Diffuse Large B-Cell Lymphoma
– Front line Therapy
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Disclosures

Consulting advice:

Hospira, Bayer, Juno Therapeutics, Teva, Oncotracker, Gilead Sciences, Celgene, Kite Pharma, Nanostring, Genmab
Diffuse large B cell lymphoma

- Median age 60, usually with advanced stage disease
  - LAN, extranodal disease, symptoms
- Practical objective of treatment – cure (70%)
- Reasonably good clinical prognostic tools
- Most patients treated same (R-CHOP)
- Unmet need – more cures, reduce toxicity
- Who should we treat differently?
- If refractory to second-line therapy, prognosis is poor
Treatment algorithm for DLBCL

CHOP-R (100%) (DA-R-EPOCH)

Cure (60-70%)  Relapsed/Refractory (30-40%)

2nd line therapy
R-ICE, R-DICE, R-DHAP, etc

Transplant eligible (20-25%)  Transplant ineligible (10-15%)

ASCT + HDC

Cure (5%)  Relapse (15-20%)  Relapse (10-15%)

3rd line or later therapy (25-35%)
## Comparison of CHOP-R and EPOCH-R

<table>
<thead>
<tr>
<th>R-CHOP</th>
<th>DA*-R-EPOCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab 375 mg/m² d1</td>
<td>Rituximab 375 mg/m² d1</td>
</tr>
<tr>
<td>Cyclophosphamide 750 mg/m² d1</td>
<td>Etoposide 50 mg/m²/d CI d1-4*</td>
</tr>
<tr>
<td>Doxorubicin 50 mg/m² d1</td>
<td>Doxorubicin 10 mg/m²/d CI d1-4*</td>
</tr>
<tr>
<td>Vincristine 1.4 mg/m² (2 mg cap) d1</td>
<td>Vincristine 0.4 mg/m²/d CI d1-4</td>
</tr>
<tr>
<td>Prednisone 40 mg/m² d1-5</td>
<td>Cyclophosphamide 750 mg/m² d5*</td>
</tr>
<tr>
<td>q3w x 6</td>
<td>Prednisone 60 mg/m² bid d1-4</td>
</tr>
<tr>
<td></td>
<td>G-CSF 5 μg/kg d6-ANC recovery</td>
</tr>
<tr>
<td></td>
<td>q3w x 6</td>
</tr>
</tbody>
</table>

* Doses increased or decreased based on degree of neutropenia.
International Prognostic Index (IPI) in aggressive NHL

Prognostic factors (APLES)
- Age > 60 years
- Performance status > 1
- LDH × normal
- Extranodal sites > 1
- Stage III or IV

Risk Category Factors
- Low (L) 0 or 1
- Low intermediate (LI) 2
- High intermediate (HI) 3
- High (H) 4 or 5

OS

Patients (%)

Years

What does the physician need or want to know when approaching a new DLBCL patient?

- **Clinical features**
  - International Prognostic Index, Stage
  - Primary mediastinal (R-EPOCH)
  - CNS, HIV, testicular (variations of rx)
- **Pathological and molecular features**
  - BM involvement (variations of rx)
  - Double hit (FISH) > Double protein (R-EPOCH)
  - Cell of origin (Germinal Center/Activated B Cell)
Double hit vs Double protein DLBCL
10-20% of DLBCL

- Double-hit lymphoma: High-grade B-cell lymphoma with translocations of MYC as well as BCL2, BCL6, or both (“triple-hit”)
  - Histologically classified as DLBCL or B-cell lymphoma unclassifiable with intermediate features between DLBCL and Burkitt Lymphoma
  - Cell of origin: Virtually always germinal center subtype
  - Outcome poor with standard therapies

- Double-expressing lymphomas: DLBCL with dual immunohistochemical expression of MYC (≥40%) and BCL2 (≥70%) in the absence of translocations
  - Cell of origin: Usually activated B cell subtype
  - Outcome inferior to other DLBCLs, but not as poor as DHL
Caveats in understanding clinical characteristics and outcomes in “double hit and double protein” lymphoma

