Disclosure

- Speaker’s Bureau for Seattle Genetics
- Advisory Board for Gilead and Seattle Genetics
- OFF Label use lenalidomide, ibrutinib, bortezomib
Objectives

- Review the histology, cell of origin and molecular profile
- Review the prognostic factors
- Update on the treatment
- Treatment of relapse
- Role of stem cell transplant
Most Common NHLs

- DLBCL, 31%
- FL, 22%
- MALTL, 8%
- MCL, 6%
- SLL/CLL, 7%
- PTCL, 7%
- ALCL, 2%
- PMLBCL, 2%
- MZL, nodal, 2%
- T-LL, 2%
- Other, 9%

EPIDEMIOLOGY OF DLBCL

- The most common lymphoma accounts for 25-30% of all NHLs in the developed world
- The incidence of DLBCL is 7 cases per 100,000 persons per year in US and England
- Incidences varies by Ethnicity, caucasian > Black > Asians > American Indian
- DLBCL is the most frequent subtype in central and South America, account for 40% of NHL
- Male predominance, 55% of cases
- Incidence increases with age, median age 64 years
- Familial aggregation of DLBCL and other NHL subtypes has been noted.
# Overview of DLBCL

## Morphology
- Centroblastic, immunoblastic, T-cell/histiocyte rich, or anaplastic

## Immuno-phenotyping
- Pan B-cell antigens (CD19, CD20, CD22, CD79a), CD45
- 50-75% express surface or cytoplasmic Ig(IgM)
- CD30+ in 25% (anaplastic), CD5 + rare

## Genetic features
- t(14;18) BCL2 oncogene (10% - 25% of cases)
  - but 60% overexpress bcl2 protein
- der 3q27 BCL6 oncogene (35% of cases)
- t(8;14) C-MYC oncogene (5-15%)

## Clinical features
- Aggressive behavior
- Heterogeneous clinical response
SUBTYPES

Subtypes included:
- DLBCL, NOS
- DLBCL coexistent with follicular lymphoma of any grade
- DLBCL coexistent with gastric MALT lymphoma
- DLBCL coexistent with nongastric MALT lymphoma
- Follicular lymphoma grade 3
- Intravascular large B-cell lymphoma
- DLBCL associated with chronic inflammation
- ALK-positive DLBCL
- EBV-positive DLBCL of the elderly
- T-cell-/histiocyte-rich large B-cell lymphoma

Subtypes not included:
- Primary cutaneous B-cell lymphomas (See CUTB-1)
- Primary DLBCL of the CNS (See NCCN Guidelines for CNS)

Primary Mediastinal Large B-Cell Lymphoma (PMBL), see BCEL-B 1 of 3.
Grey Zone Lymphoma, see BCEL-B 2 of 3.
Double Hit Lymphomas, see BCEL-B 3 of 3.

See Workup (BCEL-2)
Hans and Tally methods for determining cell of origin in diffuse large B cell lymphoma

**Hans algorithm**[1]

- **CD10**: (+) → GCB
  - (-) → BCL6
    - (+) → MUM1
    - (-) → Non-GCB
  - (-) → Non-GCB
- **MUM1**: (+) → Non-GCB
  - (-) → GCB

**Tally method**[2]

1. Measure GCB markers: CD10 (+ or -) and GCET1 (+ or -)
2. Measure ABC markers: MUM1 (+ or -) and FOXP1 (+ or -)
   (For each of the above, score 1 point for "+" and 0 points for "-"
3. Compare GCB score versus ABC score:
   - if GCB > ABC, then classify as GCB
   - if GCB < ABC, then classify as ABC
   - if GCB = ABC, then measure LMO2:
     - if LMO2 ≥30%, then classify as GCB
     - if LMO2 <30%, then classify as ABC

The Hans algorithm and Tally method use immunohistochemical stains to predict the cell of origin (GCB versus ABC or non-GCB) for cases of diffuse large B cell lymphoma. Each is approximately 80% concordant with gene expression profile results.

