Outline

Epidemiology
Initial Work-up
Burkitt Lymphoma
Double-Hit Lymphoma
Double expressor lymphoma
Grey zone lymphoma
AIDS-Related B-cell Lymphomas:
-Primary effusion lymphoma
-Plasmablastic DLCL
-HIV-DLBCL
NHL Etiology

- Immune deficiency (Congenital or Acquired)
- Autoimmune disorders (e.g. Hashimoto’s thyroiditis, Sjogren’s syndrome, RA)
- Infectious agents
  - HIV
  - Helicobacter pylori (infection of stomach and MALT)
  - EBV, Human T-cell leukemia virus, KS-associated Herpes virus, HHV-8
- Chemical and physical agents (e.g. pesticides)
- Dietary
Epidemiology
Non-Hodgkin Lymphoma

WHO Classification (2016) of Lymphoid Neoplasms

Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration*
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*
High-grade B-cell lymphoma, NOS*
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
NCCN Guidelines Version 2.2017
Diffuse Large B-Cell Lymphoma

DIAGNOSIS

ESSENTIAL:
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis and GCB versus non-GCB origin.
  - IHC panel: CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1, MYC with or without
  - Flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Additional immunohistochemical studies to establish lymphoma subtype
  - IHC panel: Cyclin D1, kappa/lambda, CD30, CD138, Epstein-Barr virus in situ hybridization (EBER-ISH), ALK, HHV8, SOX11
  - Karyotype or FISH: MYC, BCL2, BCL6 rearrangements

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Initial Workup

- History and Physical: B symptoms
- LN Biopsy: excisional, core, FNA
- Laboratory: CBC, Chem, LDH, Uric Acid
- Hep B, hep C, HIV
- CT scans C/A/P with contrast
- PET scan
- Bone Marrow Biopsy: Flow, IHC, FISH, Cytogenetics
- MUGA, Echocardiogram
- MRI, LP

B symptoms: Fever, drenching night sweats, > 10% unintentional weight loss in 6 months
Costwolds Modification of Ann Arbor Staging System
Chromosomal translocations in NHL

- **T(14;18)(q32;q21)**: Follicular Lymphoma
- **T(11;18)(q21;q21)**: MALT Lymphoma
- **T(14;18)(q32;q21)**: MALT Lymphoma
- **T(1;14)(q22;q32)**: MALT Lymphoma
- **T(3;14)(p14.1;q32)**: MALT Lymphoma
- **T(11;14)(q13;q32)**: Mantle cell Lymphoma
- **T(3;14)(q27;q32)**: DLBCL
- **T(14;18)(q32;q21)**: DLBCL
- **T(8;14)(q24;q32)**: Burkitt Lymphoma
- **T(8;22)(q24;q11)**: Burkitt Lymphoma
- **T(2;8)(p12;q24)**: Burkitt Lymphoma

80% 5% 15% 5%
Denis Parsons Burkitt
(1911-1993)
Burkitt Lymphoma
Burkitt Lymphoma
\[ t(8;14)(q24;q32) \]
Burkitt Lymphoma
\[ t(8;14)(q24;q32) \]
MYC Proto-oncogene

Diagram showing interactions with various biological processes and molecules such as BRD4, TRRAP, CDK1, AURKB, CHK1, LDHA, GLS, AMPK, ARK5, SAE2, CSNK1o, and pathways like Transcription, Gene Amplification, Chromatin Remodeling, Cell Cycle Checkpoints, Metabolism, Sumoylation, Circadian and Wnt Signaling.
<table>
<thead>
<tr>
<th>Burkitt Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Usually disseminated</td>
</tr>
<tr>
<td>Frequently leukemic</td>
</tr>
<tr>
<td>Frequent CNS involved</td>
</tr>
<tr>
<td>Require intensive Tx</td>
</tr>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>&lt; 2-3% of lymphomas</td>
</tr>
<tr>
<td>Always treat as advanced stage</td>
</tr>
<tr>
<td>Marrow often involved</td>
</tr>
<tr>
<td>Always give CNS treatment</td>
</tr>
<tr>
<td>Use intensified chemo</td>
</tr>
<tr>
<td>60% cure if treatable</td>
</tr>
</tbody>
</table>
Burkitt Lymphoma

Endemic
Equatorial Africa
Primarily children, male predominance
Extranodal sites common – jaw, gonads, abdomen
>90% EBV+

Sporadic
Western countries
Peaks in childhood and elderly, male predominance
Abdomen common site
40% EBV+

Immunodeficiency-associated
40% EBV+
Sir Michael Anthony Epstein
SUGGESTED TREATMENT REGIMENS\textsuperscript{a,b}
(in alphabetical order)

Prophylaxis for tumor lysis syndrome is mandatory (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

CHOP is not adequate therapy.

