Conference on Retroviruses and Opportunistic Infections 2015
Seattle, WA
February 23 – 26, 2015

Poster 718

Incidence and Outcomes of HIV-Associated Lymphoma in Botswana

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Supported by Harvard Medical School, Harvard Catalyst | The Harvard Clinical and Translational Science Center (UL1RR02578), Harvard University CFAR (P30AI060354), NIH/NIAID (K23AI091434), NCI/MGH Federal Share Program, Ira J. Spiro Translational Research Award, and the Paul G. Allen Family Foundation (11689)

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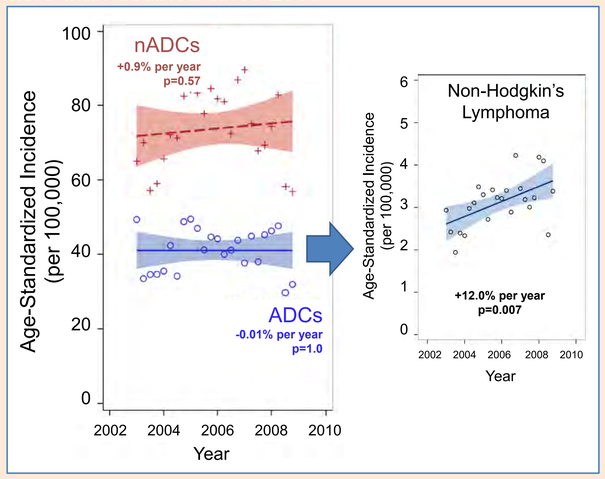
BACKGROUND

HIV & Malignancies

- Among HIV-infected people in sub-Saharan Africa, there is an emerging *second epidemic* of cancer
- The incidence of cancer is 3 – 4 fold higher in people infected with HIV
- Nearly 25% of all adults in Botswana are HIV-positive

History of Antiretroviral Therapy

- In developed nations, introduction of antiretroviral therapy (ART) led to a diminishing rate of many AIDS-defining cancers (ADCs)
- Since 2003, Botswana has deployed one of the world's most successful ART programs, with >90% coverage of eligible, known seropositive adults
- However, in Botswana rates of ADCs and non-AIDS-defining cancers (nADCs) have not decreased
  - Incidence of Non-Hodgkin's Lymphoma (NHL), an ADC has more than doubled since 2003



Specific Aims

- Characterize the incidence, demographics, and treatment of HIV-positive and HIV-negative individuals diagnosed with lymphoma in Botswana
- Analyze the outcomes of lymphoma in Botswana based on demographic and clinical predictors

METHODS

Patient Enrollment

- Enrolled all consenting adults (>18 years old) treated for any type of lymphoma, between 10/2010 and 9/2014 at 2 hospitals in Gaborone, Botswana
- Baseline and quarterly follow-up information was collected by researchers in-hospital and through home visits

Clinical Assessment and Data Analysis

- Diagnoses with accessible pathology reports were confirmed for accuracy by oncologists at MGH
- HIV and ART status were assessed at time of diagnosis
  - ART-naïve patients, and those starting ART within 6 months of lymphoma diagnosis were considered "off-ART" for survival analysis
- Data about treatment protocols and modifications were analyzed from available patient records in 41 cases (60% of total cases)
- Generated a multivariable Cox proportional hazards model to evaluate effects of HIV status and lymphoma type on survival

RESULTS

Study Cohort

- Sixty-eight patients with lymphoma were enrolled and followed for a mean of 12.9 months (73.1 person years total)
- Twelve (75%) patients with Hodgkin's Lymphoma (HL) and 38 (73%) patients with NHL were seropositive for HIV at the time of lymphoma diagnosis
- Patients with HL tended to have higher CD4 counts and better performance status than patients with NHL
- Forty-nine percent of HIV-positive patients were on ART more than 6 months prior to lymphoma diagnosis, another 31% were eligible to have been initiated on ART by CD4 count alone (<250 cells/μL)

Table 1 - Cohort Characteristics at Lymphoma Diagnosis

Characteristic	Hodgkin's Lymphoma (n=16)	Non-Hodgkin's Lymphoma (n=52)
Patient Characteristics		
Male Sex, no. (%)	8 (50.0)	30 (57.7)
Age at Diagnosis, median (IQR)	39.4 (32-42)	40.0 (35-53)
Primary School or Less, no. (%)	5 (31.3)	15 (28.9)
Unemployed, no. (%)	6 (37.5)	26 (50.0)
Income <$300/mo., no. (%)	11 (68.8)	38 (73.1)
Rural residence, no. (%)	11 (68.8)	37 (71.2)
Clinical Characteristics		
Advanced Cancer Stage (III, IV), no. (%)	4 (25.0)	20 (35.7)
Better Performance Status (0 or 1), no. (%)	15 (93.8)	34 (65.4)
HIV-Positive, no. (%)	12 (75.0)	38 (73.1)
Of HIV+ Nadir CD4 Count, median (IQR)	315 (231-487)	191 (114-296)
Of HIV+ on ART > 6 Months, no. (%)	7 (58.3)	18 (47.4)

Subtypes of Lymphoma

- The National Health Laboratory of Botswana analyzes all lymph node specimens, but lacks IHC and flow cytometry to arrive at exact diagnoses in all cases. A subset of samples are sent abroad for IHC.
- Seventy-five percent of HL diagnoses were the mixed cellularity subtype, a form commonly found in patients with immune system disorders
- The most common NHL diagnoses included the aggressive large cell lymphomas and the more indolent CLL/SLL

