary toxicity. Finally, PLWH were significantly more likely to experience treatment delays compared with their HIV-negative counterparts, largely due to neutropenia.

There were ten total deaths, two in PLWH and eight in HIV-negative patients. The cause of death was HL in seven patients, complication of HL treatment in two patients, and could not be ascertained in one patient. The patients who died of treatment-related

Characteristics	All (n = 38)	HIV negative (n = 27)	HIV positive (n = 11)	p
Male sex, n (%)	21 (55)	18 (67)	3 (27)	0.06
Female sex, n (%)	17 (45)	9 (33)	8 (73)	
Age, median [IQR]	27 [19, 36]	22 [19, 29]	39 [32, 42]	<0.01
Home district (%)				
Lilongwe	17 (45)	12 (44)	5 (45)	0.96
All Other Districts	21 (55)	15 (56)	6 (55)	
B symptoms, n (%)				
Yes	27 (73)	19 (73)	8 (73)	1.0
Stage, n (%)				
III–IV	25 (66)	17 (63)	8 (73)	0.84
ECOG performance status ≥2, n (%)	13 (35)	10 (37)	3 (27)	0.78
IPS, n (%) (N = 36)				
0	3 (8)	2 (8)	1 (10)	0.69
1	3 (8)	3 (11)	0 (0)	
2	7 (19)	4 (15)	3 (30)	
3	11 (31)	7 (27)	4 (40)	
4	10 (28)	9 (35)	1 (10)	
5	2 (6)	1 (4)	1 (10)	
Bone marrow involvement, n/N (%)	7/24 (29)	6/15 (40)	1/9 (11)	0.30
Bulky disease ≥10 cm, n (%)	9 (24)	9 (33)	0 (0)	0.08
White blood cells x 10^9/L, median [IQR]	6.7 [3.9, 9.8]	7.50 [5.3, 10.7]	4.10 [2.8, 7.2]	0.04
Haemoglobin, g/dL, mean (SD)	9.0 (2.9)	8.5 (3.2)	10.2 (1.7)	0.14
Platelets x 10^9/L, mean (SD)	386 (254)	406 (286)	337 (147)	0.48
LDH ratio per ULN, mean (SD)	0.8 (0.4)	0.8 (0.4)	0.8 (0.4)	0.85
Creatinine, mg/dL, median [IQR]	0.6 [0.5, 0.7]	0.6 [0.5, 0.6]	0.7 [0.6, 0.9]	0.18
Lymphocytes x 10^9/L, median [IQR]	1.4 [0.9, 2.3]	1.7 [0.9, 2.5]	1.4 [0.9, 1.8]	0.20
Bilirubin, mg/dL, median [IQR]	0.4 [0.3, 0.8]	0.6 [0.3, 0.8]	0.3 [0.2, 0.6]	0.27
Albumin, g/dL, mean (SD)	3.1 (0.8)	3.0 (0.9)	3.4 (0.7)	0.23
EBER positive by ISH, n/N (%)	14/17 (83)	8/11 (73)	6/6 (100)	0.46
Treatment characteristics (N = 35)				
Treatment cycles received ≥12, n (%)	28 (80)	20 (80)	8 (80)	1.0
Treatment delays, n/N (%)	18/35 (51)	9/25 (36)	9/10 (90)	0.01
HIV characteristics (N = 11)				
HIV diagnosis known prior to HL diagnosis, n (%)	–	–	8 (73)	
Time since HIV diagnosis, years, median [IQR]	–	–	1.6 [0.3, 4.0]	
Receiving ART at HL diagnosis, n (%)	–	–	8 (73)	
Duration of ART at HL diagnosis, years, median [IQR]	–	–	1.2 [0.3, 4.0]	
CD4 count, cells per µL, mean (SD)	–	–	179 (113)	
HIV viral load, detectable > 400 copies per mL, n (%)	–	–	1 (9.1)	

ART = antiretroviral therapy. EBER = Epstein–Barr virus-encoded RNA. ECOG = Eastern Cooperative Oncology Group. HIV = human immunodeficiency virus. HL = Hodgkin lymphoma. IPS = International Prognostic Score. IQR = interquartile range. ISH = *in situ* hybridisation. LDH = lactate dehydrogenase. SD = standard deviation. ULN = upper limit of normal.

