How I treat HIV-associated lymphoma

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Over the past 10 years, significant progress has been made in understanding HIV-associated lymphomas and improving the prognosis of these diseases. With the advent of combination antiretroviral therapy and the development of novel therapeutic strategies, most patients with HIV-associated lymphomas are cured. The outcome for the majority of patients with HIV-associated diffuse large B-cell lymphoma and Burkitt lymphoma in particular, is excellent, with recent studies supporting the role of rituximab in these diseases. Indeed, in the combination antiretroviral therapy era, the curability of many patients with HIV-associated lymphoma is similar to their HIV-negative counterparts. New treatment frontiers need to focus on improving the outcome for patients with advanced immune suppression and for those with adverse tumor biology, such as the activated B-cell type of diffuse large B-cell lymphoma and the virally driven lymphomas. Future clinical trials need to investigate novel targeted agents alone and in combination with chemotherapy. (Blood. 2012;119(14):3245-3255)
Common Types of HIV-Associated Lymphomas

- DLBCL – includes primary CNS lymphoma (PCNSL)

- Burkitt Lymphoma

- HIV-positive patients have a 60-200 fold increased incidence of non-Hodgkin Lymphoma.
  - Majority of which are DLBCL.

- Less frequent:
  - Primary Effusion Lymphoma (PEL)
  - Plasmablastic Lymphoma
  - Classical Hodgkin Lymphoma (HL)
  - Follicular Lymphoma
  - Peripheral T-Cell Lymphoma

- Risk of systemic or primary CNS lymphoma in HIV-infected persons is closely associated with the CD4 count!
Pathobiology

- Involves complex biologic factors that play a role
- Chronic antigen stimulation
- Co-infecting oncogenic viruses (EBV)
- Genetic abnormalities
- Cytokine dysregulation
- Most lymphomas are B-cell lineage
  - Rearrangement of immunoglobulin genes
- Occasional T-cell lymphomas
  - T-cell receptor gene rearrangements
Viral and genetic abnormalities in HIV-associated NHL

<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>30%&lt;sup&gt;2,10,11&lt;/sup&gt;</td>
<td>0</td>
<td>MYC (10%); BCL6 (20% of centroblastic DLBCL)&lt;sup&gt;19,20&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>80-90%&lt;sup&gt;2,10,11&lt;/sup&gt;</td>
<td>0</td>
<td>TP53 (40%)&lt;sup&gt;5,88&lt;/sup&gt;</td>
</tr>
<tr>
<td>Centroblastic Immunoblastic</td>
<td>0</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>Plasmablastic lymphoma</td>
<td>&gt;50%&lt;sup&gt;2&lt;/sup&gt;</td>
<td>80%&lt;sup&gt;61&lt;/sup&gt;</td>
<td>None</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td>100%&lt;sup&gt;2,8&lt;/sup&gt;</td>
<td>100%&lt;sup&gt;2,8&lt;/sup&gt;</td>
<td>None</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>30-50%&lt;sup&gt;2,9&lt;/sup&gt;</td>
<td>0</td>
<td>MYC (100%)&lt;sup&gt;2&lt;/sup&gt;; TP53 (50-60%)&lt;sup&gt;5,88&lt;/sup&gt;</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>100%&lt;sup&gt;10&lt;/sup&gt;</td>
<td>0</td>
<td>BCL6 (30-40%)&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>80-100%&lt;sup&gt;2&lt;/sup&gt;</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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Diagnosis

- Most important: Adequate and properly evaluated biopsy
- Excisional biopsies
- Core or Fine needle aspirate biopsies are inadequate.
- Centroblastic → characterized by diffuse sheets of large lymphoid cells with round or oval nuclei & prominent nucleoli.
- Express germinal center-associated markers
  - CD10
  - BCL6
  - CD20+
- Immunoblastic variant → cases containing more than 90% immunoblasts and exhibits features of plasmacytoid differentiation.
  - CD10-
  - MUM1/IRF4+
  - CD138/syndecan-1
A model for the histogenesis of HIV-associated lymphomas showing molecular and viral pathogenesis and DLBCL taxonomy

