PROFILE AND MANAGEMENT OF AIDS RELATED LYMPHOMA

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PREFACE

The work described in this manuscript was conducted at King Edward Vlll Hospital, which is a tertiary, academic hospital affiliated to the Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa under the supervision of Professor Yunus Moosa.

This work has not been submitted in any form for any diploma or degree to any tertiary institution. Work submitted to journals is indicated in the text.

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DECLARATION

I, Nadine Rapiti, declare that

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I was the primary investigator and main author on all 3 papers submitted for publication.

The contributions of others to the project was as follows:

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Nadine Rapiti

DEDICATION

This thesis is dedicated to my dad who taught me that “Knowledge is power, but humanity starts with **SHARING** knowledge”

To my wonderful mum and siblings, for the nurturing and support
To Jaiden and Jared, for teaching me to find the rainbows after the rain
To Jayan, for riding with me always
To M, I forgive you

To my family, friends, colleagues for sharing moments and creating memories

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ABSTRACT

Worldwide, HIV-associated lymphoma (HAL) is a common HIV-related malignancy. Most are aggressive, high-grade B cell malignancies and are classified as AIDS Related Lymphomas (ARL). ARL include Diffuse large B cell lymphoma (DLBCL), Burkitt lymphoma (BL), and less commonly, plasmablastic lymphoma (PBL), primary effusion lymphomas (PEL) and primary central nervous system lymphoma (PCNSL). Prior to antiretroviral therapy (ART), the incidence of lymphoma was 60-200 fold higher than that seen in HIV-negative subjects, but this has decreased to 11-25 fold with the widespread use of ART.

The prevalence of HIV in South Africa (SA) is estimated at 13.5% (8 million people), with the province of KwaZulu-Natal (KZN) leading other provinces at a seroprevalence rate of 18%. Most patients in SA access medical care through government health facilities. King Edward Vlll Hospital (KEH) is a government-funded, tertiary health care centre affiliated with the academic hospital of the Nelson R. Mandela School of Medicine of the University of KwaZulu located in Durban, KZN. Most ARL in the indigent population, other than BL, are treated at KEH. The aim of this original research was to describe the profile, outcome and prognostic variables of ARL treated in a government hospital at the epicentre of the HIV/AIDS pandemic in KZN, and compare this to data described elsewhere in South Africa and internationally.

There is limited data from South Africa on ARL, and no data from KZN. Globally, conventional chemotherapy for ARL has been supplemented by rituximab, which is a monoclonal antibody targeting CD20. A shift in treatment midway through this study period, to include the use of rituximab locally for CD20-positive ARL, provided an opportunity to compare outcomes with and without rituximab.

Plasmablastic lymphoma is a challenging ARL, in terms of diagnosis and management. As this is an unusual lymphoma, with a prevalence of 0.004% of all lymphomas, there

are no large, prospective trials. We describe our experience with the profile and outcome of this cohort of ARL patients, treated with combination chemotherapy.

Outcome in lymphoma is guided by prognostic scoring systems, the international prognostic index (IPI) or the age-adjusted IPI (aaIPI). As these prognostic scoring systems have not been validated in the local population in KZN, the utility of these scoring systems was assessed in this research.

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ABBREVIATIONS

aaIPI	Age adjusted IPI
ACVBP	Doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone
aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio
ARL	AIDS Related Lymphoma
ART	Antiretroviral therapy
BL	Burkitt lymphoma
BM	Bone marrow
CD	Cluster of differentiation
CHOEP	Cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
CNS	Central nervous system
CR	Complete response
CR_1	Complete response with 1st line chemotherapy
CR_s	Complete response with salvage chemotherapy
CRu	Complete response unconfirmed
CSF	Cerebrospinal fluid
CT	Computerised tomography
DA-EPOCH	Dose adjusted EPOCH
DFS	Disease free survival
DLBCL	Diffuse large B cell lymphoma
EBER	Epstein-Barr virus (EBV) encoded RNA
ECOG	Eastern Cooperative Oncology Group
EPOCH	Etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin
HAL	HIV associated lymphoma
HD-MTX	High dose methotrexate
HIV	Human Immunodeficiency Virus

IPI	International prognostic index
IT	Intrathecal
KEH	King Edward Vlll Hospital
KZN	KwaZulu-Natal
LDH	Lactate dehydrogenase
m-BACOD	Methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone
MINE	Mesna, ifosfamide, novantrone, etoposide
MSM	Males having sex with males
NHL	Non-hodgkin lymphoma
NHLS	National Health Laboratory Service
OS	Overall survival
PBL	Plasmablastic lymphoma
PCNSL	Primary CNS lymphoma
PD	Progressive disease
PEL	Primary effusion lymphoma
PET	Positron emission tomography
PFS	Progression free survival
PLWH	People living with HIV
PR	Partial response
R	Rituximab
SA	South Africa
SOC	Standard of care
TB	Tuberculosis
VL	Viral load

CHAPTER 1

1.1 Background and study context

Lymphomas that occur more frequently in people living with HIV(PLWH) are referred to as HIV-associated lymphomas (HAL). Three malignancies are considered AIDS-defining: high-grade non-Hodgkin lymphoma (NHL), Kaposi sarcoma and invasive cancer of the cervix.[1] The AIDS-defining high-grade NHL are collectively called AIDS-related lymphomas (ARL) and include diffuse large B cell lymphoma (DLBCL), Burkitt lymphoma (BL) and less commonly, plasmablastic lymphoma (PBL), primary CNS lymphoma (PCNSL) and primary effusion lymphoma (PEL). DLBCL and BL usually express CD20, and the other ARL are generally CD20 negative.[3] The risk of PLWH developing ARL has decreased since 1996 due to the widespread use of antiretroviral treatment (ART). Despite this, NHL remains one of the most common malignancies in PLWH and the most common cause of AIDS-related deaths due to malignancy.[1]

Sub-Saharan Africa is home to 21% of the global population of PLWH, the largest burden, but most studies on HAL or ARL are from developed countries. King Edward VIII hospital (KEH) is a government-funded, tertiary, academic hospital in the province of KwaZulu-Natal (KZN), South Africa. This province has an HIV seroprevalence of 18%. KEH manages most of the ARL in the indigent population, which is based on international practice within the constraints of local resources. In light of economic constraints and a high burden of disease, it is imperative to assess if internationally adopted treatment regimens are safe and effective in the local population.

1.2 Description of core research problem and its significance

The aim of this body of work was to describe the clinical, radiologic and laboratory characteristics of patients presenting with CD20-positive ARL and plasmablastic lymphoma in a tertiary academic hospital in KZN. In addition, the response to treatment, survival outcomes, and the value of prognostic variables were assessed.

1.3 Review of the literature

1.3.1 Profile of ARL

The profile and management of ARL have been the focus of many studies[1-3] Unlike high-grade NHL in immunocompetent patients, ARL tends to present in younger patients, with more advanced stage disease, frequent involvement of extranodal sites, B symptoms and bone marrow infiltration (**Table 1**). [2-8] It is worth noting that most of the data come from studies outside Africa, with an under-representation of African ethnic groups in these studies.[1-3,5]

An early American ARL study by Levine et al[3] described over 75% of the cohort giving a history of men having sex with men (MSM). This study found a strong male predominance, with a slightly increasing prevalence of ARL in females over the 4 study time periods. Similarly, other studies showing a strong male predilection generally described cohorts with higher MSM.[2,5,6] This is unlike the gender distribution in India[4] and Africa[8] (where the main mode of HIV transmission is heterosexual), but similar to the French (42% MSM)[5], American cohort[2] (MSM 81%) and Asian cohort[6] (MSM 41%). In the Indian study[4], the most common extranodal site of lymphoma involvement was the bone marrow. Cohorts from outside of India and Africa are overshadowed by the epidemiology of HIV in those regions. Therefore, studies from those regions which dominate the literature, are overrepresented by males, MSM, and white ethnicity.

The median baseline CD4 count in the African study[8] was reasonable, at 198 cells/μL, although none of the patients were on ART at diagnosis. This CD4 count contrasts with the baseline CD4 count of ≤100 cells/μL in the North American cohort[2] (also with none of the patients on ART) and raises the possibility of lymphoma presenting at higher CD4 counts in the African population.[9]

Table 1.1 Profile of AIDS Related Lymphoma

Author	n	Median Age (years)	Ethnicity	Gender M:F	EN (%)	BMI (%)	AAS III-IV (%)	B symptoms (%)
Levine et al[3]	369	38	W:51% H:39% B:8% A:1%	96:4	97%	16%	68%	65%
Kaplan et al[2]	192	38	W:68.8% B:10.9% H:18.8% O:1.6%	97:3	79%	15%	67%	ND
Besson et al[5]	52	52	W:92% SS:8%	87:13	81%	14%	84%	ND
Mounier et al[7]	485	37	ND	85:15	34%*	16%	62%	52%
Xiao et al[6]	17	43	A:100%	94:6	ND	ND	70%	18%
Rudresha et al[4] **DLBCL** **PBL**	 33 15	 43 40	 ND	 1.2:1 6.5:1	 58% 73%	> EN site	 55% 20%	 63% 40%
Mwanda et al[8]	49	39	ND	0.69:1	29%*	ND	69%	88%

Abbreviations: ~~ARL=AIDS related lymphoma~~, n=number, M=male, F=female, EN=extranodal disease, BMI=bone marrow involvement, AAS=Ann Arbor stage, ND=not documented, DLBCL=diffuse large B cell lymphoma, PBL=plasmablastic lymphoma, H=Hispanic, B=Black, A=Asian, W=White, O=other, SSA=sub-Saharan African

*proportion with involvement of ≥2 extranodal sites

1.3.2 Evolution of chemotherapeutic regimens for management of CD20 positive ARL

With the availability of highly effective ART and improvement in life expectancy, the management of ARL gained priority. One of the first studies looked at combination chemotherapy comprising methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD) in two different dosing schedules.[2] The patient profile is shown in **Table 1.1**, and none of the patients were on antiretroviral therapy (ART), as shown in **Table 1.2**. Both arms performed equally based on survival outcomes. However, it is noteworthy, that survival appeared more significantly associated with the CD4 count at baseline than the intensity of chemotherapy. This suggested that HIV was still the dominant factor in survival, underscoring the importance of addressing the HIV disease in addition to the malignancy.

The subsequent chemotherapy regimen explored in ARL was bolus chemotherapy in the form of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). A prospective study by Ratner et al[10] compared standard and modified doses of CHOP. The study found that the complete response (CR) was better with standard or full dose CHOP compared to reduced dose CHOP, but this was not statistically significant (**Table 1.2**). However, there was a shorter period of disease free survival (DFS) for the modified dose CHOP, hence there was still a need to optimise chemotherapy.

A novel approach, considering many of the challenges faced in low-income countries, was taken by Mwanda et al.[8] This study explored the efficacy of an oral regimen, specifically chosen for its low toxicity (omitting doxorubicin), limited impact on immunity (no steroids) and reduced need for monitoring. The short time survival was comparable with standard CHOP; however, the long-term survival was disappointing. The median overall survival (OS) was 12.3 months. 38 patients went on to receive 2nd line CHOP chemotherapy. The results are shown in **Table 1.2**. This was an interesting approach to ARL management, with first-line oral chemotherapy, and 78% of the cohort receiving what is often considered standard first-line chemotherapy as 2nd line therapy. This was based on what was considered practical in an African country, with potential

also for good patient compliance. The CR was comparable to 1st line CHOP; however, the 5 year survival was lower than that reported for upfront bolus chemotherapy.

Table 1.2 Patient characteristics and chemotherapy evolution in AIDS Related Lymphoma

Author	Study design/ Number	Median CD4 count in cells/µL	% on ART with chemo	Treatment	CR	Survival
Kaplan et al[2]	RCT PIII			M-BACOD		Median OS
LD	98	100	0		42%	35weeks
SD	94	107	0		51%	31 weeks
Mwanda et al[8]	Prospective 49	198	37%*	Oral CMT	58%	5-yr OS 33%
Ratner et al[10]	Prospective Phase II	-	100%	mdCHOP vs SD CHOP		Median DFS 16 months
mdCHOP	40				30%	DFS 16 months
CHOP	25				48%	DFS NR

Abbreviations: LD=low dose, SD=standard dose, RCT=randomised controlled trial, CMT=chemotherapy, mdCHOP=modified dose cyclophosphamide, doxorubicin, vincristine, prednisone, DFS=disease free survival, NR=not reached, P=phase, ART=antiretroviral therapy, CD4=cluster of differentiation 4, CR=complete response

*37% received ART concurrently or on completion of CMT

1.3.3 Concomitant use of ART and chemotherapy

Ambivalence around initiating ART at the time of lymphoma chemotherapy was based on concerns for overlapping toxicity (myelotoxicity and neurotoxicity), drug-drug interactions, and pill burden affecting adherence versus potential survival benefit from early treatment of HIV. A North American study[10] addressed how well co-administration of ART with chemotherapy was tolerated, with all patients receiving

concurrent ART with CHOP chemotherapy. In terms of pharmacokinetics, cyclophosphamide clearance was 1.5 times less than controls, but doxorubicin clearance and ART concentration were unaffected. In terms of the side effect profile, full dose CHOP and ART were both well tolerated, and this supported the move toward concurrent ART with full dose bolus chemotherapy in ARL.

This need to optimise chemotherapy dosing in ARL stemmed from poor survival in the pre- ART era.[2,7] From the international studies, it was known that global ART use improved CD4 count and immune function within a month of starting ART, thereby reducing the risk of opportunistic infections.[11,12] Virological response to ART was found to significantly correlate with CR, and improved OS.[11,13,14]

Other studies showed that concomitant use of ART with chemotherapy convincingly demonstrated significantly improved overall survival (OS), without the need to adjust the dose of ART or chemotherapy .[7,15,16] **Table 1.3** details the studies showing survival outcomes pre-ART and with ART or comparing outcomes with and without ART in the same study.

Table 1.3 Survival outcome with Anti Retroviral Therapy use in AIDS Related Lymphoma

Author	Pre-ART OS	OS in ART era
Kaplan et al[2]	OS 31-35 weeks	-
COHERE[13]	-	1 year OS 66%
Mounier et al[7]	3-year OS 21%	3-year OS 37%
Besson et al[5]	-	2 year OS 75%
Barta et al[15]	2 year OS 24%	2 year OS 67%
Xiao et al[6]	-	1year OS 82% Median OS 26.6 months
Lim et al[16]	8.3 months	OS 43.2 months

Abbreviations: OS=overall survival, COHERE=Collaboration of Observational HIV Epidemiological Research Europe

The limitations from COHERE[13] (a collaboration of observational cohort studies amongst 30 European countries) were the inability to separate the histological sub-types of the different ARL, apart from primary CNS lymphoma (PCNSL), and the lack of documented chemotherapeutic regimen detail; both factors affecting OS. In Africa, survival trebled with concurrent ART, even with lower intensity oral chemotherapy.[8] Consistent with this finding, irrespective of the chemotherapy regimen used, several European and Asian studies have shown a statistically significant improved OS with ART use.[5,6,7,16] The second Asian study[6] looked at 17 patients with DLBCL, all of whom received ART, and showed an even better 1-year survival than the COHERE group.[13]

The management of ARL had therefore evolved from low dose chemotherapy to full dose CHOP with ART. Better control of HIV with ART, shifted the focus to optimising lymphoma management, similar to HIV negative patients.

1.3.4 Rituximab safety and efficacy in ARL

It is intuitive to expect that by approximating the treatment of ARL to regimens used for non-HIV-related lymphomas would achieve survival rates closer to that seen in the HIV-negative subjects. Thus, investigators explored adding rituximab to the treatment regimens for ARL. 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 CR, and improved event-free and overall survival (OS) with the addition of rituximab. The next step was therefore to establish whether rituximab could safely improve **the** outcome in ARL?

Kaplan et al[17] in 2005, answered this question in his publication of the first phase 3 trial comparing CHOP with R-CHOP in HIV-NHL in North America. 150 patients with HIV-NHL were randomised to rituximab plus CHOP (n = 99) vs CHOP (n = 51). Patients on rituximab who achieved a response were put on maintenance rituximab every 3 months. 80% of the patients had DLBCL with a spattering of other histologic types of ARLs. Although the CR for R-CHOP was better than CHOP, this was not statistically significant. Of concern, infection related deaths occurred in 14% of the R-

CHOP compared to 2% of the CHOP arm (p= 0.035); 60% of deaths occurred in patients with CD4 counts < 50 cells/μL. This raised safety concerns especially for patients with CD4 counts < 50 cells/μL. It is notable that lymphoma-related deaths were fewer in the rituximab arm (14%) vs the CHOP arm (28%). This was, however, the first phase 3 study using a CD20 monoclonal antibody in combination with bolus combination chemotherapy in ARL.

In 2006, a French study,[18] looked at 61 PLWH with DLBCL (n=42), immunoblastic lymphoma (n=2), PBL (n=1) and BL (n=16). The response rate and disease-free survival (DFS) after 6 cycles of R-CHOP was evaluated, with an excellent 2-year-OS of 75%. After the 1st phase lll trial results by Kaplan in 2005[17], this paper was somewhat reassuring in terms of the use of R-CHOP in ARL, as there was no increase in life-threatening infections. Both studies above looked at ARL as a broad entity and included BL and PBL as well. So the outcomes described are not specific to the histologic subtypes of the different ARL.

Ribera et al[19] in 2008, documented the efficacy and safety of 6 cycles of R-CHOP in a Spanish phase ll trial-in HIV-DLBCL. The focus of this paper was DLBCL, which is the most common ARL seen worldwide. The adverse events were neutropenia in 48% of chemotherapy cycles, infections in 10% of chemotherapy cycles, with 7 deaths due to infection. It was surprising in this paper that the estimated 3-year OS was inferior to the 3-year DFS, as the OS is generally greater than the DFS. The paper concluded that R-CHOP "is feasible, safe, effective in HAL DLBCL".