- Clinical features of the subtype are less favorable
- Selection biases of series
- Variability in molecular testing
- Challenges and changes in morphologic/pathologic classification
- Non-uniform therapy
- Single vs multicenter
- Retrospective
FISH DH DLBCL and treatment with R-CHOP

Green et al, JCO 2012
DA-EPOCH-R in double hit lymphoma

Petrich et al Blood 2014
Oki et al BJH 2014
Planned Intergroup Trial in DH/DP DLBCL
Phase I then Phase II-III
BCL-2 inhibitor Venetoclax

Untreated DHL/DPL

DA-EPOCH-R

DA-EPOCH-R + Venetoclax (ABT199)

Ph I Investigator-initiated study (Alliance Foundation) WCM/NYP Coordinating Site (Rutherford)
Phase II/III NCI/Alliance/Intergroup (Abramson MGH)
What about new approaches in DLBCL?

- Strategies under investigation independent of cell of origin
- Strategies targeting specific cell of origin subtype
Roche GOYA Phase III: Study Design

Previously untreated DLBCL (N = 1,400)

Randomize

GA101 x 8 cycles + CHOP x 6 or 8

Rituximab x 8 cycles + CHOP x 6 or 8

GA101: 1,000 mg d1, d8, d15, cycle 1; d1, cycles 2–8, every 21 days
Rituximab: 375 mg/m² d1, cycles 1–8, every 21 days

Roche press release 7/16 – did not meet primary endpoint

Other negative studies of “unselected” DLBCL patients
R-CHOP + (maintenance) enzastaurin, everolimus, lenalidomide
Alliance/CALGB 50303: R-CHOP vs R-EPOCH in Newly Diagnosed DLBCL

- Primary endpoints: EFS, molecular predictors of outcome for each regimen
- Secondary endpoints: RR, OS, toxicity, use of molecular profiling

To be presented, ASH 2016

What about new approaches in DLBCL?

- Strategies under investigation independent of cell of origin
- Strategies targeting specific cell of origin subtype
Germinal Center vs Activated B Cell DLBCL

Dissecting a Cancer into Molecularly and Clinically Distinct Subgroups by Gene Expression Profiling

IHC surrogate (Hans) - CD10, bcl-6, MUM-1
GCB vs “non-GCB”

Outcome by GCB vs ABC gene signatures in DLBCL
N=233 patients treated with R-CHOP

Oncogenic mechanisms and potential therapeutic targets in GCB and ABC DLBCLs

<table>
<thead>
<tr>
<th>DLBCL subtype</th>
<th>Cell of origin</th>
<th>Oncogenic mechanisms</th>
<th>Potential targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCB</td>
<td>Germinal centre B-cell</td>
<td><em>BCL2 translocation</em></td>
<td>BCL6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‡<em>EZH2 mutations</em></td>
<td>EZH2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>§<em>PTEN deletions</em></td>
<td>PI3K/Akt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of PTEN expression</td>
<td></td>
</tr>
<tr>
<td>ABC</td>
<td>Post-germineral centre B-cell</td>
<td><em>NF-κB activation</em></td>
<td>BCR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‡<em>CARD11 mutations</em></td>
<td>CBM complex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>¶<em>MYD88 mutations</em></td>
<td>IRAK-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>¶<em>CD79B mutations</em></td>
<td>JAK–STAT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>¶<em>A20 deletions</em></td>
<td></td>
</tr>
</tbody>
</table>

Upfront DLBCL – Novel agent/regimen in specific clinical or molecular patient subsets

Study design

- **Subset 1**
  - CHOP-R

- **Subset 2**
  - Other regimen

- **CHOP-R**

- **Other regimen**

DLBCL
ABC DLBCL-associated signaling

Ibrutinib in relapsed DLBCL patients with ABC versus GCB subtype

<table>
<thead>
<tr>
<th></th>
<th>ABC subtype (N=29)</th>
<th>GCB subtype (N=20)</th>
<th>Unclassifiable 1 (N=16)</th>
<th>Unknown2 (N=5)</th>
<th>Total (N=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Evaluable for Response</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>PP ORR4 (CR + PR)</td>
<td>10 (40%)</td>
<td>1 (5.3%)</td>
<td>0</td>
<td>2 (66.7%)</td>
<td>13 (21.7%)</td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>2 (8%)</td>
<td>0</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>8 (32%)</td>
<td>1 (5.3%)</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>10 (16.7%)</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>2.5</td>
<td>1.28</td>
<td>0.95</td>
<td>NR3</td>
<td>1.64</td>
</tr>
</tbody>
</table>