<table>
<thead>
<tr>
<th>Germinal Center</th>
<th>Post-Germinal Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germinal Center B-cell type (GCB)</td>
<td>Activated B-cell type (ABC)</td>
</tr>
<tr>
<td>Mild immunodeficiency</td>
<td>Severe immunodeficiency</td>
</tr>
<tr>
<td>Moderate CD4 count</td>
<td>Low CD4 count</td>
</tr>
<tr>
<td>Good Prognosis</td>
<td>Poor prognosis</td>
</tr>
<tr>
<td>Post-CART</td>
<td>Pre-CART</td>
</tr>
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</table>

**Germinal Center B-cell type (GCB)**
- BL: CD20 +
- EBV +/-
- MUM1/IRF4 -
- CD10/BCL6 +
- DLBCL-CB: CD20 +
- EBV +/-
- MUM1/IRF4 -
- CD10/BCL6 +

**DLBCL-IB**
- CD20 +
- EBV +/-
- MUM1/IRF4 +
- CD10/BCL6 -

**PEL**
- CD20 -
- EBV +
- KSHV/HHV8 +
- MUM1/IRF4 -
- CD10/BCL6 -

**PB**
- CD20 -
- EBV +
- KSHV/HHV8 +
- MUM1/IRF4 -
- CD10/BCL6 -

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Evaluation

- Physical examination → include careful assessment of lymph node regions, liver & spleen.

- Laboratory studies:
  - CBC
  - Chemistry profile (LDH, uric acid levels, CD4 count & HIV viral load)

- Serology:
  - Hepatitis B & C

- Bone marrow aspirate and biopsy performed at initial diagnosis
  - 20% of cases - lymphoma will be detected

- LP in aggressive B-cell lymphomas
  - Analysis by flow cytometry and cytology

- CT & [MRI]
  - [FDG-PET if available]
Treatment Questions

- Treatment for HIV-associated lymphoma has evolved significantly over the past 30 years.

- Therapeutic Questions:
  - Should lower doses of chemotherapy be used to reduce toxicity and immune suppression?
  - What is the role of rituximab and the optimal regimen?
  - Should CART be suspended during lymphoma therapy?
# Pivotal trials in HIV-associated lymphomas

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Study design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaplan et al[53]</td>
<td>Prospective multicenter randomized phase III (n=192)</td>
<td>Randomization to standard-dose m-BACOD versus low-dose m-BACOD without GM-CSF. No cART</td>
<td>Similar efficacy of both regimens but less hematological toxicity with low-dose m-BACOD</td>
</tr>
<tr>
<td>Ratner et al[52]</td>
<td>Prospective multicenter sequential phase II (n=65)</td>
<td>First 40 patients received modified-dose (m) CHOP (50% cyclophosphamide and doxorubicin) and the next 25 patients received standard-dose CHOP. cART was administered</td>
<td>CR higher with full dose CHOP compared to mCHOP (48% vs 30%). Authors concluded that concomitant cART was safe but unable to conclude superiority of one regimen over another</td>
</tr>
<tr>
<td>Sparano et al[55]</td>
<td>Prospective multicenter sequential phase II (n=96)</td>
<td>First 43 patients received didanosine and the next 55 patients received cART with CDE</td>
<td>At 2 years, FFS and OS were 36% and 43%. Patients receiving concomitant cART had better survival and less toxicity</td>
</tr>
<tr>
<td>Mounier et al[56]</td>
<td>Prospective multicenter phase III study</td>
<td>485 patients were randomly assigned to different CHOP-based chemotherapy regimens according to an HIV score that was based on performance status, prior AIDS and CD4 count</td>
<td>Though HIV score, IPI score and cART affected survival, the intensity of CHOP-based chemotherapy had no effect on survival</td>
</tr>
<tr>
<td>Little et al[37]</td>
<td>Prospective single center phase II (n=39)</td>
<td>All patients received EPOCH and G-CSF with cART suspension</td>
<td>CR was 74%. At 53 months, DFS and OS were 92% and 60%. Patients in CR achieved CD4 recovery and HIV control following treatment. Conclusion that EPOCH with cART suspension is feasible and highly effective</td>
</tr>
<tr>
<td>Kaplan et al[53]</td>
<td>Prospective multicenter randomized phase III (n=150)</td>
<td>Randomization (2:1) to R-CHOP versus CHOP with concomitant cART. Some patients received maintenance rituximab.</td>
<td>CR rate higher with R-CHOP compared to CHOP (67.6% vs 47%). Increased infectious deaths with R-CHOP mostly in patients with low CD4 counts. Conclusion that rituximab does not improve clinical outcome</td>
</tr>
<tr>
<td>Boue et al[63]</td>
<td>Prospective multicenter phase II (n=61)</td>
<td>All patients received R-CHOP</td>
<td>CR in 77% of patients. Estimated 2 year OS was 75%</td>
</tr>
<tr>
<td>Spina et al[60]</td>
<td>Retrospective analysis of 3 phase II trials</td>
<td>Pooled results from 3 trials of CDE with rituximab</td>
<td>CR rate was 70%. At 2 years, FFS and OS were 59% and 64%. Conclusion that R-CDE is effective but rituximab may increase infections</td>
</tr>
<tr>
<td>Sparano et al[49]</td>
<td>Prospective multicenter phase II study</td>
<td>101 patients were randomized to receive either concurrent or sequential rituximab with DA-EPOCH.</td>
<td>There was a superior outcome with concurrent rituximab and DA-EPOCH (CR rate 75%) and this was considerably better when compared to the previous ANC results with CHOP +/- R</td>
</tr>
<tr>
<td>Dunleavy et al[67]</td>
<td>Prospective single center phase II (n=33)</td>
<td>All patients received SC-EPOCH-RR with cART suspension</td>
<td>79% of patients needed only 3 cycles of treatment. At 5 year follow-up, FFS and OS were 84% and 68%. Outcome was better for GCB versus non-GCB DLBCL (5 year FFS of 95% versus 44%).</td>
</tr>
</tbody>
</table>