**DLBCL**: diffuse large B cell lymphoma; **GCB**: germinal center B cell; **ABC**: activated B cell.

**References:**

Prognostic Subgroups in DLBCL

DNA microarray analysis can be used to predict survival after chemotherapy

Key oncogenic pathways in DLBCL. The 2 major molecular subtypes of DLBCL are shown: the GCB and the ABC type.

GCB
- **Histone modification**
  - EZH2 mutations
  - MLL2 mutations
  - CREBBP mutations
  - EP300 mutations
- **Blocks to terminal differentiation**
  - BCL6 expression, EZH2 mutations
- **Cell cycle activation +/- blocks to apoptosis**
  - MYC and BCL2 translocations (DHI1) and protein over-expression
- **MTOR pathway activation**
- **Signaling cascades**
  - PTEN del/loss (PI3K and AKT activation)

ABC
- **BCR/NF-κB signaling**
  - CD79A/B, CARD11, MYD88 mutations, TNFAIP3 (A20) deletions
- **Histone modification**
  - MLL2 mutations
  - CREBBP mutations
  - EP300 mutations
- **Blocks to terminal differentiation**
  - BCL6 translocations, PRDM1 loss/mutations
- **Cell cycle activation +/- blocks to apoptosis**
  - MYC translocations, MYC and BCL2 protein over-expression
- **MTOR pathway activation**
- **Signaling cascades**
  - PI3K and AKT activation
- **Cytokine signaling/JAK-STAT pathway activation**

Laurie H. Sehn, and Randy D. Gascoyne Blood
2015;125:22-32
Diffuse large B-cell lymphoma with a majority of cells staining for the Ki-67 proliferative index, indicative of rapid growth. Ki67/peroxidase stain.

Identify Disease Subtype

- Molecular risk assessment should be performed in all cases including
  - Evaluation for c-MYC, BCL-2, BCL-6 by IHC or FISH
  - Evaluation of cell of origin by IHC (Hans Algorithms), or Lymph2Cx platform, or gene expression profile
  - Subclassify cases into
    - GCB
    - ABC (non-GCB)
    - Double-Hit DLBCL
    - Double Expressor DLBCL
## Diagnostic features of DLBCL, BL and B-cell lymphoma unclassifiable with features intermediate between DLBCL and BL (“gray zone”)

<table>
<thead>
<tr>
<th></th>
<th>DLBCL</th>
<th>gray zone</th>
<th>BL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphology</strong></td>
<td>Variable, ranging from medium-sized to large, pleomorphic nuclei with a large morphological range</td>
<td>BL-like morphology with or without large cells</td>
<td>Cohesive, starry-sky, medium-sized, round nuclei with multiple small nucleoli</td>
</tr>
<tr>
<td><strong>Immunophenotype</strong></td>
<td>BCL-2, CD10, BCL-6, MUM-1 highly variable Ki-67 30-&gt;95%</td>
<td>BCL-2 often strong, CD10 mostly+, BCL-6 mostly +, MUM-1 variable Ki-67 50-&gt;95%</td>
<td>BCL-2-, CD10+, BCL-6+, MUM-1 variable Ki-67 &gt; 95%</td>
</tr>
<tr>
<td><strong>MYC translocation</strong></td>
<td>5-15%</td>
<td>80%</td>
<td>90-100%</td>
</tr>
<tr>
<td><strong>Non/G partner</strong></td>
<td>40%</td>
<td>40%</td>
<td>None</td>
</tr>
<tr>
<td><strong>BCL2 translocation</strong></td>
<td>20-30%</td>
<td>45%</td>
<td>No</td>
</tr>
<tr>
<td><strong>BCL6 translocation</strong></td>
<td>30%</td>
<td>9%</td>
<td>No</td>
</tr>
<tr>
<td><strong>Simple karyotype</strong></td>
<td>Rarely</td>
<td>Rarely</td>
<td>Typical</td>
</tr>
<tr>
<td><strong>Complex karyotype</strong></td>
<td>Generally</td>
<td>Generally</td>
<td>No</td>
</tr>
</tbody>
</table>
Diffuse Large B-Cell Lymphoma

