Temporal trends and clinical outcomes of HIV-associated diffuse large B-cell lymphoma during the antiretroviral and rituximab era.

Rafeh Naqash
PGY III Internal Medicine
Catholic Health
Epidemiology and Current Principles:

• HIV-positive patients have a 60- to 200-fold increased incidence of non-Hodgkin lymphoma (NHL), the majority of which are diffuse large B-cell lymphoma (DLBCL).(1)

• With the advent of combined antiretroviral medication (CART) a paradigm shift has been observed with respect to HIV-lymphoma. (2)

• R-EPOCH is the superior regimen in the setting of HIV-associated DLBCL.(3)

Pathogenesis:

- Chronic antigen stimulation.
- EBV: Latent membrane protein-1 and EBNA-2-oncogeneic role.\(^{(1)}\)
- Certain HIV gene products, particularly Tat, have been implicated as potentially oncogenic.\(^{(2)}\)
- Several B cell stimulatory cytokines have been found to be increased in HIV-infected people prior to a diagnosis of lymphoma, in particular IL6, IL10, CRP, sCD23, sCD27, and sCD30.

**Viral and genetic abnormalities in human immunodeficiency (HIV)–associated lymphomas:**

<table>
<thead>
<tr>
<th>Histologic subtype</th>
<th>EBV +</th>
<th>KSHV/HHV-8+</th>
<th>Common recurring chromosomal abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td></td>
<td></td>
<td>MYC (10%); BCL6 (20% of centroblastic DLBCL)</td>
</tr>
<tr>
<td>Centroblastic Immunoblastic</td>
<td>30%</td>
<td>0</td>
<td>TPS3 (40%)</td>
</tr>
<tr>
<td>Plasmablastic lymphoma</td>
<td>&gt;50%</td>
<td>80%</td>
<td>None</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td>100%</td>
<td>100%</td>
<td>None</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>30-50%</td>
<td>0</td>
<td>MYC (100%); TPS3 (50-80%)</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>100%</td>
<td>0</td>
<td>BCL6 (30-40%)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>80-100%</td>
<td>0</td>
<td>None</td>
</tr>
</tbody>
</table>

EBV, Epstein-Barr virus; KSHV/HHV-8, Kaposi sarcoma herpes virus/human herpes virus 8; CNS, central nervous system.

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**Figure (a):**

Graph showing the percentage of cases with specific chromosomal abnormalities in different lymphoma subtypes.

**Figure (b):**

Images showing EBER staining in lymphoma cells.

Cesarman, Ethel Current Opinion in Oncology. 25(5):487-494, September 2013. DOI: 10.1097/01.cco.0000432525.70099.a4
The GCB subtype arises from centroblasts, whereas the ABC subtype arises from a plasmablastic cell just prior to germinal center exit.

The cell of origin of DLBCL (GCB or non-GCB) can be reasonably predicted by the expression of 3 surface proteins (CD10, BCL6, and MUM1) on the tumor tissue using immunohistochemistry as described in the Hans algorithm.
The NF-κB pathway is activated through B-cell receptor signaling in activated B cell-like diffuse large B-cell lymphoma (ABC DLBCL).

PFS and OS Kaplan-Meier curves.

- **C**: PFS for GCB vs. Non-GCB DLBCL, $P = 0.003$
- **D**: OS for GCB vs. Non-GCB DLBCL, $P = 0.036$
- **E**: PFS for EBV Negative vs. EBV Positive DLBCL, $P = 0.008$
- **F**: OS for EBV Negative vs. EBV Positive DLBCL, $P = 0.008$
- **G**: PFS for CD4 $> 100$ cells/$m^3$ vs. CD4 $< 100$ cells/$m^3$, $P = 0.001$
- **H**: OS for CD4 $> 100$ cells/$m^3$ vs. CD4 $< 100$ cells/$m^3$, $P = 0.001$

Kieron Dunleavy, and Wyndham H. Wilson Blood 2012;119:3245-3255
Study Rationale:

- DLBCL classification based on the cell of origin (COO) is becoming therapeutically important as target agents may have selective activity at least in the immunocompetent DLBCL. It is unclear if similar principles may apply in the context of HIV-induced immunosuppression.
- Identification of primary extranodal sites of disease associated with prognosis in patients with HIV and concurrent diffuse large B-cell lymphoma (DLBCL).