In 2012, a German study[20] assessed the value of rituximab in an observational, multicentre, cohort ~~study~~ of 163 patients who were HIV positive and diagnosed with an ARL: DLBCL (60%), BL (32%), and HGBCL (8%). The different chemotherapy regimens included both bolus and infusional chemotherapy and were 3 weekly CHOP, fortnightly CHOP 14, the addition of etoposide to CHOP in the CHOEP regimen and infusional chemotherapy in the form of the etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin (EPOCH regimen). 44 patients with BL and DLBCL had the more intensive chemotherapy. Rituximab was added to CHOP in 74

patients (47%). 77% received at least 4 doses of rituximab. As the focus of this study was the effect of rituximab, the response to the different chemotherapy regimens was not documented. Instead, the OS and progression-free survival (PFS) at 2 years were estimated (**Table 1.4**). Importantly, the use of rituximab was associated with prolonged OS and progression-free survival (PFS). **Table 1.4** highlights the important studies in ARL using rituximab.

Table 1.4 Rituximab use in AIDS Related Lymphoma

Author	**N**	**Median CD4 in cells/µL**	**% on ART**	**CMT(N or %)**	**CR %**	**OS /DFS/ % alive at study endpoint**
Kaplan et al[17] (phase lll)	150	133	100%	CHOP (51) vs RCHOP (99)	47% 58%	OS 110 weeks OS 139 weeks
Boue et al[18] (phase ll)	61	172	69%	RCHOP	77%	2-year OS 75%
Ribera et al[19] (phase ll)	81	158	100%	RCHOP x 6	69%	3-year eDFS 77% 3 year OS 56%
Wyen el al[20]	163	205	96%	R-CMT in 74 (47%)	ND	2-year eOS 73% (rituximab) vs 49% (no R)
Barta et al[21]						
CMT	1004	334	43%	CMT in 65%	49%	64%
R-CMT	542	179	69%	R-CMT in (35%)	71%	32%

Abbreviations: N=number, ART=antiretroviral treatment, CR=complete response, OS=overall survival, eOS= estimated overall survival, DFS=disease free survival, eDFS=estimated disease free survival, R=rituximab, CMT=chemotherapy, ND=not documented

Differences in this study cohort[20] and in the AMC010 trial[17] to account for the benefit of rituximab were: in the AMC010 trial, the median CD4 count was 133 cells/µL vs 205

cells/µL in the German cohort.[20] There was a higher number of patients with a CD4 count < 50 cells/µL (25% vs 18%), more patients with advanced-stage lll/lV disease (79% vs 60%), and a lower number of ART naïve patients (26% vs 55%) in the AMC010 trial. Also in the AMC010 trial, routine antibiotic prophylaxis for neutropenic patients was not prescribed, and patients were given rituximab maintenance. This maintenance is not and has not been standard practice in aggressive CD20 lymphoma, even in HIV-negative patients.

In 2013, Barta et al[21] demonstrated a clear survival benefit with the addition of rituximab to standard chemotherapy. The study included 1546 patients with HAL from 19 prospective phase ll or lll clinical trials in North America and Europe, to assess the impact of the type of chemotherapy, rituximab and ART on CR, PFS and OS. Almost a third of this cohort (485 patients) was described in the Mounier et al[7] paper which intensified chemotherapy according to patients' prognostic risk score. The results showed that rituximab use resulted in a significantly higher CR and improved PFS and OS. Of significance, the improved outcome was seen in patients with a CD4 count ≥50 cells/µL, but not when the CD4 count was <50 cells/µL.

The authors concluded that rituximab added as a backbone to any combination chemotherapy almost trebled the CR and halved the risk of lymphoma progression or mortality from any cause.[21] This was the pivotal analysis that changed clinical practice. This ushered in R-CHOP or R-infusional chemotherapy as the regimen of choice for CD20-positive ARL. However, the use of rituximab in patients with CD4 counts <50 cells/µL remained an area of concern.

1.3.5 South African ARL profile, treatment and outcome

At the same time, local practice in South Africa for CD20 ARL was changing to incorporate the use of rituximab to CHOP chemotherapy. Although there was little South African data at the time, there were 3 South African studies of note. In 2013, De Witt et al[22] published the Western Cape experience, in a retrospective analysis between January 2004 and December 2010 looking at both the outcome and prognosis for 36 HIV lymphoma patients. The median CD4 count was 184 cells/µL. The study ethnicity

included 61% of patients of African ethnicity and 39% of mixed ancestry. All but 2 patients received CHOP. Concurrent Mycobacterium tuberculosis was seen in 25% of the patients. The estimated two-year OS was 40.5% (with a median OS of 10.5 months) and the estimated 2-year PFS was 34%.

Patel et al[23] in 2015, published the South African experience on the '**Impact of HIV on lymphoma in South Africa**', which comprehensively described the effect of HIV on lymphoma at a tertiary, public hospital in Gauteng, a province in South Africa. The study compared 2 time periods i.e.1993 to 2005 and 2006 to 2012. In the first 12-year timeframe, 32 patients and in the second 6-year time period, 85 patients with ARL were seen per year. From 1993 to 2012 the paper showed that the seropositivity in NHL at this hospital increased from 5% to 79%. Over this time, the gender had changed, from a male-to-female ratio of 1.35:1 in the first 12-year study time, to 1.1:1 in the last 6-year period (as an increasing number of females were presenting with HAL). HIV was diagnosed at the time of lymphoma diagnosis in 91% of the patients in the earlier time and 50% of the patients in the latter study time.

An earlier paper by the same author in 2007, compared the profile and outcome of NHL in patients with and without HIV from 1993 to 2005 (so the first time period for the current paper). In this cohort, the median OS was 11 months for the seropositive group vs 42 months for the seronegative group, and HIV was an independent predictor of poor outcome. Out of 198 patients during this 12-year time period, only 29 patients were on ART, and the median CD4 count was 177 cells/µL. This paper showed clearly the effect of the later ART rollout in South Africa (2004) compared to the international ART rollout (1996) in a Kaplan-Meier survival graph. Chemotherapy included CHOP or CHOEP (similar to Wyen et al[20]) and the outcome for the 2nd part of the study has not yet been published.

In 2020, Magangane et al[24] compared clinical features between HIV-negative and HIV-positive DLBCL cases in a tertiary hospital in Cape Town from 2003 to 2013. During this 11-year period, 263 DLBCL cases were grouped according to HIV status. There were similar findings in DLBCL in the HIV-negative (205 patients) cohort and HAL

(54 patients), apart from a younger age and more patients with elevated lactate dehydrogenase (LDH) levels in the patients with HAL. In the HAL cohort bone marrow involvement was seen in 33% and extranodal disease in 49%. The female predominance in this South African cohort differs from the male predominance described in the American and European cohorts in **Table 1.1**. The incidence of marrow involvement is also higher than that described for the other cohorts in **Table 1.1**. 56% of the study group received ≥ 5 cycles of CHOP. All PLWH were offered ART. 40% of the HAL group attained a CR, with 8% relapsing. The 5-year OS was 46%, which was significantly poorer than the HIV-negative cohort with a 5-year OS of 56%.

Table 1.5 Profile, treatment and outcome of South African patients with AIDS Related Lymphoma

Author	Number	Median age in years	Gender: M:F	Treatment	Outcome
De Witt et al[22]	36	37	53:47	CHOP in 94%	2-year OS 40.5%
Patel et al[23]					
1993-2005	198	36	1.35:1	CHOP or	OS 11 months
2006-2012	466	39	1.1:1	CHOEP	ND
Magangane et al[24]	54	40	43:57	CHOP	5-year OS 46%

Abbreviations: M=male, F=female, OS=overall survival, ND=not documented

1.3.6 ARL profile, treatment and outcome from Africa (outside of South Africa)

Despite the high number of PLWH in sub-Saharan Africa, there is little other data on ARL from this area. Gopal et al[25] in 2016, published their experience from Malawi for 58 lymphoma patients. 64% (n=37) of the patients were HIV positive, with a median age of 47 years. 60% of the patients were male (unlike another African cohort from Uganda and Kenya[8]) and the median CD4 count was 121 cells/μL, despite 84% of the ARL already on ART at lymphoma diagnosis. The study described the outcome of full-dose CHOP chemotherapy, with a 1-year OS of 45%. In this population, HIV was not associated with increased mortality and full-dose chemotherapy was well tolerated in

both groups. This study is the only prospective study on outcomes in ARL in sub-Saharan Africa.

In 2011, Bateganya et al[26] compared the outcome in 160 patients from Uganda (HIV positive and negative) with NHL. Of the HIV-positive NHL, 70% were male, with a median age of 37 years and 91% had advanced-stage disease, with 75% on ART. HIV-positive patients not receiving ART had a more than 9-fold increase in death compared to the HIV-negative cohort. However, patients who received concurrent ART and chemotherapy had similar survival to the HIV-negative cohort, and this contrasts with the better outcome in the British cohort by Coutinho et al[27] and the poorer Spanish outcome by Baptista et al.[28] The challenges with healthcare documented in Uganda in this paper resonate with the difficulty in South Africa in the public health sector.

Another Ugandan study by Okello et al,[29] retrospectively compared CHOP with infusional chemotherapy with dose adjusted etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin(DA-EPOCH). The 1 year OS was 55% for CHOP and 80% for DA-EPOCH, with more severe side effects in the latter group. The improved OS with infusional chemotherapy echoes the findings by Kaplan et al.[13] Over 80% of the patients were on ART at lymphoma diagnosis, and although the majority of the patients had DLBCL, there was a small number of PBL (4%) and BL (3%). There are similarities in the healthcare setting in Uganda and SA, with no private medical aid schemes for most patients and limited access to rituximab. Additionally, in our centre in KZN, infusional chemotherapy is not offered due to resource constraints and lack of a dedicated haematology ward, and this has precluded the use of EPOCH or other infusional chemotherapy thus far.

In 2020 Manyau et al[30] published data from Zimbabwe, where the aim of the study was to assess if rituximab improved OS at 18 months. This is a retrospective study of CD20 positive ARL treated with CHOP (n=97) or R-CHOP (n=27). The cohort included 100% African patients with a median age of 42 years and 57% of the study cohort were males. No survival benefit with rituximab was seen. The 12 month OS was 44%, and the median survival of 11.2 months is compared to the 10.5 months in South Africa,

referencing the de Witt paper.[22] However, the standard of care in South Africa is described as R-CHOP in this paper from Zimbabwe (again referencing de Witt). R-CHOP only became the standard of care in South Africa in 2013, and hence the treatment outcome described in the de Witt paper was with CHOP chemotherapy and not R-CHOP. This Zimbabwean paper though, is the first and largest ARL study from sub-Saharan Africa describing the use of rituximab.

1.3.7 Prognosis in ARL

As treatment for ARL lymphoma has improved over time, the emphasis on prognostic tools gained momentum. Shipp et al[31] first introduced the utility of the International Prognostic Index (IPI) in aggressive lymphoma by a publication in the New England Journal of Medicine. This was a retrospective analysis of 2031 patients with aggressive lymphoma, treated with a doxorubicin-based chemotherapy regimen. A point each was given for age >60 years, Ann-Arbor stage lll or lV, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or more, elevated lactate dehydrogenase (LDH) level and >1 extranodal site of disease. This IPI divided patients into four risk categories (shown in **Table 1.6**). based on the score (low, low and high-intermediate, and high risk). According to this data, patients could be grouped into the 4 categories with the associated CR and OS. Patients may further be categorised into 2 groups, with low-risk defined by an IPI score of 0-2 and high-risk having a score of 3-5.

Table 1.6 Outcome according to International Prognostic Index[31]

IPI category	Score	CR	5-year OS
Low	0-1	87	75%
Low-intermediate	2	67	51%
High-intermediate	3	55	43%
High	4-5	44	26%

Abbreviations: CR=complete response, OS=overall survival

In 2010, Ziepert et al[14] examined the utility of the IPI when rituximab was included in the treatment of CD20 positive lymphoma. This paper looked at 3 prospective trials,

where 1062 patients were treated with rituximab-combination chemotherapy. The study findings validated the prognostic significance of the IPI for PFS, event-free survival and OS when rituximab was used.

As the cohort of patients by Shipp and Ziepert et al[14,31] included all HIV negative patients, studies have examined the role of the IPI specifically in ARL. In 1998, Navarro et al [32] validated the utility of the IPI in 46 ARL patients with HIV-NHL treated with CHOP chemotherapy between 1988 to 1997. Importantly, the study excluded patients with an ECOG performance status of >2 and active opportunistic infection or other malignant AIDS-defining events. Although the study was limited in the patient selection, it paved the way for other studies assessing prognostic variables in ARL, including comparisons between HIV-positive and negative cohorts.[27]

In the 2006 French study,[18] the IPI correlated with OS. It is notable that no patient in this particular study had an IPI >3, which might explain the good 2-year survival, i.e. an unintentionally selected cohort with a better outcome. Supporting the prognostic value of the IPI in ARL, the 3-year OS in a Spanish study[19] **(Table 1.4)** was inferior to the French cohort[18], and this might be reflective of the larger number with a higher IPI in this Spanish group. The IPI and virological response to ART were prognostic factors for both response and survival.[19]

In 2008, the COHERE study group[13] looked at outcome and prognostic factors in HIV-NHL in 847 patients. Interestingly, the negative predictive value of ARL diagnosed whilst on ART compared to ART naïve patients at diagnosis would support the findings in the previously described paper by Wyen et al.[20] This same German study[20] also found that CD20 expression, CD4 count >100 cells/µL, ART use, low IPI score, absence of bone marrow involvement and use of rituximab were all predictive of better OS and PFS. The French-Italian collaboration[13] highlighted the prognostic significance of the CD4 count in ARL (which follows a similar thread to the Kaplan Meier graph by Patel et al[23]), and the different patient profile and outcome for DLBCL compared with PBL.

As ARL occurs in younger patients with a greater tendency to extranodal involvement, the age-adjusted International prognostic index (aaIPI) has been assessed in ARL. This score looks at only 3 of the 5 variables from the IPI (Ann Arbor stage of disease, LDH level and the patient performance status) and logically excludes the age and number of extranodal sites of disease. Patients are scored from 0-3, with a score of 0-1 being the low-risk category and a score of 2-3 comprising the high-risk group. With treatment for ARL evolving, in 2014, Barta et al[15] analysed the same 1546 cohort that proved the value of rituximab. The study defined pre-and post-ART outcomes-and showed that the prognostic significance of HIV-associated variables had declined over time, but the aaIPI was the most consistent predictor of OS.

In the Mwanda et al study[8], 3 prognostic scoring systems were analysed viz., the IPI, HIV score and AIDS Clinical Trials Group 142 prognostic index, the latter derived from the Kaplan et al[2] cohort and published by Straus et al in 1998.[33] Of the 3 prognostic scoring systems, the IPI was the best discriminator for OS. ART use was associated with an almost 12-fold increase in CR.

The HIV score was derived from a European study by Mounier et al [7], published in 2006. This score assigned a point each for diagnosis of AIDS prior to lymphoma diagnosis, poor patient performance status, and CD4 counts less than 100 cells/µL. The 3 categories are good risk (no factors), intermediate (1 factor) and poor risk (2-3 factors). Patients in the study were then stratified to receive chemotherapy according to this HIV score. Patients with a good score of 0 (n=218), received more intense chemotherapy with ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone) or CHOP, with 5-year OS of 51% vs 47% for the 2 chemotherapy regimens, respectively. Patients with an HIV score of 1, received either standard or low dose CHOP, with 5-year OS of 28% vs 24%, respectively. The high-risk patients with a score of 2-3, received either low dose CHOP or just vincristine/prednisone, with 5-year OS of 11% vs 3%, respectively. This is one of the few papers where therapy in ARL was tailored according to prognosis. However, there was no statistically significant difference in outcome based on the intensity of the chemotherapy for any of the 3 risk groups. So the three different chemotherapy regimens tried during this study did not

impact the outcome, suggesting the need for alternative chemotherapy or prognostic scoring system, if tailored therapy is to be of benefit in ARL.

In the South African studies, the only 2 prognostic variables that impacted 2-year OS were an ECOG performance status response to ART.[22] This paper is one of the few papers on ARL assessing the prognostic significance of TB co-infection (found not to be significant). This is a noteworthy finding as TB is endemic in South Africa.

Table 1.7 Prognosis in AIDS Related Lymphoma

Author	Variables correlating with outcome	Comments on variables
Navarro et al[32]	IPI	IPI of 1 favourable
Coutinho et al[27]	IPI	IPI also correlated with CR in the HIV-positive cohort
COHERE et al[13]	Lymphoma histology	Increased mortality in low CD4 count and lymphoma diagnosed on ART correlated with poor outcome
Barta et al[15]	aaIPI	aaIPI retained value in rituximab era
Mwanda et al[8]	IPI best predictor of OS	ART correlated with good outcome
Mounier et al[7]	IPI, HIV score, concurrent ART	Chemotherapy intensity did not affect outcome

Abbreviations: IPI=international prognostic index, aaIPI=age adjusted IPI, ART=antiretroviral treatment, OS=overall survival

In the other Western Cape study,[24] bone marrow involvement, the age of presentation, female gender, LDH and stage were all reported to be of poor prognostic significance. These are also variables analysed in this thesis. The authors did not report on the CD4 count or any HIV-associated prognostic variables. The IPI and aaIPI were not assessed, and were not validated in the other 2 South African studies either.[22-24]

Another African study showed a correlation between improved survival and patients who completed 6 or more cycles of chemotherapy.[29] A Zimbabwean study showed that variables associated with poorer outcome were male gender, age ≥ 40 years and < 3 cycles of chemotherapy. This survival benefit of more chemotherapy cycles is similar to the benefit seen in Uganda.[29] The poor prognostic significance of the male gender in this study contrasted with the poorer outcome associated with females in the Western Cape.[24]

With the evolution of ARL treatment mirroring that of HIV-negative lymphoma patients, the comparison of the efficacy of this treatment between the 2 groups yielded conflicting results. A British study[27] in 2014, showed significantly, better 5-year OS for the HIV-positive cohort, which contrasted with a Spanish cohort[28] 5-year OS in 2015. Based on these studies, the prognostic significance of HIV itself in high-grade lymphoma in the ART era is unclear, however, international data has proven the utility of the IPI and aaIPI in ARL.[7,8,15,27,32]

1.3.8 Plasmablastic lymphoma

Most of the papers on ARL have focused on CD20 positive lymphomas or DLBCL, as this is the most frequently seen lymphoma. Whilst there has been significant progress with the management of CD20 positive ARL, plasmablastic lymphoma (PBL) management has not been as well established. This is due to the rarity of this lymphoma, and lack of large, prospective studies. The papers on PBL have usually been small cohort studies of 20-40 patients (**Table 1.8**), similar to the cohort size described in this thesis.