Induction Therapy

Low Risk- Combination Regimens
- CALGB 10002 regimen (cyclophosphamide and prednisone followed by cycles containing either ifosfamide or cyclophosphamide; high-dose methotrexate, leucovorin, vincristine, dexamethasone, and either doxorubicin or etoposide or cytarabine; or intrathecal triple therapy [methotrexate, cytarabine, and hydrocortisone]) + rituximab.
- CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) ± rituximab (3 cycles)
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (minimum 3 cycles with one additional cycle beyond CR) (regimen includes intrathecal methotrexate) (Data are for patients without CNS disease.)
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab (regimen includes intrathecal therapy)

High Risk- Combination Regimens
- CALGB 10002 regimen (cyclophosphamide and prednisone followed by cycles containing either ifosfamide or cyclophosphamide; high-dose methotrexate, leucovorin, vincristine, dexamethasone, and either doxorubicin or etoposide or cytarabine; or intrathecal triple therapy [methotrexate, cytarabine, and hydrocortisone] with prophylactic CNS irradiation in select patients) + rituximab
- CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) alternating with IVAC (ifosfamide, cytarabine, etoposide, and intrathecal methotrexate) ± rituximab
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (for high-risk patients not able to tolerate aggressive treatments) (regimen includes intrathecal methotrexate) (Data are for patients without CNS disease.)
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab (regimen includes intrathecal therapy)

Second-line Therapy (select patients with reasonable remission)
While no definitive second-line therapies exist, there are limited data for the following regimens:
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (minimum 3 cycles with one additional cycle beyond CR) (regimen includes intrathecal methotrexate) (Data are for patients without CNS disease.)
- RICE (rituximab, ifosfamide, carboplatin, etoposide) intrathecal methotrexate if not received previously
- RIVAC (rituximab, ifosfamide, cytarabine, etoposide); intrathecal methotrexate if not received previously
- RGDP (rituximab, gemcitabine, dexamethasone, cisplatin)
- High-dose cytarabine + rituximab

\textsuperscript{a}See references for regimens BURK-A 2 of 2.

\textsuperscript{b}All regimens for Burkitt lymphoma include CNS prophylaxis/therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Diffuse Large B-cell Lymphoma

Centroblastic variant

Immunoblastic variant
HGBL with MYC and BCL2 and/or BCL6 rearrangements

2008 WHO Classification: B-cell lymphoma unclassifiable with features between Burkitt lymphoma and diffuse large B-cell lymphoma
Classifying Aggressive Lymphoma

MYC and Double Hit Lymphoma

- Myc rearrangement in 7-14% of DLBCL
- DHL: Rearrangement Myc with bcl-2 (60%), bcl-6 (<10%), bcl-2/bcl-6 (20%)
- DHL: Age (70), Stage III/IV, HI/H IPI, LDH > nl, extranodal sites (including CNS)
- DEL: High % of Myc (≥40%) plus BCL2 (50-70%) protein expression by IHC
- Associated with poor outcome
- R-CHOP is inadequate
- Treatment: Clinical trial, DA-EPOCH-R.
Double Hit Lymphoma

**Definition**
- Double Hit (Double Rearrangements):
  - DLBCL or HGB-NOS (intermediate between DLBCL and BL) with MYC rearrangement plus BCL2 and/or BCL6 rearrangements (as detected by FISH or standard cytogenetics) are known as "double-hit" lymphomas (if all three are rearranged, they are referred to as "triple-hit" lymphomas).
  - Vast majority are germinal center B-cell–like lymphomas

**Clinical Presentation**
- Often present with poor prognostic parameters, such as elevated LDH, bone marrow and CNS involvement, and a high IPI score.