WORKUP

ESSENTIAL:
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Uric acid
- PET-CT scan ± chest/abdominal/pelvic CT with contrast of diagnostic quality
- Adequate bone marrow biopsy (>1.6 cm) ± aspirate; bone marrow may not be needed if PET scan negative unless finding of another lymphoma subtype is important for treatment decision
- Calculation of International Prognostic Index (IPI) (See BCEL-A 1 of 2)
- Hepatitis B testing
- MUGA scan/echocardiogram if anthracycline or anthracyclene-based regimen is indicated
- Pregnancy testing in women of child-bearing age

USEFUL IN SELECTED CASES:
- Neck CT, head CT, or MRI
- Discussion of fertility issues and sperm banking
- HIV
- Lumbar puncture, consider if have 4–6 factors according to prognostic model (See BCEL-A 2 of 2), HIV lymphoma, testicular, double expressor lymphoma
- Beta-2-microglobulin
Diffuse Large B-Cell Lymphoma

STAGE

Nonbulky (<7.5 cm) → RCHOPn x 3 cycles + RT (category 1) or RCHOP x 6 cycles ± RT → See Pre RT Evaluation (BCEL-4)

Stage I, II

Bulky (≥7.5 cm) → RCHOP x 6 cycles ± RT → See Pre RT Evaluation (BCEL-4)

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## CHOP Plus Radiotherapy for Early-stage DLBCL

### ECOG trial (Glick J et al; Horning S et al)
- Stage I bulky and stage II
- CHOP (6-8 cycles) followed by RT vs CHOP in patients with CR to CHOP
- At 10 years, DFS and TTP favored CHOP-RT, but disease-specific survival was 81% in both treatment arms

### SWOG trial (Miller TP et al)
- Stage I and II, non-bulky
- CHOP (3 cycles) plus RT vs CHOP (8 cycles)
- At 9 years, DFS and TTP favored CHOP-RT, with less toxicity, but OS was similar

### GELA trial (Fillet G et al)
- Elderly, IPI = 0
- CHOP (4 cycles) plus RT vs CHOP x 4
- No improvement in CR, 5-year EFS, or 5-year OS
## Stage Adjusted International Prognostic Index
### Stage I and II

<table>
<thead>
<tr>
<th>Factors</th>
<th>IPI group</th>
<th>No. of risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60</td>
<td>Low</td>
<td>0 or 1</td>
</tr>
<tr>
<td>LDH &gt; normal</td>
<td>Low</td>
<td>0 or 1</td>
</tr>
<tr>
<td>PS 2-4</td>
<td>High</td>
<td>2-4</td>
</tr>
<tr>
<td>Stage II or IIE</td>
<td>Low</td>
<td>0 or 1</td>
</tr>
</tbody>
</table>
British Columbia Cancer Agency
PET-Based therapy for limited-stage DLBCL

Sehn LH, Cancer 2012: 18, 421-426
Treatment of Advanced Stage DLBCL

- R-CHOP is the standard regimen
- Other regimens: DA-EPOCH-R, R-ACVBP (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone)
- Older patients > 80 years old: R-miniCHOP
- Patients who can not receive anthracycline: R-CEOP, R-CEPP, or R-GCVP
- Clinical trials
- Autologous Stem cell transplant during 1CR in selected high-risk IPI cases
CHOP for Advanced-stage DLBCL: The Former Standard

- CHOP was as effective as second- and third-generation chemotherapy regimens, with less toxicity
- 50% to 60% remained uncured

First-line R-CHOP for DLBCL

- Previously untreated DLBCL > 60 yrs patients were randomized to CHOP (8 cycles) plus rituximab (R-CHOP) or CHOP alone
- Median follow-up: 24 months
- R-CHOP was superior to CHOP

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>R-CHOP (n = 202)</th>
<th>CHOP (n = 197)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (%)</td>
<td>76</td>
<td>63</td>
<td>0.005</td>
</tr>
<tr>
<td>Progression (%)</td>
<td>43</td>
<td>61</td>
<td>0.002</td>
</tr>
<tr>
<td>EFS (%)</td>
<td>57</td>
<td>38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-year OS (%)</td>
<td>70</td>
<td>57</td>
<td>0.007</td>
</tr>
</tbody>
</table>