The first reported cases of PBL was in 1997 by Delecluse et al, [34] describing a series of 16 PBL cases, of which 15 were in HIV-positive patients. There was an association between Epstein-Barr virus (EBV) positivity, with CD20 staining negatively or only weakly positive. Based on the morphology and immunohistochemistry, the name 'plasmablastic lymphoma' was proposed.

In 2012, Castillo et al[35] described the outcome in 50 patients with HIV-associated PBL from North and South America and Europe. 75% had a high-risk aaIPI. Just under two-thirds were treated with CHOP, with a CR seen in two-thirds. The 5-year OS was poor (24%), with advanced-stage disease and poor performance status having a negative predictive value. The aaIPI was prognostic for both the PFS and OS.

As the outcome for PBL with CHOP chemotherapy was poor, attempts to improve outcome included treatment intensification with infusional therapy, similar to DLBCL.[13,29] In 2014, Ibrahim et al[36] showed a significantly better OS when PBL was treated with infusional chemotherapy using EPOCH compared with CHOP. However, this contrasted with the better outcome shown by Loghavi et al[37] in 20 PBL patients treated with CHOP rather than those who received intensified chemotherapy. The optimal treatment for PBL, therefore, remains still undecided.

The largest study on PBL was published by Tchernonog et al.[38] The PBL cohort was from Belgium and France, and was separated into 3 groups: HIV-associated PBL (n=56), post-transplant PBL (n=17) and a third group who were HIV negative (n=62). The median age of the HIV-associated PBL was 46 years, with an equal gender distribution. Oral cavity involvement was seen in 27%, 30% had a high-risk IPI score, CD20 positivity was present in 7% and EBV encoded RNA (EBER positivity) in 77%. Most patients were treated with CHOP chemotherapy, and ART alone failed to induce a CR. Notably, improved OS was seen in PBL patients who were HIV positive compared to the other 2 groups. The outcome correlated with the IPI.

In sub-Saharan Africa, there are 3 papers on PBL from South Africa and 1 from Malawi. In 2014, Chiyapo et al[39] published the Western Cape experience. The study included 25 PLWH, with 48% having advanced-stage disease, bone marrow involvement seen in 12% and a median CD4 count of 196 cells/μL. The median OS was 1 year and the IPI was predictive of OS.

This was followed in 2017 by Jordaan et al,[40] describing the Free State experience in a cohort that included 59 patients treated from 2005 to 2013, a third already on ART at

lymphoma diagnosis and a median CD4 count of 109 cells/μL. Only 38 patients received chemotherapy/radiotherapy (21 were too ill or defaulted follow-up). The study follow-up was short with survival at 3 months documented as 92% (with ART) compared with 56% (for patients not on ART).

The third province in South Africa was represented by Vaughan et al,[41] who described PBL lymphoma data for both PLWH and HIV-negative patients at 2 time-points viz. 2007 (46 patients) and 2017 (53 patients) and showed no significant difference in the number of PBL cases over these 2 time points. More than 95% were HIV-associated PBL, and a significantly greater number were on ART with better HIV control at the latter time point. Poorer survival was noted for patients with high LDH levels and when the tumor stained negatively for EBER.

Table 1.8 Profile and outcome of HIV-associated Plasmablastic lymphoma

Author	Number	Age in years	M:F gender	Rx	CR or OS
Delecluse et al [34]	15	27-55	93:7	CMT	OS 1-18 months 53% mortality ≤ 12m
Castillo et al[35]	50	43	78:22	CHOP (63%)	CR 66%, OS 11m 5-year OS 24%
Ibrahim et al[36]	25	44	4:1	CHOP vs EPOCH	7m 17m
Tchernonog et al[38]	56	46	50:50	CHOP (most)	32m
Chiyapo et al[39]	25	35	1:1.08	CHOP	CR 63% 3-year OS 39%

Abbreviations: M=male, F=female, Rx=treatment, CMT=chemotherapy, OS=overall survival, CR=complete response, m=months

Data from Africa was shared by Zuze et al[42] with prospective data from Malawi in 2018; "**Plasmablastic lymphoma in Malawi"** in 12 PBL cases, 50% (n=6) were HIV-associated, with a median CD4 count of 147 cells/μL, a third being males and bone marrow involvement was also present in a third. Patients were treated with CHOP or modified dose EPOCH and although survival data was short, the 1-year OS was good at 67%. The small number of HIV-associated PBL precluded prognostic significance for the 2 different chemotherapy regimens.

1.3.9 Updated lymphoma work-up and assessment guidelines

As treatment for ARL was being consolidated, the investigational tools were also being refined and revised. Traditionally, patients with lymphoma, including ARL, have a staging work-up to define the extent of lymphomatous disease. Radiological staging was conventionally a computerised tomography(CT) scan, and then more often replaced by positron emission tomography (PET)-CT scans as PET-CT scans became more readily available. This staging is performed at baseline, and then repeated halfway through chemotherapy, and at the end of treatment if a CR is not documented at mid-cycle. The baseline work-up includes the functional status according to the Eastern Cooperative Oncology Group (ECOG) performance status, the lactate dehydrogenase level (LDH), a bone marrow aspirate and trephine and a CT or PET-CT scan. Additionally, patients with ARL may have an assessment of immune status in the form of a CD4 count and an HIV viral load estimate.

In 2014, Cheson et al[43] published a lymphoma guideline from an international group of haematologists, oncologists and radiologists who determined and updated the staging recommendations, radiological interpretation and utility of CT and PET-CT scans in DLBCL. It was decided that a CR in lymphoma is defined by the absence of any clinical or metabolic/radiological evidence of disease. If a PET-CT is the radiological assessment and re-assessment tool, the PET-CT should be negative, either halfway through chemotherapy or at the end of treatment, using the Deauville 5-point scoring system. A score of 1-2 was considered a CR, and 4-5 signified active disease. A score of 3 was initially thought to represent a CR, but needed to be interpreted with caution, A

partial response (PR) was a ≥50% decrease in the tumor mass and relapsed or progressive disease (PD) was defined by a ≥50% increase in existing tumor or any new lymphomatous lesions. Responses not meeting any of the criteria above would be classified as stable disease. This group discussed the merits of bone marrow biopsy in the age of PET-CT, and the recommendation was that a marrow biopsy was only indicated if a PET-CT was not suggestive of marrow involvement. An adequate trephine sample was a unilateral core of ≥ 2.5cm and should be performed with immunohistochemistry and flow cytometry routinely done at the same time.

1.3.10 Updated lymphoma treatment guidelines

Following the increasing experience and data published worldwide on the management of ARL, Hentrich et al[44] in June 2014, published a German-Practice Guideline. In this guideline, a panel of experts in HIV-related lymphoma performed literature searches, with agreement via a consensus process. It was agreed that 6 cycles of R-CHOP or infusional chemotherapy in the form of R-EPOCH should be the standard of care (SOC) for DLBCL, which is consistent with the Ugandan data.[29] No SOC for PBL could be reached. ART use concurrently with chemotherapy was recommended. CNS prophylaxis was recommended for patients at higher risk of CNS disease, defined as for HIV-negative patients (testicular involvement, an ECOG performance status of >1, >1 extranodal site of involvement and an increased LDH level). High-dose methotrexate was suggested as an alternative to intra-thecal chemotherapy. For PBL, CHOP was still recommended as the chemotherapy of choice, largely due to a lack of more effective therapy and a lack of randomised trials. For patients with a good IPI and performance status, a more intensive chemotherapy regimen, as well as myeloma-based therapy, were suggested as alternative options.

Also in 2014, Bower et al[45] published a British guideline from a panel of experts in Britain. This guide included good practice points, according to the group's experience and expertise as well, so this guideline was not only evidence-based from published literature. This guideline suggested that ARL be managed in a similar manner to lymphoma in HIV-negative patients. For DLBCL, CHOP or infusional chemotherapy with rituximab and ART was recommended. However, the authors stated that there was

no established 'gold standard' for treatment. Rituximab was suggested to be used with caution in patients with CD4 counts < 50 cells/μL. For the small number of patients with limited-stage 1 or ll disease, limited chemotherapy of 3 cycles with radiotherapy was a reasonable option. For plasmablastic lymphoma, the guideline recommended ART with anthracycline-based chemotherapy. Intrathecal prophylaxis was suggested for high-risk patients, as for HIV-negative patients with aggressive NHL. The place of radiotherapy was as consolidation for bulky disease or bony lesions, and as palliation for patients not eligible for salvage chemotherapy. Both the guidelines defined response criteria according to the Cheson et al[43] recommendations in 2014. These guidelines consolidated the findings from all the studies above and put in place a practice guideline for ARL.

1.4 A coherent problem statement highlighting the nature and magnitude of the problem, the discrepancy, knowledge gaps therein and possible factors influencing the problem.

At King Edward Vlll hospital in KZN, ARL is the most common malignancy seen. However, the profile, efficacy and prognosis of ARL treated at KEH is unknown. KEH mirrored the international changes in ARL management, first with lower dose m-BACOD (in the late '90s and early part of 2000), then full dose CHOP with ART became the standard of care from 2005. The ART rollout began in South Africa in 2004 and rituximab was approved for use in aggressive CD20 positive ARL for state or public patients in 2013. It was at this time that PET-CT scans also became available for lymphoma staging. Additionally, the safety and efficacy of rituximab in ARL in South Africa is unknown.

The study period is from 2006 to 2016. The availability of rituximab halfway through the study period allowed for comparison of CHOP and RCHOP chemotherapy in ARL in KZN. During the study time, 9 of the 158 patients presenting with ARL were treated with m-BACOD (**Figure 1.1**), and were not included in the analysis. The advantage of CHOP chemotherapy at our centre, was the ability to manage ARL as out-patients, especially in settings with ward and bed constraints in the hospital and when patients could often not be admitted due to social responsibilities. Due to these same socio-

economic constraints, routine prophylaxis of the CNS as suggested by the guidelines was not practiced.[44] Rather patients were investigated and treated on clinical suspicion of leptomeningeal involvement. However, the incidence of CNS involvement, and efficacy of local management has not been objectively documented.

The IPI prognostic scoring system has only been validated for PBL in South Africa.[39] There is no information on the IPI or aaIPI for CD20 ARL or DLBCL in South Africa, due to the small cohort size.[22]

1.5 Research questions, objectives and hypothesis and/or theoretical framework

Figure 1.1 shows the number and sub-types of ARL seen from 2006 to 2016, which is the time period of this study. The most common ARL seen was CD20 positive ARL, which is compatible with other studies.[13,18,20]

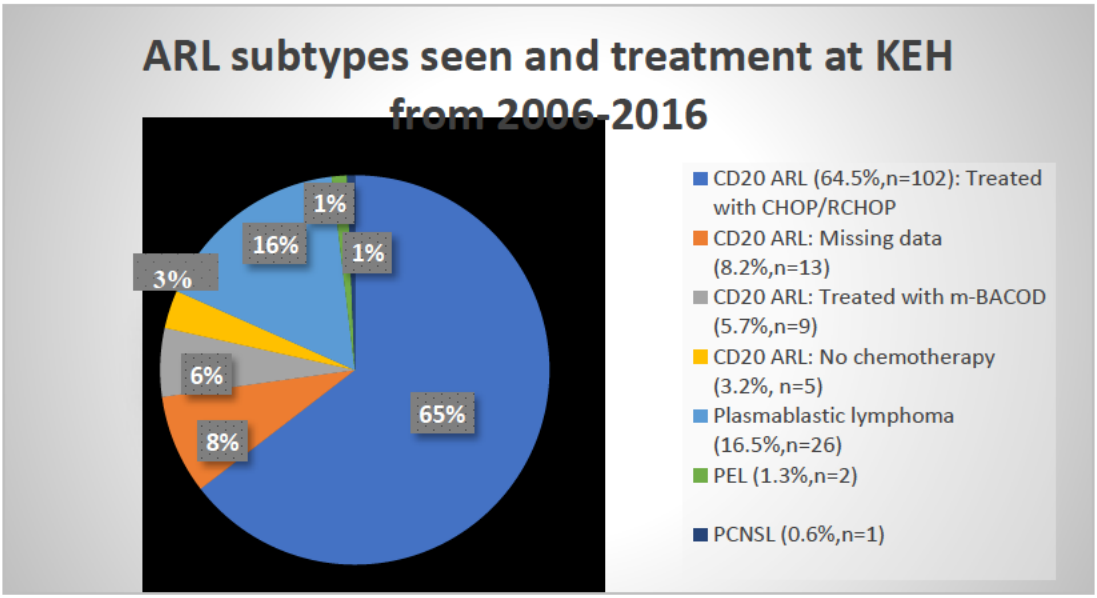

Figure 1.1 ARL sub-types and treatment seen at King Edward Vlll Hospital from 2006 to 2018
Abbreviations: ARL= AIDS Related lymphoma, KEH=King Edward Vlll Hospital, PEL=primary effusion lymphoma, PCNSL=primary CNS lymphoma, CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone, R-CHOP=rituximab-CHOP, m-BACOD= methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone

The aim of this study was to describe the clinical profile and investigational characteristics of patients with ARL in a tertiary hospital in KZN. The survival outcomes and factors predicting survival were also assessed.
The objective in Chapter 2 was to determine the profile of CD20 ARL, and compare this profile with the literature, determine the response to chemotherapy, compare CHOP and RCHOP, and describe 2-year survival outcomes. This is the first ARL description from KZN, and the 1st from South Africa comparing outcome with and without rituximab.
Plasmablastic lymphoma accounted for 16.5% of the entire cohort. The profile, response to CHOP chemotherapy and prognosis is described in Chapter 3. The German Practice guideline by Hentrich et al[44] confirms the lack of an accepted guideline for the management of plasmablastic lymphoma. Literature on this lymphoma is generally small cohort studies, including 4 studies from sub-Saharan Africa, and our local data will add to this limited pool of information.

Chapter 4 investigates the utility of the different prognostic variables, including the IPI and aaIPI in the cohort described in Chapter 2. The 2-year survival outcomes from Chapter 2 will be updated at 4 years in Chapter 4. South Africa has a unique blend of 1st and third-world medical practice and significant resource constraints. Ultimately, local data will contribute to the formulation of a practical, cost-effective guideline for ARL.

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CHAPTER 2

The literature review described in Chapter 1 highlighted the predominance of CD 20 positive ARL or DLBCL in patients with ARL. Figure 1.1 in the preceding chapter confirmed that more than two-thirds of the patients with ARL during the study time period had CD20-positive ARL. This chapter therefore describes the profile and 2-year survival outcome for this lymphoma sub-type and has been published by Journal of Egyptian National Cancer Institute (Rapiti, N., Abdelatif, N., Rapiti, A. *et al.* Patient characteristics and outcome of CD20-positive HIV-associated lymphoma: a single-center KwaZulu-Natal, South African hospital 12-year retrospective review. *J Egypt Natl Canc Inst* **34,** 32 (2022). https://doi.org/10.1186/s43046-022-00131-6).
The paper presented has been amended according to the journal reviewers' suggestions.

ABSTRACT

Patient Characteristics and Outcome of CD20 Positive HIV Associated Lymphoma: A Single Centre KwaZulu-Natal, South African Hospital 12-Year Retrospective Review

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 centre 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 two-year overall survival (OS) are described.

Results: The analysis included 102 patients, 54% females, median age 39 years, and median CD4 cell count 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 two-year OS of 59% (95% CI: 50%, 69%). A CR was attained in 46% on CHOP, and 64% on R- CHOP, with a two-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 randomised studies are required for the establishment of locally validated, cost-effective treatment guidelines.

Key words: 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 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 rate 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), 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 epicentre 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 in Durban, Kwa-Zulu-Natal, and services a population of 11.3 million.[5] The haematology 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 at this hospital.

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 haematology clinic between January 2006 and December 2016. All patients were followed up to December 2018, to capture at least two 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 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 calculated.[17] Clinical workup included a unilateral staging bone marrow biopsy. Cardiac function was assessed by multiple-gated acquisition scan. Baseline staging radiology included a computerised 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 of 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 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 centre 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 activity (Deauville score of < 3), or radiological evidence of disease respectively, either halfway through chemotherapy or at the end of treatment. A partial response was defined as a ≥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 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, two year disease-free survival (DFS) and two-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 two years post-chemotherapy. Two-year OS was the proportion alive at two years post first haematology 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, 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 survival curves are presented by the treatment group. A p-value less than 0.05 was considered statistically significant. Ninety-five percent confidence intervals (CI's) 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 CD20-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 39 years (range 21- 62 years), and a median CD4 cell count of 196 cells/μL (range 8-784 cells/μL). 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 R-CHOP. There were three failed bone marrow tests reported. The baseline profile is described in **Table 2.1**.

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 (**Figure 2.1**). 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 9thth patient defaulted therapy at 14 months).

