Aggressive Non-Hodgkin Lymphomas

Overview of Diseases and Treatment

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Rocky Mountain Cancer Centers
Leukemia and Lymphoma Society Conference
April 11, 2015
Outline

• Overview of NHL

• Diffuse large B-cell lymphoma

• Primary mediastinal large B-cell lymphoma

• Mantle cell lymphoma

• Burkitt lymphoma

• T-cell lymphomas
Non Hodgkin Lymphoma

Definition

• A diverse group of cancers that arise from one of the following cells:
  – B-lymphocytes
  – T-lymphocytes
  – Natural killer cells
  – Precursors of these cells
## Lymphoma

### Epidemiology

<table>
<thead>
<tr>
<th>Parameter (2014 estimates)</th>
<th>Non Hodgkin Lymphoma</th>
<th>Hodgkin Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of new cases</td>
<td>70,800</td>
<td>9190</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>18,990</td>
<td>1180</td>
</tr>
<tr>
<td>“Death rate”</td>
<td>27%</td>
<td>13%</td>
</tr>
<tr>
<td>M:F ratio</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Median age</td>
<td></td>
<td>30 years</td>
</tr>
</tbody>
</table>

WHO 2008 Classification of Lymphoid Neoplasms (1)

• Precursor lymphoid neoplasms (e.g. ALL)
• Mature B-cell neoplasms
  – Chronic lymphocytic leukemia/small lymphocytic lymphoma
  – Lymphoplasmacytic lymphoma
  – Mantle cell lymphoma
  – B-cell prolymphocytic leukemia
  – Follicular lymphoma
  – Diffuse large B-cell lymphoma (several subtypes)
  – Burkitt lymphoma/leukemia
  – Marginal zone lymphoma
  – Hairy cell leukemia
  – Plasma cell myeloma
WHO 2008 Classification of Lymphoid Neoplasms (2)

- Hodgkin lymphoma
- Mature T-cell and NK-cell neoplasms
  - Peripheral T-cell lymphoma (several subtypes)
  - Anaplastic large cell lymphoma
  - Primary cutaneous peripheral T-cell lymphomas
  - Adult T-cell leukemia/lymphoma
  - T-cell large granular lymphocyte leukemia
  - T-cell prolymphocytic leukemia
  - Natural killer cell large granular lymphocyte leukemia
  - Aggressive natural killer cell leukemia
Non Hodgkin Lymphoma

Classification Based on Growth Rate

• Indolent
  – Follicular
  – Small lymphocytic lymphoma/chronic lymphocytic leukemia
  – Marginal zone lymphoma
  – Occasionally mantle cell lymphoma
  – Lymphoplasmacytic lymphoma (Waldenstrom’s macroglobulinemia)

• Aggressive
  – Diffuse large B-cell lymphoma
  – Mantle cell lymphoma
  – Peripheral T-cell lymphoma
  – Anaplastic large cell lymphoma

• Highly Aggressive
  – Burkitt lymphoma
  – Acute lymphoblastic leukemia
Lymphoma

Clinical Presentation

- Enlarging lymph node(s)
- B symptoms: fever, night sweats, weight loss
- Enlargement of liver
- Enlargement of spleen
- Others possible: bowel involvement, brain involvement

- Patients may have no symptoms
- Indolent much different from aggressive
Lymphoma
Making the Diagnosis

- Lymph node biopsy
  - Fine needle aspiration usually inadequate but can be used for screening
  - Core needle biopsy often adequate
  - Excisional biopsy may be necessary

- Studies on tissue
  - Histology
  - Immunophenotype (flow cytometry)
  - Genetic studies

- Bone marrow examination can be diagnostic or used for staging
Lymphoma
Staging Evaluation

