RESEARCH

Patient characteristics and outcome of CD20-positive HIV-associated lymphoma: a single-center KwaZulu-Natal, South African hospital 12-year retrospective review

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Abstract

Background: Due to the high prevalence of HIV, HIV-associated lymphoma (HAL) is a common malignancy in South Africa. However, there is a paucity of literature on HAL from this region. The objective of this study was to profile the clinical characteristics and outcome of CD20-positive HAL treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), with or without rituximab (R), from a single center in KwaZulu -Natal, South Africa.

Methods: Retrospective chart review of adult patients treated from 2006 to 2018 for HIV-associated CD20-positive lymphoma. The clinical characteristics, complete response (CR), and 2-year overall survival (OS) are described.

Results: The analysis included 102 patients, 54% females, median age of 39 years, and median CD4 cell count of 196 cells/μL. Bone marrow involvement was noted in 5%. Eighty-six percent of the cohort received concomitant antiretroviral therapy and chemotherapy, 76% of the CHOP group, and 92% of the R-CHOP group. Overall, a CR was seen in 55% (95% CI 45%; 65%), with a 2-year OS of 59% (95% CI 50%, 69%). A CR was attained in 46% on CHOP and 64% on R-CHOP, with a 2-year disease-free survival (DFS) for CHOP of 42% and 50% for R-CHOP.

Conclusion: Although the clinical characteristics and laboratory findings are similar to other higher-income cohorts, there was a difference in gender and incidence of marrow involvement. The low incidence of marrow involvement has prompted more routine use of immunohistochemistry and flow cytometry in staging marrows of HAL locally. Further randomized studies are required for the establishment of locally validated, cost-effective treatment guidelines.

Keywords: HIV-associated lymphoma, CD20-positive lymphoma, AIDs-related lymphoma, Rituximab

Background

Worldwide, HIV-associated lymphoma (HAL) is a common HIV-related malignancy [1]. Most are aggressive, high-grade B cell malignancies and are classified as AIDS-related lymphomas [2]. Prior to antiretroviral therapy (ART), the incidence was 60–200-fold higher than that seen in HIV-negative subjects, but has decreased to 11–25-fold with the widespread use of ART [3]. The prevalence of HIV in South Africa (SA) is estimated at 13.5% (8 million people), with the province of KwaZulu-Natal leading the provinces at a seroprevalence of 18% [4, 5].

Treatment for HAL has evolved from low dose chemotherapy to full dose cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) with ART [6–8]. Rituximab (R), a chimeric anti-CD20 monoclonal antibody, was initially added to the treatment of CD20-positive lymphomas in HIV-negative patients after randomized controlled trials showed improved complete response (CR)

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and improved event-free and overall survival with the addition of rituximab [9]. A meta-analysis by Barta et al., using individual patient data of 1546 patients with HAL, from 19 clinical trials from North America and Europe, demonstrated a clear survival benefit with the addition of rituximab to standard chemotherapy [10]. This ushered in R-CHOP as the regimen of choice for CD20-positive HAL [11–13].

There is limited data from South Africa on HAL, particularly on outcomes with rituximab [14]. Here we describe the presentation and outcomes of CD20-positive HAL from a resource-constrained, single institute, at the epicenter of the HIV AIDS epidemic. A shift in treatment midway through the study period, from CHOP to R-CHOP, provided an opportunity to describe outcomes with and without rituximab.

Methods

Clinical setting

King Edward VIII Hospital is a tertiary government hospital and services a population of 11.3 million [5]. The hematology clinic attends to approximately 600 in-patients and out-patients and 30 new referrals per month. All indigent patients with HAL, except Burkitt lymphoma, are managed here.

Study design

A retrospective chart review was performed on all patients with CD20-positive HAL who met inclusion criteria and were started on treatment at the hematology clinic between January 2006 and December 2016. All patients were followed up to December 2018, to capture at least 2 years of survival data. Clinical information was obtained from patient charts, and laboratory data was obtained from the National Health Laboratory Service database. The study protocol was approved by the Biomedical Research Ethics Committee (BE043/17) and complied with the principles of the Declaration of Helsinki.