Table 1: **Baseline characteristics of adolescents and adults with newly diagnosed classical Hodgkin lymphoma in Lilongwe, Malawi, from 2013 to 2021.**

complications had the following details: one patient died about a week after the first dose of chemotherapy with anaemia, vomiting and shortness of breath and the other died ten days after the eighth dose of chemotherapy from neutropenic sepsis. For the death that could not be ascertained, the patient likely died from HIV-associated opportunistic infection or HL relapse that could not be confirmed. This patient had stage IV HL with lung involvement, received 12 doses ABVD and was in complete remission. However, this patient returned three months after chemotherapy with anaemia, seizures, and decreased level of consciousness. CSF showed elevated protein, but cytology was negative for disease involvement; bone marrow biopsy was also negative for relapse.

Of 35 patients treated with ABVD, 33 were evaluable as one died during treatment prior to response assessment and one absconded prior to response assessment. Of 33 evaluable patients, there were 27 (82%) patients with a complete response (CR), 3 (9%) with a partial

response (PR) and 3 (9%) with progressive disease (PD). Among PLWH, there were ten evaluable patients and all ten (100%) had a CR. Among HIV-negative patients, there were 23 evaluable participants; of these, 17 (74%) had a CR, 3 (13%) had a PR, and 3 (13%) had PD. Of note, of participants with partial response, only one had bulky disease at baseline evaluation.

Median follow-up time among those still alive was 2.7 years (IQR 1.5–4.9). One (3%) patient was lost to follow up. We excluded three patients from survival analysis who had initial treatment with CHOP (doxorubicin, cyclophosphamide, vincristine, and prednisone) chemotherapy. One patient was initially diagnosed with non-Hodgkin lymphoma and one patient was initially diagnosed with anaplastic large cell lymphoma, and one patient had nodular lymphocyte predominant HL and was therefore treated with CHOP plus rituximab. For all patients treated with ABVD, 2-year OS was 82% (95% CI 70–96). 2-year OS was 80% (95% CI 59–100) for PLWH and 83% (95% CI 69–100) for HIV-negative patients. 2-year PFS was 64% (95% CI 50–83) with a median PFS of 4.3 years. 2-year PFS was 79% (95% CI 60–100) for PLWH and 59% (95% CI 40–80) for HIV-negative patients. Though not statistically significant, OS and PFS appear to be better in patients with limited stage, favourable risk disease (Fig. 1), as expected.

For both the unadjusted and adjusted cox regression models, there were no significant associations between baseline characteristics and OS (Table 2). However, in both univariate and multivariate analyses of PFS, PLWH had superior outcomes compared with HIV-negative patients (unadjusted HR 0.26 (0.06, 1.15), p = 0.08; adjusted HR 0.23 (0.05, 1.02) p = 0.05), though did not meet statistical significance. We also analysed additional characteristics of interest (haemoglobin, albumin, bone marrow involvement, gender, performance status, treatment delay, and age) for association with OS (Supplementary Fig. S1, Appendix 1) and PFS (Supplementary Fig. S2, Appendix 1) by univariate cox regression models, but none of these factors were significantly associated with OS or PFS. Most notably, treatment delays were not associated with worse OS or PFS.

The total cost for ABVD treatment was $2708 per patient. Total cost for palliative care only, which included diagnostic costs was $1304 per patient. ABVD chemotherapy made up about 30% of the total costs (Fig. 2). Using the GLOBOCAN estimates of 117 annual cases of HL, the estimated total costs for ABVD treatment across Malawi is $317,057 annually; this is approximately 0.1% of the $270 million 2022 Malawi healthcare budget.[18] Total costs across Malawi for a palliative care only approach would be $152,597 annually.

Discussion

This study represents one of the most detailed prospective cohort studies regarding HL treatment in SSA. Patients presented with advanced disease as only three