First-line R-CHOP for DLBCL

- EFS and OS significantly greater with R-CHOP vs CHOP
- Incidence of severe or serious adverse events similar in 2 arms

Disease-free survival in patients treated with CHOP and R-CHOP - 10 yrs F/U

R-CHOP Improved Survival of Patients With DLBCL in British Columbia

Progression-Free Survival by Treatment Era: Elderly Patients ≥ Age 60 Years (n = 294)

Progression-Free Survival by Treatment Era: Young Patients < Age 60 Years (n = 127)

# Phase 3 Trials Evaluating Alternative Regimens to R-CHOP 21

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Regimens</th>
<th>Outcome</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recher et al</td>
<td>380</td>
<td>R-ACVBP</td>
<td>3-year PFS 87% vs 73%</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vs R-CHOP</td>
<td>3-year OS 92% vs 84%</td>
<td>.007</td>
</tr>
<tr>
<td>Cunningham et al</td>
<td>1080</td>
<td>R-CHOP 14</td>
<td>2-year PFS 75% vs 75%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vs R-CHOP</td>
<td>2-year OS 83% vs 81%</td>
<td>NS</td>
</tr>
<tr>
<td>Delarue et al</td>
<td>602</td>
<td>R-CHOP 14</td>
<td>3-year EFS 56% vs 60%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vs RCHOP</td>
<td>3-year OS 83% vs 72%</td>
<td>NS</td>
</tr>
</tbody>
</table>
Rituximab Maintenance in DLBCL: ECOG 4494

ECOG, CALGB, SWOG intergroup phase 3 trial

**Elderly:** Diffuse large B-cell lymphoma

**Stratify by number of risk factors:** 0-1 vs 2, 3, 4

**Randomized**

- **CHOP**
  - every 21 days (6–8 cycles)
  - (n = 314)

- **CHOP + Rituximab**
  - every 21 days (6–8 cycles)
  - (n = 318)

**Restaging**

- Stratify by CR vs PR

**Randomized**

- **Rituximab Maintenance**
  - Rituximab 375 mg/m² x 2 years
  - (n = 207)

- **Observation**
  - (n = 208)

Maintenance Therapy
Evaluable CR/PR Patients: TTF

Evaluatable Patients, n = 352

Graph courtesy of Michael Williams, MD.
Conclusions: ECOG 4494
R-CHOP vs CHOP

- Addition of rituximab to induction CHOP did not influence RR or early (6-month) progression
- Induction R-CHOP (followed by MR or observation) significantly prolonged TTF
- MR significantly prolonged TTF in responders, but only in patients with CHOP induction
  - No benefit for MR if R-CHOP induction
- No statistically significant differences in OS observed with median follow-up of 2.7 years

Original Article

Autologous Transplantation as Consolidation for Aggressive Non-Hodgkin's Lymphoma


N Engl J Med
Volume 369(18):1681-1690
October 31, 2013
Survival Rates among All Eligible Patients Who Underwent Randomization.

CHOP ± R x 6 cycles

CR/PR

CHOP ± R x2

HDT + ASCT

Survival Rates among Eligible Patients Who Underwent Randomization, According to IPI Risk Category.
Which patients should receive CNS prophylaxis?

- Should be given in patients with testicular, epidural, or sinus involvement.
  - Should be considered in patients with breast, ovarian, bone marrow involvement, high IPI or numerous extranodal sites of diseases.
- Novel prognostic scores from BC and German High Grade lymphoma study group using IPI risk factors including
  - age > 60, LDH> norma ,PS>1, stage 3-4, >1 extranodal site and Renal or adrenal gland involvement
- Which Prophylaxis? Depending on the chemotherapy
  - IT chemotherapy given with each cycle
  - Systemic high-dose MTX 3.5 gm/m2 with leucovorin rescue at day +15 on cycle 2,4.and 6, or at completion of induction chemotherapy
Prognostic Model to Assess the Risk of CNS Disease

