A 10-year Retrospective Analysis of the Clinical Characteristics and Outcomes of mature B-Cell Non-Hodgkin Lymphoma in children treated in a tertiary South African Hospital.

By

Bhavisha Lackhoo

Student number: 0606831Y

BSc (Wits), MD (USAIM), Dip HIV Man (SA), DCH (SA), FCPaeds (SA)

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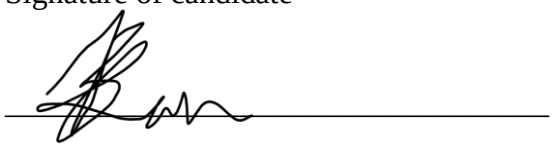
DECLARATION

I, Bhavisha Lackhoo, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Paediatrics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature of candidate



____30th_day of ____October_____ 2024.

Dedication

To my beloved husband Tyral
and my son Khai
my pillars of strength and inspiration.

ABSTRACT

Background: Mature B-cell Non-Hodgkin lymphoma(B-NHL) is a common childhood malignancy with excellent cure rates in developed countries. There is limited data in Sub-Saharan Africa(SSA) especially with regard to HIV-infected children with B-NHL.

Aim: The aim of this study was to compare clinicopathologic characteristics and outcomes in HIV-infected and HIV non-infected children with mature B-NHL.

Setting: Chris Hani Baragwanath Academic Hospital, South Africa.

Methods: Data were collected for all children diagnosed with mature B-NHL over a 10-year period. This included demographic, clinical, laboratory, radiological, treatment and outcome data. Descriptive statistics, multivariate analysis and a Cox proportional hazard model to determine the hazard ratio were calculated using the statistical programme IBM SPSS version 2.

Results: A total of 61 patients were included in this study. The majority of patients were HIV-infected(n=41, 67%). The predominant histological subtype was Burkitt Lymphoma in both groups(40%). The median age of diagnosis in the HIV-infected group was 9.5 years and 5.7 years in the HIV non-infected group (p=0.07). Males were the majority sex in both groups (69%). More HIV-infected patients had a previous history of TB (n=18, p=0.002) and the majority were virally unsuppressed (61%). HIV-infected patients with B-NHL are 19 times more likely to succumb to death compared to HIV non-infected patients with B-NHL (HR=18.8, 95% CI 3.2-110.3, p=0.001).

Conclusion: This study has shown that HIV-infected patients with B-NHL are 19 times more likely to die compared to their HIV-negative counterparts. Advanced disease at presentation, malnutrition, and treatment toxicity contributed to deaths in the HIV-infected group.

Acknowledgements

I would like to acknowledge my supervisor Dr B Rowe for her encouragement, patience and guidance throughout this research. I would also like to thank my family for their endless support and love.

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ABBREVIATIONS

BL	Burkitt lymphoma
B-NHL	B-cell Non-Hodgkin lymphoma
CHBAH	Chris Hani Baragwanath Academic Hospital
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computerized Tomography
DLBCL	Diffuse large B-cell lymphoma
FBC	Full blood count
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HGBL-11q	High-grade B-cell lymphoma with 11q aberration
HREC	Human Research Ethics Committee of the University of the Witwatersrand
LDH	Lactate dehydrogenase

LMIC	Low to middle income countries
MRI	Magnetic resonance image
NHL	Non-Hodgkin lymphoma
NOS	Not otherwise specified
SSA	Sub-Saharan Africa
TB	Tuberculosis
WITS	University of the Witwatersrand

SUBMISSIBLE PAPER

A 10-year Retrospective Analysis of the Clinical Characteristics and Outcomes of mature B-Cell Non-Hodgkin Lymphoma in children treated in a tertiary South African Hospital

B Lackhoo[1], MD DCH (SA) ; **B Rowe[2],** MBChB (UP) DCH (SA) FC Paed(SA) MMed Paed (WITS) Cert Med Paed Onc (SA)

[1]*Department of Paediatrics and Child Health, University of the Witwatersrand and Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa.*

[2]*Paediatric Haematology-Oncology department, University of the Witwatersrand and Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa*

***Corresponding author*:** *Bhavisha Lackhoo* (Bhavisha.l@hotmail.com)

1. INTRODUCTION

Non-Hodgkin lymphoma(NHL) is a common childhood malignancy that accounts for 7% of all childhood cancers diagnosed between the ages of 5 and 19 years in industrialised countries(1,2). The incidence of NHL in low to middle income countries(LMIC) is often underestimated due to substandard cancer registries, diagnostic challenges and comorbid conditions(1,3–5). It is estimated that 90% of paediatric NHL occurs in LMIC(1)The median incidence of NHL among the general paediatric population in Sub-Saharan Africa is estimated to be 1.98/100,000(6). B-cell NHL(B-NHL) are high grade neoplasms originating from mature B-lymphocytes and follow an aggressive clinical course(3). In contrast with adults, the subtypes of B-NHL comprise mainly Burkitt lymphoma(BL) and diffuse large B-cell lymphoma(DLBCL) in children(3). Rarer forms reported in children are plasmablastic lymphoma, primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma not otherwise specified, and mediastinal grey zone lymphoma(7).

The incidence of HIV-infected children with B-NHL in SSA is unknown due to a paucity of data from SSA countries with the highest HIV prevalence(6).

BL is characterised by the over-expression of the MYC oncogene(8). This overexpression is most commonly due to a chromosomal translocation between chromosome 8 and 14(8). The t(8;14) is the classical translocation found in BL. Variant translocations found in BL involve the light-chain Ig genes and consists of translocations between chromosomes 2, 8, and 22(9). There are 3 clinical variants of BL: endemic (seen in equatorial Africa which is associated with Ebstein Barr virus(EBV) and *Plasmodium falciparum* malaria infection), sporadic, and immunodeficiency-associated(10). Endemic BL has a male predominance and a peak incidence of four to seven years (11). Sporadic and immunodeficiency-associated BL is more common in South Africa(3). Sporadic BL is four times more common in males and has a peak incidence in children of 11 years old(11). Endemic BL often presents with a jaw mass whereas sporadic BL more commonly presents as an abdominal mass or involvement of the bone marrow(3,12). Sporadic BL has a 5-year overall survival (OS) of 96% in HIV) negative patients with stage 3 disease(3). Immunodeficiency-associated BL has a greater mortality rate in higher risk groups, with an estimated 5-year OS of 33.3%(3). High grade B-cell lymphoma with 11q aberration (HGBL 11q), previously known as Burkitt-like lymphoma, is recognized by the WHO since 2016(7). It morphologically resembles BL but lacks the MYC rearrangement.

DLBCL represents 10-20% of all paediatric NHL(3,13). Genetic abnormalities in DLBCL may include t(8;14) and t(14;18)(9). DLBCL has a male predominance and mainly occurs in the second decade of life((13). The abdomen is the most common site of primary disease(13). DLBCL is more prevalent amongst HIV infected patients(14).

Plasmablastic lymphoma(PBL) is an aggressive B-NHL that occurs in immunosuppressed children and adults(15). It has a higher prevalence in South Africa due to the higher prevalence of HIV-infection and carries a poor prognosis(15).

Paediatric B-NHL is staged according to the Murphy staging system and is based on imaging findings, bone marrow aspirate and biopsy, and evaluation of the central nervous system (CNS) through imaging and/or examination of the cerebrospinal fluid (CSF)(16)

Paediatric B-NHL is treated according to established risk stratified international multi-agent chemotherapy protocols(Table 1)(17,18). Patients are stratified into low, intermediate or high risk categories based on disease stage and tumour burden (Figure 1). The objective of risk stratified therapy is to reduce acute and long-term complications for low risk patients(19),whilst more intensive regimens are employed for patients at a higher risk for treatment failure(19). The Non-Hodgkin Lymphoma-Berlin-Frankfurt-Munster 95(NHL-BFM95) and Lymphome-Maline-de Burkitt (LMB) are chemotherapy protocols based on these principles(17,18). Disease stage and Lactate dehydrogenase(LDH) levels at diagnosis are used to risk stratify patients in BFM-based protocols(17). Lactate dehydrogenase is an important prognostic marker and represents tumour burden(2). An LDH level two-times the upper limit of normal or greater than 1000IU significantly decreases event free survival (EFS) in children with B-NHL(20).