• Fertility preservation
• Labs
  – CBC, CMP, LDH
  – Immunoglobulin studies (esp. indolent NHL)
  – HIV, hepatitis B and C serologies
• CT chest, abdomen, pelvis
• PET/CT scan
  – Best in DLBCL, Hodgkin
  – No role in following patients in remission
• Bone marrow aspirate and biopsy
• Lumbar puncture in 4 high-risk groups
  – Testicular non Hodgkin lymphoma
  – Bone marrow involvement with DLBCL (not indolent)
  – Paranasal sinus non Hodgkin lymphoma
  – Immunodeficiency
• Echocardiogram if doxorubicin planned
• Pulmonary function tests if bleomycin planned
Example of a PET/CT scan in a patient with aggressive NHL
## Cotswald Modification of Ann Arbor Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of one lymph node region</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of 2 or more lymph node regions on same side of the diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm</td>
</tr>
<tr>
<td>IV</td>
<td>Involvement of extranodal sites beyond that designated as E (e.g. bone marrow, liver, lung)</td>
</tr>
</tbody>
</table>

**Other Designations Applicable to Any Stage**

<table>
<thead>
<tr>
<th>Designation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No B symptoms</td>
</tr>
<tr>
<td>B</td>
<td>Fever 100.4° or higher, drenching night sweats, unexplained weight loss &gt; 10% of body weight</td>
</tr>
<tr>
<td>X</td>
<td>Bulky disease (&gt; 10 cm)</td>
</tr>
<tr>
<td>E</td>
<td>Involvement of a single extranodal site adjacent to a known nodal site</td>
</tr>
</tbody>
</table>

Outline

• Overview of NHL

• **Diffuse large B-cell lymphoma**
  - Primary mediastinal large B-cell lymphoma
  - Mantle cell lymphoma
  - Burkitt lymphoma
  - T-cell lymphomas
Diffuse Large B-Cell Lymphoma: Most Common Subtype of NHL

- Diffuse large B cell (30%)
- Follicular (25%)
- Mantle cell (6%)
- Small lymphocytic (7%)
- MALT type marginal zone B cell (7.5%)
- Nodal type marginal zone B cell (< 2%)
- Lymphoplasmacytic (< 2%)
- T and NK cell (12%)
- Other subtypes (9%)
- Burkitt (2.5%)

Lichtman. Williams Hematology, 7th Ed. 2006;1408.
Diffuse Large B-Cell Lymphoma

- Most common NHL: 31%
  - Peak incidence in sixth decade
- Clinical outcomes and molecular features highly heterogeneous
- Large cells with loss of follicular architecture
  - 30% to 40% present with rapidly enlarging, symptomatic mass with B symptoms
  - May present as extranodal disease (stomach, CNS, testis, skin)
- Curable in 50% or more of cases
- Median survival: wks to mos if not treated

Diffuse Large B-Cell Lymphoma

Pathology, low-power view
Diffuse Large B-Cell Lymphoma
Pathology, high-power view
International Prognostic Index (1)

- Developed to identify factors related to the prognosis of DLBCL

- 5 factors with adverse implications identified (APLES)
  - Age > 60
  - ECOG performance status 2 or higher
  - LDH above normal range
  - Extranodal sites: 2 or more
  - Stage III or IV

N Engl J Med 1993
## International Prognostic Index (2)

<table>
<thead>
<tr>
<th>Risk level</th>
<th>IPI score</th>
<th>3-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1</td>
<td>91%</td>
</tr>
<tr>
<td>Low-intermediate</td>
<td>2</td>
<td>81%</td>
</tr>
<tr>
<td>High-intermediate</td>
<td>3</td>
<td>65%</td>
</tr>
<tr>
<td>High</td>
<td>4-5</td>
<td>59%</td>
</tr>
</tbody>
</table>

Ziepert M et al., JCO 2010.
Gene Expression Profiling

• Uses DNA microarrays to characterize gene expression by tumor cells

• Identifies 3 major groups
  – Germinal center-type DLBCL
    • Profile similar to that of normal germinal center B cells
    • Better prognosis
  – Activated B-cell type DLBCL
    • Profile resembles that of activated B cell
    • Worse prognosis
  – Primary mediastinal
Microarray Analysis and Diffuse Large B-Cell Lymphoma Heterogeneity

Gene Expression Defines Molecurally and Clinically Distinct Subgroups in DLBCL

DLBCL Subtype Retains Prognostic Value With R-CHOP Therapy

Treatment of DLBCL

• What is current standard treatment?
  – R-CHOP in previously untreated patients
  – Chemo then autologous transplant in relapsed patients

• How are we trying to improve on current standard treatment?
Increasing the intensity of chemotherapy by adding chemotherapy drugs to CHOP does not improve outcome in patients with DLBCL.