**Treatment**
- Clinical trial is recommended.
- While the standard of care is not established, the following regimens have been used at NCCN Member Institutions:
  - DA-EPOCH-R
  - RHyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
  - R-CODOX-M/R-IVAC (rituximab-cyclophosphamide, vincristine, doxorubicin with methotrexate/ifosfamide, etoposide, and cytarabine)
  - RCHOP has been associated with inferior outcomes.
- Consider consolidation with high-dose therapy with autologous stem cell rescue. While its role is not established, this is done at some NCCN Member Institutions.
- These patients are at higher risk for CNS involvement (See BCEL-A 2 of 2); consider CNS prophylaxis according to institutional standards.
Double Hit Lymphoma

cloned genes injected into fertilized mouse eggs

eggs implanted in uterus of pseudo-pregnant female

some embryos yield mice carrying transgene in all their cells, including gametes

breed with one another

mice carrying IgG-myc transgene in all their cells
mice carrying both transgenes in all their cells
mice carrying IgG-bcl-2 transgene in all their cells

% of mice surviving

age (days)

bcl-2 alone
myc alone
myc + bcl-2
Case #1

48 M presents with progressive, burning flank pain without fevers, night sweats or weight loss.

CT scan is notable for multiple enlarged mesenteric and retroperitoneal nodes, largest measuring 5.2 x 3.2 cm.

On exam, he has a right anterior cervical node measuring 2 cm and a 1.5 cm left supraclavicular node.

Biopsy reveals diffuse large B-cell lymphoma, positive for CD20, CD10, bcl-6, bcl-2 and Ki67 fraction is 80%. MYC is positive in 80-90% of cells.

Laboratory studies reveal a normal CBC and LDH is 180.
Baseline PET
Case #1

Given the patient is symptomatic, he initiates RCHOP chemotherapy while his cytogenetics are pending. His symptoms promptly resolve 10 days later, FISH reveals concurrent rearrangements in MYC and BCL-2, consistent with double-hit lymphoma.
Case #1

What would you do now?

1. Escalate to DA-R-EPOCH
2. Escalate to R-CODOX/M-IVAC
3. Escalate to R-HyperCVAD
4. Continue R-CHOP
5. Continue RCHOP and consolidate with autologous stem cell transplant
Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis

Table 2. Treatment patterns (N = 311)

<table>
<thead>
<tr>
<th>Induction regimen</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP</td>
<td>100 (32)</td>
</tr>
<tr>
<td>R-Hyper-CVAD</td>
<td>65 (21)</td>
</tr>
<tr>
<td>DA-EPOCH-R</td>
<td>64 (21)</td>
</tr>
<tr>
<td>R-CODOX-MIVAC</td>
<td>42 (14)</td>
</tr>
<tr>
<td>R-ICE</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Other/multiple</td>
<td>31 (10)</td>
</tr>
</tbody>
</table>

Rituximab Included

- Yes: 268 (86)
- No: 15 (5)
- NA: 27 (9)
- Median # Cycles administered (range): 5 (0-9)

CNS prophylaxis

- None: 130 (42)
- MTX: 102 (33)
- Ara-C: 6 (2)
- Both: 66 (21)
- NA: 7 (2)

Stem cell transplantation

- At any time: 83 (27)
- In first CR: 53 (17)
- Autologous SCT in first CR: 39 (13)
- Allogeneic SCT in first CR: 14 (5)

Salvage chemotherapy

- R-ICE: 50 (16)
- R-ESHAP: 6 (2)
- R-DHAP: 2 (<1)
- Other: 48 (15)
- NA: 208 (65)