- Age >60 years
- Serum LDH > normal
- Performance status >1
- Stage III or IV
- Extranodal involvement >1 site
- Kidney or adrenal gland involvement

<table>
<thead>
<tr>
<th>No. of risk factors</th>
<th>2-year CNS relapse risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>0.8%</td>
</tr>
<tr>
<td>2-3</td>
<td>3.9%</td>
</tr>
<tr>
<td>4-6</td>
<td>12%</td>
</tr>
</tbody>
</table>

Low risk 0–1
Intermediate-risk 2–3
High-risk 4–6

Prognostic Factors for DLBCL

- Clinical factors: International Prognostic Index (IPI), Absolute lymphocyte and monocyte count
- Functional Imaging: FDG PET
- Immunohistochemistry for cell of origin, Germinal center B-cell (GCB) vs. activated B-Cell (ABC) using Hans algorithm
- Gene expression profile for cell of origin
- Molecular factor, FISH for MYC and BCL2 rearrangement
- Provisional prognostic factors
  - Free light chain
  - Serum 25-hydroxyl vitamin D levels
  - Serum cytokines/chemokines
## International Prognostic Index (IPI)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adverse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;60 years</td>
</tr>
<tr>
<td>PS</td>
<td>≥2</td>
</tr>
<tr>
<td>LDH</td>
<td>&gt;Normal</td>
</tr>
<tr>
<td>Extranodal sites</td>
<td>≥2</td>
</tr>
<tr>
<td>Stage</td>
<td>III-IV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Number of Factors Present</th>
<th>5-year DFS (%)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>Low/Intermediate</td>
<td>2</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>High/Intermediate</td>
<td>3</td>
<td>49</td>
<td>43</td>
</tr>
<tr>
<td>High</td>
<td>4-5</td>
<td>40</td>
<td>26</td>
</tr>
</tbody>
</table>

### Age-Adjusted

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adverse</th>
<th>Number of Factors Present</th>
<th>5-year OS Age&gt;60 (%)</th>
<th>5-year OS Age≤60 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS</td>
<td>≥2</td>
<td>0</td>
<td>56</td>
<td>83</td>
</tr>
<tr>
<td>LDH</td>
<td>&gt;Normal</td>
<td>1</td>
<td>44</td>
<td>69</td>
</tr>
<tr>
<td>Stage</td>
<td>III-IV</td>
<td>2</td>
<td>37</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>21</td>
<td>32</td>
</tr>
</tbody>
</table>

Outcome according to the number of International Prognostic Index (IPI) factors in patients treated with R-CHOP.

Outcome according to the revised International Prognostic Index (R-IPI).

Revised International Prognostic Index (R-IPI) for diffuse large B-cell lymphoma

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk group</th>
<th>4-yr OS, percent</th>
<th>4-yr PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Very good</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>1 or 2</td>
<td>Good</td>
<td>79</td>
<td>80</td>
</tr>
<tr>
<td>3 or more</td>
<td>Poor</td>
<td>55</td>
<td>53</td>
</tr>
</tbody>
</table>

One point is given for each of the above characteristics present in the patient, for a total score ranging from zero to five. When applied to patients with DLBCL who were treated with R-CHOP, 4 year overall survival (OS) and progression free survival (PFS) rates according to the score were as follows:

Data from: Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 2007; 110:1227.
Event-free survival according to "early PET" status and IPI

A. Event-Free Survival According to PET Response
   Low and Low-Intermediate Risk Group

   PET (-), n=26
   PET (+), n=11

   Probability of Event-Free Survival

   Years After Randomization

   \[ P = .01 \]

B. Event-Free Survival According to PET Response
   High and High-Intermediate Risk Group

   PET (-), n=28
   PET (+), n=25

   Probability of Event-Free Survival

   Years After Randomization

   \[ P = .004 \]
Multi-center study of DA-EPOCH-rituximab in untreated diffuse large B-cell lymphoma outcomes based on biomarkers.

Gene-Expression Predictors of Survival among Patients with Diffuse Large-B-Cell Lymphoma Treated with R-CHOP

Outcomes in patients with DLBCL after treatment with R-CHOP according to cell of origin.