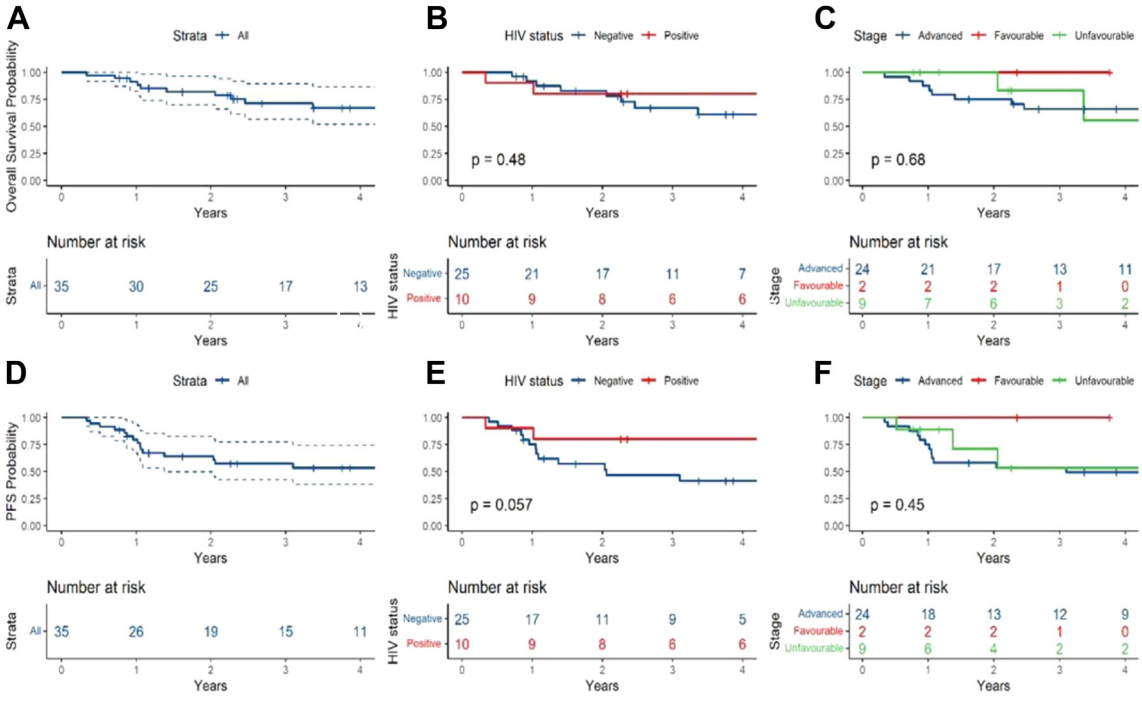

Fig. 1: **Kaplan–Meier curves for overall survival (OS) and progression-free survival (PFS).** OS curves shown for entire cohort (A), by HIV status (B), and by advanced stage, favourable and unfavourable risk (C). PFS curves shown for entire cohort (D), by HIV status (E), and by advanced stage, favourable and unfavourable risk (F).

Variable	Value	Unadjusted		Adjusted	
		HR (95% CI)	p	HR (95% CI)	p
Overall survival					
Stage	III–IV	1.58 (0.33, 7.49)	0.56	1.38 (0.28, 6.89)	0.70
ECOG PS	≥2	128 (0.36, 4.56)	0.70	1.24 (0.34,4.60)	0.74
HIV	Positive	0.58 (0.12, 2.72)	0.49	0.52 (0.11,2.46)	0.41
Progression-free survival					
Stage	III–IV	1.90 (0.54, 6.70)	0.32	2.08 (0.58, 7.49)	0.26
ECOG PS	≥2	0.80 (0.28, 2.30)	0.68	0.71 (0.24, 2.08)	0.53
HIV	Positive	0.26 (0.058, 1.15)	0.08	0.23 (0.051, 1.02)	0.05

All variables of interest were binary and all three (stage, ECOG, and HIV) were included in the adjusted Cox proportional hazard model. Stage III–IV versus stage I–II; ECOG ≥2 versus <2 and HIV positive versus negative. ABVD = doxorubicin, bleomycin, vinblastine, and dexamethasone. ECOG PS = Eastern Oncology Cooperative Group performance status. HIV = human immunodeficiency virus. HR = hazard ratio.

Table 2: **Unadjusted and adjusted Cox proportional hazard estimates for overall and progression-free survival among Hodgkin lymphoma patients treated with ABVD in Lilongwe, Malawi 2013–2021.**

patients had limited stage, favourable risk HL and 65% of patients had an International Prognostic Score > 2. Despite high-risk disease, 2-year OS in our cohort was 82% and 2-year PFS was 64%.