Patient selection

Chart review was restricted to HIV-positive patients over the age of 12 years, with histologically proven CD20-positive HAL. Burkitt lymphoma was excluded from this analysis. Patients with misplaced clinical notes, untraceable HIV test results, or missing histology results were excluded from the analysis. For inclusion, patients had to have received at least one cycle of CHOP or R-CHOP.

Patient diagnosis, investigation, and staging

Tissue biopsies were examined by certified histopathologists and reporting followed World Health Organization guidelines [15, 16]. All patients had Eastern Cooperative Oncology Group performance status assessments and the International Prognostic Index was calculated [17]. Clinical workup included a unilateral staging bone marrow biopsy. Cardiac function was assessed by a multiple-gated acquisition scan. Baseline staging radiology included a computerized tomography (CT) scan or a positron emission tomography (PET)-CT scan, and the Cotswolds-modified Ann Arbor system was used to stage disease [18].

Patient treatment

All patients were offered ART at time of diagnosis of lymphoma as per national guidelines [19]. Chemotherapy for lymphoma comprised one of two regimens: intravenous cyclophosphamide, doxorubicin, vincristine, and oral prednisone (CHOP), or CHOP with rituximab (R-CHOP) [20]. Regimens were designed to be repeated every 21 days for a total of six to eight cycles. From 2006 to 2013, CHOP chemotherapy was the standard of care. When rituximab became available in 2013 all patients were offered R-CHOP as the standard of care. Patients not achieving a complete response (CR) with first-line chemotherapy, were offered salvage chemotherapy and/ or radiotherapy.

Central nervous system (CNS) prophylaxis was not routinely practiced. CNS involvement was assessed clinically. If suspected, confirmation was by cerebrospinal (CSF) cytology or flow cytometry. CNS involvement was managed with alternate day intra-thecal (IT) methotrexate, cytarabine, and hydrocortisone until two consecutive CSF evaluations showed the absence of malignant cells [21]. Patients were then offered a further two to four cycles of high-dose intravenous methotrexate in addition to completing the remaining cycles of CHOP or R-CHOP chemotherapy based on willingness to be admitted for the former [22].

Neutropenia was managed with growth factors as secondary prophylaxis [23]. Patients receiving rituximab were offered isoniazid as treatment of latent tuberculosis (TB).

Response to treatment

After three to four cycles of chemotherapy, a mid-cycle PET-CT or staging CT scan was performed. PET-CT scans were reported consistently at a single center using the Deauville scoring system [24]. Response was assessed by CT scans using the revised evaluation criteria in solid tumors to define CR, partial response, and progressive disease [25]. For a complete response (CR), the PET-CT or CT scan had to show the absence of metabolic or radiological evidence of disease respectively, either halfway through chemotherapy or at the end of treatment. On PET-CT a Deauville score of < 3 was classified as a CR. A

partial response was defined as a $\geq 50\%$ reduction in the tumor size. Relapsed or progressive disease was a ≥ 50 increase in tumor or the appearance of new lesions. Stable disease was a response not meeting any of the aforementioned criteria.

Bone marrow biopsy was only repeated if the initial biopsy showed infiltration by lymphoma. If the mid-cycle staging showed a CR, patients received a further 3–5 cycles of chemotherapy. If a mid-cycle PR was noted, patients underwent repeat radiological staging at the end of 6–8 cycles [26]. Patients with CR were reviewed quarterly. Patients with no response or progressive disease at mid-cycle or with partial or no response at the end of 8 cycles were offered second-line salvage therapy.

Outcome
Study outcomes included CR, 2-year disease-free survival (DFS), and 2-year overall survival (OS). CR was defined as the absence of clinical and radiological evidence of lymphoma. Two-year DFS was the proportion free of disease at 2 years post-chemotherapy. Two-year OS was the proportion alive at 2 years post first hematology clinic presentation. As the cohort was an intent to treat group, the patients who demised or defaulted follow-up during the study were considered non-responders in the analysis.

Statistical analysis
The baseline characteristics, and responses to treatment, were compared using means (with standard deviations) for normally distributed variables, medians (with interquartile ranges and ranges) for variables that were skewed, and frequencies (with percentages) for categorical variables. To determine statistically significant differences between the arms, the chi-square test, proportion test, quantile regression, and the *t* test were used for categorical and binary variables, medians, and means, respectively. For the study outcomes (DFS and OS), Kaplan-Meier curves are presented by treatment group. A *p* value less than 0.05 was considered statistically significant. Ninety-five percent confidence intervals (CIs) were constructed for the main outcomes. All analyses were done using Stata version 15.1 (Statacorp, 2015).