N=70
Median age=63
Median prior treatments=3 (range 1-7)
IPI high-intermediate/high risk 59%

Upfront DLBCL – Novel agent/regimen in specific clinical or molecular patient subsets

Study design

- **GCB**
  - CHOP-R

- **Non-GCB**
  - CHOP-R
  - Ibrutinib + CHOP-R

Other regimen

**CHOP-R**
Alliance 51301 Study Schema

**Randomization**
Stratify by time to relapse, conditioning regimen

- **Arm A**
  - Relapsed/Refractory DLBCL-ABC
  - Salvage ≥PR, stem cells collected
  - ASCT: CBV or BEAM
  - Ibrutinib 560 mg + Ibrutinib x 12 months
  - Follow Up

- **Arm B**
  - ASCT: CBV or BEAM
  - Placebo x 12 months
  - Follow Up

Crossover if Progression
ABC DLBCL-associated signaling

Response to Lenalidomide in Relapsed and Refractory DLBCL Based on Subtype

- Retrospective analysis of patients with relapsed DLBCL treated with lenalidomide as a single agent or in combination with rituximab/steroids at several institutions (N=56) suggests activity in the non-GCB subset.

Hernandez-Illizaliturri et al. Cancer 2011
Upfront DLBCL – Novel agent/regimen in specific clinical or molecular patient subsets

Study design

- GCB
  - CHOP-R

- Non-GCB
  - CHOP-R
  - Lenalidomide + CHOP-R
  - Other regimen
ABC DLBCL-associated signaling

ABC DLBCL is associated with high expression of target genes of NF-kB

Investigator-Initiated Trial of R-CHOP+bortezomib in DLBCL
Similar PFS and OS in GCB and non-GCB

N=40

GCB N=14
Non-GCB N=18

2Y PFS 64%
2Y OS 70%

Randomized phase 2 open-label study of R-CHOP ± bortezomib in patients with untreated non-germinal center B-cell-like subtype diffuse large cell lymphoma: Results from the PYRAMID trial (NCT00931918) ASH 2015

**Study design**

- **Arm A (n=95)**
  - Bortezomib 1.3 mg/m² IV, Days 1 and 4
  - R-CHOP† 21 X 6 cycles

- **Arm B (n=95)**
  - R-CHOP† 21 X 6 cycles

**Previously untreated DLBCL**
- Measurable disease
- ECOG PS 0–2

**Non-GCB Selection**
- Assay/scoring in real time at central US lab*
- Hans method¹
  (CD10, bcl-6, MUM-1)
- 48–72 hour turnaround
- Retrospective molecular analyses

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*Local IHC testing by certified local pathologists was also employed, confirmed by central review;
†R-CHOP standard dose (rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² [max 2 mg], all IV on Day 1, and prednisone 100 mg PO on Days 1–5)
## Demographics and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP N=91*</th>
<th>VR-CHOP N=92*</th>
<th>Total N=183*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>62 (24–85)</td>
<td>65 (20–83)</td>
<td>64 (20–85)</td>
</tr>
<tr>
<td>Age &gt;65 years, %</td>
<td>44</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>Male, %</td>
<td>58</td>
<td>49</td>
<td>54</td>
</tr>
<tr>
<td>IPI Risk Group, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>24</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Low/Intermediate</td>
<td>25</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>High/Intermediate</td>
<td>38</td>
<td>34</td>
<td>36</td>
</tr>
<tr>
<td>High</td>
<td>12</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>LDH &gt; ULN, %</td>
<td>55</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>ECOG PS 0/1/2, %</td>
<td>44/44/12</td>
<td>59/40/1</td>
<td>52/42/7</td>
</tr>
</tbody>
</table>

*mITT population*
Overall response rate

*Response-evaluable population (confirmed non-GCB DLBCL, measureable disease and at least one post-baseline response assessment); response assessments based on the 2007 Revised Response Criteria for Malignant Lymphoma†; †Investigator-assessed
Progression-Free Survival