In our analysis, we had two distinct groups of patients: the HIV-negative cohort was younger and had more men (not statistically significant) and more bulky disease (not statistically significant) whereas PLWH experienced more treatment delays, though admittedly the numbers in each group were relatively small. Notably, PLWH had increased frequency of grade 3/4 neutropenia and subsequent treatment delays at provider discretion. Thus, there was concern that delayed treatment may be associated with poorer outcomes. However, treatment delays were not associated with worse OS or PFS and, in fact, when controlling for stage and performance status, PLWH had improved PFS in our population. Similarly, PLWH in a study in South Africa were more at risk for experiencing treatment delays when compared with HIV-negative counterparts.[10]

The impact of HIV on HL treatment outcomes in SSA, and globally, in the literature has been mixed. Just over a decade ago, researchers in South Africa found that OS of HL was poorer in PLWH and another more recent study from South Africa redemonstrated largely the same findings.[10,19] Conversely, high-income countries have reported that PLWH treated with standard ABV and ART are not at increased risk of cancer-specific mortality compared with HIV-negative counterparts.[20,21] For example, in the United Kingdom, investigators found that PLWH who were treated with ABVD did not have different outcomes when compared with HIV-negative participants.[22] Further, a French cohort study found that although PLWH tend to present with more advanced stage HL with high risk features, there were no significant survival differences when compared with HIV-negative counterparts.[23] Finally, similar to our findings, a prospective cohort study on patients with HL in Botswana found that PLWH had better survival when compared with HIV-negative individuals.[12]

There are plausible explanations for improved outcomes in PLWH and HL. First, PLWH who regularly receive ART are more likely to be connected to their local healthcare systems thus receive earlier diagnosis at less advanced stage.[12] However, in our population there were no significant differences in stage, IPS, or ECOG between PLWH and HIV-negative participants. In addition, PLWH, especially if recently started on ART may derive some benefits from immune reconstitution. In our study, there may be some immune reconstitution in PLWH as the median time on ART at enrollment was only 1.2 years. Additionally, the underlying disease biology may be different in the setting of HIV and underlying immunosuppression. Further investigation is needed to understand these intersecting factors to optimise therapy for PLWH and HL around the world, especially as this reflects only a single-centre experience from a tertiary referral hospital with a limited number of patients.

Survival estimates in our study are similar to other studies from the region and most deaths were from disease progression. OS in our cohort was similar to studies from Ethiopia and Botswana.[11,12] Notably most deaths were a result of disease progression rather than from complications of treatment. Compared with high-income countries, treatment options for relapsed/refractory HL (e.g., radiotherapy, stem cell transplant) are more limited in our setting[24] so outcomes after relapse were especially poor in this study. Thus, although PFS was in the expected range for such advanced disease, outcome disparities persist, especially after relapse. Combining this lack of salvage therapies with the fact that almost all patient deaths in this cohort were from progressive disease emphasised the need for access to novel therapies that maximise disease control.

Finally, in this article, we also provide a comprehensive micro-costing analysis for HL treatment in Lilongwe. We conducted this micro-costing analysis in the context of an observational cohort with comprehensive longitudinal assessment. We captured real-world costs, including those associated with