Short, dose intense courses of chemotherapy with CNS prophylaxis through intrathecal therapy are the backbone of modern treatment regimens for B-NHL(17).

Rituximab, a CD20 monoclonal antibody, is well established in adult chemotherapy protocols treating CD20-positive B-cell lymphomas(21). It is increasingly used in first-line therapy paediatric protocols for CD20-positive B-NHL(21)

Cure rates in developed countries are more than 80% however, in LMICs, cure rates may be lower secondary to limited diagnostic and treatment resources(3). Delayed diagnosis, misdiagnosis, far distances from treatment centres and supportive care limitations including restricted access to advanced life support, intravenous antibiotics and blood products further exacerbate low cure rates in LMIC. Malnutrition complicates the treatment of B-NHL by affecting the pharmacokinetics of cytotoxic drugs and contribute to poorer outcomes(22).

South Africa has a high Tuberculosis (TB) and HIV burden(23,24). The clinical features of TB and HIV may overlap with those of NHL(24). This poses a challenge to healthcare workers, where NHL may be misdiagnosed as TB(24), leading to delays in the diagnosis of NHL. HIV is the most common acquired immunodeficiency and infected children have a 100-fold increased risk for developing B-NHL(23,25). HIV-infected patients with B-NHL have a higher mortality rate, however, HIV infected children on highly active antiretroviral therapy(HAART) have similar outcomes to HIV non-infected children(3,25). There is a paucity of information regarding treatment modification and outcomes of HIV-infected children with B-NHL in South Africa.

2. METHODS

This study aims to describe the experience with mature B-NHL in a tertiary level hospital, and contribute knowledge about presenting features, treatment modalities and outcome in a South African paediatric population with a high HIV-prevalence.

Study Objectives

2.1 To determine the incidence of B-NHL among all newly diagnosed paediatric patients with malignancy diagnosed at CHBAH from 1 January 2010 until 31 December 2019.

2.2 To compare the presenting features, treatment-induced toxicity, treatment delays and protocol modifications between HIV-positive and HIV-negative patients with B-NHL.

2.3 To describe the overall outcome of patients with B-NHL and in the subgroup of patients with and without HIV-infection.

A retrospective cohort study was performed between 1 January 2010 and 31 December 2019 where patient records were reviewed at the Paediatric Oncology unit (POU) at Chris Hani Baragwanath Academic Hospital (CHBAH). CHBAH is a referral centre for patients across Gauteng and the North West province of South Africa, and accepts foreign patients from eSwatini, Botswana and Zimbabwe.

All newly diagnosed paediatric patients, both HIV-infected and HIV-non infected, less than 20 years of age with histologically confirmed mature B-cell neoplasms, according to the revised 2016 WHO classification of lymphoid neoplasms, were included (26). Baseline demographic data, clinical information on the mode of presentation, nutritional status, and concomitant or previous TB treatment were collected. Patients were staged according to the St Jude/Murphy staging system(16) and risk stratified according to the BFM-NHL 95 protocol.
Staging investigations included physical examination, imaging (chest X-Ray and/or abdominal ultrasound and/or CT of the affected area in addition to a CT of the chest and abdomen), bone marrow aspiration and trephine biopsy, and lumbar puncture with cerebrospinal fluid (CSF) analysis. Bone marrow involvement was defined as the presence of >5% malignant cells. More than 25% of malignant cells in the BM defined a mature B-leukaemia. Any malignant cell present in the CSF was regarded as involvement of the CNS, in addition to the presence of new, unexplained focal neurological signs with or without abnormal intracranial imaging. A tumour or lymph node more than 6cm in diameter was considered bulky disease(3).

The Murphy/St. Jude staging system defines stages I and II as limited stage disease and stages III and IV as advanced stage disease. All primary intra-thoracic (mediastinal, pleural, thymic), extensive primary intra-abdominal sites and any paraspinal or epidural sites are defined as criteria for stage III. Bone marrow and CNS involvement defines stage IV.

Baseline evaluation of peripheral full blood counts, renal function and laboratory markers of tumour lysis syndrome (uric acid levels, LDH levels, metabolic panel including calcium, magnesium and phosphorus levels) were recorded and the HIV-status confirmed as positive or negative. If found to be HIV-positive, the viral load and CD4-count was recorded. LDH-levels were used as a marker of tumour burden.

Risk stratification was done according to the BFM B-NHL 1995 protocol(27). Risk stratification was informed by disease stage and serum LDH-level. The assigned risk group

guided the intensity of chemotherapy, from less intensive chemotherapy for early stage and low risk patients (risk groups R1 and R2) to more intensive chemotherapy for patients with advanced disease (risk groups R3 and R4).

Risk group	Definition	Therapy Courses
R1	Stage I and II, completely resected	**A** **B**
R2	Stage I and II, not resected Stage III and LDH <500	**V** **A** **B** **A** **B**
R3	Stage III and LDH ≥500-<1000 U/L Stage IV+B-AL and LDH <1000U/L and CNS negative	**V** **AA** **BB** **CC** **AA** **BB**
R4	Stage III+IV+B-AL and LDH ≥1000U/L or/and CNS positive	**V** **AA** **BB** **CC** **AA** **BB** **CC**

Figure 1: Risk stratification and determination of chemotherapy regimen according to BFM B-NHL 95 protocol(17)

In view of the larger disease burden in R2,R3 and R4 patients, a cytoreductive prephase "V" is given to cytoreduce the tumour and minimize the risk of tumour lysis and acute kidney injury. The prephase consists of 5 days of dexamethasone in increasing doses and 2 days of cyclophosphamide IV. Block A (for limited disease) and Block AA (for advanced disease) includes methotrexate (1g/m² in block A and 5g/m² in Block AA respectively), dexamethasone, vincristine, ifosfamide, cytarabine, etoposide and triple IT therapy with

prednisone, methotrexate and cytarabine. Block B (for limited disease) and Block BB (for advanced disease) includes methotrexate (1g/m² in block B and 5g/m² in Block BB respectively), dexamethasone, vincristine, cyclophosphamide, doxorubicin, and triple intrathecal (IT) therapy with prednisone, methotrexate and cytarabine.

Block CC (only used in advanced disease (R3 and R4) included dexamethasone, vincristine, cytarabine, etoposide and triple IT therapy with prednisone, methotrexate and cytarabine.

Details of the chemotherapy course are shown in table 1.

