Welcome & Introductions

Dr. Roschewski’s slides are available for download at www.LLS.org/programs, under the program listing.

Information for Patients with Aggressive Lymphomas

Mark Roschewski, MD

CDR, Commissioned Corps, Public Health Service

Lymphoid Malignancies Branch, Center for Cancer Research

National Cancer Institute, National Institutes of Health

Bethesda, MD
Disclosures

Mark Roschewski, MD, has no affiliations with commercial interests to disclose.

Agenda

- Understand the current approach to DLBCL and BL
- Discuss strategies to overcome chemotherapy resistance
- Describe “precision medicine” approaches to aggressive NHL
- Introduce the role of circulating tumor DNA to monitor therapy
PTCL is far behind B-cell NHL in all 3 categories.

**Challenge of precision medicine**

- Biology of disease
- Pathologic classification
- Treatment

Outcomes by molecular subtype after R-CHOP

Outcomes by molecular subtype after DA-EPOCH-R


Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma

A Event-free Survival (NCI Patients)

B Overall Survival (NCI Patients)

Frontline treatment of DLBCL
Rituximab improves overall survival

Cure rate ~60%

**Coiffier et al. Blood 2010 Sep 23;116(12):2040-5**

---

**Pre-rituximab**

CHOP vs. m-BACOD, ProMACE-CytarBOM, or MACOP-B

CHOP-14, CHOEP-14, CHOP-21, or CHOEP-21

**CHOEP-21** benefits > 60 yrs and CHOP-14 ≤ 60 yrs

**CHOP remains standard**

**Improved outcome with R-CHOP**

**R-CHOP-21** vs. R-CHOP-14

R-CHOP not superior

**R-CHOP-14**

**Ongoing studies**

R-CHOP vs. DA-EPOCH-R

R-CHOP vs. DA-ECOPH-R

RB-CHOP vs. R-CHOP*

R-CHOP-I vs. R-CHOP*

R2-CHOP vs. R-CHOP

---

**Dunleavy, Roschewski, Wilson Clin Cancer Res 2014**

### CALGB 50303: R-CHOP vs. DA-EPOCH-R

**EFS**

- **HR:** 1.14 (95% CI: 0.82-1.61; P=0.4386)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events, n</th>
<th>3 Yrs (95% CI)</th>
<th>5 Yrs (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP</td>
<td>233</td>
<td>64</td>
<td>0.81 (0.75-0.86)</td>
<td>0.69 (0.62-0.76)</td>
</tr>
<tr>
<td>DA-EPOCH-R</td>
<td>232</td>
<td>70</td>
<td>0.79 (0.75-0.84)</td>
<td>0.66 (0.59-0.72)</td>
</tr>
</tbody>
</table>

**OS**

- **HR:** 1.18 (95% CI: 0.79-1.77; P=0.42)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events, n</th>
<th>3 Yrs (95% CI)</th>
<th>5 Yrs (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP</td>
<td>233</td>
<td>44</td>
<td>0.85 (0.80-0.89)</td>
<td>0.76 (0.70-0.81)</td>
</tr>
<tr>
<td>DA-EPOCH-R</td>
<td>232</td>
<td>50</td>
<td>0.85 (0.79-0.89)</td>
<td>0.74 (0.69-0.79)</td>
</tr>
</tbody>
</table>

*Median follow-up 5 yrs

Targeted therapy for ABC
Oncogenic activation of NF-κB in ABC DLBCL

Chronic Active BCR signaling

Constitutive MYD88 signaling

Forms covalent bond with cysteine-481 in BTK

High BTK specificity

IC$_{50}$ = 0.5 nM

Daily oral dosing produces 24-hr BTK inhibition

Blocks NF-κB activation in DLBCL cell lines$^{1,2}$

Ibrutinib: first in-class inhibitor of BTK
Blocking chronic active B-cell receptor signaling with through BTK

Ibrutinib (PCI-32765)

Ibrutinib selective for ABC DLBCL

Ibrutinib adds no toxicities to R-CHOP

Combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treatment-naive patients with CD20-positive B-cell non-Hodgkin lymphoma: a non-randomised, phase 1b study

Ibrutinib safe to add to R-CHOP at 560mg
Phase III study R-CHOP +/- ibrutinib accrued

Lenalidomide active in ABC DLBCL

<table>
<thead>
<tr>
<th>T-Cell Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation and proliferation</td>
</tr>
<tr>
<td>Immune synapse formation</td>
</tr>
<tr>
<td>CD8+ T-effector cell activity</td>
</tr>
<tr>
<td>Stimulation of cytotoxic CD8+ and helper CD4+ T cells</td>
</tr>
<tr>
<td>Dendritic cell antigen presentation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Malignant B-Cell Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>p21G1, AP-1</td>
</tr>
<tr>
<td>CDK2, CDK4, CDK6, Rb</td>
</tr>
<tr>
<td>Akt, Gab1 phosphorylation</td>
</tr>
<tr>
<td>G2/M, arrest, proliferation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NK-Cell Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number and activity of NK cells</td>
</tr>
<tr>
<td>Enhanced ADCC</td>
</tr>
<tr>
<td>Immune synapse formation and direct NK killing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microenvironment Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-inflammatory cytokines: IL-2, IL-8, IFN-γ, TNF-α</td>
</tr>
<tr>
<td>Inflammatory cytokines: IL-1, IL-6, IL-12, TNF-α</td>
</tr>
</tbody>
</table>