Table 2.1. Baseline profile of patients with CD20 positive HIV Associated Lymphoma presenting to King Edward Vlll Hospital from 2006 to 2016

	Total n=102 (%)	CHOP n=50 (%)	R-CHOP n=52 (%)	p value(CHOP vs R-CHOP)
Histology				
DLBCL	70 (70%)	35 (70%)	35 (67%)	
HGBCL	31 (61%)	14 (28%)	17 (33%)	0.540
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 count ≤ 200 cells/µL	53 (52%)	30 (60%)	23 (44%)	0.210
CD4 count > 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*	36 (35%)	18 (36%)	18 (35%)	0.778
Stage lll/lV disease	46 (45%)	21 (42%)	25 (48%)	0.180
IPI score				
1 (low risk)	17 (17%)	9 (18%)	8 (15%)	
2 (Low intermediate	31 (30%)	18 (36%)	13 (25%)	0.398
3 (High intermediate)	23 (23%)	11 (22%)	12 (23%)	
4-5 (High risk)	30 (29%)	12 (24%)	19 (37%)	

Abbreviations:DLBCL=diffuse large B cell lymphoma, HGBCL=high grade B cell lymphoma, ECOG= Eastern Cooperative Oncology Group, ART=antiretroviral treatment, IPI=International prognostic index, * Bulky disease defined as tumor measuring ≥ 10cm

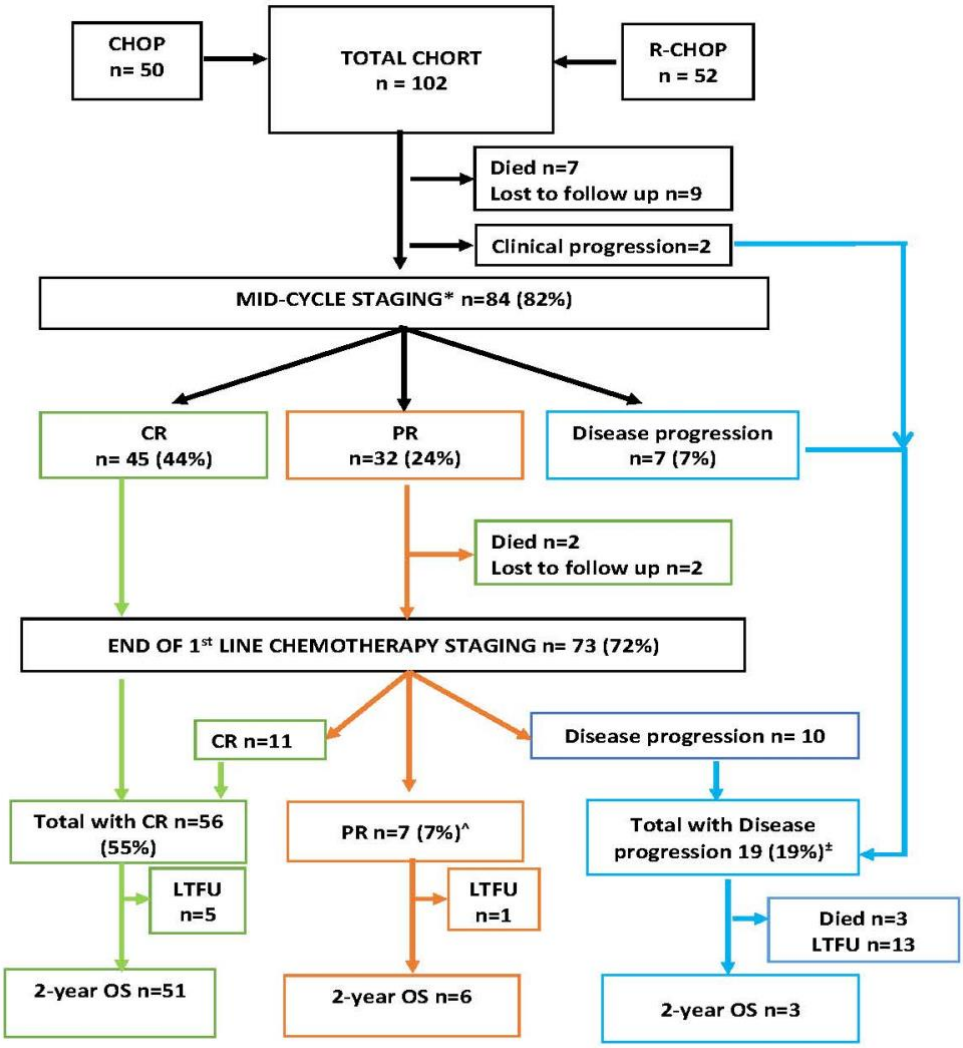

Figure 2.1. Treatment, response and 2-year outcome in CD20 positive HIV Associated Lymphoma

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 CT scans and 74 patients had PET-CT scans at mid-cycle re-staging

^6 patients received 2nd line chemotherapy and/or radiotherapy

±10 patients received 2nd line chemotherapy

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 respectively. 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 **Figure 2.2** and **Figure 2.3,** respectively. Overall, 12 patients died during treatment. 9 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 progression of lymphoma (4 patients) or toxicity of chemotherapy or lymphoma (2 patients). The results are described in **Table 2.2**

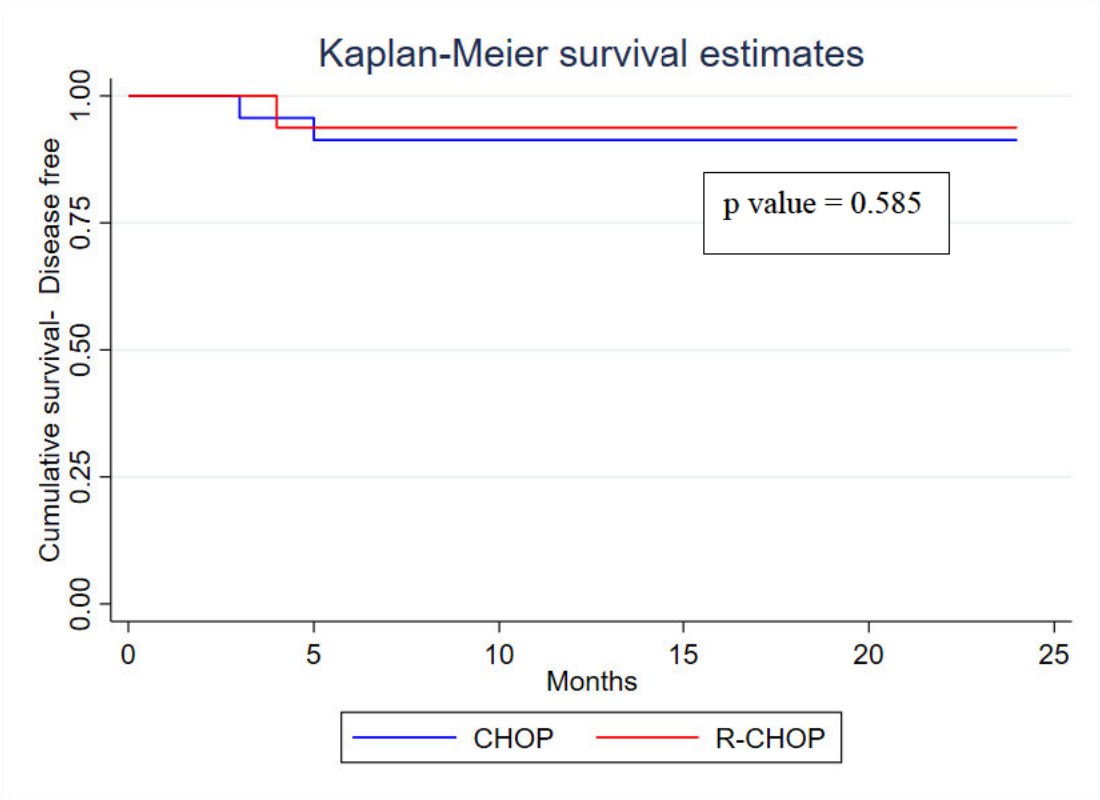

Figure 2.2 Disease-free survival for CHOP and R-CHOP chemotherapy groups
Abbreviations: CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone, R=rituximab

Infectious complications

The overall incidence of infectious complications were similar in the two treatment arms (**Table 2.2**). 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 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 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.

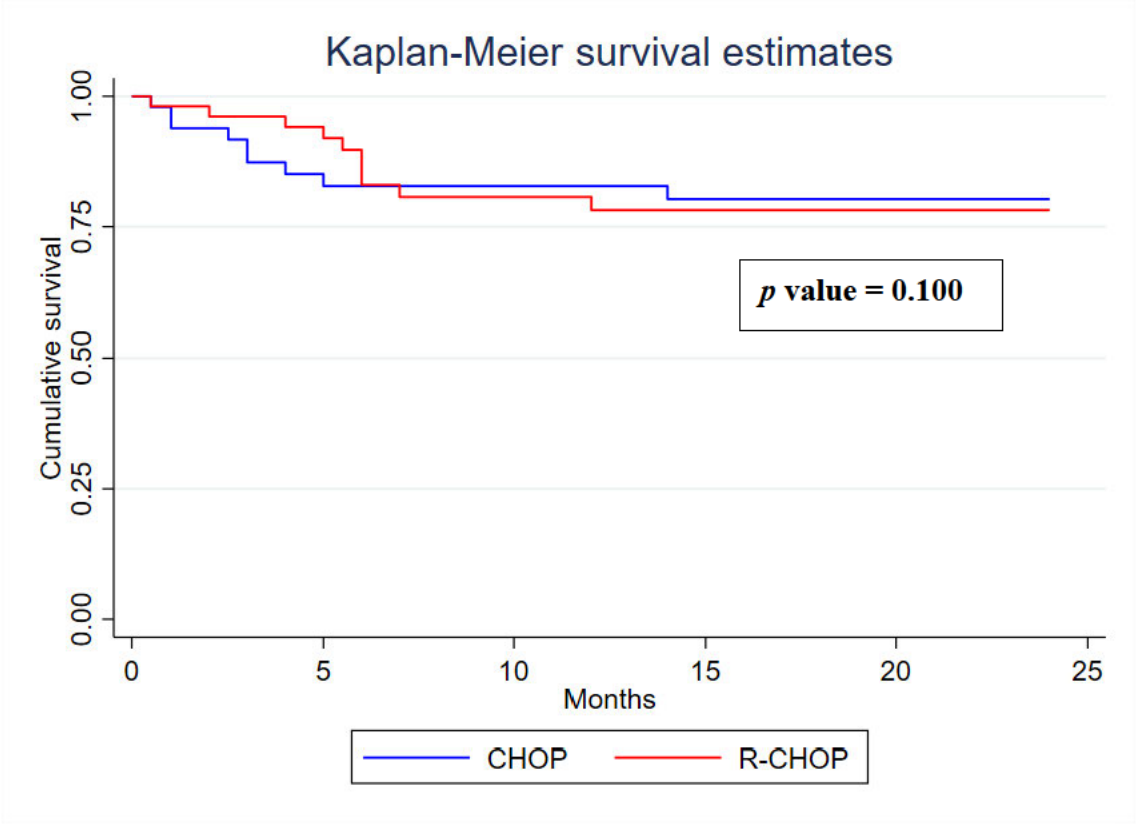

Figure 2.3. Overall survival at 2 years for CHOP and R-CHOP chemotherapy groups,
Abbreviations: CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone, R=rituximab

Of 13 infections in the CHOP group, seven led to admission and were due to Klebsiella septicaemia, 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 pneumonias and one had shingles. Infections managed as outpatients involved the upper respiratory, lower respiratory and gastro-intestinal 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).

Table 2.2 Response to first line chemotherapy for patients with CD20 positive HIV Associated Lymphoma treated at King Edward Vlll 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 count > 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

Abbreviations: HAL= HIV associated lymphoma, CHOP= cyclophosphamide, doxorubicin, 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 time of loss of follow up
[#]3 patients had progressive disease at time of death

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 an 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 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 gender 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 behaviour 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 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 two-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 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 randomised 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 were 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 haematology patients in general.[42-44] However, when interpreting this, one should consider 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 amongst 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 favoured. 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% two-year progression-free survival; with our OS exceeding 24 months for the three patients that attained CR.[49] Although the numbers are small the findings here suggest that 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 Vlll Hospital were not available for most patients, and the difference in baseline haemoglobin between treatment groups could not be accurately determined. Biopsy and 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, resource-limited setting were 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 health-care challenges.

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CHAPTER 3

HIV ASSOCIATED PLASMABLASTIC LYMPHOMA: A SINGLE CENTRE 12 YEAR EXPERIENCE IN KWA-ZULU NATAL, SOUTH AFRICA

The previous chapter described the most common ARL seen at King Edward Vlll hospital over the study period. The 2nd paper in this chapter therefore focuses on the 2nd most frequently seen subtype of ARL, and has been published in HIV Medicine (HIV Medicine. 2022; 00:1–12. DOI: 10.1111/hiv.13266). The paper has been submitted according to the journal format and the manuscript includes changes according to the journal reviewers' comments.

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ORIGINAL RESEARCH

HIV-associated plasmablastic lymphoma: A single-centre 12-year experience in Kwa-Zulu Natal, South Africa

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Abstract

Objective: To describe the clinical profile and outcome of patients with HIV-associated plasmablastic lymphoma (PBL) treated with cyclophosphamide, doxorubicin, oncovin, prednisone (CHOP) chemotherapy in a tertiary hospital in KwaZulu-Natal, South Africa.

Methods: This 12-year retrospective clinical chart review, from 2006 to 2018, of patients with PBL treated with CHOP chemotherapy describes their clinical presentation, complete response (CR), progression-free survival (PFS) and disease-free survival (DFS). Response to salvage chemotherapy was also assessed, as was the overall survival (OS).

Results: Of 26 patients included in the study, PBL was the presenting manifestation of underlying HIV infection in 58% ($n = 15$). The median age was 35 years (range 13–49), and 62% ($n = 16$) were males. The median CD4 count was 285 cells/μL (range 45–863). All patients had extranodal disease, with 4% having bone marrow involvement ($n = 1$) and > 60% presenting with advanced stage and high-risk PBL. Central nervous system (CNS) involvement was present in 15% ($n = 4$). A CR was attained in 46% ($n = 12$). The median DFS was 23.5 months (range 5–91 months), with an overall 2-year survival of 42% ($n = 11$).

Conclusions: Patients with PBL had a low CR with CHOP chemotherapy and poor OS. Use of alternative chemotherapy regimens needs to be investigated to optimally manage this aggressive lymphoma. The surprisingly low incidence of marrow involvement is the focus of ongoing local research.

KEYWORDS

CHOP chemotherapy, HIV-associated lymphoma; South Africa, plasmablastic lymphoma

INTRODUCTION

Plasmablastic lymphoma (PBL), which is classified as a large cell lymphoma, is uncommon, with a reported prevalence of 0.004% of all non-Hodgkin's lymphoma [1]. Plasmablastic lymphoma usually occurs in immunosuppressed or elderly patients but may also be seen in association with autoimmune conditions and other haematological disorders. It also occurs in patients with HIV infection who are profoundly immunocompromised with low CD4 counts and high viral loads or have good CD4 counts and undetectable viral loads

[2,3]. In the setting of HIV, PBL is an AIDS-related lymphoma (ARL) or HIV-associated lymphoma (HAL) [4]. Plasmablastic lymphoma was first described with HIV in 1997 [5], and accounts for 2% of all HAL. It tends to affect the oral cavity and jaw [5]. Due to its rarity and the absence of large prospective studies, there is currently no evidence-based guideline on the management of PBL [6,7].

Plasmablastic lymphoma shares histological features and also immunophenotypic characteristics with plasma cell dyscrasias [8,9]. Therefore, a diagnosis of PBL may require exclusion of a plasma cell dyscrasia. Further confounding the diagnosis is the weak cluster of differentiation 20 (CD20) positivity in 10% of PBL [10].

Treatment for PBL is complicated by an absence of randomized trials, leading to a lack of standardized treatment regimens and conflicting data. For example, chemotherapy regimens commonly include cyclophosphamide, doxorubicin, oncovin and prednisone (CHOP) with an overall survival (OS) ranging from 4 to 11 months [11,12]. However, an Italian study using predominantly CHOP in conjunction with antiretroviral therapy (ART) reported an improved 3-year OS of 67% [13]. Another study using intensified infusional chemotherapy reported improved median OS of 17 months compared with 7 months for patients treated with CHOP [14]. However, the benefit of chemotherapy more intensive than CHOP has not been corroborated by other studies [15]. Due to the overlapping features with multiple myeloma, case reports with myeloma-directed therapy have shown OS exceeding 10 years [16]. The role of ART has also shown promise, with two cases of HIV-associated PBL regressing with the institution of ART [17,18]. Treatment of PBL with ART and chemotherapy showed a 1-year OS of 67%, supporting concurrent chemotherapy and ART [19]. However, even with chemotherapy intensification, outcome remains generally poor and optimal treatment remains undefined [20].

Treatment of PBL may be guided by prognosis, which is stratified according to the International Prognostic Index (IPI) [21]. This IPI has been shown to correlate with OS in PBL. Interestingly, there is no consistent correlation between OS and a low CD4 count, a variable that is not routinely included in the IPI [11–13]. The utility of this IPI in the local population in the KwaZulu-Natal (KZN) province is not known.

South Africa has an HIV seroprevalence of 13.5%, with 7.97 million people living with HIV infection [22]. KwaZulu-Natal is recorded to have the highest HIV seroprevalence, at 18% [23]. Although PBL also occurs in other immunocompetent patients, with incidence rates as high as 44% [15,20], in Gauteng, another South African province, over 95% of PBL cases were seen in HIV-positive patients [24]. Despite the high HIV seroprevalence in KZN, there are no data on the profile, prognosis and outcome of HIV-associated PBL in KZN. Of the four sub-Saharan African studies, three are from other South African provinces [24–26] and the fourth is a small study of six patients in Malawi [27]. This would be the first such report from KZN, the epicentre of the HIV epidemic in South Africa.

Practioner points

1. Aggressive lymphoma seen in HIV-positive patients, all presenting with extranodal disease.
2. Patients may have overlapping features with multiple myeloma, and multiple myeloma needs to be actively excluded.
3. The 2-year survival for plasmablastic lymphoma with CHOP chemotherapy is only 42%; however, there is a good outcome when combined with radiotherapy with curative intent

METHODS

Study design, setting, participants and data collection

This is a retrospective chart review of PBL patients treated at King Edward VIII Hospital (KEH) between 2006 and 2018. KEH provides tertiary clinical haematology care to all public patients in KZN, and services a population of 11.3 million (19.2% of the South African population). All HAL, apart from Burkitt lymphoma, is treated at this hospital. The study protocol was approved by the Biomedical Research Ethics Council (BREC) of the University of KwaZulu Natal (BE043/17), and the study complied with the principles of the Declaration of Helsinki. All study data were anonymized, with patients given unique personal identification numbers.