David W. Scott et al. JCO 2015;33:2848-2856
Time to progression for patients with DLBCL after treatment with R-CHOP according to cell of origin and immunohistochemistry for MYC and BCL2.

David W. Scott et al. JCO 2015;33:2848-2856
Outcomes in patients with DLBCL after treatment with R-CHOP according to groups defined by immunohistochemistry for MYC and BCL2.

David W. Scott et al. JCO 2015;33:2848-2856
Treatment of Activated B cell (ABC) type DLBCL

- R-ACVBP
- R-CHOP plus lenalidomide (R2-CHOP)
- R-CHOP plus bortezomib
- R-CHOP plus ibrutinib
- VR-CAP (rituximab, CY, doxorubicin, prednisone and bortezomib)
- Clinical Trials
Intensified chemotherapy with ACVBP plus rituximab versus standard R-CHOP for the treatment of DLBCL (LNH03-2B): an open-label randomised phase 3 trial

Figure 1. Protocol outline R-ACVBP=rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone. R-CHOP=rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone.

Christian Récher, Bertrand Coiffier, Corinne Haioun, Thierry Jo Miina, Christophe Fermé, Olivier Casasnovas, Catherine Thiéblemont, André Bosly, Guy Laurent, Franck Morschhauser, Hervé Ghesquières, Fabrice Jardin, Serge Bologna, Christophe Fruchart, Bernadette Corront, Jean Gabarre, Christophe Bonnet, Maud Janvier, Danielle Canioni, Jean-Philippe Jais, Gilles Salles, Hervé Tilly, for the Groupe d’Etude des Lymphomes de l’Adulte
Intensified chemotherapy with ACVBP plus rituximab versus R-CHOP the treatment of DLBCL (LNH03-2B): an open-label randomised phase 3 trial.
CONSORT diagram.
R-ACVBP vs R-CHOP in Young Patients with Non-GCB DLBCL
GELA Phase III Trial LNH 03-2B

Thierry Jo Molina et al. JCO 2014;32:3996-4003
Progression-free survival and overall survival according to (A and B) GCB vs. non-GCB, (C and D) among patients with GCB tumors according to treatment arm, and (E and F) among patients with non-GCB tumors.

GCB vs. non-GCB

GCB

Non-GCB

Thierry Jo Molina et al. JCO 2014;32:3996-4003
Lenalidomide plus R-CHOP21 in elderly patients with untreated DLBCL
Results of the REAL07 open-label, multicentre, phase 2 Trial

45 patients
Age 60-80 yrs
Stage II-IV

Treatment
Lenalidomide 15 mg day 1-14
+R-CHOP 21x 6 cycles

Toxicity
Grade 3-4 neutropenia 31%
Grade 3-4 thrombocytopenia 13%,
No grade 4 non-hematologic ADR

Response
92% response
86% CR, 6% PR

Conclusion
Lenalidomide + CHOP 21 is safe and effective in elderly DLBCL

Lenalidomide plus R-CHOP overcome negative Prognostic impact of Non-GCB Phenotype in DLBCL (Nowakowski et al. 2014)

- Phase II study
- Newly diagnosed DLBCL stage II-IV
- Treatment
  - Lenalidomide 25 mg daily days 1-10
  - R-CHOP every 21 days x 6 cycle
  - Neulasta day 2 of each cycle
  - Aspirin prophylaxis
  - Molecular subtype using IHC
  - Compared with 87 control DLBCL treated with R-CHOP
Outcomes of 64 patients with DLBCL treated with R2CHOP (lenalidomide added to R-CHOP)

ORR = 98%
CR=80%

Grzegorz S. Nowakowski et al. JCO 2015;33:251-257
Historical control R-CHOP compared to R2CHOP based on germinal center B-cell (GCB) versus non-GCB.
Ibrutinib +R-CHOP as Frontline Therapy for DLBCL
Phase 1b study (Younes et al. 2014)

• Treatment plan
  – Ibrutinib 280, 420, or 560 mg daily +R-CHOP q 3 wks
  – Phase 2 dose Ibrutinib 560 mg daily +R-CHOP x 6