Table 1: Chemotherapy course for treatment according to BFM B-NHL 95 protocol (17)

Drug	Route	Dose	1	2	3	4	5
Prephase V							
Dexamethasone	Oral/IV	mg/m²¶	5	5	10	10	10
Cyclophosphamide	IV	200mg/m²	X	X			
Methotrexate	IT	12mg	X				
Cytarabine	IT	30mg	X				
Hydrocortisone	IT	10mg	X				
Course A							
Dexamethasone	Oral/IV	10mg/m²¶	X	X	X	X	X
Vincristine	IV	1.5mg/m²‖	X				
Ifosfamide	IV	800mg/m²	X	X	X	X	X
Cytarabine	IV	150mg/m²*				X-X	X-X
Etoposide	IV	100mg/m²				X	X
Methotrexate	IV	1g/m²	X				
Methotrexate	IT	12mg	X				
Cytarabine	IT	30mg	X				
Hydrocortisone	IT	10mg	X				
Course B							
Dexamethasone	Oral/IV	10mg/m²¶	X	X	X	X	X
Vincristine	IV	1.5mg/m²‖	X				
Cyclophosphamide	IV	200mg/m²	X	X	X	X	X
Doxorubicin	IV	25mg/m²				X	X
Methotrexate	IV	1g/m²	X				
Methotrexate	IT	12mg	X				
Cytarabine	IT	30mg	X				
Hydrocortisone	IT	10mg	X				
Course AA§ and BB§							
Methotrexate	IV	5g/m²¶	X				
Methotrexate	IT	6mg	X				X
Cytarabine	IT	15mg	X				X
Hydrocortisone	IT	5mg	X				X
Course CC							

Dexamethasone	IV	20mg/m^2¶	X	X	X	X	X
Vincristine	IV	1.5mg/m^2‖					
Cytarabine	IV	3g/m^2*	X-X	X-X			
Etoposide	IV	100mg/m^2*			X-X	X-X	X
Methotrexate	IT	12mg					X
Cytarabine	IT	30mg					X
Hydrocortisone	IT	10mg					X

¶ Subdivided in 3 doses
§ Courses AA and BB are the same as A and B, respectively, with the exceptions listed
‖ Maximum dose was 2 mg
*Doses are 12 hours apart

Modifications to the chemotherapy protocol were made on an individual basis. Patients with severe malnutrition (-2 to -3 SD for weight, height or weight for height(28), severe immunosuppression (CD4 count of less than 200 cells/µl or 15%), with or without extensive bone marrow involvement, may have had their chemotherapy protocol modified on an individualized basis to include an extended period of corticosteroids or a dose reduction of their first or subsequent chemotherapy blocks. The aim of these modifications was to minimize treatment-related morbidity and mortality over and above the risk-adapted strategy as described above.

Patients with advanced disease had response-assessment evaluation after the fifth course of chemotherapy. If a residual mass was detected, the patient underwent a biopsy or resection of the residual mass. If viable lymphoma tissue was identified, the patient proceeded to high-dose chemotherapy and autologous stem cell transplant. If no viable lymphoma was found on biopsy, patients in R3 received no further therapy and patients in R4 received a sixth course of chemotherapy as consolidation. Patients in R4 with bone marrow involvement at diagnosis, had repeat bone marrow sampling at the start of each block of chemotherapy until clearance of bone marrow involvement was obtained. Routine surveillance of the CSF was done during IT procedures to document CNS-status.

Documentation was made if a patient received radiation therapy or immunotherapy(Rituximab).

Data was captured using password protected Google Forms and this was exported to an Excel spread sheet. Parametric continuous variables were described with means and standard deviations and non-parametric continuous variables were described with medians and

interquartile ranges. Associations between continuous variables were described with a student t-test if normally distributed, otherwise with a Wilcoxson-Rank sum test if not normally distributed. Categorical variables were described with frequencies and percentages. Associations between categorical variables were described with Chi-square tests and Fischer-exact tests were appropriate. The date of diagnosis was the date of histology confirming B-NHL**.** The last date of follow up was used in survival analysis. Overall survival (OS) was calculated from the date of diagnosis to the date of death from any cause. Kaplan-Meier graphs illustrated the overall survival and the log-rank test described the significance in survival outcomes between groups. A logistic regression model describes the odds of survival given certain predictive variables. A P-value <0.05 was chosen as the level of significance for all analyses. Missing data were addressed by adjusting group totals for analyses.

Statistical analysis was conducted with the assistance of a statistician using the statistical programme IBM SPSS version 28.

.Ethical considerations

Patient anonymity was maintained by assigning sample numbers to each patient. Data was stored in a password-secured database with access only available to the researcher. No consent or assent were required due to the retrospective and anonymous nature of the study and the absence of any direct influence of the study on the individual patient's treatment protocol. Permission to conduct the study was obtained from the Chief Executive Officer of CHBAH and the Head of Department of the Paediatric Oncology Unit, as well as the Human Research Ethics Committee of the University of the Witwatersrand (HREC). WITS HREC (Medical) Clearance certificate no: M1906102.

3. RESULTS

Sixty one patients with histologically confirmed B-NHL, treated at CHBAH from 1 January 2010 to 31 December 2019 were included. Sixty eight files were reviewed and seven files did not meet the inclusion criteria. Of the 61 files reviewed, 41 cases (67%) were HIV infected and 20 cases (33%) were HIV non infected. Burkitt Lymphoma was the most commonly

diagnosed B-NHL in both groups (n=25, 40%), followed by B-NHL NOS (n=12, 19.6%) and DLCBL (n=12, 19.6%). HGBL-11q (n=3) accounted for 5% of total B-NHL diagnosed. Nine cases of plasmablastic lymphoma were diagnosed exclusively in the HIV-infected cohort. The clinical characteristics are depicted in table 2.

Table 2: Clinical characteristics of patients

Characteristics	HIV Non-Infected n=20 (%)	HIV Infected n=41 (%)	*P-value*
Age at diagnosis			0.07
1-5	11 (55)	12 (29)	
6-10	5 (25)	9 (22)	
>10	4 (20)	20 (48)	
Mean	9	10.7	
Sex			0.77
Male	13 (65)	29 (71)	
Female	7 (35)	12 (29)	
Nutritional status			
Weight for age			**0.03**
Normal weight	13 (65)	14 (34)	
Underweight	3 (15)	11 (27)	
Severely underweight	4 (20)	16 (39)	
Height for age			**0.02**
Normal Height	16 (80)	16 (39)	
Stunted	2 (10)	15 (37)	
Severely stunted	2 (10)	10 (24)	
History of previous TB			**0.002**
No	19 (95)	23 (56)	
Yes	1 (5)	18 (44)	
TB treatment at diagnosis			**0.02**
Yes	0 (0)	9 (22)	
Presentation			0.35
Abdominal	12 (60)	16 (39)	
Extra-abdominal	8 (40)	25 (61)	
Duration of symptoms prior to diagnosis(Weeks)			0.29
0-2	6 (30)	11 (27)	
2-4	3 (15)	8 (20)	
4-6	1 (5)	9 (22)	
>6	10 (50)	13 (32)	
Lactate dehydrogenase(U/L)			1.00
<500	6 (30)	11 (27)	
>500 but <1000	4 (20)	10 (24)	
>1000	10 (50)	20 (49)	
Murphy Staging			**0.04**
1	0 (0)	1 (2)	
2	2 (10)	9 (22)	
3	14 (70)	13 (32)	

4	4 (20)	18 (44)	
CNS involvement	1 (5)	8 (20)	0.25
Bone Marrow involvement	3 (15)	16 (39)	0.08
Risk group			0.66
R1	0	0	
R2	4 (20)	6 (15)	
R3	3 (15)	10 (24)	
R4	13 (65)	25 (61)	

Table 3: Patient characteristics specific to the HIV-infected cohort (n= 41)

	n(%)	Mean	Median	IQR
Treatment status				
On HAART	18 (44)			
Defaulted or not initiated on treatment	23 (56)			
Viral load				
Suppressed(<50 copies/ml)	4 (9)			
Unsuppressed(>50 copies/ml)	37 (91)			
CD4 count (cells/µl) (1 unknown)	40	442	314	427
Immunological Category				
Not significant	12 (29)			
Mild	5 (12)			
Advanced	7 (17)			
Severe	16 (39)			
Unknown	1 (2)			
WHO Clinical staging				
I	0			
II	1 (2)			
III	10 (24)			
IV	30 (74)			

Most children were South African (n=57, 93%), whilst others were from Malawi(n=1), Gabon(n=1), Mozambique(n=1) and Swaziland(n=1).

The majority of patients with B-NHL were male in both HIV-infected (n=29, 70.7%) and HIV non-infected patients(n=13, 65%). In the HIV-infected cohort, the age at diagnosis was greater than 10 years old(n=48) whilst the HIV non-infected cohort was younger at diagnosis between 1 and 5 years old(n=11, 55%). A significantly higher proportion of HIV-infected children were severely underweight (n=16, 39%), (p=0.03) and stunted (n=10, 24%, p=0.02) compared to HIV non-infected children .