Improved PFS without difference in OS according to induction chemo regimen
<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk factor</th>
<th>Reference univariate analysis</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥60</td>
<td>&lt;60</td>
<td>1.622 (1.177, 2.234)</td>
<td>.003</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>2-4</td>
<td>0-1</td>
<td>1.772 (1.304, 2.805)</td>
<td>.001</td>
</tr>
<tr>
<td>WBC</td>
<td>≥10³</td>
<td>&lt;10³</td>
<td>2.249 (1.694, 4.349)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Albumin</td>
<td>&lt;4</td>
<td>≥4</td>
<td>1.864 (1.318, 3.026)</td>
<td>.001</td>
</tr>
<tr>
<td>LDH</td>
<td>&gt;3× ULN</td>
<td>≤3× ULN</td>
<td>1.907 (1.131, 2.609)</td>
<td>.011</td>
</tr>
<tr>
<td>B symptoms</td>
<td>Present</td>
<td>Absent</td>
<td>1.587 (1.083, 2.414)</td>
<td>.019</td>
</tr>
<tr>
<td>Extranodal disease</td>
<td>&gt;1 site</td>
<td>0-1 site</td>
<td>1.518 (1.099, 2.294)</td>
<td>.014</td>
</tr>
<tr>
<td>Ann Arbor Stage</td>
<td>3-4</td>
<td>1-2</td>
<td>2.607 (1.373, 3.138)</td>
<td>.001</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>Positive</td>
<td>Negative</td>
<td>1.906 (1.357, 2.851)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>Present</td>
<td>Absent</td>
<td>4.700 (3.763, 24.77)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Multivariate analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk factor</th>
<th>Reference univariate analysis</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>≥10³</td>
<td>&lt;10³</td>
<td>1.710 (1.001, 2.923)</td>
<td>.05</td>
</tr>
<tr>
<td>LDH</td>
<td>&gt;3× ULN</td>
<td>≤3× ULN</td>
<td>1.727 (1.000, 3.018)</td>
<td>.05</td>
</tr>
<tr>
<td>Ann Arbor Stage</td>
<td>3-4</td>
<td>1-2</td>
<td>1.585 (1.351, 1.389)</td>
<td>.014</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>Present</td>
<td>Absent</td>
<td>2.000 (1.169, 3.423)</td>
<td>.011</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group performance status; WBC, white blood cell count, in 10³ cells/mL; LDH, lactate dehydrogenase, in U/L; CNS, central nervous system; ULN, upper limit of normal.
Complete Response to Induction Therapy in Patients With Myc-Positive and Double-Hit Non-Hodgkin Lymphoma Is Associated With Prolonged Progression-Free Survival

TABLE 1. Demographic and Clinical Characteristics of Patients With Myc-Positive and Double-Hit Non-Hodgkin Lymphoma

CR to induction therapy and age associated with OS
No difference according to rearrangement type or histology except grade 3 FL

Oki et al. 2014
R-EPOCH appears to be associated with improved EFS and OS
Double expressor DLBCL

Definition of MYC positivity = 40% in most series, though BCL2 positivity varied

20-35% of DLBCL associated with adverse outcome in patients treated RCHOP and variants

Swerdlow. ASH 2014
Concurrent Expression of MYC and BCL2 in Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone


In DLBCL rx RCHOP: MYC and BCL-2 over expression associated with poor PFS/OS, though DHL had the worst overall survival
Similar findings to Johnson study with inferior outcomes of DHL and double expressors.
Case #1
Post remission therapy?

1. Autologous stem cell transplant
2. Rituximab maintenance
3. Observation
4. Allogeneic stem cell transplant
Clinical Significance of MYC Expression and/or “High-grade” Morphology in Non-Burkitt, Diffuse Aggressive B-cell Lymphomas
A SWOG S9704 Correlative Study
James R. Cook, MD, PhD,* Bryan Goldman, MS;† Raymond R. Tubbs, DO,* Lisa Rimsza, MD,‡ Michael Leblanc, PhD,‡ Patrick Steff, MD,§ and Richard Fisher, MD,¶

Am J Surg Pathol • Volume 38, Number 4, April 2014

(R)CHOP x 5

(R)CHOP x 3

(R)CHOP x 1
followed by ASCT

TABLE 1. Clinical Features at Presentation Based on Morphologic Features (P-values for All Comparisons >0.05)