Results
Baseline characteristics
From 2006 to 2018, 129 patients with CD 20 positive HAL were seen. Twenty-seven were excluded; thirteen due to untraceable histology and/or HIV results, five did not receive chemotherapy, and nine received a regimen other than CHOP or R-CHOP. Of the remaining 102, 54% were female, median age of 39 years (range 21–62), and median CD4 cell count of 196 cells/µL (range 8–784). Fifty-six patients (55%) were not on ART at lymphoma diagnosis, 40 (39%) were started on ART, and 16 (16%) did not consent to ART. Overall, five patients (5%) had bone marrow involvement by lymphoma, with three of these patients receiving CHOP and two having R-CHOP. There were three failed bone marrow tests reported. The baseline profile is described in Table 1.

Treatment and outcomes
Fifty patients received CHOP and 52 R-CHOP, with an overall CR in 56 (55%) (95% CI 45; 65%). All 45 patients who achieved a mid-cycle CR remained in CR at the end of first-line chemotherapy (Fig. 1). Of the nine patients with progressive disease at mid-cycle, 2 patients received 2nd-line chemotherapy and were then lost to follow-up within 6 months. Three of these 9 patients demised and another 4 were lost to follow-up (3 within 6 months and the 9th patient defaulted therapy at 14 months).

Twenty-three patients (46%) receiving CHOP achieved a CR (95% CI 32%; 61%) and 33(64%) on R-CHOP attained a CR (95% CI 49%; 76%). At the end of first-line chemotherapy, 56 patients were in a CR (45 patients at mid-cycle and 11 patients converted from mid-cycle PR to end-of-treatment CR). Two patients with a CR relapsed at 4 and 5 months. Both patients received salvage chemotherapy, with 1 achieving a second CR with salvage chemotherapy and remaining in CR at 2 years and the second patient defaulted follow-up after 12 months. The disease-free survival and overall survival for the 2 treatment groups are shown in Figs. 2 and 3, respectively. Overall, 12 patients died during treatment. Nine patients died before completing chemotherapy and 3 patients died after being re-staged and assessed as having progressive disease. Eleven patients died within 6 months and the twelfth patient died at 10 months with sepsis. Sepsis accounted for four deaths (8%) in the CHOP arm and two (4%) in the R-CHOP group. The remaining six deaths were attributed to the progression of lymphoma (4 patients) or toxicity of chemotherapy or lymphoma (2 patients). The results are described in Table 2.

Infectious complications
The overall incidence of infectious complications was similar in the two treatment arms (Table 2). Eleven patients were on TB treatment at diagnosis of lymphoma, seven received CHOP and four R-CHOP. Two were diagnosed with TB based on findings on the initial staging bone marrow examination. One had granulomatous

Table 1 Baseline profile of patients with CD20-positive HAL presenting to King Edward VIII Hospital from 2006 to 2018

	Total *n* = 102 (%)	CHOP *n* = 50 (%)	R-CHOP *n* = 52 (%)	*p* value (CHOP vs R-CHOP)
Histology				0.540
DLBCL	70 (70%)	35 (70%)	35 (67%)	
HGBCL	31 (61%)	14 (28%)	17 (33%)	
Other	1 (2%)	1 (2%)	0	
Median age in years (IQR)	39 (12)	38 (9)	39 (12)	0.525
Female	55 (54%)	31 (62%)	24 (46%)	0.108
ECOG ≥ 2	88 (86%)	44 (88%)	44 (85%)	0.618
Median CD4 in cells/µL (IQR)	196 (209)	143 (175)	228 (211)	0.166
CD4 ≤ 200 cells/µL	53 (52%)	30 (60%)	23 (44%)	0.210
CD4 > 200 cells/µL	49 (48%)	20 (40%)	29 (56%)	
ART at lymphoma diagnosis	46 (45%)	18 (36%)	28 (54%)	0.021
Extra nodal disease	72 (71%)	36 (72%)	36 (69%)	0.711
B symptoms	32 (31%)	17 (34%)	15 (29%)	0.437
Bulky disease[a]	36 (35%)	18 (36%)	18 (35%)	0.778
Stage III/IV disease	46 (45%)	21 (42%)	25 (48%)	0.180
IPI score				0.398
1 (low risk)	17 (17%)	9 (18%)	8 (15%)	
2 (low intermediate)	31 (30%)	18 (36%)	13 (25%)	
3 (high intermediate)	23 (23%)	11 (22%)	12 (23%)	
4–5 (high risk)	30 (29%)	12 (24%)	19 (37%)	