Almost half (n=18, 48%) of the HIV-infected group had a previous history of TB compared to only one patient in the HIV non-infected group (5%), (p=0.002). At diagnosis, nine HIV infected children were already on TB treatment (22%) and a further three (7.3%) children were initiated on TB treatment during treatment for B-NHL. No HIV non-infected children were on TB treatment at diagnosis nor were any children initiated on TB treatment. Data regarding the basis of TB diagnosis was not consistently documented.

In the HIV-infected group 56% (n=23) of cases were HAART naïve at the time of B-NHL diagnosis. More than half the HIV-infected cohort had severe or advanced HIV-associated immunodeficiency as reflected by CD4 count.

Both cohorts had a similar duration of symptoms of longer than 6 weeks prior to diagnosis.. Both groups presented with bulky disease and neither group had a significant number of patients who presented with oncological emergencies.

The majority of patients were diagnosed with stage 3 or stage 4 disease in both groups. In the HIV-infected cohort, there were more patients with stage 4 disease(n=18, 43%) than in the HIV non-infected cohort(n=4, 20%, p=0.04). Neither group had large numbers of acute kidney injury and only one patient in the HIV-infected cohort required dialysis. LDH-levels were elevated for most patients in both groups.

The majority of patients in both groups(70%) were treated with multi agent chemotherapy More protocol modifications were seen in the HIV-infected group (n=24, 59%). Protocol modifications included dose adjustments, which occurred more often in the HIV-infected cohort. Dose adjustments involved a reduction of 50%,60% or 80% of chemotherapy dose for the first and/or subsequent blocks of chemotherapy on an individualized basis. Seven patients had tumour resection at diagnosis, three patients in the HIV-infected group and four patients in the HIV non-infected group.

In the HIV-infected group, more patients required ICU admission(n=5, 12%) compared to the HIV non-infected group(n=1, 5%). Three HIV-infected patients were admitted to ICU for supportive care and disease related complications(n=3, 7.3%) compared to one patient in the HIV non-infected group (n=1, 5%). Two patients in the HIV-infected cohort required admission to ICU for toxicity related complications(n=2, 4.9%) while none of the patients in the HIV non-infected cohort required admission.

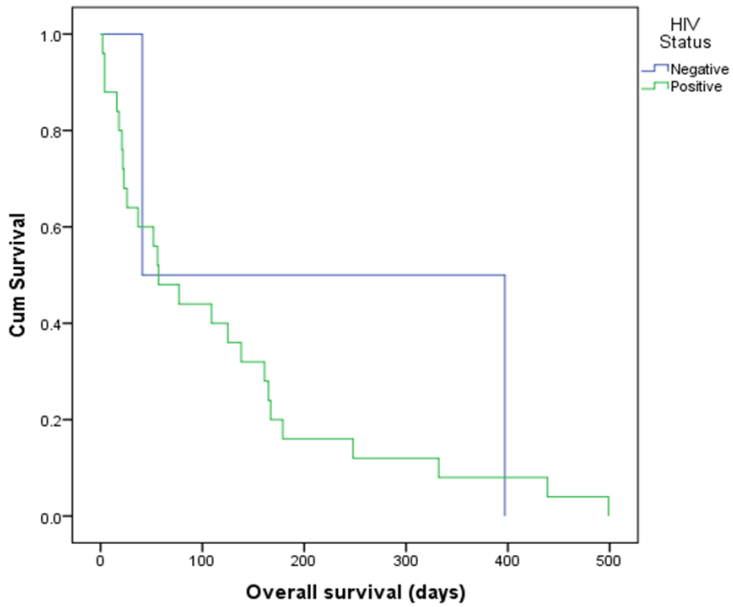
More HIV-infected patients died(n=25, 80.6%) compared to the HIV non-infected group (n=2, 18.2%)($p < 0.001$). Eleven HIV-infected patients died of treatment toxicity(n=11, 27%) compared to one HIV non-infected patient(n=1, 5%). More HIV non-infected patients are alive and disease free (n=9, 45%) compared to HIV-infected patients (n=6, 15%) ($p = 0.001$). Similar numbers of patients who have been lost to follow up were seen in both groups.

Table 4: Overall outcomes of patients with B-NHL in HIV infected and HIV non-infected cohorts.

	HIV negative, n=20 **n (%)**	HIV positive, n=41 **n (%)**
Outcomes		
Alive disease free	9 (45)	6 (15)
Dead of disease	1 (5)	14 (34)
Dead of treatment toxicity including septic deaths	1 (5)	11 (27)
Lost to follow up	9 (45)	10 (24)
p-value		***0.001****

*p<0.05=statistically significant

HIV-infected patients with B-NHL are 19 times more likely to demise compared to HIV non-infected patients with B-NHL(OR=18.8, 95% CI 3.2-110.3, p=0.001). Factors such as nutritional status, risk group and protocol modifications were included in the model as predictor variables.



p-value 0.001

Figure 2: Kaplan Meier graph of overall survival based on HIV status

4. Discussion

There is a paucity of data in LMIC concerning B-NHL in general and in HIV-infected patients specifically. In this study, more than half (67%) of the cohort were HIV-infected as compared to a study done in Cape Town between 2005 and 2014, where 25% of the patients with B-NHL were HIV infected(3). Chris Hani Baragwanath Hospital has one of the largest paediatric HIV clinics in South Africa which explains the higher prevalence of HIV infected patients in our setting. The prevalence of HIV-infected children in Gauteng in 2010 was 2.8% , this decreased to 1.5% in 2019(29). The Western Cape had a much lower prevalence of HIV-infected children in 2010(0.9%) and 2019(0.7%) compared to Gauteng(29). In view of this increased HIV prevalence, increased numbers of plasmablastic lymphoma and DLBCL were seen in our cohort. Burkitt lymphoma remains the predominate diagnosis in both HIV infected and non-infected groups in keeping with previous studies(3).

A concern in our study is that the majority of HIV-infected children with B-NHL were not on HAART at diagnosis or had a history of defaulting treatment. Most of these patients had an unsuppressed viral load and a low CD4+ count. The majority of children were of South African descent and had access to HAART since its nationwide roll-out in 2004. Issues such

as access to treatment, social and financial support, and adequate follow-up to ensure treatment compliance should be addressed.
A male predominance was seen in our study, correlating well with other studies(30). Studies from Israel, Netherlands, Pakistan and Yemen, showed that gender did not have an influence on the prognosis of survival (31–34).

The mean age at diagnosis of B-NHL in HIV non-infected patients in our study (9) is higher compared to the mean age of presentation documented in another South African study done between 1995 and 2010 (6.8 ±3.8 years) in a predominantly HIV non-infected cohort(11,12). The mean age for HIV-infected patients in our study, was older 10.7years). There were more cases of DLBCL in the HIV infected group and the peak incidence of DLBCL is in the second decade of life(11). This explains why the predominant age of presentation in the HIV-infected group was higher. .

Most HIV-infected patients presented with varying degrees of malnutrition, and this can be a contributing factor to their poor outcome(22). Almost half of the HIV-infected cohort were previously diagnosed with TB. A diagnosis of TB is difficult to confirm in children and therefore empiric treatment may be started based on clinical suspicion. Children infected with HIV are at increased risk for TB infection (3). In a study from two South African centres, a third of children with BL and HIV infection had concomitant TB (35). The overlap in clinical features of B-NHL and TB, along with poor documentation about the basis of TB-diagnosis, make it difficult to conclude whether B-NHL was misdiagnosed as TB, and therefore presented at a later and more advanced stage with consequent poorer outcomes(24). In our study, HIV-infected children with previously diagnosed TB had significantly worse overall survival($p=0.02$). This finding may be due to patients being delayed in diagnosis of B-NHL (where TB and B-NHL co-exist), misdiagnosed as TB instead of B-NHL, or they may have a higher level of immunosuppression (and a true higher incidence of TB) compared to the group that had no previous TB.