- 2-year PFS: 78% R-CHOP vs 82% VR-CHOP HR (95% CI): 0.73 (0.43, 1.24); p=0.611
PFS by IPI Risk Group

**Low/Low-Intermediate:** 2-year PFS, 90% R-CHOP vs 89% VR-CHOP

HR (95% CI): 0.85 (0.35, 2.10)

p = 0.958

**High-Intermediate/High:** 2-year PFS, 65% R-CHOP vs 72% VR-CHOP

HR (95% CI): 0.67 (0.34, 1.29)

p = 0.606
Overall Survival

2-year OS: 88% R-CHOP vs 93% VR-CHOP
- HR (95% CI), 0.75 (0.38, 1.45); p=0.763
A Prospective Randomised Trial of Targeted Therapy for Diffuse Large B-Cell Lymphoma (DLBCL) Based upon Real-Time Gene Expression Profiling
The REMoDL-B Study of the UK NCRI and SAKK Lymphoma Groups

Patients with DLBCL in need of full course R-CHOP (stage II\textsubscript{A}-IV)

- Consent
- Biopsy sent to HMDS for molecular profiling
- R-CHOP #1
- Randomisation Stratified for molecular phenotype and IPI
- 5x R-CHOP + bortezomib 1.3mg/m\textsuperscript{2} days 1+8
- 5x R-CHOP

Follow-up

Davies et al, ASH 2015
Progression-free survival by molecular profile

Davies et al, ASH 2015

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FAIL (n=159)</th>
<th>ABC (n=248)</th>
<th>GCB (n=477)</th>
<th>Unc. (n=201)</th>
<th>Total (n=1085)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS at 12 months – % (95% CI)</td>
<td>79.3 (71.2, 85.4)</td>
<td>76.0 (73.0, 83.9)</td>
<td>79.5 (75.3, 83.1)</td>
<td>77.6 (70.2, 83.4)</td>
<td>79.0 (76.2, 81.5)</td>
</tr>
<tr>
<td>OS at 24 months – % (95% CI)</td>
<td>70.5 (61.0, 78.1)</td>
<td>68.9 (61.5, 75.1)</td>
<td>75.0 (70.2, 79.1)</td>
<td>67.8 (58.1, 75.8)</td>
<td>71.7 (68.4, 74.8)</td>
</tr>
<tr>
<td>No. of events observed</td>
<td>28</td>
<td>36</td>
<td>51</td>
<td>23</td>
<td>136</td>
</tr>
<tr>
<td>Proportion of patients with an event</td>
<td>17.9%</td>
<td>14.7%</td>
<td>10.7%</td>
<td>11.6%</td>
<td>12.8%</td>
</tr>
<tr>
<td>Median follow up, in months (95% CI)</td>
<td>16.9 (14.3, 24.7)</td>
<td>17.2 (15.8, 21.6)</td>
<td>16.5 (15.7, 17.7)</td>
<td>14.3 (12.9, 15.8)</td>
<td>16.3 (15.7, 17.0)</td>
</tr>
</tbody>
</table>
Comparison of R-CHOP in ABC/Non-GCB Retrospective vs Prospective studies

- **Retrospective (Lenz, NEJM 2008)**
  - 2-year PFS 40% ABC by GEP with R-CHOP, GCB > ABC subtype

- **Prospective**
  - 2-year PFS 80% non-GCB by IHC with R-CHOP

Spectrum of ABC/Non-GCB DLBCL patients

Less Favorable  |  More Favorable

Randomized in an unselected patient population or Assessed retrospectively (as in Lenz)

“Standard outcome”
Spectrum of ABC/Non-GCB DLBCL patients

Less Favorable  More Favorable

Excluded due to concerns about delays/risk

Randomized in a selected patient population (patients who could wait for screening/enrollment)

“Favorable outcome”
Some reasons why demonstrating benefits of DLBCL precision medicine may be challenging

- Targeted drug might not be effective
- Assay used to define subsets may not be sufficiently robust or rapid
- Patient selection issues

How do we go forward?

- Control groups
- Improved drugs and better/faster biomarker assays
- Innovative study designs