What is R-CHOP?

<table>
<thead>
<tr>
<th>Name of Drug</th>
<th>Dose and Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375 mg/m² IV on day 1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/m² IV on day 1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>50 mg/m² IV push on day 1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>2 mg IV push on day 1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>50 mg/m² or 100 mg PO on days 1-5</td>
</tr>
</tbody>
</table>

- 1 cycle = 21 days
- 3-6 cycles administered, depending on stage
- Often administered with growth factor support (e.g. Neulasta 6 mg subcutaneously on day 6)
**CHOP ± Rituximab in DLBCL: GELA LNH-98.5 Phase III Study**

- **Primary endpoint:** EFS
- **Secondary endpoints:** OS, RR

Untreated elderly patients with stage II-IV DLBCL

- \( R-\text{CHOP} \) every 3 wks for 8 cycles \( (n = 202) \)
- \( \text{CHOP} \) every 3 wks for 8 cycles \( (n = 197) \)

Stratified by risk factors (0-1 vs 2-3)

**CHOP ± Rituximab in DLBCL: 10-Yr Survival Results (GELA LNH-98.5 Study)**

- **Median OS:** 3.5 yrs with CHOP vs 8.4 yrs with R-CHOP

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**Parameter, %[^2]**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, &lt; 70 vs ≥ 70 yrs</td>
<td>58.0</td>
<td>49.0</td>
</tr>
<tr>
<td>LDH, NI vs &gt; NI</td>
<td>69.0</td>
<td>45.0*</td>
</tr>
<tr>
<td>Stage, I/II vs III/IV</td>
<td>67.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Bone marrow, yes vs no</td>
<td>60.0</td>
<td>34.5*</td>
</tr>
<tr>
<td>Tumor size, &lt; 10 vs ≥ 10 cm</td>
<td>60.0</td>
<td>36.5</td>
</tr>
<tr>
<td>β₂-microglobulin, NI vs &gt; NI</td>
<td>64.5</td>
<td>39.0*</td>
</tr>
<tr>
<td>Serum albumin, ≥ 35 vs &lt; 35 g/L</td>
<td>60.0</td>
<td>40.0</td>
</tr>
</tbody>
</table>

[^2]: *P < .05 (multivariate analysis).

PARMA Study: Bone Marrow Transplantation vs Salvage Chemotherapy

Selected Investigational Therapies

• Targeting all subtypes
  – R-ACVBP
  – Dose-adjusted EPOCH-R
  – New anti-CD20 antibodies
  – Antibody-drug conjugates
  – CAR T-cell therapy
  – Many more!

• Targeting activated B-cell subtype with R-CHOP-X
  – Bortezomib (proteasome inhibitor)
  – Ibrutinib (Bruton tyrosine kinase inhibitor)
  – Lenalidomide (Cereblon inhibitor)
Design of study comparing R-ACVBP with R-CHOP for DLBCL.

Ages 18-59; median age 47 years
N = 380
About 96% had good prognosis (age-adjusted IPI 1)

Christian Récher, Bertrand Coiffier, Corinne Haioun, Thierry Jo Molina, Christophe Fermé, Olivier Casasnovas ...

Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial

The Lancet, Volume 378, Issue 9806, 2011, 1858 - 1867
http://dx.doi.org/10.1016/S0140-6736(11)61040-4
Compared with R-CHOP, R-ACVBP improves EFS, DFS, PFS, OS, but severe toxicity was increased.

Christian Récher, Bertrand Coiffier, Corinne Haioun, Thierry Jo Molina, Christophe Fermé, Olivier Casasnovas ...

Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial

The Lancet, Volume 378, Issue 9806, 2011, 1858 - 1867

http://dx.doi.org/10.1016/S0140-6736(11)61040-4
Dose-adjusted EPOCH-R results in good outcomes in patients with DLBCL, though patients with high-risk disease by IPI continue to fare poorly.

Even with DA-EPOCH-R, patients with non-GCB subtype (dotted line) have worse outcomes than patients with GCB subtype (solid line).