Lactate dehydrogenase is used as a prognostic factor in B-NHL. The serum level of LDH at diagnosis is used to risk stratify the intensity of treatment required for each patient(36). Significantly worse outcomes were seen in patients with stage III disease and LDH concentrations of >500 U/L(36). This correlates well with our study where 67% of the patients who demised had a serum LDH of more than two times the upper limit see figure 3.

Advanced stage disease was present in both cohorts in this study regardless of HIV-status and these results were comparable to other South African studies(3,25). Advanced disease presentations in both the HIV-infected and HIV non-infected cohorts could reflect a delay in diagnosis due to a lack of awareness of the early signs of childhood cancer, misdiagnosis, complicated referral pathways, or the preferential use of traditional medicine prior to presenting to a healthcare facility.

In this study, HIV-infection was a strong predictor of death as an outcome and patients with HIV and B-NHL were 19 times more likely to die compared to patients with B-NHL without HIV-infection. Higher mortality in HIV-infected patients is well documented in adult and paediatric studies(37,38). Burkitt lymphoma had a more severe course, with increased mortality in children with advanced immunosuppression as shown by studies from Malawi (39,40). In South Africa, the mortality ratio was three times higher in HIV-infected children with BL, especially in those with low CD4+counts(35).
In our study, deaths among the HIV-infected cohort can be attributed to advanced disease at diagnosis, underlying severe malnutrition, disease progression and toxicity–all of which were higher in the infected cohort. A higher proportion of HIV-infected patients had more ad hoc protocol modifications, although not statistically significant, it could be a contributing factor to the poor outcome in this group. There was an increased use of anti-CD20 monoclonal antibody therapy in the HIV-infected group in an attempt to reduce the dose of cytotoxic chemotherapy and thereby ameliorating toxicity. Patients in the HIV non-infected cohort had a significant survival advantage compared to patients infected with HIV. Infection with HIV was an independent prognostic factor, after controlling for risk group, malnutrition and protocol modifications.

Given the high mortality rate in our HIV-infected cohort, future studies should address the feasibility of high intensity, toxic treatment regimens in this patient population with underlying malnutrition and low functional reserve. Immunotherapy, in the form of monoclonal anti CD-20 antibody, is now included in first-line chemotherapy regimens for treatment of advanced B-NHL since 2021for both HIV infected and non-infected patients(21). The use of immunotherapy in initial treatment cycles allows for a lower dose of conventional cytotoxic chemotherapy to be given whilst nutritional rehabilitation is pursued. Protocol modifications should be minimized, and if used, standardized, in order to examine the true effect on outcome.

5. Study limitations and strengths

Nineteen patients(31%) were lost to follow-up and attempts to enquire about their whereabouts were unsuccessful. Proportionally more HIV non-infected patients were lost to follow up and are presumed alive.

In keeping with a retrospective data review, documentation pertaining to initiation of HAART, basis of concomitant diagnosis like TB, reasons for protocol modifications etc were not accurately done and limits conclusions that can be reached. Patient numbers were small with only 20 patients in the HIV non-infected cohort and this precludes accurate statistical analysis and underscores the need for collaboration across different POU's in South Africa to be able to analyse data from larger groups treated consistently with standardized protocols.

This study represents a diverse population and forms a good database for possible future comparison studies between a pre- and post-immunotherapy era.

6. Conclusion

Mature B-NHL is a common childhood cancer that has good cure rates in developed countries. South Africa is challenged by a high HIV and TB burden and socioeconomic difficulties that affect children. This study has shown that HIV-infected patients with B-NHL are 19 times more likely to die compared to their HIV-negative counterparts. Advanced disease at presentation, malnutrition, and treatment toxicity contributed to deaths in the HIV-infected group.

Competing interests
The authors declare that there are no financial or personal relationships that could have influenced the writing of this article.

Author's contributions
Conceptualisation, manuscript writing were done by B.L and B.R. Data collection was done by B.L. Data analysis were done by B.L, with the assistance of a statistician for final checking. Corrections and final manuscript was done by B.R.

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Data availability

Data sharing is not applicable in this study. No new data were created or analysed in this study.

Disclaimer
The views and opinions expressed in this article are those of the author and are the product of professional research. It does not reflect the official policy or position of the affiliated institution.