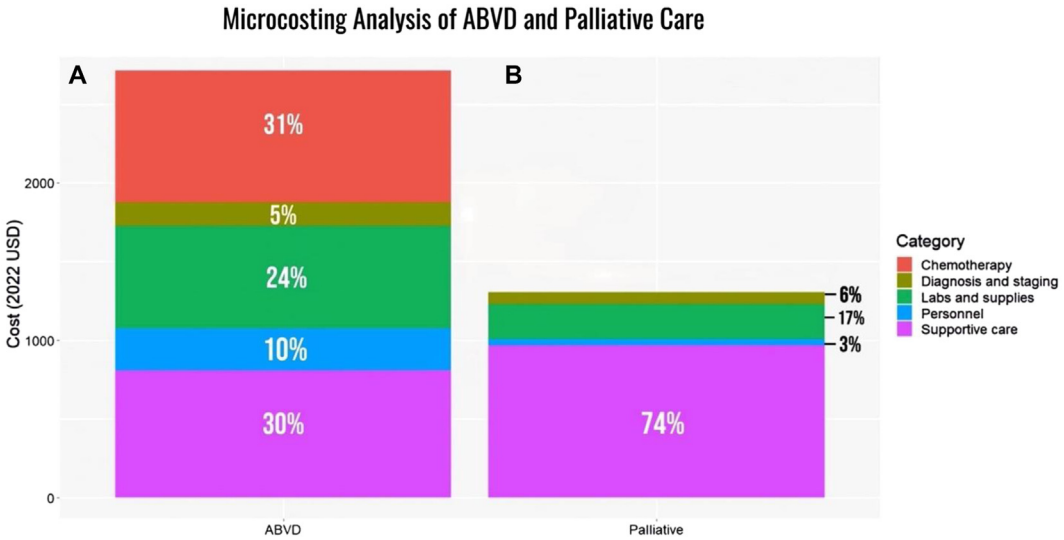

Fig. 2: **Micro-costing analysis of cancer care for patients with Hodgkin lymphoma.** Data are shown as cost estimates on a per-patient basis for treatment with ABVD (doxorubicin, bleomycin, vinblastine, and dexamethasone) (column A) and best supportive care only (column B). Percentages of different costs are displayed and categories of costs are color coded.

complications and hospitalisations. We estimate that it costs $2708 (2022 USD) to treat a patient over the course of 2 years of follow-up with first line ABVD chemotherapy, an estimated budget impact of around 0.1% of the Malawian healthcare budget. Palliative care costs were much lower ($1304). Chemotherapy costs accounted for approximately 30% of the cost. To our knowledge, this is the first published effort to characterise the costs of HL treatment in adults in SSA. This cost compares extremely favourably to the costs of the same treatment in high-income countries; one study from Canada estimated a full treatment course of ABVD to be $12,701 for the chemotherapy alone in 2018, while a PET scan costs close to $2000 per scan, not to mention labor and physician time.[23] Given the young age of the patients treated and the many years of quality life to be lived in those cured, a cost-effectiveness analysis is likely to demonstrate a remarkably low cost per Disability Adjusted Life Year averted. A formal cost-effectiveness analysis is planned.

The strengths of our study include a prospective, deeply characterised HL cohort with complete treatment and outcome data. Further, we had only one patient lost to follow-up during the study period.

There are numerous limitations to this study that should be noted. First, our study is limited by a small cohort size and being from a single institution which may limit generalisability. In addition, PET-CT was unavailable for staging. However, most participants had advanced stage disease detected even without PET-CT. We also recognise that treatment delays were common and are generally advised against in Hodgkin lymphoma; however, this did not seem to have a marked inpact on outcomes as those with treatment delay did not have worse outcomes than those who did not have treatment delay. In fact, if anything, delay was more common in PLWH and PLWH had superior PFS compared HIV negative patients. That being said, quality improvement approaches are needed to improve dose intensity. In addition, radiation therapy was unavailable for treatment of residual disease which may contribute to worse outcomes for patients presenting with bulky disease. This was likely a neglible effect in this study as only one of three participants with partial response had original bulky disease; however, over time and with more patients, this would certainly be another contributing factor to treatment disparities in Malawi compared to high-income countries. Thankfully, Malawi is expected to begin radiation therapy in two centres in 2024.

In conclusion, most patients with HL in Malawi present with advanced or unfavourable risk. Treatment with ABVD is effective and well tolerated—and can be provided at an affordable price. Challenges remain in improving long-term survival in our population and to understand the mechanisms driving treatment disparities relative to high-income countries. Given high rates of death from disease progression, especially in those who relapse after ABVD, access to more effective salvage therapies is urgently needed (e.g., checkpoint inhibitors). Furthermore, in the absence of PET-CT, novel biomarkers such as circulating tumour DNA or viral biomarkers may be deployed and maintained at a significantly reduced cost compared to PET-CT, which would allow for the risk stratification of patients who are likely to benefit from alternative therapies earlier in the disease course. Additional investment and research are

warranted to help elucidate the ways in which patient outcomes can become more equitable for this curative disease that often strikes young patients and causes significant losses to society.

Contributors

Contribution: SG and MSP conceived and designed the analysis. MM, EKu, DMC, LCE, and MSP analysed, accessed, verified, and interpreted data and drafted and revised the manuscript; MM, MC, EKa, LS, NM, SG, LCE, and MSP acquired clinical data; TT, SMR, and YF acquired pathologic data; and all authors provided final approval of the manuscript.

Data sharing statement

Deidentified analytical datasets, study protocol, and analysis code are stored in a password-protected open access repository and are available upon request to the corresponding author for reproducibility upon manuscript publication (available at: http://tinyurl.com/mr34sy65).

Declaration of interests

We declare no competing interests. This work was completed while Dr. Satish Gopal was employed at the University of North Carolina at Chapel Hill. The opinions expressed in this article are the authors own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States Government.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102480.

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