Mechanism of action of anti-CD20 antibodies

Obinutuzumab (GA-101)

- **Mechanism**
  - Monoclonal antibody that binds to protein called CD20 on surface of B cells
  - “Glycoengineered”: sugar molecules removed from part of antibody that induces immune reaction
  - Glycoengineering makes it a better killer of cancer cells than rituximab
Structure of antibody-drug conjugates

**Antibody**
The antibody, brentuximab, specific for CD30[^1]

**Cytotoxic agent**
The synthetic microtubule-disrupting agent, monomethyl auristatin E (MMAE), that induces target cell death[^1]

**Linker**
A synthetic protease-cleavable linker that covalently attaches MMAE to the CD30-directed antibody and releases the agent within the target cell[^1]

Chimeric antigen receptors.

First Generation CAR

Second Generation CAR

Third Generation CAR


©2014 by American Society of Hematology
Chimeric Antigen Receptors: MOA

- Chimeric antigen receptors[1]
  - Genetically engineered receptors that combine anti-CD19 single chain variable fragment of an antibody with intracellular signaling domains of T cells
  - With the use of lentiviral-vector technology, CTL019 T cells express a CAR with CD3 zeta and 4-1BB (CD137) signaling domains[2]

CAR T Cells Against CD19 in Rel/Ref CD19+ Lymphomas: Results


Best response ≥ 3 mos after CTL019 infusion

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>CR/CRu</th>
<th>PR</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL n = 5</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>DLBCL n = 11</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>
Complete remissions (CRs) of chemotherapy-refractory large-cell lymphomas in patients receiving anti-CD19 chimeric antigen receptor T cells.

James N. Kochenderfer et al. JCO 2015;33:540-549
A Roadmap of Immunotherapy Agents in the Cancer: Immune System Interaction

- Release of cancer cell antigens: chemotherapy, radiation, targeted therapy
- Tumor antigen
- Dendritic cell: Cancer antigen presentation: vaccines
- Activated T cell
- Resting T cell
- TCR, CD28
- MHC, B7
- Killing of cancer cells: anti–PD-1, anti–PD-L1
- Priming and activation: anti–CTLA-4
CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment

Examples of Companies Developing T-cell Treatments

• CAR T cell therapy
  – Novartis
  – Juno Therapeutics
  – Kite Pharmaceuticals
  – BluebirdBio

• PD1/PD-L1 Antibodies
  – BMS
  – Merck
  – Roche/Genentech
  – MedImmune

There is lots of enthusiasm and lots of research in this field!
B-cell receptor signaling is derailed in lymphomas.

Klein U and Pasqualucci L. Immunology and Cell Biology 2010; 88:346.
Targeting the ABC Subtype of DLBCL

*ABC subtype has a unique biology*

Adding bortezomib to R-CHOP may overcome the adverse prognostic significance of the ABC subtype.

Jia Ruan et al. JCO 2011;29:690-697
Addition of lenalidomide to R-CHOP (R2-CHOP) may overcome adverse prognostic implications of ABC subtype.

Grzegorz S. Nowakowski et al. JCO 2015;33:251-257
Ibrutinib

- Inhibitor of Bruton’s tyrosine kinase
- Orally administered
- Approved by FDA in 2013 for relapsed mantle cell lymphoma
- Approved by FDA in February 2014 for previously treated chronic lymphocytic leukemia
Ibrutinib in de Novo DLBCL

- Relapsed/refractory de novo DLBCL (median number of previous systemic therapies: 3); ibrutinib 560 mg PO QD; CT and PET scanning pretreatment and every 2 cycles; primary endpoint: ORR, categorized by molecular subtype

- Ibrutinib showed a clinically meaningful response rate in relapsed/refractory ABC DLBCL, but not in other molecular subtypes

<table>
<thead>
<tr>
<th>Response</th>
<th>ABC Subtype (n = 29)</th>
<th>GCB Subtype (n = 20)</th>
<th>Unclassifiable* (n = 16)</th>
<th>Unknown* (n = 5)</th>
<th>Total (N = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not evaluable for response, n</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>ORR (CR + PR, per protocol), n (%)</td>
<td>10 (40.0)</td>
<td>1 (5.3)</td>
<td>0</td>
<td>2 (66.7)</td>
<td>13 (21.7)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>2 (8.0)</td>
<td>0</td>
<td>0</td>
<td>1 (33.3)</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>8 (32.0)</td>
<td>1 (5.3)</td>
<td>0</td>
<td>1 (33.3)</td>
<td>10 (16.7)</td>
</tr>
</tbody>
</table>

*GEP performed, but not assignable to ABC or GCB subtypes, or GEP not yet performed or tissue not available.