<table>
<thead>
<tr>
<th></th>
<th>BCLU Morphology N = 31</th>
<th>DLBCL Morphology N = 229</th>
<th>All Cases N = 260</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n [%])</td>
<td>19 (61)</td>
<td>130 (57)</td>
<td>149 (57)</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>54 (25-65)</td>
<td>49 (18-66)</td>
<td>50 (18-66)</td>
</tr>
<tr>
<td>Randomized (n [%])</td>
<td>15 (48)</td>
<td>150 (66)</td>
<td>165 (63)</td>
</tr>
<tr>
<td>IPI score (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>13 (45)</td>
<td>115 (51)</td>
<td>128 (51)</td>
</tr>
<tr>
<td>3</td>
<td>7 (24)</td>
<td>80 (36)</td>
<td>87 (34)</td>
</tr>
<tr>
<td>4-5</td>
<td>9 (31)</td>
<td>29 (13)</td>
<td>38 (15)</td>
</tr>
<tr>
<td>Not available</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>IPI risk factors (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS &gt; 1*</td>
<td>12 (41)</td>
<td>84 (37)</td>
<td>96 (38)</td>
</tr>
<tr>
<td>&gt; 1 extranodal sites</td>
<td>10 (32)</td>
<td>61 (27)</td>
<td>71 (27)</td>
</tr>
<tr>
<td>LDH &gt; ULN†</td>
<td>30 (100)</td>
<td>202 (90)</td>
<td>232 (91)</td>
</tr>
<tr>
<td>Age &gt; 60</td>
<td>7 (23)</td>
<td>32 (14)</td>
<td>39 (15)</td>
</tr>
<tr>
<td>Stage III or greater</td>
<td>29 (94)</td>
<td>214 (93)</td>
<td>243 (93)</td>
</tr>
<tr>
<td>Extranodal sites (median [range])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2 (7)</td>
<td>15 (7)</td>
<td>17 (7)</td>
</tr>
<tr>
<td>III</td>
<td>14 (45)</td>
<td>64 (28)</td>
<td>78 (30)</td>
</tr>
<tr>
<td>IV</td>
<td>15 (48)</td>
<td>150 (65)</td>
<td>165 (63)</td>
</tr>
</tbody>
</table>
MYC + by IHC associated with inferior PFS/OS. BCLU histology not predictive.
*MYC*+ associated with inferior PFS and OS
Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis

No clear difference in OS with autologous transplant in CR1
Double hit lymphoma: the MD Anderson Cancer Center clinical experience

No significant benefit to transplantation in first CR

Oki et al. 2014
Case #1

What would you do now?

1. Escalate to DA-REPOCH
2. Escalate to R-CODOX/M-IVAC
3. Escalate to R-HyperCVAD
4. Continue R-CHOP
5. Continue RCHOP and consolidate with autologous stem cell transplant
Case #1
Post remission therapy?

1. Autologous stem cell transplant
2. Rituximab maintenance
3. Observation
4. Allogeneic stem cell transplant
DHL lymphoma summary

- Double hit (<10% of DLBCL) and double expressor (up to 30% of DLBCL) represent distinct subsets of aggressive lymphoma
- Outcomes with chemotherapy poor, particularly in patients with DHL
- Retrospective data mixed on benefit of intensified regimens
- No clear benefit of transplantation CR 1
- DA-REPOCH promising in small phase 2 study of MYC rearranged DLBCL
- DHL inherently chemotherapy resistant and improved outcomes will require novel agents
Grey Zone Lymphoma
(Intermediate between DLBCL and cHL)

**Synonyms**
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (CHL)
- Large B-cell lymphoma with Hodgkin features
- Hodgkin-like anaplastic large cell lymphoma

**Clinical Presentation**
- Present with large anterior mediastinal mass with or without supraclavicular lymph nodes
  - More common in males, presenting between 20–40 y
  - Non-mediastinal grey zone lymphoma is more likely compared to mediastinal cases to occur in older individuals and typically have higher risk features, more advanced-stage disease, and higher IPI.

**Immunophenotype**
- Often transitional features between CHL and PMBL
- CD45 often positive; CD30, CD15, CD20, CD79a frequently positive
- EBV -
- PAX5, BOB.1, OCT-2 are often positive, BCL6 variable
- CD10, ALK are negative
- If morphology closer to PMBL, or absence of CD20, CD15+ would suggest the diagnosis of grey zone lymphoma
- If morphology closer to CHL, CD20 strong positivity and other B-cell markers and absence of CD15 would suggest grey zone lymphoma.

**Prognosis and Treatment**
- A worse prognosis than either CHL or PMBL has been suggested.
- While there is no consensus on the treatment, aggressive large B-cell lymphoma regimens are preferred.
- If the tumor cells are CD20+, the addition of rituximab to the chemotherapy treatment should be considered.
- Data suggest that the use of rituximab-anthracycline-based chemotherapy as in other B-cell lymphomas (See BCEL-C) is helpful. If localized disease, then RT is preferred.
- There is no ostensible difference in outcome between mediastinal and non-mediastinal grey zone lymphoma.