Patients were included in this study if they were HIV-positive with a histological diagnosis of PBL and received at least one cycle of CHOP chemotherapy. Patients were excluded if the histology was inconclusive, patients refused chemotherapy, they died before the first cycle of chemotherapy, or preceived a chemotherapy regimen other than CHOP. All information was obtained from the patients' in- and outpatient records. Histology and all laboratory data were retrieved from the National Health Laboratory System (NHLS) Laboratory Information System, TrakCare. Information was collated into a computer program, Excel, for analysis.

Clinical assessments and investigations of study participants

All patients referred to KEH had a tissue diagnosis of PBL with histology assessed by qualified histopathologists and reported according to the WHO guidelines [28]. As part of routine care, presenting symptoms, including B symptoms and the Eastern Cooperative Oncology Group (ECOG) performance status, were recorded [29].

The work-up of the patients was based on established lymphoma guidelines and included a physical examination, blood testing for full blood count, chemistry profile, urate level, lactate dehydrogenase level and a unilateral staging bone marrow aspirate and trephine [30]. HIV testing, CD4 count and viral load were checked if the HIV status was unknown. A baseline cerebrospinal fluid (CSF) cytocentrifuge cytology was performed routinely in patients with no suspicion of meningeal involvement, if the patient was agreeable to admission, and in all patients with a clinical suspicion of leptomeningeal involvement.

Baseline radiological staging was done with either a computed tomography (CT) or positron emission tomography (PET) scan [31]. Patients were staged using the Ann Arbor staging [32].

Management and outcomes

All study patients were treated according to the algorithm in Figure 1. Radiotherapy was offered for localized or bulky disease, with bulky disease defined as any tumour measuring 10 cm or more in maximum diameter.

Outcome was assessed as the response status and was determined by clinical response, CT or PET-CT and bone marrow histology. Mid-cycle restaging was a repeat CT lymphoma staging or PET-CT scan after three to four cycles of chemotherapy. The bone marrow biopsy was repeated at this time if there was marrow involvement at baseline. The PET-CT or CT lymphoma staging was repeated after six to eight cycles of CHOP [33–35] if the interim scans did not show complete response (CR) [36].

Response was assessed using the Lugano criteria [37]. Patients with complete response (CR), partial response (PR) or stable disease at mid-cycle restaging completed six to eight cycles of CHOP. Patients with progressive disease (PD) were switched to second-line chemotherapy [38]. Overall survival was calculated from time of diagnosis to death or last recorded follow-up. Disease-free survival was calculated from time of CR to relapse, and PFS was calculated from the time of presentation to clinical or radiological disease progression or death with CHOP chemotherapy.

Statistical analysis

Data analyses were conducted using Stata 16 (StataCorp LLC, College Station, TX, USA). Descriptive statistics were calculated for demographic and clinical characteristics. Frequencies and percentages were calculated for categorical variables and median and interquartile range for the continuous variables. For CR, the χ^2 test was used to determine whether risk factors were statistically significant. Univariate analysis for PFS and OS at 2 years was done using Kaplan–Meier survival analysis, and the log-rank test was used to generate the *p*-values. Survival curves were generated for IPI score [high (3–5) vs. low (0–2)] and compared using the log-rank test. *p*-values < 0.05 were considered statistically significant.

RESULTS

Over a 12-year period, 34 HIV-positive patients with PBL were seen at KEH in KZN. Eight patients were excluded from the study analysis (one with inconclusive histology, one patient refused chemotherapy, three died prior to chemotherapy and three received a different chemotherapy regimen). Of the 26 patients treated with CHOP chemotherapy, 62% were male (Table 1). All patients had extranodal disease, with a single patient having lymphomatous involvement of the bone marrow.

Nine patients (35%) were on ART prior to the diagnosis of PBL with five having undetectable viral loads on diagnosis of PBL.

One patient had concurrent hypercalcaemia with lytic lesions. Clonal marrow plasmacytosis was not detected in any of the samples. A single patient had a complete myeloma work-up, with no evidence of a monoclonal protein or Bence–Jones proteinuria.

The CR for patients treated with CHOP chemotherapy was 46% ($n = 12$), with a 2-year survival of 42% ($n = 11$) and median PFS of 8 months (range 1–97), as shown in Figure 2. For the two patients who refused ART during chemotherapy; one died with CNS disease after 2 months, and the other patient was lost to follow-up after 3 months. About a quarter ($n = 6$) of all patients received second-line salvage chemotherapy with mesna, ifosfamide, novantrone and etopside (MINE) [38], with half of these ($n = 3$) attaining a CR or PR. A single patient received high-dose methotrexate (HD-MTX) as salvage therapy post-MINE, with three

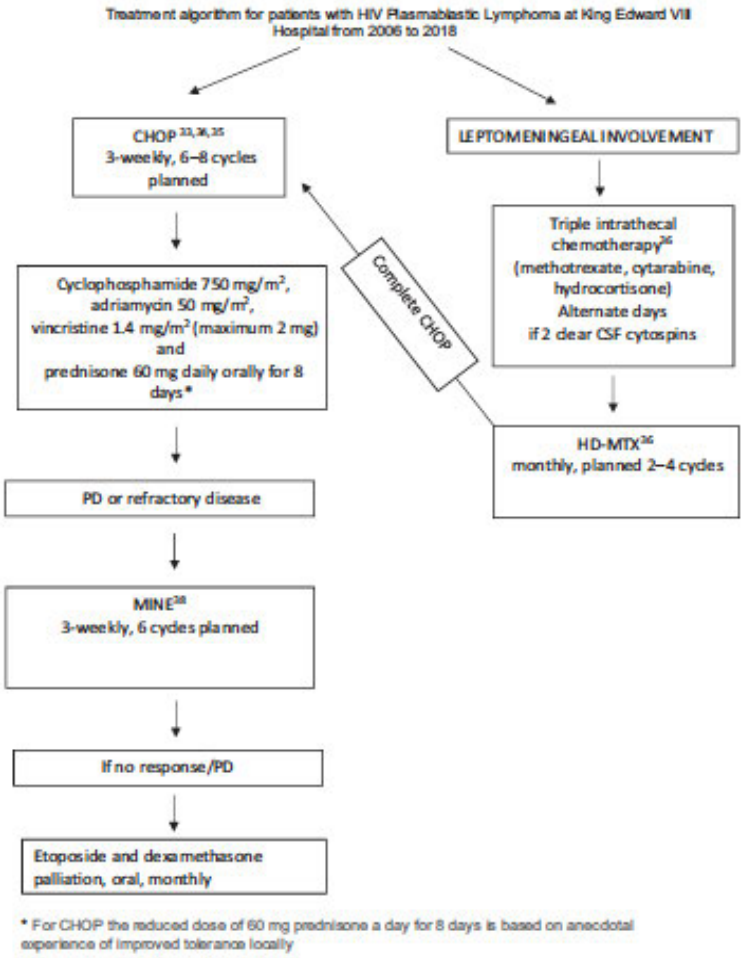

FIGURE 1 Treatment algorithm for patients with HIV plasmablastic lymphoma at King Edward VIII Hospital from 2006 to 2018. CSF, cerebrospinal fluid, HD-MTX, high-dose methotrexate; MINE[38], mesna, ifosfamide,norvantrone,etoposide for 3 days; PD, progressive disease

patients requiring HD-MTX for CNS involvement by lymphoma. The median OS for the study cohort was 16 months (range 1–111).

Central nervous system involvement by lymphoma was seen in four patients (15%), whose profiles and outcomes are presented in Table 2. CSF cytocentrifuge was performed at baseline (routinely or for suspicion of CNS disease) in 11 patients (42%), with three patients (12%) having leptomeningeal involvement. A single 37-year-old female patient presented and relapsed with CNS lymphomatous involvement. She had leptomeningeal CNS involvement at baseline and cleared CNS disease with 13 cycles of triple intrathecal chemotherapy but defaulted scheduled consolidation with HD-MTX. She returned 3 months later with paraparesis with a T8 sensory level, not responsive to HD-MTX.

Radiotherapy was planned for seven patients presenting with bulky disease or those having a partial response to chemotherapy. The details are described in Figure 3. The two patients who received curative radiotherapy had a complete response with OS of 78 and 111 months, respectively.

The profile of the 12 patients who achieved a CR with CHOP chemotherapy is shown in Table 3. All 12 patients were on ART prior to or during chemotherapy. Of the four patients who had undetectable HIV viral loads prior to chemotherapy and achieved a CR, one remains well after 78 months, while the other three were lost to follow-up at 22, 25 and 29 months, respectively.

The difference between the survival curves of IPI scores for OS at 2 years (Figure 4) and PFS (Figure 5) were not statistically different. CD4 count, age, presence of B symptoms, viral load, presence of CNS disease, stage of disease and EBV-encoded RNA (EBER) positivity were not associated with significantly improved CR, OS or PFS (Table 4).

TABLE 1 Baseline clinical and laboratory findings for patients with HIV-associated plasmablastic lymphoma treated at King Edward VIII Hospital from 2006 to 2018

Patient number [*n* (%)]	26
Age (years) [median (range)]	35 (13–49)
Male	16 (62%)
Histology	
CD20-negative	16 (100%)[a]
EBER-positive	9 (90%)[a]
Ann Arbor stage	
Stage I	4 (15%)
Stage II	5 (19%)
Stage III	4 (15%)
Stage IV	13 (50%)
Extranodal disease	26 (100%)
Biopsy site	
Oral cavity	8 (31%)
Nasal/nasopharynx	8 (31%)
Ano-rectal	3 (12%)
Other: scrotum, pelvic mass, humerus, tonsil, ethmoid sinus, caecum, mandible (1 each)	7 (27%)
'B' symptoms	7 (27%)
Bulky disease[b]	4 (15%)
IPI score	
0–1	0 (0%)
2	8 (31%)
3	11 (42%)
4–5	7 (27%)
ECOG PS ≥ 2	26 (100%)
PBL presentation of HIV	15 (58%)
CD4 (cells/μL) [median (range)][c]	285 (45–863)
CD4 < 200 cells/μL at diagnosis[c]	5 (19%)
On ART pre-PBL diagnosis	9 (35%)
ART started during chemotherapy	15 (58%)
No ART during chemotherapy	2 (8%)
Bone marrow involvement[d]	1 (4%)
Hypercalcemia > 2.75 mmol/L	3 (12%)
Lytic lesions	5 (19%)

Abbreviations: ART, antiretroviral therapy; CD20, cluster differentiation 20; EBER, Ebstein–Barr virus (EBV)-encoded RNA; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, International Prognostic Index; PBL, plasmablastic lymphoma.

[a]Results available in 16 patients for CD20 and 10 patients for EBER, respectively.

[b]Bulky disease defined as tumour lesion measuring ≥ 10 cm in maximum diameter.

[c]One result not found.

[d]One bone marrow aspirate and trephine (BMAT) result not found, one failed BMAT.

DISCUSSION

This study is the first in KZN, South Africa, to describe the clinical features and chemotherapy response for patients with HIV-associated PBL. The 2-year survival with CHOP and salvage chemotherapy was poor, at 42%. These findings highlight the need to identify local prognostic factors, optimize ART with chemotherapy intensification [13] and explore novel chemotherapeutic approaches in these patients.

Profile

In this study, PBL showed a slight male predominance (male:female ratio = 1.6:1.0), which is well documented in the literature [11,15,20,25,27], The study cohort had a median age of 35 years, which is similar to that described in two other South African provinces [25,26], but younger than that reported in Europe [39] and India [40], where participants were older than 45 years of age. This could be reflective of the younger age of HIV diagnosis in South Africa compared with other countries [22,40–42].

Although described as an AIDS-defining lymphoma, the median CD4 count of our study cohort was 285 cells/μL, which is within a non-AIDS-defining range. A CD4 count > 200 cells/μL has also been described in the US, Europe and South America [11] and a CD4 count of almost 200 (196 cells/μL) in another South African study [26]. This suggests that factors other than immunosuppression may be involved in the development of PBL in the HIV- positive population. However, most other studies have reported low CD4 counts of 115 (mean) [43], 85 (median) [12] and 68 cells/μL (median) [44] in patients with PBL. Similar to our study, the latter three studies were carried out in the post-ART era. The CD4 count in our study is the highest in HIV PBL described to date. However, this did not improve the CR or OS, which probably suggests the influence of other variables on outcomes. The impact of HIV-associated factors, including CD4, warrants further investigation.

The development of PBL is unlikely to be related solely to high viral loads because approximately 20% of patients had undetectable viral loads at presentation in this study. These findings concur with another South African study [24] and a German study [12]. This contrasts with Mai et al. [43], who postulated that the high incidence of PBL in their study may have been associated with poor control of HIV. However, the surprisingly high incidence of PBL described in HIV-negative, immunocompetent patients indicate that

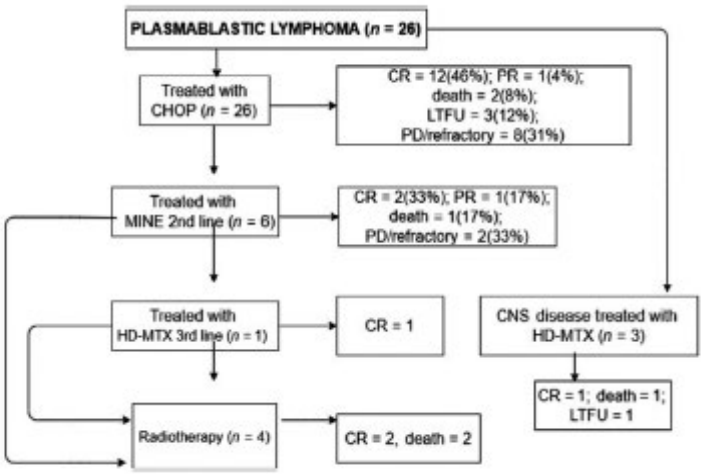

FIGURE 2 Outcomes associated with chemotherapeutic regimens in HIV patients with plasmablastic lymphoma treated at King Edward VIII Hospital from 2006 to 2018. CR, complete response; PR, partial response; PD, progressive disease; LTFU, lost to follow-up; CHOP, cyclophosphamide, adriamycin,vincristine, prednisone; MINE, mesna, ifosphamide, norvantrone, etopposide; HD-MTX, high-dose methotrexate

TABLE 2 Profile and outcomes of patients with central nervous system involvement in plasmablastic lymphoma treated at King Edward VIII Hospital from 2006 to 2018

Age (years)	41	37	32	41
Sex	Male	Female	Male	Female
Stage	IV	IV	IV	IV
CD4 count (cells/μL)	461	168	863	625
On concurrent ART with chemotherapy	Yes	Yes	Yes	Yes
Time to CNS involvement (months)	11	Baseline	Baseline	Baseline
Leptomeningeal involvement	No	Yes	Yes	Yes
Parenchymal involvement	Yes	No	No	No
Treatment of CNS disease	HD-MTX × 2	CHOP × 1 TIC, HD-MTX	CHOP × 8 TIC	TIC, CHOP × 4 HD-MTX × 2
CR	No	No	Yes	Yes
OS post-CNS disease (months)	1[a]	3[b]	12[a]	86
OS (months)	12[a]	6[a]	12[a]	86

Abbreviations: ART, antiretroviral therapy; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone; CNS, central nervous system; CR, complete response; HD-MTX, high-dose methotrexate; OS, overall survival; TIC, triple intrathecal chemotherapy.

[a]Patient lost to follow-up.

[b]Patient died.

factors other than immunosuppression alone contribute to pathogenesis of PBL [15,20]. Longitudinal studies in large samples are required to explore the risk factors associated with the development of PBL in HIV-infected people.

Only 4% of the patients had bone marrow involvement by lymphoma, which is significantly lower than the 44% described by Castillo et al. [11] and other studies [13,26]. The surprisingly low incidence of marrow involvement by lymphoma seen in this study is currently the focus of ongoing research, looking at trephine quality and the utility of ancillary testing with routine immunohistochemistry and immunophenotyping on marrow samples.

Histology/immunophenotype

None of the patients in this study exhibited CD20 immunopositivity, which is in keeping with the general evidence [12,19].

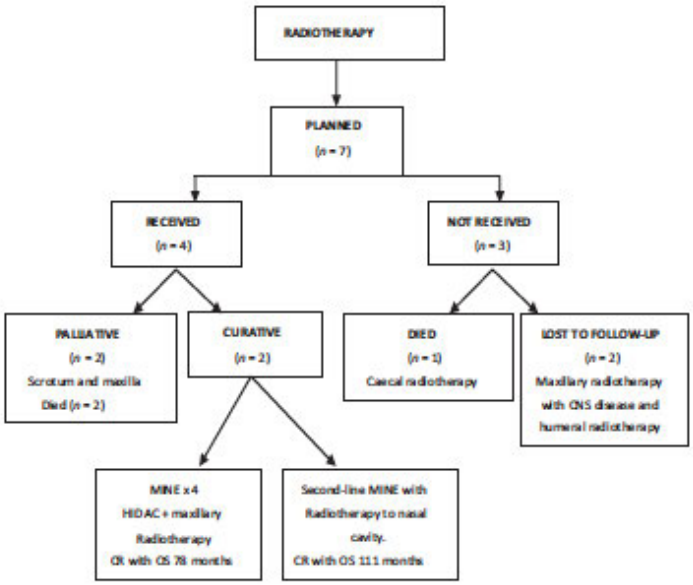

FIGURE 3 Outcome with radiotherapy for patients with HIV plasmablastic lymphoma treated at King Edward VIII Hospital from 2006 to 2018. MINE, mesna, ifosphamide, norvantrone, etoposide; HD-MTX, high-dose methotrexate; HIDAC, high-dose cytarabine; CNS, central nervous system; CR, complete response; OS, overall survival

TABLE 3 Profile of patients with HIV-Associated plasmablastic lymphoma from 2006 to 2018 treated with cyclophosphamide, doxorubicin, oncovin, prednisone (CHOP) chemotherapy achieving a complete response ($n = 12$)

Age (years)	Sex	Biopsy site	ECOG PS	Stage	IPI	CD4 (cells/μL)	CNS disease	DFS in CR_1	OS
40	M	Oral (maxilla)	2	II	2	522[a]	No	27[b]	78[b]
29	F	Pelvic floor	3	IV (bone)	3	217	No	18[b]	27[b]
29	M	Oral (maxilla)	3	II	2	219	No	33	38[d]
13	F	Nasopharynx	2	IV (liver)	3	578	No CSF	5	17[c]
35	M	Oral cavity	3	IV (liver, bone)	4	393	No	91[b]	97[b]
35	F	Oral cavity	2	IV (bone)	4	597	No CSF	42[b]	48[b]
32	M	Ethmoid sinus	3	IV(CNS)	3	863	Yes	8	12[c]
41	F	Tonsil	3	IV (CNS)	4	625	Yes	80	86[c]
49	M	Tonsil	2	I	2	492[a]	No CSF	18	22[c]
29	M	Oral cavity	2	I	2	201[a]	No CSF	19	25[c]
39	M	Peri-anal	2	II	2	215[a]	No CSF	22	29[c]
35	M	Oral (maxilla)	3	II	3	368	No	25[b]	28[b]

Abbreviations: CNS, central nervous system; CR, complete response; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; F, female; IPI, International Prognostic Index; M, male; OS, overall survival.