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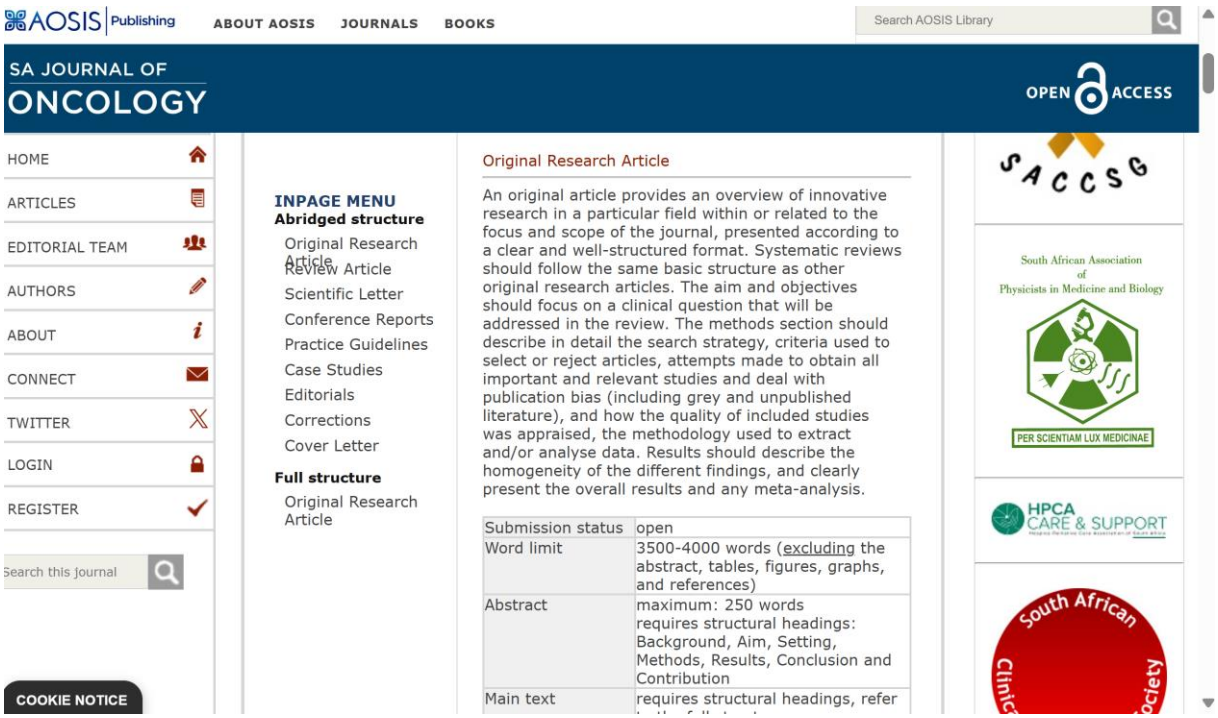
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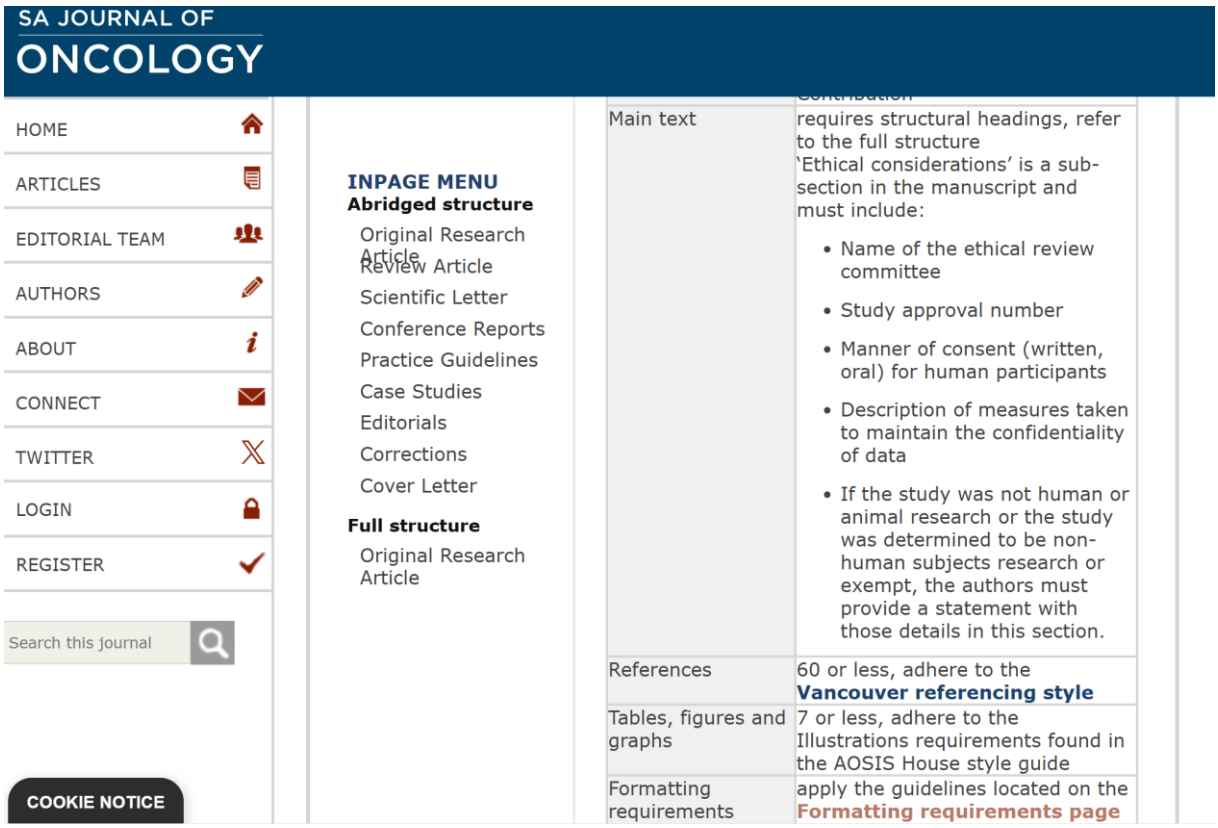
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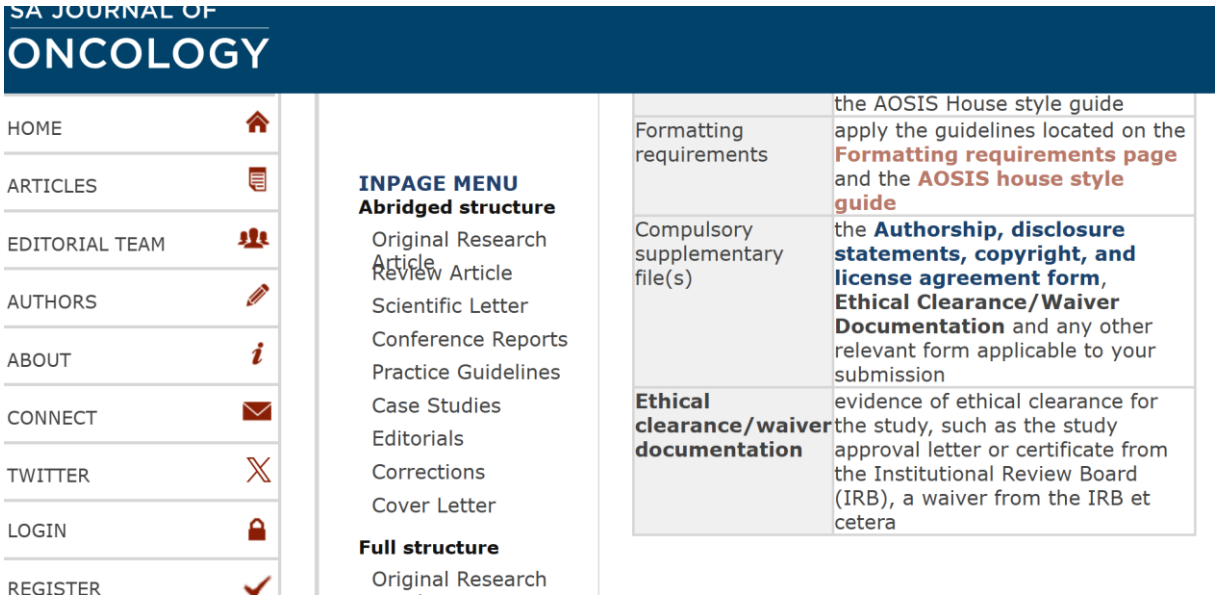

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maximum: 250 words
requires structural headings: Background, Aim, Setting, Methods, Results, Conclusion and Contribution

Main text

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Name of the ethical review committee
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CC: Supervisor: Dr B Rowe
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Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2022/08/05

REF: R14/49

PROTOCOL NO: **M220382** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *A 10 year retrospective analysis of the clinical characteristics and outcomes of mature B-Cell Non-Hodgkin Lymphoma in children treated in a tertiary South African hospital*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

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Appendix A: Data capture sheet

Study number:

A.) Demographic data:

- *Date of diagnosis* (will be the date of the diagnostic biopsy) MMDDYYYY

B.) Clinical and presentation characteristics:

a) *Age at diagnosis* in months

b) *Sex* (M/F) **m=0, f=1**

c) *Nutritional status: Anthropometry* (weight in kg for age, height/length in cm for age, weight for age (Z-score), and/or body mass index (BMI) for age (Z-score)) will be plotted using WHO Growth Charts and categorised using z-scores as +3/+2/+1/0/-1/-2/-3/unknown.

*e.) HIV infected***: pos =1; neg =0 unknown =2** Determined by HIV-ELISA(>18months) or HIV-PCR 0-18months)

- WHO clinical stage: **Stage 1-4** (appendix C)
- CD4 count: Immune category reflecting immunological classification (appendix D)
- Absolute CD4 count: (continuous)
- HIV viral load (HIVVL), **1-yes 0-no (Definition in Appendix D)**
- Treatment status: **On HAART at dx: 1-yes 0-no (Definition in Appendix D)**

f.) TB History

- Whether on TB-treatment at diagnosis **(yes/no):**
  - If yes, state the basis of the TB-diagnosis: [text]
  - If yes, was TB-treatment continued after B-NHL diagnosis: **(yes/no)**
- Was a TB-diagnosis made during treatment for B-NHL **(yes/no)**

g.) Duration of symptoms in weeks:

h.) *Clinical presentation with bulky disease* **(yes/no):yes-1, no-0 (Definition Appendix D)**

i.) Oncologic emergency at diagnosis: **yes/no yes-1, no-0 (Definition in appendix D)**

- Type of emergency: (1 – 5)
- Obstructive/Compressive syndrome:
    - Superior vena cava (1) or Superior mediastinal syndrome (2) or Extradural spinal compression (3)
- Tumour lysis syndrome (4)
- Other (5)

j.) *Tissue histology* ***(*****1-5) (Definition in appendix B)**

BL (1)

BL-like (2)

Definition: Morphologically and immunophenotypically similar to BL, but lacks the t(8;14)

DLBCL(3)

Plasmablastic lymphoma (4)

Other (5)

k.) *Primary disease site* **(1-8)**

Abdominal mass/nodes/ascites (1), Jaw mass (2), Other head and neck mass including orbital (3), intracranial (4), mediastinal (5), peripheral nodes (6), extradural, paraspinal (7), Other (ovary, uterus, primary bone involvement (8)

l.) *Bone marrow* involvement: **yes/no yes-1 no-0 (Definition in Appendix D)**

m.) *CNS* involvement: **yes/no yes-1 no-0 (Definition in Appendix D)**

n.) *Staging* **(1-4)**

a. Murphy staging-system (1-4) (**Appendix C**).