Endpoints

Primary:
- Difference in DLBCL based on COO in HIV patients.
- Role of extranodal sites in influencing outcomes.
- Role of HIV-viremia in influencing outcomes.

Secondary
- Assessing clinico-biochemical features influencing survival outcomes measured objectively by progression free and overall survival.
Methodology:

- Database: cancer registry and institutional network database of RPCI and ECMC (Jan 2000-Dec 2015)

- Eligibility: Patients with HIV and lymphoma age 18 and above.

- Retrospective chart review/EMR review after obtaining appropriate IRB approval of RPCI and ECMC along with data sharing/usage agreements.
Statistical analysis:

• All analysis was conducted in SPSS v-22 with a $P \leq 0.05$ being significant

• Overall survival (OS), progression free survival (PFS) were assessed with respect to multiple variable

• Chi-square test and Independent samples t-test were used for categorical and continuous variables respectively. Log-rank Kaplan Meier method was used for survival function and cox-regression was used for multivariate analysis.
Lymphoma distribution in our patient population:

CD20+ DLBCL (n=25) meeting criteria of age >18 and presence of HIV were included for the purpose of this study.
Demographic characteristics of patients with DLBCL:

Frequency Polygram for age distribution

Gender distribution with respect to race
Staging at diagnosis of DLBCL.

IPI scores of patients with DLBCL

Age > 60 years
Stage III or IV disease
Elevated serum LDH
ECOG/Zubrod performance status of 2, 3, or 4
More than 1 extranodal site
DLBCL stratification based on COO:

No differences in viral loads, cd4 counts or survival.

Hans Algorithm:
Type of frontline chemo effecting survival?

![Bar chart showing percentages of survival for different chemotherapy regimens]

- R-EPOCH: 44.00%
- R-CHOP: 36.00%
- No-chemo: 20.00%

![Survival curve showing overall survival in days]

P=0.26
Role of GI involvement on survival:

- **Overall Survival**
  - GI involvement:
    - No
    - Yes

- **Progression free survival**

<table>
<thead>
<tr>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95.0% CI for Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30</td>
<td>3.944</td>
<td>1.146 13.578</td>
</tr>
</tbody>
</table>

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<tr>
<th>Sig.</th>
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</tr>
</thead>
<tbody>
<tr>
<td>0.20</td>
<td>4.415</td>
<td>1.264 15.420</td>
</tr>
</tbody>
</table>
Multivariate Cox regression analysis for GI involvement

Adjusted for differences in IPI (high vs low)
Gender
Race (AA vs non-AA)

<table>
<thead>
<tr>
<th>P</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.031</td>
<td>5.146</td>
<td>1.18-29.11</td>
</tr>
</tbody>
</table>
Did patients with GI involvement have higher degree of HIV viremia?
RESEARCH ARTICLE

Sites of extranodal involvement are prognostic in patients with diffuse large B-cell lymphoma in the rituximab era: An analysis of the Surveillance, Epidemiology and End Results database

Jorge J. Castillo,1* Eric S. Winer,2 and Adam J. Olszewski3

Approximately a third of the patients with diffuse large B-cell lymphoma present with extranodal involvement. Our study aims to identify primary extranodal sites of disease associated with prognosis in patients with diffuse large B-cell lymphoma (DLBCL) in the rituximab era. A secondary objective is to describe epidemiological and clinical characteristics of patients with extranodal DLBCL. We included adult patients from the Surveillance, Epidemiology and End Results (SEER) database (2004–2009) in whom DLBCL was the first malignancy diagnosed. Extranodal primary sites were divided into 12 groups according to the topography code reported by SEER. Multivariate overall survival (OS) analyses were performed using Cox proportional-hazard regression models adjusted for age, sex, race, and stage. From a total of 25,992 adult DLBCL patients included in our analysis, 32% presented with extranodal primary sites. Gastrointestinal tract (34%), head/neck (H&N; 14%), and skin/soft tissue (11%) were the most common. In comparison with nodal DLBCL, patients with extranodal involvement were older (mean age, 67 vs. 63 years; P < 0.001), with worse OS rates were gastrointestinal (Hazard ratio (HR) 1.24, 95% confidence interval (CI) 1.15–1.33; P < 0.001), pulmonary (HR 1.56, 95% CI 1.38–1.75; P < 0.001), and liver/pancreas (HR 1.58, 95% CI 1.35–1.85; P < 0.001), whereas H&N was associated with better survival (HR 0.79, 95% CI 0.70–0.89; P < 0.001). In this population-based study, primary extranodal sites of involvement are associated with distinct outcomes in patients with DLBCL. Gastrointestinal, pulmonary, and liver/pancreas sites had a significant worse outcome than nodal sites.