**Morphology**
- Pleomorphic cells in a diffusely fibrous stroma
- Typically larger and more pleomorphic than in PMBL, sometimes resembling lacunar or Hodgkin-like cells
- Necrosis without neutrophilic infiltrate is frequent
HIV and Lymphoma

- 40% of HIV positive individuals will get malignancy
- NHL 1.2% per year
  - Chronic antigenic stimulation
  - Co-infecting oncogenic viruses (EBV, KSHV)
  - Cytokine dysregulation (light chains)

66 pts HIV NHL vs 225 HIV controls (sex, age, CD4, dx date)
Increasing kappa/lambda FLC levels 2-5 yr before dx increases risk
Association CD4 and FLC
AIDS-Related B-cell Lymphomas

**Burkitt lymphoma**
- Suggested regimens:\(^e\) (alphabetical order)
  - CDE (cyclophosphamide, doxorubicin, etoposide) + rituximab
  - CODOX-M/IVAC (modified): cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine ± rituximab
  - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab\(^f\)
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
  - If CD4 <50, maximize supportive care
  - GCSF for all patients

**Diffuse large B-cell lymphoma**
- HHV8-positive DLBCL, NOS
- Primary effusion lymphoma
- Suggested regimens:\(^e\)
  - Dose-adjusted EPOCH + rituximab\(^f\) (preferred)
  - CDE + rituximab
  - CHOP + rituximab
  - GCSF for all patients
  - Intrathecal therapy (IT)\(^g\)
  - If CD20-rituximab is not indicated
  - If CD4 <50, maximize supportive care

For relapse, see BCEL-6

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)
# AIDS-Related B-cell Lymphomas

<table>
<thead>
<tr>
<th>Plasmablastic lymphoma</th>
<th>Primary CNS lymphoma</th>
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<tbody>
<tr>
<td><strong>Suggested regimens:</strong>&lt;br&gt; - CODOX-M/IVAC (modified)&lt;br&gt; - Dose-adjusted EPOCH&lt;br&gt; - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine)&lt;br&gt; - Standard CHOP is not adequate therapy</td>
<td><strong>Initiate HAART, if not already receiving</strong>&lt;br&gt; <strong>Even with poorly controlled HIV and/or marginal performance status, consider high-dose methotrexate</strong>&lt;br&gt; <strong>For select patients with good performance status on HAART, see <a href="#">NCCN Guidelines for CNS- Primary CNS Lymphoma</a></strong>&lt;br&gt; <strong>Consider RT alone for palliation of patients who are not candidates for systemic therapy</strong>&lt;br&gt; <strong>Best supportive care (See <a href="#">NCCN Guidelines for Palliative Care</a>)</strong></td>
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</tbody>
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[Source: VCU Health](#)
Primary effusion lymphoma

- Epidemiology: 1-4% of AIDS-related lymphoma
- Clinical presentation: pleural, pericardial, peritoneal effusion, joint spaces
- CD45+, CD30 (50%), CD19- CD20-
- Prognostic factors: KPS, ART, inflamm cytokines
- HIV neg PEL (chronic immunosuppressed)
- HHV-8 KSHV
- EBV
Primary effusion lymphoma
 Treatment

- CHOP (DA EPOCH)
- Methotrexate (CODOX/HYPERCVAD)
- CDE (cyclophosphamide, doxorubicin, etoposide)
- Monoclonal Ab (brentuximab/Rituximab)
- Bortezomib
- Lenalidomide
- Autologous Stem Cell Transplant
Plasmablastic Diffuse Large Cell NHL

Originally described in 1997
< 2% of HIV NHL
Oropharyngeal cavity
CD20 -, CD38+, CD138+, MUM1+, hi K67
Myc-IgH translocation poor prognostic
Median survival 15 months
EBER/ISH 78%
Plasmablastic Diffuse Large Cell NHL

No randomized trial
CHOP based therapy; High RR but short OS
Bortezomib (case reports) + Gem Ox Dexamethasone