BFM-risk group classification (R1-R4) **(1-4)** (**Appendix C)**

<u>C.)</u> Biochemical and haematological characteristics:

i.) Full blood count

- White cell count (10^9/L), absolute neutrophil count (10^9/L), absolute monocyte count (10^9/L), absolute lymphocyte count (10^9/L), haemoglobin (10^9/L), platelet count

ii.) Chemistry

- Acute kidney injury (AKI) at diagnosis: (yes/no) (**Definition in Appendix C**)
- * Define AKI in Appendix D
- Dialysis needed for AKI: **y/n**
- Serum LDH (U/L)
- LDH ≥2 ULN: y/n
- Serum Uric acid:

D.) Treatment details, protocol modifications, treatment delays and treatment toxicity

i. Chemotherapy delivery, delays & protocol modifications:

a. Were there delay/s of >4 weeks in delivery of chemotherapy blocks: **y/n**

b. Number of times where chemotherapy-blocks were >4 weeks delayed in delivery:

c. Reason for delay in chemotherapy delivery: **0 – prolonged cytopenia without sepsis 1-sepsis or other infection with or without cytopenia 2-non-sepsis related organ-dysfunction 3-other (specify) 4- no delay**

d. Protocol modifications done: **yes/no** yes-1 no-0 (**definition in Appendix D**)

e. Reason for protocol modification: **0 – prolonged count recovery (> 4 weeks) delaying block delivery 1-severe sepsis with previous blocks 2- severe organ dysfunction with previous blocks 3-severely debilitated state at diagnosis due to malnutrition 4-severely debilitated state at diagnosis due to HIV-infection 5-Other (specify) 6- No protocol modification**

f. Number of protocol modifications:

i. Extended prephase (corticosteroids > 5 days) only: **y/n** yes-1 no-0

ii. Dose adjustment < 2 blocks: **y/n** yes-1 no-0

iii. Dose adjustment ≥ 2 blocks: **y/n** yes-1 no-0

g. Type of protocol modification:

i. Dose adjustment: **yes/no** yes-1 no-0 not applicable-2

ii. Omission of intravenous or intrathecal chemotherapy drug: **yes/no** yes-1 no-0 not applicable-2

1. <60% dose < 2 blocks y/n/not applicable
2. <60% dose ≥ 2 blocks: y/n/not applicable
3. 60-80% dose <2 blocks: y/n/not applicable
4. 60-80% dose ≥2 blocks: y/n/not applicable
5. > 80% dose <2 blocks: y/n/not applicable
6. >80% dose ≥2 blocks: y/n/not applicable

o.) Toxicity: (**Definitions in appendix C**)

i.) Episodes of grade III or grade IV mucositis: **yes/no**

ii.) Episodes of any other grade III or grade IV toxicity: yes/no (Categorisation of organ toxicity categories (1-10)

iii.) Episodes of febrile neutropenia: **yes/no**

i.) Episodes of BC positive febrile neutropenia during treatment:

ii.) Episodes of ICU-admissios: 1-Febrile neutropenia 2-Disease related 3-Other

iii.) Outcome after ICU admission: 1-Alive 2-Dead

iv.) Death from treatment-related toxicity (non-septic): **y/n**

v.) Death from treatment-related toxicity (septic): **y/n**

p.) Surgery:

i.) Tumour resection at diagnosis (EXCLUDING Biopsy only): **y/n**

ii.) Second look surgery: **y/n**

iii.) Viable tumour after second look surgery (refractory disease): **y/n (appendix C)**

q.) *Autologous Blood Stem Cell Transplant*: **y/n**

i.) If y: After how many blocks of chemo:

r.) Monoclonal antibody use: **y/n**

i.) If y: How many courses

ii.) If y: Upfront or in refractory/relapse setting

s.) Radiation use: **y/n**

i.) If y: After how many blocks:

ii.) If y: As part of first or refractory/relapse setting

E.) Response to treatment (Categories 1-4) (Definitions in Appendix C)

i.) Remission with first line therapy: **(1)**

ii.) Refractory disease: **(2)**

iii.) Progressive disease: **(3)**

iv.) Relapsed disease: **(4)**

F.) Outcome (Categories 1-7)

- Date last seen: MMDDYYYY
- Alive disease free (ADF) (1)
- Dead of disease (DOD) (2)
- Dead of treatment toxicity including septic deaths: (DOT) (3)

- Relapsed, progressive or refractory disease on 2nd line Rx: (4)
- Relapsed, progressive or refractory disease on palliative care: (5)
- Lost to follow up – Presumed alive (LTFU-A) (6)
- Lost to follow up – Presumed dead (LTFU-D) (7)

Appendix B: WHO 2016 classification of lymphoid neoplasms

	• Distinction of GCB vs ABC/non-GC type required with use of immunohistochemical algorithm acceptable, may affect therapy.
	• Coexpression of MYC and BCL2 considered new prognostic marker (double-expressor lymphoma).
Diffuse large B-cell lymphoma, NOS	• Mutational landscape better understood but clinical impact remains to be determined.
	• This term replaces EBV+ DLBCL of the elderly because it may occur in younger patients.
EBV+ DLBCL, NOS	• Does not include EBV+ B-cell lymphomas that can be given a more specific diagnosis.
EBV+ mucocutaneous ulcer	• Newly recognized entity associated with iatrogenic immunosuppression or age-related immunosenescence.
Burkitt lymphoma	• *TCF3* or *ID3* mutations in up to ~70% of cases.
Burkitt-like lymphoma with 11q aberration	• New provisional entity that closely resembles Burkitt lymphoma but lacks *MYC* rearrangement and has some other distinctive features.
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* translocations	• New category for all “double-/triple-hit” lymphomas other than FL or lymphoblastic lymphomas.
	• Together with the new category for the “double-/triple-hit” lymphomas, replaces the 2008 category of B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BCLU).
High-grade B-cell lymphoma, NOS	• Includes blastoid-appearing large B-cell lymphomas and cases lacking *MYC* and *BCL2* or *BCL6* translocations that would formerly have been called BCLU.

Appendix C: Murphy staging :BFM- Risk grouping and treatment strategy

Murphy staging system for Non-Hodgkins lymphoma in children:

Stage	Clinicopathologic feature
Stage I	Single tumour (extranodal) or single anatomical area (nodal), with exclusion of mediastinum or abdomen
Stage II	Single tumour (extranodal) plus regional node involvement Two single extranodal sites on same side of diaphragm Two single extranodal sites with or without regional node involvement on the same side of the diaphragm Primary gastrointestinal (GI) tract tumour, usually in ileocecal area, with or without involvement of associated mesenteric nodes.
Stage III	Two single tumours (extranodal) on opposite sides of diaphragm Two or more nodal areas above and below diaphragm All primary intrathoracic tumours (mediastinal, pleural, thymic) Extensive primary intra-abdominal disease All paraspinal or epidural tumours, regardless of other tumour sites
Stage IV	Any of the above with bone marrow or CNS involvement or both.

CNS involvement is considered when any of the following are present:

1. Any CNS tumour mass diagnosed on computed topography (CT) or Magnetic resonance image (MRI).
2. Cranial nerve palsy that cannot be explained by an extradural lesion.
3. The presence of malignant cells on CSF.
4. **Bone marrow involvement** is considered if there is a presence of more than 5% of blasts identified morphologically.