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- Overview of NHL
- Diffuse large B-cell lymphoma
- **Primary mediastinal large B-cell lymphoma**
- Mantle cell lymphoma
- Burkitt lymphoma
- T-cell lymphomas
Primary Mediastinal Large B-cell Lymphoma

- Distinct subtype of DLBCL
- 10% of cases of DLBCL
- Arises in thymus
- Affects predominantly young women
- Bulky mass, possibly with pleural or pericardial effusions
- Unique gene mutations on molecular testing

DA-EPOCH-R leads to excellent outcomes in primary mediastinal DLBCL.

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• Overview of NHL

• Diffuse large B-cell lymphoma

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• **Mantle cell lymphoma**

• Burkitt lymphoma

• T-cell lymphomas
Mantle Cell Lymphoma

- Usually aggressive, though can be indolent

- Characteristic immunophenotype: CD5, CD19, CD20 positive (like CLL) but CD23-negative. Cyclin D1-positive.

- Genetic feature: t(11;14) between cyclin D1 locus and Ig heavy chain locus
FISH showing t(11;14)
Mantle Cell Lymphoma

**Therapy**

- Watchful waiting only rarely (elderly, indolent)

- Induction therapy options
  - R-bendamustine
  - VR-CAP
  - R-hyper CVAD
  - R-CHOP alternating DHAP

- Usually autologous transplantation offered in first remission

- Bortezomib, ibrutinib, and lenalidomide used in relapsed disease
Compared with R-CHOP, BR improves PFS in MCL.

Figure 3 Progression-free survival in histological subtypes of follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Waldenstrom's macroglobulinaemia (D) B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.

Mathias J Rummel, Norbert Niederle, Georg Maschmeyer, G Andre Banat, Ulrich von Grünhagen, Christoph Losem, ...

Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

The Lancet, Volume 381, Issue 9873, 2013, 1203 - 1210
http://dx.doi.org/10.1016/S0140-6736(12)61763-2
Replacement of vincristine with bortezomib leads to improved PFS in patients with newly diagnosed MCL.

Ibrutinib therapy results in a high response rate in patients with relapsed mantle cell lymphoma.

Table 3. Best Response to Therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Prior Treatment with Bortezomib (N = 63)</th>
<th>Prior Treatment with Bortezomib (N = 48)</th>
<th>All Patients (N = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>43 (68)</td>
<td>32 (67)</td>
<td>75 (68)</td>
</tr>
<tr>
<td>Complete</td>
<td>12 (19)</td>
<td>11 (23)</td>
<td>23 (21)</td>
</tr>
<tr>
<td>Partial</td>
<td>31 (49)</td>
<td>21 (44)</td>
<td>52 (47)</td>
</tr>
<tr>
<td>None†</td>
<td>20 (32)</td>
<td>15 (31)</td>
<td>35 (32)</td>
</tr>
<tr>
<td>Response duration — mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>15.8</td>
<td>NR</td>
<td>17.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.6–NR</td>
<td>NR–NR</td>
<td>15.8–NR</td>
</tr>
<tr>
<td>Progression-free survival — mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7.4</td>
<td>16.6</td>
<td>13.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.3–19.2</td>
<td>8.3–NR</td>
<td>7.0–NR</td>
</tr>
<tr>
<td>Overall survival — mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>95% CI</td>
<td>10.0–NR</td>
<td>11.9–NR</td>
<td>13.2–NR</td>
</tr>
</tbody>
</table>

* Response data included only those patients who received ibrutinib and had at least one postbaseline efficacy assessment. CI denotes confidence interval, and NR not reached.
† No response was defined as stable or progressive disease.