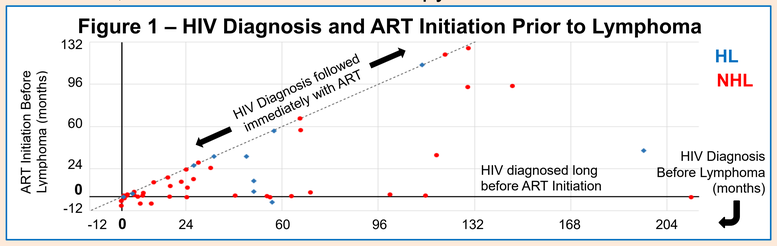
Table 2 – Most Common Subtypes of Lymphoma

Hodgkin's Lymphoma		Non-Hodgkin's Lymphoma	
Subtype	**n (%)**	**Subtype**	**n (%)**
Mixed Cellularity	12 (75.0)	DLBCL	19 (36.5)
Unspecified	3 (18.8)	Large Cell NHL (no IHC)	14 (26.9)
Nodular Sclerosis	1 (6.3)	CLL/SLL	3 (5.8)

Clinical Course

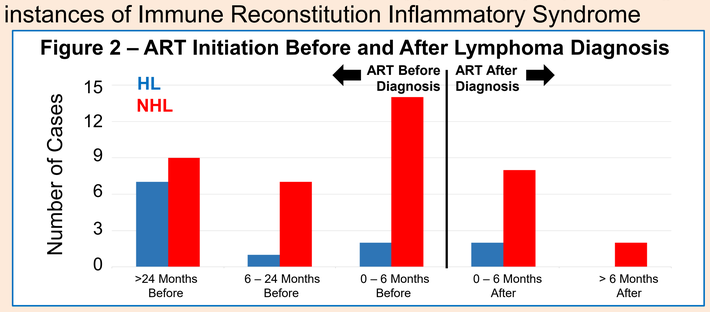
- Mean time to diagnosis after symptomatic clinical presentation was 58 and 98 days for HL and NHL respectively, and not associated with HIV status (p = 0.42)
- Mean duration of HIV seropositivity before diagnosis was 47.7 months, mean duration of ART therapy was 20.7 months

Figure 1 – HIV Diagnosis and ART Initiation Prior to Lymphoma



- ART was initiated less than 6 months before diagnosis in 17% and 35% of HL and NHL cases respectively, potentially representing instances of Immune Reconstitution Inflammatory Syndrome

Figure 2 – ART Initiation Before and After Lymphoma Diagnosis



RESULTS

Clinical Course, Continued

- All 41 patients with available medical records received standard treatment:
  - HL: 6 cycles of ABVD
  - NHL: 6 cycles of CHOP (6 most recent cases with rituximab)
- Treatment modifications between cycles were common and due to toxicity (22 instances) and chemotherapy drug stock out (6)
  - HIV status was not associated with rates of observed drug toxicities (typically leukopenia)

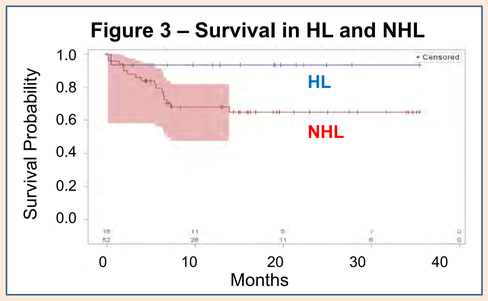
Table 3 - Delays in Treatment due to Clinical Factors

Hodgkin's Lymphoma				Non-Hodgkin's Lymphoma			
	Tox	No Tox	p-value		Tox	No Tox	p-value
HIV-negative	0	1	0.19	HIV-negative	3	12	0.60
HIV-positive	8	4		HIV-positive	11	30	

Survival

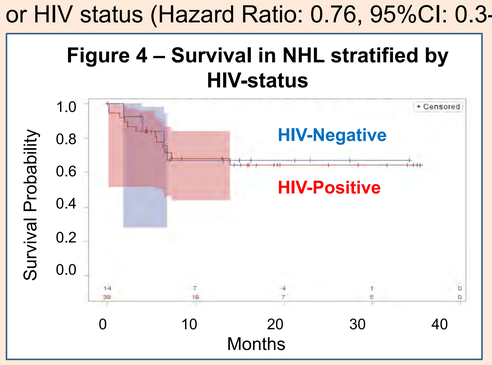
- One HL patient (6%) and 16 NHL patients (31%) died during a median follow up of 13 and 10 months for HL and NHL respectively
- One-year survival rates were 93% (95%CI: 59-99%) for HL and 74% for NHL (95%CI: 58-84%)

Figure 3 – Survival in HL and NHL



- Mean survival in patients with NHL was 10.7 months (95%CI: 9.3-12.2)
- While power was low, no significant differences in survival were detected with stage at presentation (p = 0.76), treatment modification (p = 0.60), or HIV status (Hazard Ratio: 0.76, 95%CI: 0.3-2.2)

Figure 4 – Survival in NHL stratified by HIV-status



CONCLUSIONS

- Despite ART coverage exceeding 90% by government estimates, 23% of incident HIV-associated lymphomas occurred prior to ART and 31% during the first 6 months of ART
- Delayed diagnosis and frequent treatment modifications due to chemotherapy stock-outs and toxicity were large barriers
- Relatively low mortality rates were achieved with standard treatments of HL and NHL, though the 1-year survival rates are somewhat lower than would be expected in the USA
- HIV-infection was not associated with reduced survival, although sample size was limited

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