[a]Indicates patients with undetectable HIV viral load at baseline.

[b]Ongoing.

[c]Patient lost to follow-up.

[d]Patient died.

A few studies [10,25,39,40] have reported faint CD20 positivity. This can pose a diagnostic dilemma because of difficulties in separating PBL from other CD20 expressing large cell lymphomas. Additionally, this will affect the management of CD20-positive PBL cases as targeted CD20 immunochemotherapy shows a trend towards improved OS [39].

In this study, just over 10% had other myeloma-defining criteria in the form of lytic lesions or hypercalcaemia

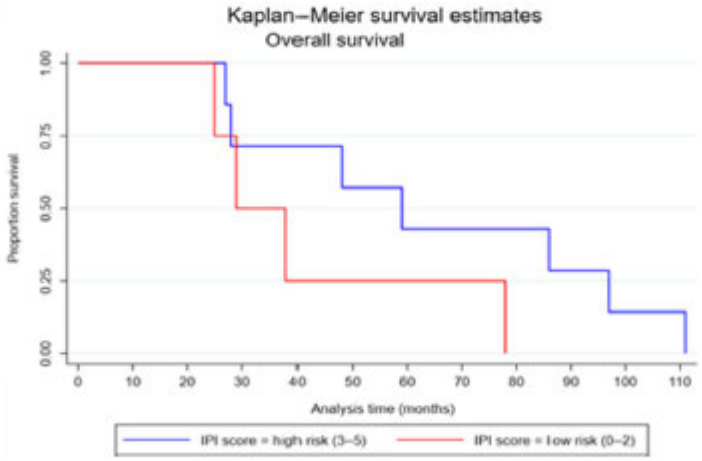

FIGURE 4 Overall survival at 2 years by International Prognostic Index (IPI) score ($p = 0.1709$)

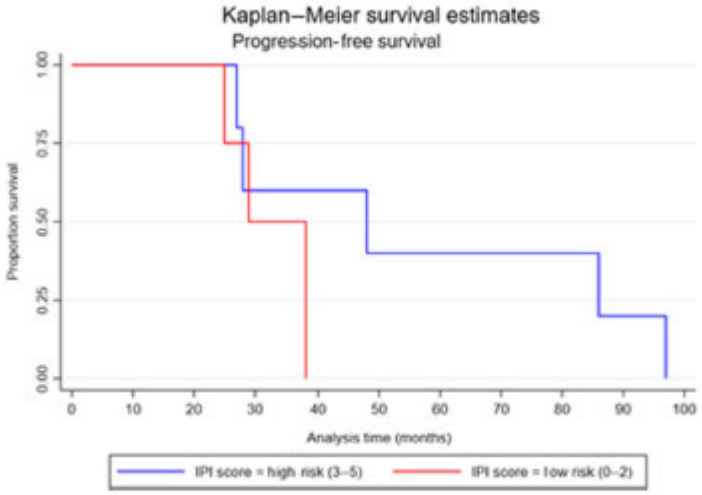

FIGURE 5 Progression-free survival by International Prognostic Index (IPI) score ($p = 0.2091$)

which highlights that the diagnosis may be confounded further. As this tumour shares morphology and immunophenotype with plasmablastic myeloma, it can be difficult to differentiate the two [9]. However, differentiation from plasmablastic myeloma in this study was made easier because 90% were EBER-positive, the latter being a helpful marker in differentiating PBL from plasmablastic myeloma [45]. The EBER findings in our study cohort are within the EBER 75–100% positivity range described in the literature [15,20]. Although the prognostic value of EBER yields conflicting results, the poor survival outcome of < 2 months in the single EBER-negative patient would support the inferior outcome reported in EBER-negative HIV PBL [15,24].

Response to CHOP, second-line, radiotherapy

The CR for first-line CHOP chemotherapy was 46%, which falls in the range of the other South African studies. A CR of 27% was reported in the Free State [25] and 63% in the Western Cape [26]. The poorer response in our study compared with the Western Cape study is probably attributable to a larger number of our patients presenting with high-risk IPI. The 2-year OS and PFS in our study of 42% and 8 months, respectively, are similar to the 2-year OS of 43% described in a German cohort [46] and the PFS of 5 months described in North America [47] and India [48]. Attempts to intensify

TABLE 4 Indicators of survival for: (a) progression-free survival (PFS) at 2 years; (b) overall survival (OS) at 2 years; and (c) complete remission (CR) ($N = 26$)

		(a) PFS at 2 years	(b) OS at 2 years	(c) CR
		n (%)		
ART	CD4 < 50 cells/μL	0 (0)	1 (9)	0 (0)
	CD4 50–200 cells/μL	0 (0)	1 (9)	0 (0)
	CD4 > 200 cells/μL	9 (100)	9 (82)	9 (100)
'B' Symptoms	No	7 (78)	8 (73)	6 (67)
	Yes	2 (22)	3 (27)	3 (33)
Age	< 40 years	7 (78)	9 (82)	7 (78)
	≥ 40 years	2 (22)	2 (18)	2 (22)
Stage	Early	6 (67)*	6 (55)	5 (56)
	Late	3 (33)	5 (45)	4 (44)
Viral load	Detectable	6 (67)	8 (73)	6 (67)
	Undetectable	3 (33)	3 (27)	3 (33)
IPI	Low risk	4 (44)	4 (36)	4 (44)
	High risk	5 (56)	7 (64)	5 (56)
CNS disease	No	8 (89)	10 (91)	8 (89)
	Yes	1 (11)	1 (9)	1 (11)
EBER positivity	No	0 (0)	0 (0)	0 (0)
	Yes	3 (100)	4 (100)	4 (100)

Abbreviations: ART, antiretroviral therapy; CNS, central nervous system; EBER, Ebstein–Barr virus (EBV)-encoded RNA; IPI, International Prognostic Index.
*Significant with $p = 0.028$.

CHOP chemotherapy have not shown any benefit [11,12], apart from the improved OS with infusional chemotherapy by Ibrahim et al. [14] Nevertheless, resource limitations at our centre restrict infusional chemotherapy.

There was a reasonable CR of 50% with salvage chemotherapy, which also highlighted the utility of combined treatment modalities. Combination radiotherapy with chemotherapy both involved field radiotherapy with salvage chemotherapy, and survival exceeding 5 years in 50% of the study group is encouraging, albeit the small number in this study. The latter findings are supported by the findings in 10 consecutive PBL patients in America [49] as well as South African data [26].

IPI correlation with outcome

Our study showed that stage of disease did not correlate with PFS, unlike findings in the Western Cape [26] and the multi-site American and European studies [11]. Also, contrary to the latter study we found no association with CR and OS [11]. More importantly, in our setting, the IPI did not have prognostic utility, which may be partially attributable to a small sample size. This contrasted with the other South African [26] and European studies [39]. A German study found a significantly poorer OS associated with intermediate and high-risk IPI [12]. Although our sample size was small, it was comparable to the South African [26] and German [12] cohort size. Therefore, identifying other factors that influence prognosis in our setting is an area for further study.

CNS involvement

Although the 15% incidence of CNS involvement with PBL in this study is higher than that described in other studies [5,27], our small number ($n = 4$) precludes any definitive conclusions. The Southwest Oncology Group (SWOG) 8516 analysis demonstrated no proven benefit to routine intrathecal chemotherapy to prevent secondary CNS lymphomatous involvement [50]. Hence primary intrathecal prophylaxis was not routinely administered in this study. A 20-year follow-up on CNS involvement in the SWOG 8516 study showed a median time to CNS relapse of 5.4 months and median survival of 2.2 months, which is similar to our findings [50]. Despite HD-MTX, intrathecal

chemotherapy and/or radiotherapy in our study, the outcomes were consistently poor in 75% of patients with CNS involvement and warrant investigation of alternative treatment.

STUDY STRENGTHS AND LIMITATIONS

Although this is a small sample cohort, this is the first study on PBLin the ethnic population in KZN. This study also describes outcome with salvage therapy, adding to this limited literature. The retrospective nature of the study meant that available data were restricted to the patients' notes and the laboratory information systems. Viral loads and ART regimens were not available for many patients. CD20, EBER, Human herpesvirus 8 (HHV8) and anaplastic lymphoma kinase (ALK) results were not available for all samples, and the myeloma work-up was not completed for all patients.

CONCLUSIONS

This study highlights the unique profile of PBL in HIV-infected patients managed in the public health sector in KZN. In this province, PBL occurs in younger HIV-infected patients who have higher CD4 counts and are more likely to have extranodal involvement than patients described in the literature. Larger, prospective studies are required in the local setting to assess the utility of the IPI and other prognostic variables and optimise management.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

NR: concept design, drafting of paper, final approval of version to be published; accountable for all aspects of work. NP: contribution to design concept, draft revision, final approval of version to be published; accountable for all aspects of work. NA: analysis of data, draft revision, final approval of version to be published; accountable for all aspects of work. PR: contribution to concept design, draft revision, final approval of version to be published; accountable for all aspects of work. YM: contribution to design concept, draft revision, final approval of version to be published; accountable for all aspects of work.

ETHICAL APPROVAL

All patients granted verbal or written consent and/or assent prior to investigation or treatment. As the study is retrospective, there was no specific study consent. The Biomedical Research Ethics Committee (BREC) in KwaZulu Natal approved this study.

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CHAPTER 4

The previous 2 chapters described the profile and outcome of the 2 most frequently seen ARL at King Edward Vlll Hospital in KZN. This survival outcome in ARL is correlated with different prognostic scoring systems. The ability to identify accurate prognostic tools can help tailor therapy according to predicted outcomes. In Chapter 3, the prognostic variables associated with plasmablastic lymphoma in our cohort were described, together with the profile and outcome. This chapter, therefore, focuses on the prognostic variables seen specifically in CD20 positive ARL, which is the patient cohort from Chapter 2. The manuscript has been submitted to Plos One, and has been revised according to the journal reviewers and accepted for publication. Nadine Rapiti[1], Nada Abdelatif[2], Mahomed-Yunus S. Moosa[3]

Abstract

Prognostic variables and 4-year survival outcomes in CD20 Positive AIDS-Related Lymphoma in the Anti-retroviral treatment era: A Retrospective Review from a Single Centre in KwaZulu-Natal, South Africa

Objective: To describe 4-year survival outcomes and assess the value of established and additional relevant variables to predict complete response (CR), four-year progression free survival (PFS) and overall survival (OS) of CD20 positive AIDS-Related Lymphoma (ARL) treated with standard combination chemotherapy.

Method: We performed a retrospective review of patients diagnosed with CD20-positive ARL between 2006 and 2016. All patients over 12 years of age who received at least one cycle of combination chemotherapy with curative intent were included in the analysis. Variables assessed included International Prognostic Index (IPI), age-adjusted-IPI, age, gender, B symptoms, extent of disease, functional performance status, CD4 cell count, viral load, concurrent ART with chemotherapy, rituximab inclusion, and number of chemotherapy cycles used. Kaplan-Meier survival curves for OS and PFS at 4 years were compared for IPI and aaIPI using the log-rank test. A Cox proportional

hazards model was used to investigate the effects of prognostic variables for patients achieving OS and PFS at 4 years and logistic regression for patients achieving CR.

Results: A total of 102 patients were included in the analysis. At year four of follow-up, the OS was 50% (n=51) and PFS was 43% (n=44). Attaining a CR and male gender were significantly associated with improved 4-year OS ($p<0.001$ and $p=0.028$ respectively) and PFS ($p<0.001$ and 0.048 respectively). A viral load of < 50 copies/ml was associated with a higher complete response rate (aOR 6.10 [95% CI 1.15, 24.04], $p=0.01$). Six or more cycles of chemotherapy was superior to fewer cycles for both PFS (aHR 0.17 [95% CI 0.10, 0.29]) and OS (aHR 0.12 [95% CI 0.07, 0.22]) with p-value < 0.001 for both PFS and OS. The Kaplan-Meier survival estimates demonstrated the prognostic utility of the IPI and aaIP for OS ($p=0.002$ and 0.030 respectively) and the IPI for PFS ($p=0.002$).

Conclusion:
This study is a first from a high-prevalence HIV area in KwaZulu-Natal, South Africa, and confirms the utility of the internationally accepted prognostic scoring systems in predicting survival in CD20-positive ARL in the local population.

Keywords: AIDS-related lymphoma (ARL), HIV-associated lymphoma (HAL), international prognostic score (IPI), overall survival (OS), progression-free survival (PFS)

Introduction

Lymphomas that occur more frequently in people living with human immunodeficiency virus (HIV) are referred to as HIV-associated lymphomas (HAL).[1,2] Three malignancies are considered AIDS-defining: high-grade non-Hodgkin lymphoma (NHL), Kaposi sarcoma and invasive cancer of the cervix.[1] The AIDS-defining high-grade NHL are collectively called AIDS-related lymphomas (ARL) and are aggressive with diverse

histologic characteristics.[1] These ARL include diffuse large B cell lymphoma (DLBCL), Burkitt lymphoma (BL), plasmablastic lymphoma (PBL) and less commonly, primary CNS lymphoma (PCNSL) and primary effusion lymphoma (PEL).[2,3] DLBCL and BL usually express CD20, and the other ARL are generally CD20 negative. The introduction of antiretroviral therapy (ART) in 1996 not only reduced the incidence of ARL but also improved outcomes.[4-6] Despite the widespread use of ART, ARL remains a common malignancy and a primary cause of AIDS-related malignant deaths.[7-9] South Africa is home to just over 20% of the global population living with HIV.[10] KwaZulu-Natal is a province in South Africa that has an HIV prevalence of 18%.[11] Ascertaining reliable and valid prognostic tools for rational utilization of scarce resources for the management of ARL is critical, particularly for these resource-limited settings.

Outcomes in ARL, both CD 20 positive and CD20 negative, are associated with characteristics of the host, malignancy, and HIV disease. The former two variables are incorporated into the well-established international prognostic index (IPI), which consists of the patient's age, performance status, lactate dehydrogenase (LDH) level, stage of lymphoma and the number of extranodal sites involved.[12] This index for aggressive lymphoma was initially derived from an HIV-negative cohort treated with combination chemotherapy.[12] This scoring system was subsequently validated for ARL treated with standard cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy as well as chemotherapy supplemented with CD20 monoclonal antibodies (rituximab).[13-15] Another scoring index, the age-adjusted international prognostic index (aaIPI), which is a modified IPI score utilizing three variables of the IPI, viz., performance status, LDH level and stage of disease, strongly correlates with outcomes of ARL.[12] This score was validated in a pooled analysis of 1546 patients from 19 prospective trials conducted in the United States and Europe.[16] This study population included predominantly male patients, with a good median CD4 count, and differs from the stronger female representation and poorer CD4 count in ARL described in two South African studies as well as East Africa.[17-19]

Unlike the IPI and aaIPI, the HIV-specific prognostic variables for ARL are less well-defined. Studies have variably analysed the prognostic significance of the viral load, CD4 count and history of prior AIDS-defining illness, showing a poorer outcome with the latter two variables [20,21] However, the significance of these variables has evolved over time with the use of ART, with less prognostic significance attributed to the CD4 count.[22] In this post-ART era, it is unclear if a specific ARL prognostic score would better determine prognosis in ARL than the IPI or aaIPI, and which variables would need to be included in such a score.[23]

The therapeutic advances in ARL have resulted in outcomes comparable to HIV-negative patients, spurring the need to optimise current prognostic tools to improve management.[13,20,24] This is especially pertinent in countries with a high HIV prevalence where a significant portion of the health care budget is utilised in the management of ARL. The IPI and aaIPI prognostic scoring systems have not been validated in the local cohort or in the three other South African studies on ARL.[17,18,25] In KwaZulu-Natal, the significance of other lymphoma-related, or HIV-associated variables, including the CD4 count, concurrent ART and viral load in CD20-positive ARL is also unknown. In these settings, accurate prognostic tools for an African cohort will guide the implementation of risk-adapted, cost-effective treatment strategies.

Methods

This was a retrospective review of patients with histologically confirmed CD20-positive ARL managed at King Edward Vlll Hospital between January 2006 and December 2016. To be included, patients had to be over the age of 12 years, have received at least one cycle of CHOP chemotherapy, with or without rituximab (R), with curative intent and have had at least four years of follow-up. Patients with Burkitt lymphoma were not included in this study, as these patients are treated with a more intensive chemotherapy protocol. Patients with primary central nervous system (CNS) lymphoma were also excluded from this analysis. Anonymized data from the patients' haematology charts was captured onto an Excel electronic spreadsheet. Laboratory data was further obtained from the National Health Laboratory Service laboratory information system.

Data was exported into Stata 16 programme for analysis. The study protocol was approved by the Biomedical Research Ethics Council of the University of KwaZulu-Natal (BE043/17), and the study complied with the principles of the Declaration of Helsinki.