Lenalidomide + Rituximab for MCL: Efficacy


24-mos PFS: 84.6% (95% CI: 66.6% to 93.4%)
Median follow-up: 26 mos (range: 5-38)

24-mos OS = 92.4% (95% CI: 72.3% to 98.1%)
Median follow-up: 26 mos (range: 5-38)
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• Mantle cell lymphoma

• **Burkitt lymphoma**

• T-cell lymphomas
Burkitt Lymphoma

- Highly aggressive non-Hodgkin lymphoma
- 3 variants
  - Endemic (Africa)
  - Sporadic
  - Immune-deficiency-associated
- Characterized by translocation between chromosomes 8 and 14, which places MYC gene adjacent to Ig promoter region
- Historically treated with multi-agent chemotherapy regimens, as per ALL

Variants of EPOCH-R lead to favorable outcomes in patients with Burkitt lymphoma. Immune-deficiency-associated BL is shown in panels E-F.

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T-Cell Lymphoma

- Accounts for ~ 10% to 15% of all NHL
- Clinically and biologically heterogeneous group of disorders
- Classification relies on
  - Morphology
  - Immunophenotype
  - Clinical/anatomical presentation
- No recurrent genetic or molecular lesions
- Expert hematopathology review essential

International T-Cell Lymphoma Project: PTCL Subtype Distribution

- Peripheral T-cell lymphoma (N) 25.9%
- Angioimmunoblastic (N) 12.2%
- NK/T-cell lymphoma (E) 18.5%
- Adult T-cell leukemia/lymphoma (L) 10.4%
- ALCL, Alk+ (N) 9.6%
- ALCL, Alk- (N) 6.6%
- Enteropathy-associated T cell (E) 5.5%
- Primary cutaneous ALCL (Ec) 4.7%
- Hepatosplenic T cell (E) 9.6%
- Subcutaneous panniculitis-like (E) 1.7%
- Unclassifiable PTCL 1.4%
- Other disorders 0.9%
- Other disorders 2.5%

Majority of patients (> 85%) received an anthracycline-containing regimen

- Anaplastic large cell lymphoma, ALK+
- Anaplastic large cell lymphoma, ALK-
- All natural killer/T-Cell lymphomas
- Peripheral T-cell lymphoma, not otherwise specified
- Angioimmunoblastic lymphoma
- Adult T-cell leukemia/lymphoma

CHOP+ Etoposide: German High-Grade NHL Study Group Analysis

<table>
<thead>
<tr>
<th>PTCL Subtype</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCL, ALK+</td>
<td>78</td>
</tr>
<tr>
<td>ALCL, ALK-</td>
<td>113</td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>70</td>
</tr>
<tr>
<td>AITL</td>
<td>28</td>
</tr>
<tr>
<td>Other</td>
<td>31</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>320</strong></td>
</tr>
</tbody>
</table>

# Relapsed/Refractory PTCL: FDA-Approved Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose/Schedule</th>
<th>N</th>
<th>ORR, %</th>
<th>CR, %</th>
<th>DOR, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pralatrexate$^1$</td>
<td>30 mg/m$^2$/wk x 6</td>
<td>111</td>
<td>29*</td>
<td>11</td>
<td>10.1</td>
</tr>
<tr>
<td>Romidepsin$^2$</td>
<td>14 mg/m$^2$/wk x 3 q28 days</td>
<td>131</td>
<td>25</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Brentuximab vedotin (ALCL)$^3$</td>
<td>1.8 mg/kg q21 days</td>
<td>58</td>
<td>86</td>
<td>57</td>
<td>12.6</td>
</tr>
</tbody>
</table>

*ORR of 8% in AITL

Phase II Study: Brentuximab Vedotin for R/R Systemic ALCL

Best clinical response
- CR
- PR
- SD
- PD
- Histologically ineligible

Tumor Size (% Change From Baseline)

Individual Patients (N = 57)

Crizotinib in Advanced, Chemoresistant ALK+ Lymphoma Patients: Main Findings

- **At 40-mo follow-up**
  - 4 patients in CR under continuous crizotinib treatment
  - 2 patients with DLBCL and 2 with ALCL had disease progression and 3 died
  - 2-yr PFS: 63.7% (95% CI: 30.8-89.2)
  - 2-yr OS: 72.7% (95% CI: 39.1-94.0)


<table>
<thead>
<tr>
<th>Response, n(%)</th>
<th>Crizotinib (N = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>10 (90.5)</td>
</tr>
<tr>
<td>CR</td>
<td>9 (81.8)</td>
</tr>
<tr>
<td>PR</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>
Summary