HAL HIV-associated lymphoma, *DLBCL* diffuse large B cell lymphoma, *HGBCL* high-grade B cell lymphoma, *ECOG* Eastern Cooperative Oncology Group, *ART* antiretroviral treatment, *IPI* International Prognostic Index

[a] Bulky disease defined as tumor measuring ≥10 cm

inflammation consistent with TB with no acid-fast bacilli seen or cultured. In the other bone marrow, acid-fast bacilli were seen and *Mycobacterium tuberculosis* was cultured. During chemotherapy, six patients on CHOP and three on R-CHOP developed TB, eight pulmonary, and one both pulmonary and meningeal TB. None of the patients on CHOP received TB chemoprophylaxis while 69% on R-CHOP did.

Of 13 infections in the CHOP group, seven led to admission and were due to *Klebsiella septicemia*, TB meningitis, cellulitis, cryptococcal meningitis, lung abscess, bronchitis, and neutropenic sepsis. Eight of 16 infections in the R-CHOP group led to admission. One had sepsis at the site of tumor biopsy, four had neutropenic sepsis, two had pneumonia and one had shingles. Infections managed as outpatients involved the upper respiratory, lower respiratory, and gastrointestinal tracts. In the subgroup with CD4 cell count < 50 cells/µl, three of eight in the CHOP and one of three in the R-CHOP group developed sepsis. All of the former died from sepsis. Overall in the whole cohort, infections were seen in 36% of patients with CD4 < 50 cells/µl, and 28% with CD4 > 50 cells/µl (*p*=0.580).

CNS disease

Seven patients had CNS disease at presentation, four with leptomeningeal and three with parenchymal involvement. Of the four that presented with leptomeningeal disease, three were treated with CHOP and triple IT chemotherapy. One attained CR and survived 72 months. The other two had leptomeningeal relapse within a year of presentation; one achieved a CR with high dose methotrexate (HD-MTX) and survived 71 months, then defaulted and the other also defaulted treatment with OS of 14 months. The remaining patient presenting with leptomeningeal disease, cleared the CNS disease after completing six cycles of R-CHOP and triple IT chemotherapy but was lost to follow-up after eight months. An additional patient was noted to have leptomeningeal involvement after two cycles of R-CHOP. This patient died after receiving four more cycles of R-CHOP and three doses of IT chemotherapy.