BFM-NHL Risk grouping schema: (33)

Risk group	Therapy Course
R1	A B
R2	V A B A B
R3	V AA BB CC
R4	V AA BB CC AA BB CC

NHL-BFM95 risk groups and treatment outcomes: (33)

Risk Group	Definition
R1	Stage I and II, completely resected
R2	Stage I and II, not resected Stage III and LDH <500 U/L
R3	Stage III, LDH ≥500-<1000 U/L, Stage IV+B-AL and LDH <1000 U/L and CNS negative
R4	Stage III and IV+B-AL and LDH >1000 U/L or/and CNS positive

BFM-NHL ’95 - Treatment protocol (33)

Drug	Dose	Day 1	Day 2	Day 3	Day 4	Day 5
Prephase V						
Dexamethasone oral/IV	mg/m^2	5	5	10	10	10
Cyclophosphamide IV over 1 hour	200mg/ m^2	X	X			
Methotrexate IT	12mg	X				
Cytarabine IT	30mg	X				
Prednisolone IT	10mg	X				
Course A						
Dexamethasone oral/IV	10mg/m^2	X	X	X	X	X
Vincristine IV	1.5mg/m^2	X				
Ifosfamide IV over 1 hour	800mg/ m^2	X	X	X	X	X
Cytarabine IV over 1 hour	150mg/ m^2				X-X*	X-X*
Etoposide IV over 1 hour	100mg/ m^2				X	X
Methotrexate IV	1g/m^2	X				
Methotrexate IT	12mg	X				
Cytarabine IT	30mg	X				
Prednisolone IT	10mg	X				
Course B						
Dexamethasone oral/IV	10mg/m^2	X	X	X	X	X

Vincristine IV	1.5mg/m^2	X				
Cyclophosphamide IV over 1 hour	200mg/m^2	X	X	X	X	X
Doxorubicin IV over 1 hour	25mg/m^2				X	X
Methotrexate IV	1g/m^2	X				
Methotrexate IT	12mg	X				
Cytarabine	30mg	X				
Prednisolone IT	10mg	X				
Courses AA and BB (Same as A and B-with exceptions from the below)						
Methotrexate IV	5g/m^2	X				
Methotrexate IT	6mg	X				
Cytarabine IT	15mg	X				
Prednisolone IT	5mg	X				
Course CC						
Dexamethasone oral/IV	20mg/m^2	X	X	X	X	X
Vindesine IV	3mg/m^2	X				
Cytarabine IV 3 hour	3g/m^2	X-X*	X-X*			
Etoposide IV 2 hour	100mg/m^2			X-X	X-X	X
Methotrexate IT	12mg					X
Cytarabine IT	30mg					X
Prednisolone IT	10mg					X

*Given 2 hours apart

Appendix D: Study definitions

Acute kidney injury: GFR decrease by 25% or urine output of less than 0.5ml/kg/hr

Bone marrow involvement: Defined by presence of lymphoma cells or ≥5% blasts on aspirate or trephine biopsy

Bulky disease: Tumour mass or lymph node aggregate ≥6cm

Protocol modification: A change made to the protocol that involve the downward-adjustment of dosages of chemotherapy or omission of intravenous or intrathecal chemotherapy but still with the ultimate aim to effect cure (eg non-palliative treatment)

CNS involvement: Defined by the presence of lymphoma cells on CSF-examination, a CNS-mass on imaging, or an unexplained cranial nerve palsy.

Event Free survival (EFS): Calculated from the date of diagnosis (MMDDYYYY) to the date of disease progression, relapse or death (from disease-related causes)

Febrile Neutropaenia: Defined as a single fever of ≥38.3°C, a temperature of ≥38°C for more than one hour, or two episodes of fever of more than 38°C within a 12 h period with an accompanying absolute neutrophil count of <500 cells.

HIV Immune classification according to CD4 % and Absolute count

Degree of immune suppression	Up to 12 months	13-59 months	>5years
Not significant	>35%	>25%	>500/mm^3
Mild	25-34%	20-24%	350-499/mm^3
Advanced	20-24%	15-19%	200-349/mm^3
Severe	<20%	<15%	<200/mm^3

Mucositis (severe): Defined by WHO classification (Grade III/IV). Grade III-Ulcers requiring liquid diet and/or opioid analgesia. Grade IV- Ulcers, alimentation not possible (due to mucositis).

Overall survival (OS): Calculated from the date of diagnosis to the date of death from any cause.

Progressive disease: New sites of disease development despite treatment.

Refractory disease: Disease that persists despite treatment.

Relapsed disease: Return of signs or symptoms of disease or return of return after a period of documented disease remission.

Remission: Defined as no visible/viable tumour at end of treatment assessment or post cycle 5 in R4 patients

Superior vena cava syndrome (SVS): Any Clinical features of facial swelling, upper body oedema, plethora and dilated prominent chest veins, dyspnoea or cough.

Superior mediastinal syndrome (SMS): Any clinical signs of obstruction of airways. Stridor, orthopnoea, wheeze, dyspnoea and chest pain.

Toxicity: Occurring 10 days after chemotherapy, adapted from WHO handbook for reporting results of cancer treatment.

Category	Grade 1	Grade 2	Grade 3	Grade 4
Neurologic (1): State of consciousness OR	Temporary lethargy	Somnolence <50% of waking hours	Somnolence >50% of waking hours OR	Coma OR
Peripheral (1)	Paraesthesia or decreased tendon reflexes	Severe paraesthesia or mild weakness	Intolerable paraesthesia or motor loss	Paralysis
Haematological Haemoglobin(g/dL) (2)	9.5-10.5	8.0-9.4	6.5-7.9	<6.5
Neutrophils(10^9/L) (3)	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
Platelets(10^9/L) (4)	75-99	50-74	25-49	<25
Gastrointestinal Bilirubin (UNL) (5)	1.26-2.5	2.6-5	5.1-10	>10
Transaminase(UNL) (6)	1.26-2.5	2.6-5	5.1-10	>10
Nausea/Vomiting (7)	Nausea	Transient vomiting	Vomiting requiring therapy	Intractable Vomiting
Diarrhoea (8)	<2 days	>2days	Requires therapy	Dehydration

Renal (9) Urea and creatinine	1.26-2.5	2.6-5	5.1-10	>10
Haematuria (10)	Microscopic	Mild gross loss	Gross blood loss plus clots	Obstructive uropathy

Tumour lysis syndrome: Electrolyte and metabolic derangements because of rapid death of tumour cells. Typically there is hyperuricemia, hyperphosphatemia and hypercalcaemia.

Viral suppression: <50 viral copies/ml of blood

WHO Clinical staging of HIV for infants and children

Stage 1	Asymptomatic, Persistent generalised lymphadenopathy
Stage 2	Hepatosplenomegaly, Papular purpuric eruptions, seborrheic dermatitis, extensive human papilloma infection, extensive molluscum contagiosum, Fungal nail infections, recurrent oral ulcers, Lineal gingival erythema, angular cheilitis, Parotid enlargement, Herpes zoster,
Stage 3	Unexplained persistent diarrhoea(>14 days), Moderate acute malnutrition not responding to standard therapy, unexplained fever for >1 month, oral candidiasis outside the neonatal period, oral hairy leukoplakia, pulmonary TB, Presumed recurrent bacterial pneumonia, acute necrotising ulcerating gingivitis/periodontitis
Stage 4	Unexplained severe wasting or sever acute malnutrition not responding to standard therapy, Pneumocystis pneumonia, Recurrent severe presumed bacterial infections(Empyema, pyomyositis, bone or joint infection), Chronic herpes infection, extrapulmonary TB, Kaposi's sarcoma, Oesophageal candidiasis, CNS toxoplasmosis, HIV encephalopathy