GM-CSF, granulocyte macrophage colony-stimulating factor; G-CSF, granulocyte colony stimulating factor; cART, combined anti-retroviral therapy; CR, complete remission; FFS, failure-free survival; OS, overall survival; DFS, disease-free survival; m-BACOD, methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; R, rituximab; CDE, Cyclophosphamide, doxorubicin, and etoposide; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DA, dose adjusted; SC short course

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Outcome of CART and role of Rituximab

- Variety of trials performed to evaluate dose modifications and effects of CART on treatment.

- French group performed phase 2 study of CHOP + rituximab in HIV-associated NHL.
  - CR rate of 77%
  - 2-year survival rate of 75%
  - Suggested rituximab was beneficial and could be given safely.

- Additional phase 2 randomized study performed.
  - Randomized patients to receive concurrent versus sequential rituximab with EPOCH
  - Concurrent rituximab was not associated with increased infectious deaths
  - Examined whether the complete response rate with EPOCH-R was superior to CHOP with or without rituximab
  - Also whether concurrent vs. sequential rituximab was more toxic/or more effective.
  - No difference in toxicity.

- Based on study → unwise to omit rituximab from upfront therapy in HIV-associated lymphomas.

- Results suggest EPOCH-based treatment of HIV-associated lymphoma may be an optimal treatment regimen.
### SC-EPOCH-RR drug doses and schedule

<table>
<thead>
<tr>
<th></th>
<th>Dose mg/m²/day</th>
<th>Treatment Days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infusional Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>0.4</td>
<td>Days 1 to 4</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Bolus Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750</td>
<td>Day 5</td>
</tr>
<tr>
<td>Prednisone</td>
<td>60 od</td>
<td>Days 1 to 5</td>
</tr>
<tr>
<td><strong>Biologic Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G-CSF</td>
<td>300 mcg</td>
<td>Days 6 to 15</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375</td>
<td>Days 1 and 5</td>
</tr>
</tbody>
</table>

*od=once daily*

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SC-EPOCH-RR treatment paradigm

To determine how many cycles of SC-EPOCH-RR are needed

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PFS and OS Kaplan-Meier curves

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Treatment of Relapse

- Usually associated with a poor prognosis.
- Median survival tends to be <1 year
- Italian study presented high-dose therapy and transplantation.
  - Median OS was 33 months
  - Chemo-sensitive disease had a relatively favorable outcome.
  - Disease free at 44 months of follow-up
- Reasonable to approach relapsed HIV-associated lymphomas similarly to their HIV-negative counterparts.