All three patients with parenchymal disease received HD-MTX. The one patient that received CHOP and two cycles of HD-MTX attained a PR and was lost to follow-up after 27 months. Of the two that received R-CHOP, one was lost to follow-up after six cycles of
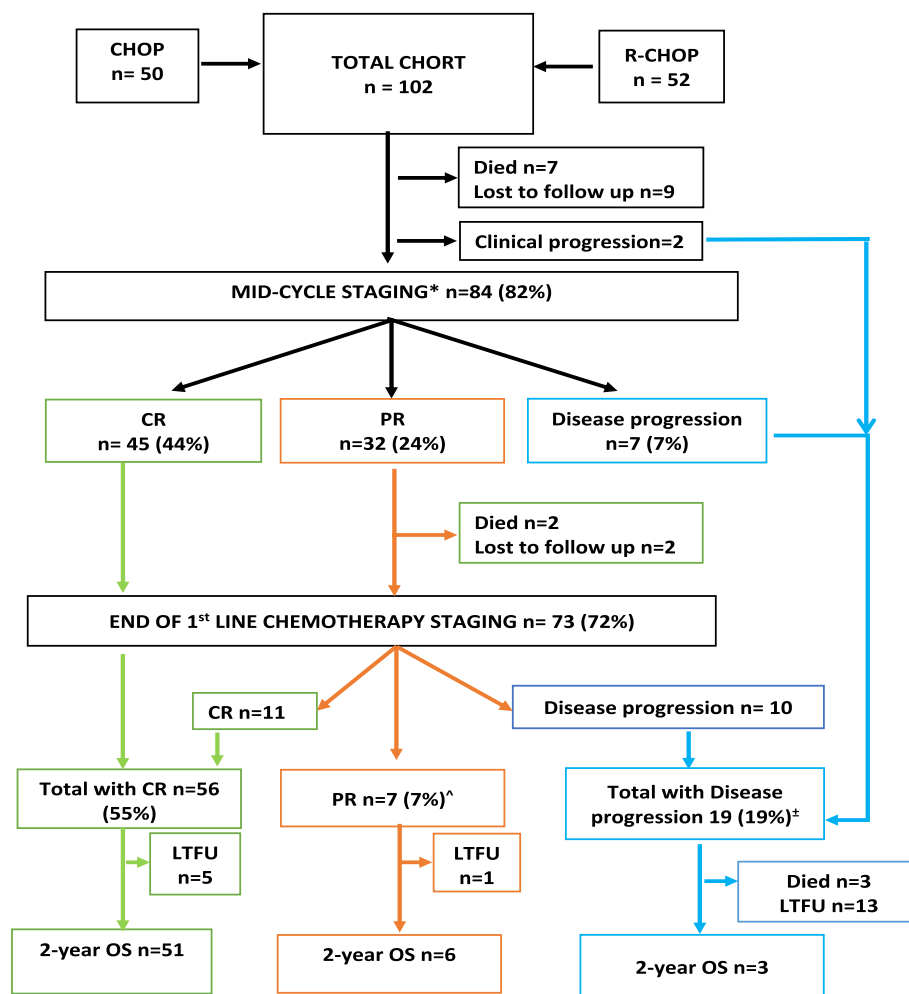
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Fig. 1 Treatment, response, and 2-year outcome in CD 20 positive HAL

Abbreviations:*CHOP* cyclophosphamide, doxorubicin, vincristine, prednisone, *R* rituximab, *CR* complete response,*PR* partial response, *LTFU* lost to follow up, *OS* overall survival. *10 patients had CTscans and 74 patients had PET-CT scans at mid-cycle re-staging. ^6 patients received 2nd linechemotherapy and/or radiotherapy. ±10 patients received 2nd linechemotherapy

chemotherapy and the other achieved a CR and survived 30 months.

Discussion

This is the first study from KZN, South Africa, to describe the profile and outcomes of CD20-positive HAL. The median age of the cohort was 39 years, 54% females, and approximately 50% with advanced-stage disease and high-risk International Prognostic Index scores. This is similar to cohorts described in Europe and Asia with the exception of the sex distribution [27–29]. From 2008 to 2013, during which time 49% of the cohort had already presented, the standard of treatment was CHOP chemotherapy. The female predominance during that period is best explained by the demographic profile of HIV in SA [30, 31], which is consistent with other reports from SA [32, 33]. From 2013 onwards the treatment of choice was R-CHOP. The male predominance during this period was likely due to a combination of improved uptake of ART by males as the rollout of ART in SA matured and a shift in health-seeking behavior of males from traditional to conventional medical care [34].

HAL is associated with more extranodal disease and bone marrow involvement [35, 36]. Here, consistent with other reports, more than 70% of patients presented with extranodal disease [36]. The 5% bone marrow involvement contrasts with other studies from SA and Europe
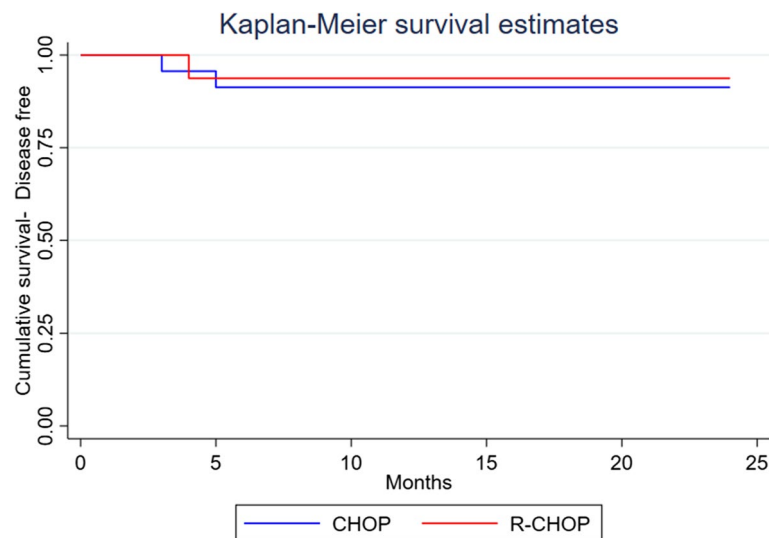
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Fig. 2 Disease-free survival by group