All patients in the study cohort were managed according to standard lymphoma treatment guidelines.[26,27] Between 2006 and 2013, CHOP was the main chemotherapy regimen. In 2013 local guidelines added rituximab to CHOP chemotherapy. CHOP and RCHOP were given at standard doses, except for prednisone, which was given at a dose of 60mg daily, orally for 8 days rather than 100mg daily for 5 days, according to the centre practice. Here we report on the effect of established and individual prognostic variables on CR, 4-year OS and 4-year PFS. Patient-related variables considered for their prognostic value included age, gender, and Eastern Cooperative Oncology Group (ECOG) functional status. Tumor-related variables considered included B symptoms, Ann Arbor stage, use of rituximab, number of chemotherapy cycles, radiotherapy, and CNS involvement. HIV-specific variables included baseline CD4 cell count, viral load, ART status, and timing of ART relative to initiation of chemotherapy. The cut-off for the age of 40 and CD4 of 100 cells/μL was chosen to allow for comparison with existing data, which shows prognostic significance to these variables at these limits.[16,21,25,28] The IPI score was categorized as low risk (0-2), and high risk (3-5). An aaIPI of 0-1 was considered low risk and a score of 2-3 as high risk.

CNS involvement was determined by imaging or cerebrospinal fluid examination using cytocentrifuge or flow cytometry. Response to therapy was assessed at mid-cycle and at completion of chemotherapy. CR was defined by the absence of disease assessed by clinical, radiological, and laboratory measures. All records were available, except for viral load, where only 65 patients had information.

Statistical analysis

Kaplan-Meier survival curves for OS and PFS at 4 years were compared for IPI and aaIPI (low versus high risk) using the log-rank test. Cox proportional hazards model was used to investigate the effects of prognostic variables on patients achieving OS and

PFS during the study period. Logistic regression was used to determine the effects for the different prognostic variables in patients who achieved CR. Unadjusted and adjusted hazards and odds ratios are reported. All variables and outcome measures were evaluated on an intention-to-treat basis. All time-to-event analyses were measured from presentation to event or last recorded follow-up. P-values of <0.05 were considered statistically significant. Stata 16 was used for all data analyses.[29]

Results

During the study time period, 157 ARL were managed at this hospital. There were 102 patients with CD20 positive ARL included in this analysis (histological subtypes were 70 DLBCL, 31 high-grade B cell lymphomas, and 1 high-grade B cell lymphoma not otherwise specified). 13 patients were excluded due to missing data (either histology or HIV results), 9 patients for receiving an alternative chemotherapy regimen, 5 patients who did not receive chemotherapy and 2 patients with primary effusion lymphoma. The data for 26 plasmablastic patients has been published. The chemotherapy regimens and 4-year survival outcomes are shown in **Figure 4.1.**

From the 102 patients, 50% (n=51) were alive at 4 years, with 43% (n=44) showing no disease progression, 12% (n=12) demising and 38% (n=39) were lost to follow up during the 4 years. 64% (25/39) of the patients defaulting treatment were lost to follow-up within a year and none of these patients were in a CR at the time. There were 5 patients defaulting treatment between 12-24 months, and of the nine patients lost to follow-up after 2 years, 4 were treated with CHOP (2 with a partial response [PR] who chose not to continue further therapy, and 2 in CR) and 5 were treated with R-CHOP (all in CR). There were 3 patients who relapsed post first-line chemotherapy, with 2 receiving salvage (s) therapy and the third patient was lost to follow-up immediately after documented relapse. For 21 patients receiving salvage therapy with mesna, ifosfamide, novantrone, etoposide (MINE) and/or high dose methotrexate and/or radiotherapy, 9 achieved a CR_s, 9 were lost to follow-up and 3 demised.

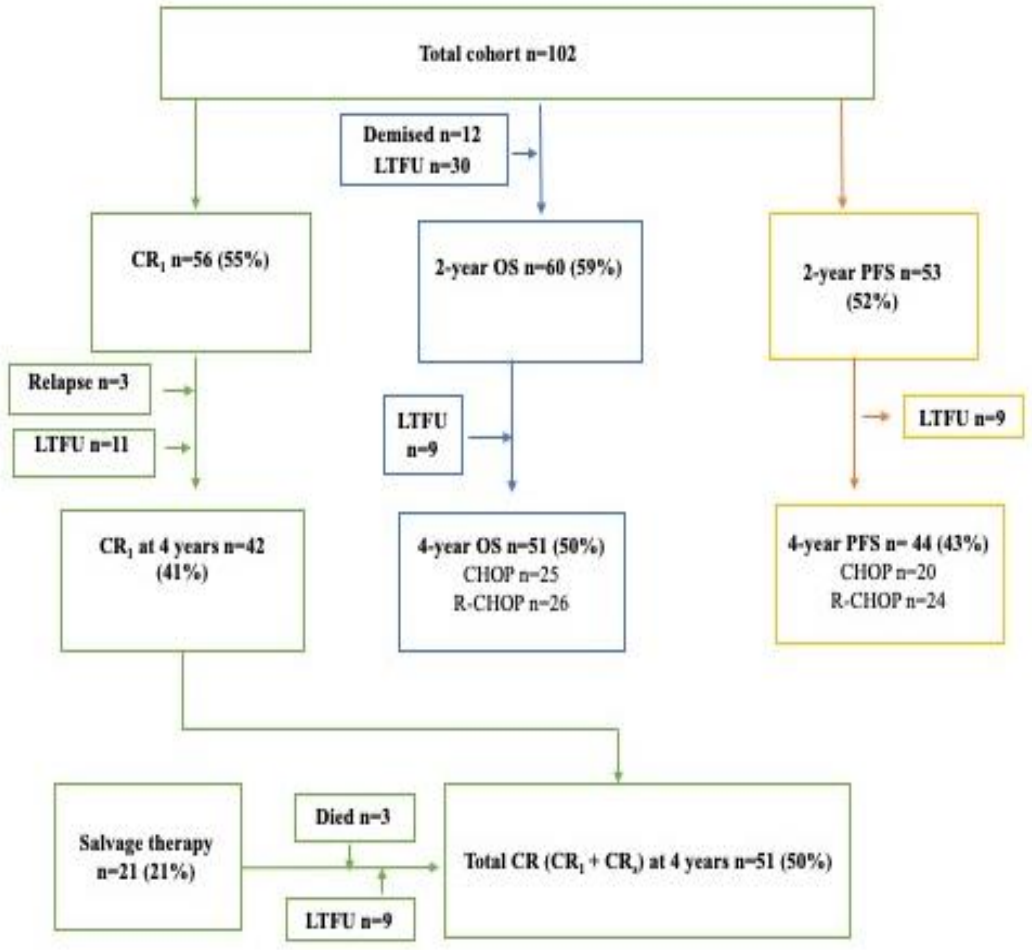

Figure 4.1. Treatment and outcomes for CD20 positive AIDS Related Lymphoma
Abbreviations: CR=complete response, PFS=progression free survival, OS=overall survival, CR_1=CR with 1st line chemotherapy, CR_s=CR with salvage therapy, LTFU=lost to follow up

For the patient and HIV prognostic variables shown in **Table 4.1**, the HIV viral load was the only variable that significantly affected the achievement of CR. Patients having undetectable viral loads of <50 copies/ml had a greater likelihood of CR (adjusted OR 6.10 [95% CI 1.55, 24.04]). Attaining a CR was significantly associated with improved PFS (HR = 0.08 [CI: 0.04, 0.16]; p-value <0.001) and OS (HR = 0.11 [CI: 0.06, 0.22)]; p-value <0.001). At lymphoma diagnosis, 45% (n=46) of the patients were already on ART, 39% (n=40) initiated ART concurrently with chemotherapy and 16% (n=16) remained ART naïve during chemotherapy. Of the 86 patients who received concurrent

Table 4.1. Impact of patient and HIV variables on Complete Response

		Complete Response (n=56)		
Predictor (%)		**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**p-value**
Age in years	**<40 (55%)**	**ref**	**ref**	**ref**
	≥40 (45%)	**1.32 (0.60, 2.91)**	**0.88 (0.26, 3.04)**	**0.841**
Gender	**Female (54%)**	**ref**	**ref**	**ref**
	Male (46%)	**1.03 (0.47, 2.26)**	**1.70 (0.51, 5.62)**	**0.386**
B symptoms	**Absent (70%)**	**ref**	**ref**	**ref**
	Present (30%)	**0.83 (0.35, 1.93)**	**0.84 (0.22, 3.24)**	**0.798**
ART timing	**Pre-diagnosis (53%)**	**ref**	**ref**	**ref**
	Concurrent with chemotherapy (47%)	**0.79 (0.33, 1.89)**	**1.01 (0.25, 4.11)**	**0.994**
CD4 count in cells/µL	**< 100 (25%)**	**ref**	**ref**	**ref**
	≥ 100 (75%)	**1.60 (0.66, 3.93)**	**1.15 (0.18, 7.52)**	**0.885**
VL	**Undetectable or <50 copies/ml (49%)**	**8.21 (2.68, 25.17)**	**6.10 (1.55, 24.04)**	**0.010**
	≥50 copies/ml (51%)	**ref**	**ref**	**ref**

Abbreviations: CR=complete response, OR=odds ratio, ART=antiretroviral therapy, VL=viral load, ref=reference

ART with chemotherapy, 60% (n=50) achieved a CR and 25% (n=4) of the ART naïve group achieved a CR (p=0.994). Of the 16 ART naïve patients, 12 received CHOP. Four of these 12 patients attained a CR and two a PR, with five of these patients having an OS exceeding five years and the sixth patient defaulted therapy after 10 months. Of the remaining six patients on CHOP, one had disease progression, two demised after three months, and three defaulted follow-up, with OS ranging from 2 weeks to six months. Four ART naïve patients received R-CHOP; one had disease progression and

Table 4.2. Impact of patient and HIV variables on outcome for CD20-positive ARL

	PFS			OS		
Predictor (%)	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)**	**p-value**	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)**	**p-value**
Age in years						
<40 (55%)	**ref**	**ref**	**ref**	**ref**	**ref**	**ref**
≥40 (45%)	**0.91 (0.54, 1.52)**	**1.02 (0.47, 2.22)**	**0.952**	**0.93 (0.53, 1.61)**	**0.95 (0.43, 2.10)**	**0.906**
Gender						
Female (54%)	**ref**	**ref**	**ref**	**ref**	**ref**	**ref**
Male (46%)	**0.77 (0.46, 1.29)**	**0.46 (0.21, 0.99)**	**0.048**	**0.78 (0.45, 1.37)**	**0.41 (0.19, 0.91)**	**0.028**
B symptoms						
Absent (70%)	**ref**	**ref**	**ref**	**ref**	**ref**	**ref**
Present (30%)	**1.04 (0.59, 1.81)**	**0.95 (0.41, 2.21)**	**0.901**	**1.18 (0.66, 2.12)**	**1.02 (0.43, 2.41)**	**0.959**
ART						
Pre-diagnosis (53%)	**ref**	**ref**	**ref**	**ref**	**ref**	**ref**
Concurrent with chemotherapy (47%)	**1.01 (0.56, 1.82)**	**0.84 (0.35, 2.04)**	**0.702**	**0.96 (0.51, 1.78)**	**0.85 (0.34, 2.11)**	**0.719**
CD4 count in cells/μL						
< 100 (25%)	**ref**	**ref**	**ref**	**ref**	**ref**	**ref**
≥ 100 (75%)	**0.81 (0.45, 1.44)**	**1.28 (0.38, 4.35)**	**0.694**	**0.93 (0.50, 1.74)**	**1.18 (0.35, 4.06)**	**0.787**
VL						
Undetectable or <50 copies/ml (49%)	**0.45 (0.23, 0.88)**	**0.45 (0.19, 1.07)**	**0.070**	**0.41 (0.21, 0.82)**	**0.43 (0.18, 1.05)**	**0.063**
≥50 copies/ml (51%)	**ref**	**ref**	**ref**	**ref**	**ref**	**ref**

Abbreviations: ARL=AIDS related lymphoma, HR=hazard ratio, CR=complete response, PFS=progression free survival, OS=overall survival, ART=antiretroviral therapy, VL=viral load

died 25 months later, and the three remaining patients were lost to follow-up during chemotherapy (none in CR). Using the chi-squared test, the 4-year OS of 59% (46/86) for concurrent ART with chemotherapy and 31% (5/16) for those who remained ART naïve during chemotherapy was not significantly associated with improved OS(p=0.111). The impact of patient and HIV variables on PFS and OS are detailed in Table 4.2 and lymphoma and treatment-related variables in Table 4.3.

Table 4.3. Lymphoma and treatment-related variables in CD20 positive ARL

	PFS			OS		
Predictor (%)	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)**	**p-value**	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)**	**p-value**
CNS involvement by lymphoma						
Absent (93%)	**ref**	**ref**	**ref**	**ref**	**ref**	**ref**
Present (7%)	**1.20 (0.48, 3.00)**	**1.04 (0.35, 3.10)**	**0.951**	**1.04 (0.38)**	**1.58 (0.49, 5.04)**	**0.444**
Rituximab use						
No (49%)	**ref**	**ref**	**ref**	**ref**	**ref**	**ref**
Yes (51%)	**0.81 (0.48, 1.36)**	**0.76 (0.45, 1.27)**	**0.289**	**1.04 (0.60, 1.80)**	**0.89 (0.51, 1.55)**	**0.675**
Radiotherapy use						
No (91%)	**ref**	**ref**	**ref**	**ref**	**ref**	**ref**
Yes (9%)	**0.86 (0.34, 2.16)**	**0.70 (0.23, 2.09)**	**0.519**	**0.33 (0.08, 1.37)**	**0.23 (0.05, 1.14)**	**0.071**
Number of chemotherapy cycles						
< 6 (30%)	**ref**	**ref**	**ref**	**ref**	**ref**	**ref**
6-8 (70%)	**0.16 (0.10, 0.29)**	**0.17 (0.10, 0.29)**	**<0.001**	**0.13 (0.07, 0.23)**	**0.12 (0.07, 0.22)**	**<0.001**

Abbreviations: ARL=AIDS related lymphoma, HR=hazard ratio, ARL=AIDS related lymphoma, CR=complete response, PFS =Progression free survival, OS=overall survival, CNS=central nervous system, ref=reference

For the 56 patients that attained a CR at the end of first-line chemotherapy, two patients received 3 cycles, one had 4 cycles, and another 5 cycles of chemotherapy (all four patients having refused additional chemotherapy). Of the 9 patients who received radiotherapy, 83% on CHOP (5/6) and 67% on R-CHOP (2/3) achieved a 4-year OS, respectively. Of the total cohort, 9% (n=9) received radiotherapy; 4 patients with bulky disease, 1 patient with a tonsillar relapse (who received salvage chemotherapy and radiotherapy), and progressive disease treated with salvage chemotherapy in the remaining four patients. A third of our study patients who received radiotherapy (3/9) had a good response with the sole addition of curative dose radiotherapy to 1st line chemotherapy, converting partial responses to CR in all three patients (all 3 had bulky disease). There was a 78% (7/9) 4-year OS for patients receiving radiotherapy compared with 47% (44/93) for patients who did not receive radiotherapy (p=0.071).
There was no significant association between individual prognostic variables of the aaIPI and OS or PFS (**Table 4.4**).

Table 4.4. aaIPI prognostic variables on outcome of CD20 positive ARL

	PFS			**OS**		
Predictor (%)	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)**	**p- value**	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)**	**p-value**
Ann Arbor stage						
Early - I/II (55%)	**ref**	**ref**	**ref**	**ref**	**ref**	**ref**
Late - III/IV (45%)	**1.92 (1.14, 3.23)**	**1.93 (0.95, 3.90)**	**0.067**	**2.05 (1.17, 3.59)**	**2.04 (0.96, 4.37)**	**0.065**
ECOG PS						
< 2 (32%)	**ref**	**ref**	**ref**	**ref**	**ref**	**ref**
≥ 2 (68%)	**1.66 (0.91, 3.04)**	**1.05 (0.47, 2.35)**	**0.899**	**1.70 (0.89, 3.25)**	**1.03 (0.43, 2.46)**	**0.941**
LDH increased						
No (4%)	**ref**	**ref**	**ref**	**ref**	**ref**	**ref**
Yes (96%)	**0.71 (0.22, 2.26)**	**0.56 (0.17, 1.85)**	**0.340**	**1.01 (0.24, 4.14)**	**0.77 (0.18, 3.27)**	**0.727**

Abbreviations: ARL=AIDS related lymphoma, aaIPI=age adjusted International Prognostic Index, CR=complete response, PFS=progression free survival, OS=overall survival, HR=hazard ratio, ECOG PS= Eastern Cooperative Oncology group performance status, LDH=lactate dehydrogenase, ref-reference

However, the IPI and aaIPI significantly correlated with OS (**Figure 4.2** and **Figure 4.3** respectively) and the IPI also significantly correlated with PFS and not OS (**Figure 4.2).**

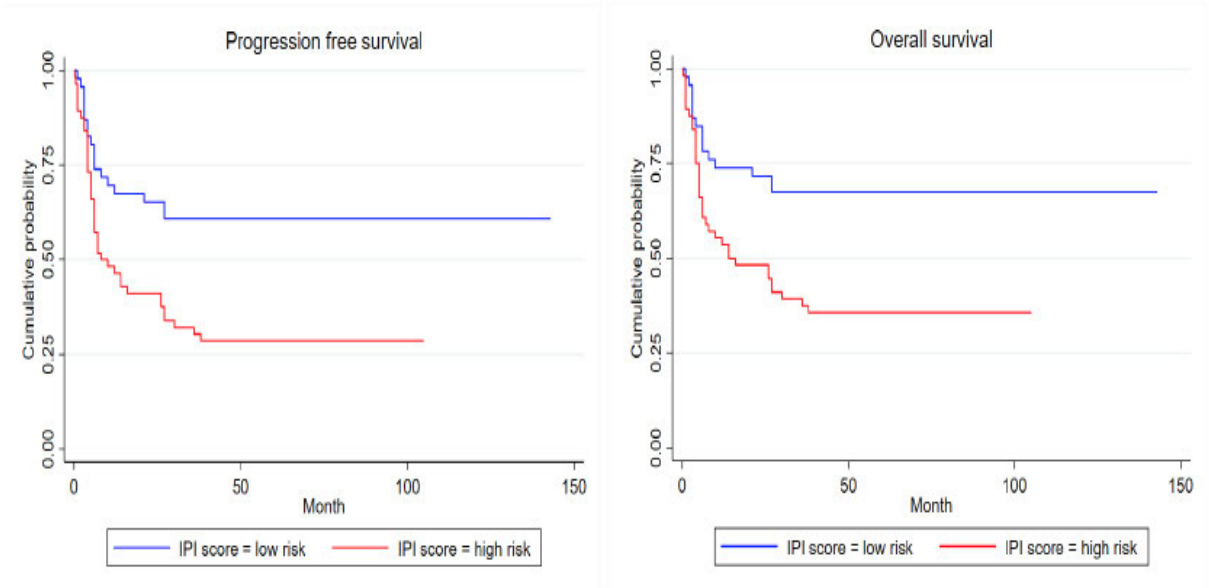

Figure 4.2. Kaplan Meier survival estimates: IPI for for PFS, p-value = 0.002 (left) and IPI for OS, p-value = 0.002 (right)
Abbreviations: IPI=International Prognostic Index, low risk (score 0-2), high risk (score 3-5)