• DLBCL
  – Standard therapy is R-CHOP
  – Promising new therapies include R-ACVBP, EPOCH-R
  – ABC subtype may be susceptible to bortezomib, lenalidomide, ibrutinib

• MCL
  – Standard is chemo followed by ASCT
  – Effective targeted therapies include bortezomib, lenalidomide, ibrutinib

• Burkitt lymphoma – EPOCH-R very effective

• Better understanding of biology leading to new therapies
Backup Slides
Survival by Subgroups in DLBCL

Diffuse Large B-Cell Lymphoma


<table>
<thead>
<tr>
<th>DLBCL Subgroup</th>
<th>5-Yr OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMBL</td>
<td>64</td>
</tr>
<tr>
<td>GCB DLBCL</td>
<td>59</td>
</tr>
<tr>
<td>ABC DLBCL</td>
<td>30</td>
</tr>
</tbody>
</table>
## Cytogenetic Changes Associated With Subgroups in DLBCL

<table>
<thead>
<tr>
<th>Cytogenetic Change, %</th>
<th>GCB DLBCL</th>
<th>ABC DLBCL</th>
<th>PMBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-Rel amplification</td>
<td>16</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Bcl-2 translocation</td>
<td>45</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Gain of 3q</td>
<td>0</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Gain/amplification of 9p24</td>
<td>0</td>
<td>6</td>
<td>43</td>
</tr>
<tr>
<td>Constitutive NF-κB activation</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Molecular Changes Associated With DLBCL

- Prevalence of genetic abnormalities
  - Recurring chromosomal translocations: ~ 50%
  - DNA imbalances: up to 67%

<table>
<thead>
<tr>
<th>Gene(s) Affected/Disregulated</th>
<th>Frequency, %</th>
<th>Predominant Causal Genetic Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple</td>
<td>45</td>
<td>Aberrant SHM</td>
</tr>
<tr>
<td>Bcl-6</td>
<td>35-40</td>
<td>3q27 translocations</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>13/24</td>
<td>t(14;18)/amplification</td>
</tr>
<tr>
<td>Fas(CD95)</td>
<td>20</td>
<td>10q24 mutations</td>
</tr>
<tr>
<td>p53</td>
<td>16</td>
<td>17p mutations/deletions</td>
</tr>
<tr>
<td>c-Myc</td>
<td>15</td>
<td>t(8;14) deregulation</td>
</tr>
<tr>
<td>Potentially c-Rel</td>
<td>14</td>
<td>2p13 amplification</td>
</tr>
</tbody>
</table>

**GELA Study Median Follow-up: 5 yrs**

**Event-Free Survival**
- R-CHOP: 3.8 yrs
- CHOP: 1.1 yrs
- \( P = .00002 \)

**OS**
- R-CHOP: 3.1 yrs
- CHOP: 
- \( P = .0073 \)

R-CHOP-14 vs R-CHOP-21 in Newly Diagnosed DLBCL (Phase III Study)

- **Primary endpoint:** OS
- **Secondary endpoint:** FFS, toxicity, response rates

Stratified by IPI score and age

- Newly diagnosed CD20+ DLBCL patients
  - (N = 1080)

- R-CHOP-14 x 6 cycles + Rituximab x 8 cycles + Lenogastim on Days 4-12
  - (n = 540)

- R-CHOP-21 x 8 cycles + Rituximab x 8 cycles
  - (n = 540)

Giving R-CHOP every 14 days instead of every 21 days has no impact on PFS (A) or OS (B).

Crizotinib in Advanced, Chemoresistant ALK+ Lymphoma Patients: Study Design

- Crizotinib monotherapy administered at 250 mg BID; until disease progression
- ALK+ NHL patients; N = 11
  - Diagnosed by immunohistochemistry and/or FISH
  - Median age: 28 yrs (range: 19-55 yrs)
    - ALCL: 9 patients
    - DLBCL: 2 patients
- Criteria
  - Refractory/relapsed disease after at least 1 prior chemotherapy regimen (median: 3, including 3 patients who received autologous BMT and 2 allogeneic BMT)
  - Measurable disease; all pts had involvement at multiple sites (nodal and extranodal), B symptoms
  - ECOG PS: 1-4; response to therapy assessed by RECIST