**Lenalidomide safely added to R-CHOP in DLBCL**

> R2-CHOP 2 year EFS of 59% in DLBCL


---

**Chronic active B-cell receptor signaling in rare lymphomas**

VIII. Figure 2: Meta-analysis of CD79B and MYD88 sequencing data in PCNSL

- PCNSL (n=213)
- MYD88 L265P (56%)
- CD79B ITAM (53%)
- Both (37%)
- 19%
- 17%
- 24%
Ibrutinib monotherapy in primary CNS lymphomas

Ibrutinib monotherapy (n=18)

- Relapsed/refractory
- Previously untreated

Ibrutinib + chemotherapy impressive responses in PCNSL

DA-TEDDI-R treatment (n=16)

Response (%)

Complete remission
Partial remission
Progressive disease

Prior treatment status:
- Refractory
- Untreated

Months on study:
- 0
- 3
- 6
- 9
- 12
- 15
- 18
- 21
- 24
- 27

Burkitt lymphoma

NCI Study: DA-EPOCH-R in adults with BL

7-year EFS 95%

NCI 9177: Pre-treatment categories

**Low-Risk**
- Stage I or II
- Normal LDH
- ECOG P.S. 0-1
- Mass size < 7cm

**High-Risk**
- All Other Patients

NCI 9177: Treatment schema

**Low Risk**
- DA-EPOCH-RR x 2
- CT-PET
- NO IT MTX

**High Risk**
- DA-EPOCH-R x 2
- CT-PET
- IT MTX

- DA-EPOCH-R x 4
- DA-EPOCH-RR x 1
- CT-PET
**NCI 9177: Event-free survival**

Median follow-up 35.7 months

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>EFS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>113</td>
<td>85.7%</td>
<td>(77.3-91.1)</td>
</tr>
</tbody>
</table>

**NCI 9177: Event-free survival in age groups**

Median follow-up 35.7 months

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>EFS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18-39</td>
<td>43</td>
<td>83.3%</td>
<td>(68.1-91.7)</td>
</tr>
<tr>
<td>Age 40-59</td>
<td>41</td>
<td>87.1%</td>
<td>(71.6-94.4)</td>
</tr>
<tr>
<td>Age 60+</td>
<td>29</td>
<td>87.4%</td>
<td>(65.2-95.8)</td>
</tr>
</tbody>
</table>
How can we monitor tumor response?

Monitoring the blood for tumor-specific molecules

Interim monitoring: early signs of resistance

Real-time tumor dynamics

Response: define molecular remissions

Complete molecular remission

Roschewski et al. Curr Treat Options Oncol. 2016 Sep;17(9):47
Surveillance monitoring: detect relapse earlier

Molecular relapse

3/27/2018

Window of opportunity

Cell-free DNA for as a “liquid biopsy”


Precision monitoring of ctDNA in lymphomas

Information for Patients with Aggressive Lymphomas

Q&A Session

**Ask a question by phone:**
- Press star (*) then the number 1 on your keypad.

**Ask a question by web:**
- Click “Ask a question”
- Type your question
- Click “Submit”

Due to time constraints, we can only take one question per person. Once you have asked your question, the operator will transfer you back into the audience line.
The Leukemia & Lymphoma Society Offers:

- **LLS Information Specialists:** Master’s level oncology professionals who can assist you through cancer treatment, financial and social challenges, and give accurate up-to-date disease, treatment, and support information.
  - EMAIL: infocenter@LLS.org
  - TOLL-FREE PHONE: 1-800-955-4572

- **Free Education Booklets:**
  - www.LLS.org/booklets

- **Free Telephone/Web Programs:**
  - www.LLS.org/programs

- **Live, Weekly Online Chats:**
  - www.LLS.org/chat

---

The Leukemia & Lymphoma Society Offers:

- **Support Resources:** LLS Community, discussion boards, blogs, support groups, financial assistance, and more: www.LLS.org/support

- **LLS Podcast, The Bloodline with LLS:** Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: www.thebloodline.org

- **Education Video:** Free education videos about survivorship, treatment, disease updates, and other topics: www.LLS.org/educationvideos

- **Patti Robinson Kaufmann First Connection Program:** Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection

- **Free Nutrition Consults:** Telephone and email consultations with a Registered Dietitian: www.LLS.org/nutrition

- **What to ask:** Questions to ask your treatment team: www.LLS.org/whatask
THANK YOU FOR PARTICIPATING!

We have one goal:
A world without blood cancers