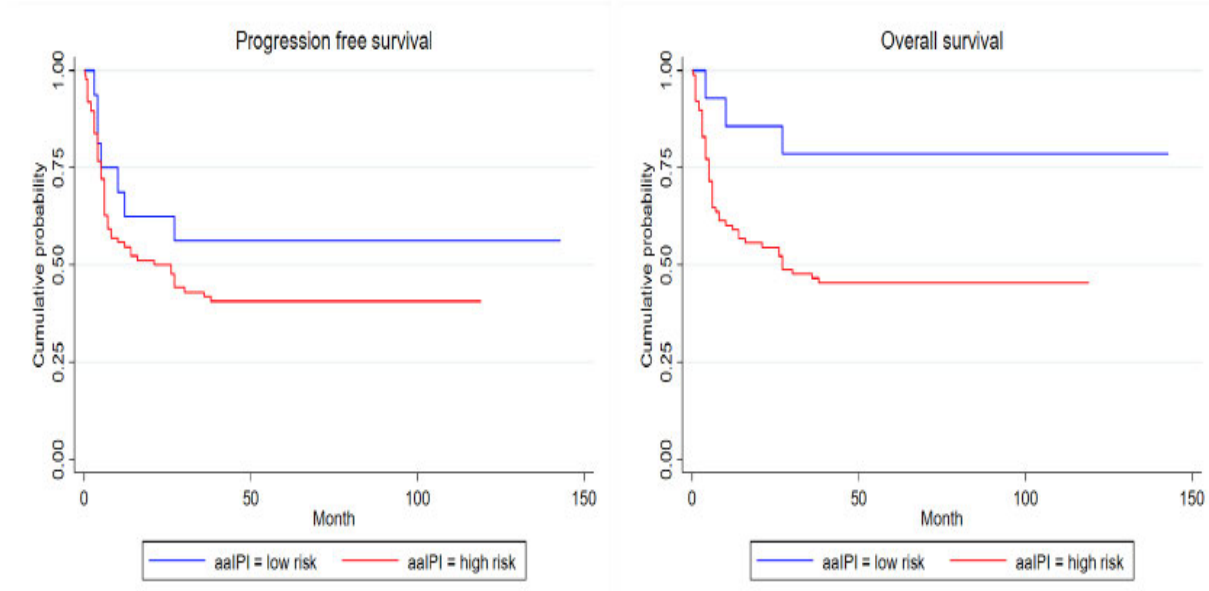

Figure 4.3. Kapan Meier survival estimates: aaIPI for PFS, p-value = 0.266 (left) and aaIPI for OS, p-value = 0.030 (right)
Abbreviations: aaIPI=age adjusted International Prognostic Index, low risk (score 0-1), high risk (score 2-3)

Discussion

Better HIV control in ARL has allowed for chemotherapy intensification with monoclonal antibodies similar to HIV-negative patients with lymphoma, and this is the first study from South Africa describing the prognostic significance of rituximab use in ARL. This study 4-year OS of 50% is within the reported 5-year survival of 46-55% for ARL[20,24] and comparable to the reported 46% 5-year survival in another South African study.[18] This improved 4-year survival in the ART era, compared with the 11-month median OS described in Gauteng, South Africa with 85% of the cohort not on ART[17], highlights the need for an accurate prognostic system to guide therapy in ARL.
The CR for the study cohort of 55% is at the lower spectrum of reported CR; 65% described by Miralles et al in the multicentre Spanish study[20] and 58-77% in American and European studies.[30,31] However this CR correlated with 4-year OS and PFS in our cohort. This finding is in accordance with the positive predictive value of the CR for OS found in a retrospective British cohort.[13]

The only patient-related variable that correlated with survival, was gender, with males having both improved PFS and OS. This prognostic significance of gender has been confirmed by other studies in Africa, including South Africa[18,32] These findings, however, contrast with the poorer outcome shown for male patients in Zimbabwe, and lack of significance for gender in studies outside of Africa.[28] Whether gender remains a unique prognostic variable for an African cohort in the ART era warrants further study.
There was no improvement in 4-year OS in patients who received ART with chemotherapy compared with those who remained ART naïve during chemotherapy (p=0.111). This result contrasts with the Lim et al[21] analysis which showed that median survival increased significantly from 8.3 months in ART naïve patients to 43.2 months for those on ART. Our study findings also contrast with an African study from Uganda which found similar survival outcomes in ARL treated with concurrent ART and chemotherapy compared with HIV-negative lymphoma patients, but an almost 9-fold increase in mortality in ARL patients not taking ART compared with HIV-negative patients. [32] Barta et al demonstrated that survival increased from 24% pre-ART to 67% in the ART era.[22] All 3 studies show a clear survival benefit with ART, which is not evident in our cohort. A similarly matched South African cohort to our study cohort

also showed poor outcome pre-ART.[17] This lack of prognostic significance in our study is therefore most likely due to the smaller number of patients not on ART (n=16), rather than a true lack of significance.

Although a low or undetectable viral load in our study significantly affected CR (p=0.01), this did not translate to a significantly improved PFS or OS. Our findings are similar to a Spanish study in terms of viral load correlating with CR but did not match the correlation with virological response and improved OS seen in this Spanish cohort.[31] The lack of impact on the OS in our cohort may be due to small sample size, or lymphocyte dysregulation, even whilst on ART being driven by immune activation [33,34] rather than HIV viral replication. [35,36] This could negate the benefit of a low or undetectable viral load on OS.

The CD4 count was not associated with improved OS (p=0.787), and this shift away from the significance of the immune status reflected by the CD4 count in the ART era has been well documented.[13,22,37] A retrospective analysis of ARL patients pre and post ART, found that a low CD4 count of < 100cells/μL was associated with poorer survival only in the pre-ART era.[21] However, the prognostic value of the CD4 cell count in the post-ART era is not entirely lost. When used in a composite score with the viral load and past history of AIDS-defining illness, it showed a strong association with mortality.[23]

There was no association between the timing of ART and survival in our cohort (aHR 0.85 [95% CI 0.34, 2.11] p=0.719), which is borne out by a Chinese study on 100 patients with ARL.[38] However, this is contradictory to the multicentre study in sub-Saharan Africa by Gopal et al[39] and a Brazilian study[40] which found a significantly lower OS in ARL diagnosed in patients already on ART. A German study also found poorer OS in ARL patients already on ART at lymphoma diagnosis compared with ART initiated post lymphoma diagnosis.[41] The conflicting results on the prognostic significance of the timing of ART in ARL is worthy of further study.

In this study, there was no improvement in outcome with the use of rituximab, in contrast to the clearly proven benefit in multiple international studies.[16,41-43] Unsurprisingly, patients who received 6-8 cycles of chemotherapy had a significantly better outcome than patients receiving < 6 cycles of chemotherapy (p=<0.001). The FLYER trial demonstrated non-inferiority of 4 cycles of R-CHOP and 2 additional rituximab doses compared to 6 cycles of R-CHOP.[44] However this group included only HIV-negative patients with DLBCL and an excellent aaIPI of 0. In our cohort, only 1 patient had an aaIPI of 0. This patient had progressive disease on R-CHOP and required radiotherapy and salvage chemotherapy to attain a 4-year OS. Compatible with our study findings, another cohort in Africa found that patients with ARL who received < 3 cycles of chemotherapy had a significant increase in mortality at 18 months.[28] In the absence of randomised trials, and noting that most patients with ARL have an aaIPI >0, our findings would support current guidelines of 6-8 cycles of R-chemotherapy in CD20 positive ARL.[45,46]

Although the numbers are small, with only 9% receiving radiotherapy, the trend toward significance in survival is different to another small study on consolidative radiotherapy in HIV DLBCL, which found no significant difference in OS in patients who received radiotherapy.[47] Unlike this latter study, the indications for radiotherapy in our study were more diverse and included bulky disease, relapse and progressive disease. For the only 2 patients who received radiotherapy but did not reach 4-year OS, both had high-risk IPI of 4, with one patient having additional risk with testicular involvement. There is limited literature on the value of radiotherapy in ARL apart from primary central nervous system lymphoma. Radiotherapy as a therapeutic tool in ARL management merits further investigation.

Both the IPI and aaIPI were associated with OS. The IPI also correlated with PFS (**Figure 4.2**). These findings are supported by other studies.[48-50] However, unlike the latter studies, the individual components in the aaIPI in our cohort did not correlate with outcome, either in univariate or multivariate analysis. The skewed LDH results, with 96% of the study cohort having a raised LDH, would also account for it not being of predictive value.

Study limitations

The retrospective design of the study limited the nature and extent of patient and laboratory information available (viral load was only available for 65 patients). Data related to ART regimens and prior diagnosis of AIDS or opportunistic infections were not available for all patients and the significance of these variables could not be determined. The sample size, in assessing the value of rituximab and ART, was a further limitation, that will be addressed in a local, prospective study. The large number of patients lost to follow-up (38%) was a further limitation.

Conclusion

This study demonstrates reasonable 4-year survival outcomes with combination chemotherapy and ART in CD20 positive ARL. It validates the utility of the IPI and aaIPI in determining prognosis in ARL in an HIV endemic province in South Africa. Further studies are required to explore the prognostic significance of ART timing, gender and the feasibility of individualized chemotherapy as stratified by prognostic factors.

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CHAPTER 5
CONCLUSION

5.1 Synthesis

This work focuses on ARL, with the aim of using the data collected toward establishing a locally validated treatment guideline for this malignancy. Of the nine provinces in South Africa, the province of KwaZulu-Natal has the highest HIV seroprevalence. The management of this lymphoma is largely borne by the public sector and the Department of Health. Identifying the patient profile and response to current therapy will determine the efficacy of therapy locally, and the need to change or intensify treatment. Identifying factors that impact outcome, will allow for therapy to be adapted in the most cost-effective manner.

This body of work has highlighted points of interest and potential for further study in the 3 manuscripts:

- 5.1.1 Low incidence of bone marrow involvement in ARL locally
- 5.1.2 Lack of statistically significant improved survival with rituximab use in CD20-positive ARL
- 5.1.3 Acceptable response to treatment of CNS involvement by systemic ARL when treated on clinical suspicion, without routine CNS prophylaxis
- 5.1.4 The highest CD4 count reported to date for PBL, and the development of PBL even with virological suppression, supporting the involvement of other factors in driving PBL tumor development
- 5.1.5 Lack of correlation of IPI/aaIPI with PBL outcome
- 5.1.6 The utility of the IPI and aaIPI in predicting OS in CD20 positive ARL
- 5.1.7 Gender having prognostic significance in CD20-positive ARL

The first manuscript in Chapter 2 showed a slightly greater female gender presenting with CD-20 positive ARL overall. However, there was a shift in the gender, with the male: female ratio during the first 7 years of the study period (2006-2013), of 38%:62%(1:1.6), changing to 54%:46%(1:0.8) in the latter 3 years (2013-2016). The female predominance was explained by the HIV population demographics in South Africa, as well as this centre's anecdotal experience with the initial reluctance by male

patients to accept ART. However, this shift in gender in the latter study period is contrary to other studies from South Africa.[1,2] Unlike the stronger representation of MSM cohorts described in North America and Europe,[3,-5] the main mode of HIV transmission in South Africa, is heterosexual, and this explains the fairly even gender distribution in South Africa.[6] The additional significance of gender correlating with the prognosis of CD20-positive ARL was an unexpected finding in Chapter 4, and worthy of further study.

There was an unexplained lower incidence of marrow involvement by lymphoma in both CD-20 positive ARL and PBL.[7,8] This contrasts also with the much higher incidence of marrow involvement in DLBCL in another province in South Africa.[2] In the early '90s, when routine ancillary testing was not performed on the staging marrows, lymphoma involvement was documented in as many as 15% of ARL cases.[3] Ancillary testing with flow cytometry and immunohistochemistry on the marrow has been shown to improve the sensitivity of marrow detection, thereby increasing the IPI score.[9,10] This need for accurate assessment of the marrow is reinforced by the poor prognostic significance attributed to the marrow involvement by lymphoma.[11]

The manuscript on prognostic variables has confirmed the utility of the IPI and aaIPI in determining prognosis in CD20 positive ARL, but not in plasmablastic lymphoma. This is the first study from South Africa that validates the IPI and aaIPI in CD20-positive ARL. Whilst this lack of correlation between the IPI/aaIPI and OS in PBL may be due to the small PBL cohort, other similarly small studies have shown a correlation.[7,12] The significance of this is especially pertinent in 'high-risk' patients with plasmablastic lymphoma, where alternative therapeutic modalities need to be explored.[13,14]

A key finding of this study was the lack of significant improvement in CR, 2-year or 4-year OS with the addition of rituximab to CHOP chemotherapy. However, rituximab was well tolerated, with a trend toward increasing transfusion requirements. There was no increase in infection in the rituximab-treated arm.

5.2 Recommendations

Following the findings in the 1st manuscript, more routine use of flow cytometry and immunohistochemistry has been recommended on staging ARL bone marrows. It has to be noted that these routine ancillary tests on the bone marrow are costly and labour-intensive, especially for flow cytometry; hence the added value needs to be objectively determined before establishing this as the standard of care locally. Therefore, two six-month time periods are currently being compared, with routine ancillary tests on the bone marrow being compared to morphology alone. The data for this review is currently being analysed, and the findings will contribute to the local guidelines for staging work-up of ARL patients.

Additionally, the bone marrows are being assessed to determine the sample quality and identify referral hospitals in KwaZulu-Natal that would benefit from teaching on the marrow sampling technique (as this is postulated to potentially contribute to the lower marrow incidence). The haematology department at this centre has already initiated outreach and teaching of junior doctors in these referral hospitals. The plan is to also review the PET scans, as described by the Cheson guideline, and correlate this result with the bone marrow biopsy.[15] Many of the patients locally have PET-CT staging scans, and this tool might prove helpful, especially if the marrow sample is of sub-optimal quality.

The high CD4 count and suppressed viral loads for many patients with PBL was a notable study finding. This points to other factors apart from immunosuppression, contributing to PBL pathogenesis. This finding is also supported by literature suggesting a higher CD4 count at lymphoma diagnosis in African patients.[16,17] Documenting clearly the profile and background of all the ARL patients will further enhance understanding, and these details should ideally be captured in a local registry. A protocol for a population-based registry has therefore been drafted, and is being revised.

Although rituximab did not significantly improve CR and OS in CD20 ARL, this may be due to the limited sample size. The aim is, therefore, to further investigate the value

of rituximab in this setting, in a prospective study. As the prognostic significance of gender has yielded conflicting results in CD20 ARL,[18,19] and appears to be more pertinent to African cohorts, this will be further studied prospectively in the same study.

There is no established optimal chemotherapy for PBL. For the limited number of patients with CD20-positive, PBL, a trial of rituximab combination therapy is recommended.[20] Ideally, myeloma-containing regimens need to be investigated for clinical effect in PBL locally. Infusional chemotherapy has also shown conflicting results when compared with bolus chemotherapy in CD20 ARL and PBL and merits further prospective study.[21] However, this centre has limited access to the full spectrum of myeloma containing therapeutic regimens, and infusional chemotherapy is not possible due to resource constraints.[22,23] The centre is therefore exploring the possibility of intensifying chemotherapy with available drugs eg. etoposide in the CHOEP regimen as tried by another South African researcher or collaborating with other centres.[1]

Study limitations/strengths

The study limitation was the retrospective nature of the study, which limited the data availability. A major limitation was the sample cohort for the CD20-positive ARL, which was not powered to detect a significant difference in outcome between the 2 chemotherapy arms. The study strengths are the first description of ARL in KZN and the first description of the outcome as well as the prognostic significance of rituximab use in ARL in SA.

5.3 Conclusion

This dissertation highlights similar response to bolus chemotherapy for ARL in the local population compared to other cohorts, despite the socio-economic challenges. There is a need for further refinement of the investigational and therapeutic modalities for ARL in the local population, and review of ancillary tests on staging bone marrows has already been initiated. Prospective studies looking at the utility of the accepted prognostic

scoring systems and alternative therapeutic modalities in PBL, and rituximab use in CD20 ARL, are being investigated.

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Foundation; European Organisation for Research; Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Médula Ósea; German High-Grade Lymphoma Study Group; German Hodgkin's Study Group; Japanese Lymphorra Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68. doi: 10.1200/JCO.2013.54.8800. PMID: 25113753; PMCID: PMC4979083.

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APPENDIX

1. **Study Ethics approval**

1 October 2017

Dr N Rapiti (863585748)
Discipline of Haematology
School of Laboratory Medicine and Medical Sciences

Dear Dr Rapiti

Protocol: Efficacy of R-CHOP chemotherapy versus chemotherapy in patients wi HIV associated lymphoma. BREC reference number: BE043/17

NEW TITLE: Profile and efficacy of chemotherapy in HIV associated lymphoma
Degree: PhD

Your correspondence received on 05 October 2017 submitting an application for Amen the title to the above and other amendments has been **noted and approved** by a s the Biomedical Research Ethics Committee.

The above approval be **ratified** at the next meeting to be held on **14 November**

Yours sincerely

Mrs A Marimuthu
Senior Administrator: Biomedical Research Ethics

administrator:


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