Southern African HIV Clinicians Society
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Sandton Convention Centre
Johannesburg

Our Issues, Our Drugs, Our Patients

www.sahivsoc.org
www.sahivsoc2016.co.za
HIV ASSOCIATED LYMPHOMA

Dr N Rapiti
HIV ASSOCIATED LYMPHOMA: OVERVIEW

- Classification
- Pathogenesis
- Prognosis
- cART
- Chemotherapy/Radiotherapy/SCT
- Supportive
CASE

40 yr old male, Mr BM, p/w

- Symptomatic anemia April ’15
- Constitutional sympt

Known HIV, on HAART, CD4 800, ?VL

PTB 2008, 2013, May 2014

Clinically:

- Pale, cervical, axillary, inguinal LN 15cm hepatomegaly

Ix: BMAT=> variable cellularity, ill-defined granulomas, Z-N –ve

Axillary LN biopsy: HV CD with HHV8 LANA-1 positivity

?Mx

NDT meeting Nov 2015
INTRODUCTION

- Pre-cART, HIV px 60-200x higher risk NHL
- Risk of NHL increases with declining CD4 count
- cART era incidence reduced, but still high 11-25x
- 4% with AIDS will have NHL at diagnosis
- 10% will develop during course of illness
- Pre-ART, malig → 10% HIV deaths
- Post-ART, malig → 28% HIV deaths
WHO CLASSIFICATION OF HIV LYMPHOID MALIGNANCIES

1) Lymphoma also in immunocompetent px

1.1 DLBCL
   - Centroblastic
   - Immunoblastic (PCNS)

1.2 Burkitt and Burkitt-like

1.3 Extranodal MALT lymphoma (rare)

1.4 PTCL (rare)

1.5 Classical Hodgkin's Dx

2) Lymphoma more specifically in HIV +ve px

2.1 PEL

2.2 Plasmablastic lymphoma of oral cavity

2.3 Lymph assoc HHV8+ Castleman dx

3) Lymphoma in other immunodef states

3.1) Polymorphic B cell lymphoma (rare)
CLASSIFICATION: INVOLVEMENT SITES

1. Systemic
   ✦ 80% of all ARL
      ✦ 1.1) Small non-cleaved(Burkitt and Burkitt-like)
      ✦ 1.2) DLBCL(centroblastic, immunoblastic plasmablastic). CD4 low

2. PCNSL: < common, CD4< 50/µL

3. PEL: rare
AETIOLOGY

- **Chronic Ag stimulation** → polyclonal B cell expansion → monoclonal B cell (circ free LC)

- **Co-infecting oncogenic viruses:**
  - EBV exp LMP1 → cell prolif NFkB → bcl-2 over exp → B cell survival
  - HHV8 all PEL

- **Molecular abn:** myc, BCL6

- **Cytokine/chemokine dysreg:** IL6, IL10 (EBV, HHV8 assoc lymphoma)
<table>
<thead>
<tr>
<th>HISTO</th>
<th>EBV</th>
<th>BCL-6</th>
<th>C-myc</th>
<th>p53</th>
<th>BCL-2</th>
<th>HHV 8</th>
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</thead>
<tbody>
<tr>
<td>Burkitt</td>
<td>30-50%</td>
<td>-</td>
<td>100%</td>
<td>50-60%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DLBCL</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>30%</td>
<td>20%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Immunoblastic</td>
<td>90% LMP1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>high</td>
<td>-</td>
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<td></td>
<td>65-75%</td>
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<tr>
<td>Plasmablastic</td>
<td>50%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>80%</td>
</tr>
<tr>
<td>PCNSL</td>
<td>90% LMP1</td>
<td>Most</td>
<td>-</td>
<td>high</td>
<td>-</td>
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<tr>
<td></td>
<td>90%</td>
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</tr>
<tr>
<td>PEL</td>
<td>90-100%</td>
<td>60%</td>
<td>NO</td>
<td>-</td>
<td>-</td>
<td>100%</td>
</tr>
</tbody>
</table>
PATHOGENESIS:
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>
</tbody>
</table>

**Germinal Center**
- **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 -

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

©2012 by American Society of Hematology
INVESTIGATION

- Excisional LN biopsy
- FBC, chemistry, LDH, urates
- CD4, VL, Hep B/C
- BMAT 20% involv
- LP with CSF flow
- CT staging vs PET
  - HIV nodal reactive hyperplasia
  - Lipodystrophy
  - infection
- MRI brain
HISTOLOGY: DLBCL: Centroblastic

- 25% HAL
- diffuse sheets of large lymphoid cells, oval nuclei, prominent nucleoli
- GCB $\rightarrow$ CD10, BCL6, CD20+
PLASMABLASTIC LYMPHOMA

- CD 38, 138, MUM1/IRF4 +ve
- CD20, 45 –ve
- Jaw, oral cavity, overlap with PEL
- CART appears beneficial
- ?infusional regimens
- ?Bortezomib ?Lenalidomide
PROGNOSIS