Abbreviations: *CHOP* cyclophosphamide, doxorubicin, vincristine, prednisone, *R* rituximab
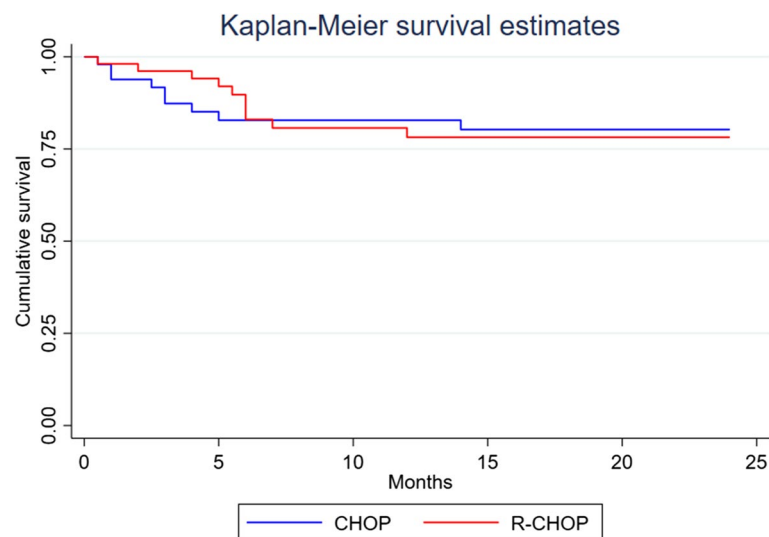

Fig. 3 Overall survival at 2 years by group

Abbreviations: *CHOP* cyclophosphamide, doxorubicin, vincristine, prednisone, *R* rituximab

where marrow involvement ranged from 13 to 35% [33, 37]. It is noteworthy that in this clinical cohort bone marrow involvement was determined exclusively by histology, without the use of the more sensitive routine immunohistochemical and immunophenotyping techniques currently available [38].

The complete response of 55% (95% CI 45%; 65%) and 2-year OS of 59% (95% CI 50%, 69%) was an improvement on a study from the Western Cape province of SA which reported a CR of 39% and 2 year OS of 40.5% [14]. Of interest a study from Uganda, which like the Western Cape study reported exclusively on the use of CHOP, showed a CR of 27% [14, 39].

As rituximab became available in 2013, a change in treatment regimen halfway through the study to include

Table 2 Response to first-line chemotherapy for patients with CD20-positive HAL treated at King Edward VIII Hospital

			Total $n = 102$ (%)	CHOP $n = 50$ (%)	R-CHOP $n = 52$ (%)	P value (CHOP vs R-CHOP)
Complete response			56 (55%)	23 (46%)	33 (64%)	0.147
Total no. of chemotherapy cycles received by 56 patients that achieved CR	**3–5**		4 (7.2%)	1 (4.3%)	3 (9.1%)	0.240
	6–8		52 (92.8%)	22 (95.7%)	30 (90.9%)	
Partial response			7 (7%)	6 (12%)	1 (2%)	0.220
No response/progressive disease*			14 (14%)	7 (14%)	7 (14%)	
Lost to follow-up**			13 (13%)	7 (14%)	6 (12%)	
Died#			12 (12%)	7 (14%)	5 (10%)	
2-year DFS			47 (46%)	21 (42%)	26 (50%)	0.585
2-year OS			60 (59%)	30 (60%)	30 (58%)	0.100
Concurrent ART			86 (84%)	38 (76%)	48 (92%)	0.027
Hospitalization			29 (28%)	12 (24%)	17 (33%)	0.331
Infections±			29 (28%)	13 (26%)	16 (31%)	0.594
Infectious complications CD4 > 50 cells/µL ($n = 91$)			25 (28%)	10/42 (23%)	15/49 (30%)	0.381
Received red cell transfusion			27 (26%)	9 (18%)	18 (35%)	0.057
Received granulocyte colony-stimulating factor			35 (34%)	17 (34%)	18 (35%)	0.915