Conclusions and future directions:

- Certain EN sites (GI) can serve as prognostic indicators of survival outcomes in HIV related DLBCL especially in older individuals.
  - GI involvement with DLBCL does not seem to have a significant association with the degree of HIV viremia or cell of origin i.e. GCB/non-GCB

- It would be important to elucidate potential genetic and pathological markers to differentiate EN from nodal DLBCL that may serve as therapeutic targets to improve outcomes.

- Role of early endoscopic evaluations in HIV –DLBCL
Clinical significance of gastrointestinal involvement in human immunodeficiency virus (HIV) patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL).

Abdul Rehman Niazi, Parlaa Ponika, Malika Hanz, Sobha Bhat, Jaspreet Dhillon, Vishal Nappuli, Otman Salim Akhtar, Junaid Ansari, Mohammed Umer Butt, Usman Khan, Haider Ali Khadim, Francisco J. Hernandez-Llizzafuri. Catholic Health/ Roswell Park Cancer Institute, Buffalo, NY; Roswell Park Cancer Institute, Buffalo, NY; Government Medical College Srinagar, Srinagar, India; Erie County Medical Center, Buffalo, NY; Weill Cornell Medical Center, New York, NY; Feist-Weiller Cancer Center, Shreveport, LA; Catholic Health/University of Buffalo, Buffalo, NY

Abstract Text:

Background: DBLCL is a heterogeneous group of aggressive lymphomas with distinct subtypes, and efforts to identify patients at high risk for treatment failure and poor clinical outcomes are ongoing. Specific sites of extra nodal (EN) involvement are known to impact response rates, progression free survival (PFS), and overall survival (OS) among immune-compotent patients; however, less is known regarding the same in DLBCL patients concomitantly infected with HIV (HIV-DLBCL). Methods: We studied differences in clinical outcomes of HIV-DLBCL based on EN involvement and cell of origin in patients treated at Erie County Medical Center and Roswell Park Cancer Institute (2000-2015). Results: 25 patients with HIV-DLBCL were identified. Median age was 49 years; 85% were males. Median time from HIV to DLBCL was 188 months; median CD4 count was 189/ml. Stage distribution was: I-II, 16%, III-IV, 32% and IV-48%. 32% were germinal center B-cell (GCB) and 24% were non-GCB; rest could not be classified. 76% had EN involvement, most common being gastrointestinal tract (GIT-32%). 84% received rituximab (DA EPOCH-44%, CHOP-32%), rest died without therapy. 52% achieved a complete response. 84% received anti-retroviral therapy with front-line chemotherapy; 29% utilized a protease inhibitor (PI) containing regimen. Clinical outcomes between GCB and non-GCB DLBCL did not differ. Patients with GI involvement were older (p = 0.02); no association was seen with CD4 count, viral load, disease stage or DLBCL subtype. After adjusting for age, race and gender in multivariate analysis, GI involvement was a predictor of PI involvement. Clinical outcomes between GCB and non-GCB DLBCL did not differ. Patients with GI involvement were older (p = 0.02); no association was seen with CD4 count, viral load, disease stage or DLBCL subtype. After adjusting for age, race and gender in multivariate analysis, GI involvement was a predictor of poor PFS (p = 0.02) and OS (p = 0.03). Concurrent use of PI showed better OS (p = 0.01) in patients with GI involvement. Conclusions: GI involvement at diagnosis is an independent predictor of adverse clinical outcomes in HIV-DLBCL patients. While endoscopic evaluation of the GI tract in asymptomatic patients may predict prognosis, it is unclear how front-line therapy can be modified to improve their clinical outcomes. Though restricted by sample size, our preliminary assessment also shows that administration of PI may benefit HIV DLBCL patients with GI involvement.
Limitations

- Sample size

- Information bias: medical records might not clearly reflect the reasoning behind the individual patients receiving the specific intervening cancer treatments

- Retrospective nature leading to observer bias: certain patient specific socioeconomic and cultural factors might influence the decision making process which might not be evident on review of medical records
We are all humans **TILL**
Race disconnects us;
Religion separates us;
Politics divides us;
And wealth classifies us.