- 70% advanced dx, with B symptoms and extranodal dx

- Prognosis: IPI with CD4 count

<table>
<thead>
<tr>
<th>NCCN IPI</th>
<th>AGE</th>
<th>LDH</th>
<th>STAGE 111/1V</th>
<th>ENDx</th>
<th>PS ≥ 2</th>
<th>CD4</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>40-60yr</td>
<td>1-3 x normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>60-75yr</td>
<td>&gt;3x normal</td>
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<tr>
<td>3</td>
<td>&gt;75yr</td>
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0-1: low
2-3: LI
4-5: HI
≥ 6: High
ANTIRETROVIRAL Rx

- Concurrent with chemo
- Interaction cytotoxics and ART
- May potentiate chemotherapy toxicity
- Highest with combinations with strong enzyme inhibitors eg Ritonavir-boosted protease inhibitors
- Integrase inhibitor containing ARV regimen suggested
- CD4 not prevented with cART, returns baseline 12/12
- No controlled studies
<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th>POST</th>
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<tbody>
<tr>
<td>INCIDENCE</td>
<td>36.6</td>
<td>8.4 per 1000p/y</td>
</tr>
<tr>
<td>CD4 &gt;200</td>
<td>3%(70)</td>
<td>21%(94)</td>
</tr>
<tr>
<td>VL(copies/ml)</td>
<td>264 667</td>
<td>35 500</td>
</tr>
<tr>
<td>% FEMALE</td>
<td>2%</td>
<td>14%</td>
</tr>
<tr>
<td>OI</td>
<td>83%</td>
<td>36%</td>
</tr>
<tr>
<td>MEDIAN S</td>
<td>3/12</td>
<td>13/12</td>
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Rx

- DLBCL: R-CHOP or R-EPOCH x 6 = SOC
- BL (good performance status): GMALL B-ALL/NHL protocol
- Plasmablastic and PEL, no standard Rx
- 1st relapse, sensitive dx, HDT with ASCT
- Resistant dx, 2nd line or palliate
- cART concurrent with bolus chemo
- Rx as for HIV-ve px
## DLBCL Rx

<table>
<thead>
<tr>
<th></th>
<th>CHOP</th>
<th>R-CHOP</th>
<th>R-EPOCH</th>
<th>R-CDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>48-60%</td>
<td></td>
<td>↑ 10%</td>
<td></td>
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<tr>
<td>Infection +</td>
<td>2%</td>
<td>14%</td>
<td></td>
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<td></td>
<td>1 randomised trial c-Art era</td>
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<tr>
<td>CR with R</td>
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<tr>
<td>Infection +</td>
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<tr>
<td>2-3yr OS</td>
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- Several prospective and Phase 2 studies CR 69-76%
- 2-9% mortality with Rituximab inclusion
- 56-75% > than CHOP or historical controls
INFUSIONAL REGIMENS

DLBCL or BL

SC-EPOCH-RR x 2

CT/FDG-PET

CR

PR

SC-EPOCH-RR x 1

SC-EPOCH-R x 2-4 (1 past CR)

No CART

IT Prophylaxis
MTX 12mg IT on days 1 and 5 of cycles 3-5 (6 doses total)
(see text for treatment of lymphomatous meningitis)

Therapy cessation*

Routine follow-up

Resume CART

*Therapy is stopped when:
1) There is < 25% reduction in bidimensional products compared to previous interim CT scan
2) SUV on PET have decreased > 50% compared to the pre-treatment PET
CASTLEMANS DX AND NHL

- 18% association 1 series
- Higher predisposition in HIV px
- HDx also associated MCD
- Prospective study MCD with HIV: 60px f/u 20/12
- 23% dev NHL (incidence 14x > HIV pop) → 50% plasmablastic
- CD4, VL not predictive of risk
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NDT meeting Nov 2015
PLASMABLASTIC CD

Fig. 5. Castleman disease, plasmablastic variant with large plasmablasts (immunoblasts) in the mantle zone. Original magnification

Haematology Meeting Nov 2015
SUMMARY: Diseases with Castleman-like lymph node histopathological features

"Castleman" Lymph Node

UCD

MCD

Diseases with CD-like histopathology

Autoimmune (ex: SLE, RA)

Malignancy (ex: Hodgkin Lymphoma)

Infectious (ex: HIV, EBV)

Hyaline Vascular

Plasma Cell

Mixed

HHV-8 associated

HHV-8-neg: idiopathic MCD

Plasmablastic

Hyaline Vascular

Plasma Cell

Mixed

2014 by American Society of Hematology
FUTURE

- Practical: delayed diagnosis, concurrent pathology, clinician awareness, dx evolution
- Identify cell of origin ie. GCB verses non
  - Tailored Rx eg Bortezomib
- ID MYC +ve DLBCL, poor outcome with R-CHOP
- Monitoring risk with serum free LC
- Rx: bolus vs infusional
- Novels agent eg. Bortezomib, Lenalidomide