ASCT
-EBMT n=68 (20 institutions) MVA for relapse
ASCT: Case-control analyses
-40 HIV + vs 46 HIV-
-Stage, IPI, age, year dx, dz status at ASCT, histology NHL/HL
-OS: 62% vs 69% in HIV-
BMT CTN 0803: HDT with ASCT for Aggressive and HL in HIV

40 pts (5% plasmablastic), BEAM conditioning, TRM 2.5%
Treatment for HIV-DLBCL

Burkitt’s Lymphoma
A 24-year-old man presents with a 4-week history of rapidly increasing right axillary lymphadenopathy, night sweats, and a weight loss of 25 lb (11.3 kg; baseline weight, 210 lb [95.3 kg]). He has no significant medical history, and his Eastern Cooperative Oncology Group (ECOG) performance status is 1. On physical examination, right axillary lymphadenopathy measuring 10 × 6 cm is noted, and the examination is otherwise unremarkable. The serum lactate dehydrogenase level is 1,200 U/L (reference range, 100-240 U/L). Positron emission tomography is done (see figure). Evaluation of the axillary lymph node obtained by excision biopsy indicates Burkitt lymphoma, with the tumor expressing CD20. Ki67 staining is 100%
Question #1b (continued)

Which of the following is the most appropriate management option for this patient?

- Bendamustine and rituximab (BR)
- Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)
- Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)
- Rituximab plus cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC)
- 7+3 chemotherapy
Which of the following is the most appropriate management option for this patient?

- Bendamustine and rituximab (BR)
- Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)
- Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)
- **Rituximab plus cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC)**
- 7+3 chemotherapy
Explaination

Burkitt lymphoma is characterized by rapid proliferation of lymphoma cells, which requires intensive alkylator-based chemotherapy for adequate control. As such, bendamustine-rituximab; Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD); or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is insufficient. Although 7+3 chemotherapy is intensive, it does not include an alkylator. The most commonly used approaches today include intensive short-duration chemotherapy. In a phase 2 study, low-risk patients (defined as having a single extra-abdominal mass or completely resected abdominal disease and a normal serum lactate dehydrogenase level) received three cycles of cyclophosphamide, vincristine, doxorubicin, and methotrexate (CODOX-M) only, and high-risk patients received CODOX-M alternating with ifosfamide, etoposide, and high-dose cytarabine (IVAC) for a total of four cycles (two cycles of each regimen). The patient in this clinical scenario was treated with rituximab–CODOX-M/IVAC with excellent results (see figure).
Question #1b

Rearrangement of which genes is most likely to be found on fluorescent in situ hybridization of the axillary node sample in this patient?

- BCR/ABL
- IGH/BCL2
- IGH/Cyclin D1
- IGH/MALT-1
- IGH/MYC
Question #1b

Rearrangement of which genes is most likely to be found on fluorescent in situ hybridization of the axillary node sample in this patient?

• BCR/ABL
• IGH/BCL2
• IGH/Cyclin D1
• IGH/MALT-1
• IGH/MYC
Burkitt lymphoma is characterized by the presence of MYC rearrangements with immunoglobulin heavy-chain (IGH) or, less commonly, light-chain genes. IGH/BCL2 translocation can occur in most patients with follicular lymphoma and may be seen in diffuse large B-cell lymphoma and other non-Hodgkin lymphomas, but it is relatively uncommon in Burkitt lymphoma (so-called double-hit lymphoma). IGH/Cyclin D1 translocation is diagnostic of mantle cell lymphoma, whereas IGH/MALT-1 translocation is typically seen in mucosa-associated lymphoid tissue marginal zone lymphomas and is unusual in Burkitt lymphoma. BCR/ABL rearrangement is typical in chronic myelogenous lymphoma and may be seen in acute lymphoblastic leukemia/lymphoma, but it is not seen in Burkitt lymphoma.
Other therapeutic approaches have included the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (HyperCVAD)/methotrexate-cytarabine regimen and other regimens similar to those used for acute lymphocytic leukemia. The findings of small phase 2 studies suggest that Burkitt lymphoma can be successfully treated with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab (DA-EPOCH-R), and this regimen may be an option for older patients who cannot tolerate more dose-intensive regimens. However, large or randomized studies to support its use are missing.