HAL HIV-associated lymphoma, *CHOP* cyclophosphamide, adriamycin, vincristine, prednisone, *R-CHOP* rituximab with CHOP, *CR* complete response, ±Excluding TB, *DFS* disease-free survival, *OS* overall survival, *ART* anti-retroviral therapy

*An additional 5 patients with disease progression were lost to follow-up or demised

**2 patients had progressive disease at the time of loss of follow-up

3 patients had progressive disease at the time of death

rituximab created an opportunity to report on the response to rituximab. The CR increased by 18% with rituximab. These results are similar to the first randomized trial comparing CHOP and R-CHOP by Kaplan et al. [40]. It is worth noting that the benefit of rituximab internationally was only demonstrated when individual patient-level data was pooled to achieve adequate power for analysis [10, 41]. Of interest, the CR and OS with R-CHOP here were similar to that described in studies from Europe [36, 40].

Case reports of rituximab use in rheumatology practice have shown an increased incidence of TB. In this study, rituximab did not increase the incidence of TB, which is consistent with reports on its use in hematology patients in general [42–44]. However, when interpreting this one should take into account that Isoniazid prophylactic therapy was taken by 69% of patients receiving R-CHOP and none that were taking CHOP, which might have biased the outcome. British and European guidelines do not recommend TB prophylaxis with rituximab, even in high prevalence settings which is our current practice [45].

Anemia is an established side effect of rituximab, but poorly described in this context [40]. Here, there was a trend towards increased transfusion requirements among patients receiving rituximab. A possible confounder was

the increased use of ART with R-CHOP which might have contributed to the anemia [46].

Due to multiple challenges, including patient and health care factors, routine CNS prophylaxis was not practiced. In resource-limited settings, a more cost-effective and pragmatic approach is favored. This includes high vigilance for clinical signs of CNS disease and a low threshold to perform imaging or spinal fluid examination. Interestingly this strategy detected a comparable proportion of CNS disease as that reported in a UK cohort with routine CNS cytology [47], even though it is generally accepted that up to 25% of CNS involvement may be clinically silent [48]. Our findings compare with Barta et al. who described a 5% risk of CNS relapse and 50% 2-year progression-free survival; with our OS exceeding 24 months for the three patients that attained CR [49]. Although numbers are small the findings here suggest a clinically based approach to CNS involvement is not unreasonable.

Limitations of the study

The retrospective study design hampered the availability of, and access to, clinical and laboratory data. Red cell transfusion records prior to referral to King Edward VIII Hospital were not available for most patients, and the difference in baseline hemoglobin between treatment groups could not be accurately determined. Biopsy and

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bone marrow examinations were reported on by different pathologists possibly introducing observer bias. A serious limiting factor in comparing outcomes between the two treatment groups was the size of the groups. To see a statistically different CR of 10%, a sample size of 388 patients per group was needed based on a test of equality [50].

Conclusion

The clinical characteristics of patients presenting with HAL in a high HIV prevalence, the resource-limited setting was no different to cohorts described elsewhere except for a preponderance of females and a lower incidence of bone marrow involvement. Overall treatment outcomes were very similar to other cohorts despite the unique socio-economic and healthcare challenges.

Abbreviations

HIV: Human immunodeficiency virus; HAL: HIV-associated lymphoma; R: Rituximab; CR: Complete response; ART: Antiretroviral therapy; DFS: Disease-free survival; OS: Overall survival; CHOP: Cyclophosphamide, adriamycin, vincristine, prednisone; SA: South Africa; CT: Computerized tomography; PET: Positron emission tomography; CNS: Central nervous system; CSF: Cerebrospinal fluid; IT: Intrathecal; TB: Tuberculosis.

Availability of data and materials

All patient files are stored in the hematology clinic filing room at King Edward VIII Hospital and are available for review.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE043/17) in October 2017. As the study was retrospective, there was no study-specific consent. All patients granted verbal or written consent prior to and investigation or treatment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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