• Toxicity
  – neutropenia 73%, thrombocytopenia 21%, febrile neutropenia 18%, anemia 18%

• Results
  – Overall response rate 95%
    • 71% CR for GCB subtype (7 patients)
    • 100% CR for non-GCB (4 patient)

• Conclusion
  – Ibrutinib 560 mg can be given safely with R-CHOP
  – Phase 3 study R-CHOP vs Ibrutinib +R-CHOP in Non-GCB DLBCL is being conducted
Kaplan-Meier survival curves in Previously Untreated DLBCL treated with Bortezomib plus R-CHOP

40 patients
Median age=56 (20-87)
IPI low 39%, IPI 3-5 49%
28 received bortezomib 1.3 mg/m2, 12 got 0.7-1 mg/m2

Results
ORR=88 % CR= 75%, PR=13%
2-year PFS 64%, OS 70%

Toxicity
Neuropathy 64%, neutropenia 55%, anemia 79%, ↓platelet 78%

Conclusion
Bortezomib+R-CHOP 21 is safe and may improve outcome in Non-GCB DLBCL

Jia Ruan et al. JCO 2011;29:690-697
Phase 2 study untreated non-GCB DLBCL
- R-CHOP 21 x 6 cycles vs bortezomib 1.3 mg/m2 IV on days 1 and 4 of each cycle (VR-CHOP)

Best Overall response
- VR-CHOP (n=90): 56% CR, 96% CR/PR
- R-CHOP (n=86): 49% CR, 98% CR/PR
- 53% R-CHOP and 59% VR-CHOP had negative FDG-PET at end of treatment

Median follow-up 31 months
- 2-year PFS: 78% R-CHOP vs 82% VR-CHOP

NO Benefit from the addition of bortezomib
Higher rate of toxicity from peripheral neuropathy.

Leonard JP. et al ASH 2015, abstract 811
R-CHOP
vs.
R-Bortezomib 1.3 mg IV day 1,4,8,11 + CAP (VR-CAP)

IHC (Hans Method)
Kaplan-Meier analysis of survival outcomes. R-CHOP vs. VR-CAP for Non-GCB DLBCL

Fritz Offner et al. Blood 2015;126:1893-1901
Treatment of Relapsed DLBCL

- Salvage chemo-immunotherapy
- Autologous Stem cell transplant for chemosensitive relapse
- Allogeneic Stem cell transplant in selected cases: persistent BM involvement or inability to collect stem cell
- Clinical trials
- CAR-T cell
Second-line R-ICE for DLBCL

- R-ICE in patients with relapsed or refractory DLBCL being considered for ASCT (n = 36)
- R-ICE appears to induce very high CR rate

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>R-ICE</th>
<th>ICE Historical Controls</th>
<th>P value</th>
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<tbody>
<tr>
<td>CR (%)</td>
<td>53</td>
<td>27</td>
<td>0.01</td>
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<tr>
<td>Post-ASCT 2-year PFS (%)</td>
<td>54</td>
<td>43</td>
<td>0.25</td>
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# Second-line Regimens for Relapsed and Refractory DLBCL

<table>
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<th>Regimen</th>
<th>n</th>
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<th>CR (%)</th>
<th>OS (mo)</th>
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<tr>
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<td>70</td>
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<tr>
<td>ICE</td>
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<td>DHAP</td>
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<td>18</td>
<td>6</td>
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<tr>
<td>Rituximab</td>
<td>30</td>
<td>37</td>
<td>10</td>
<td>NA</td>
</tr>
</tbody>
</table>

Courtesy of Michael Williams, MD.
High-Dose Chemotherapy With ABMT in Relapsed Chemosensitive NHL

- 215 patients treated with 2 cycles of DHAP (dexamethasone, cisplatin, cytarabine)
- 109 patients showed CR or PR and were randomized to
  - Conventional treatment: 4 more cycles of DHAP (n = 54)
  - High-dose treatment: BEAC (carmustine, etoposide, cytarabine, cyclophosphamide, and mesna) + ABMT (n = 55)

Randomised phase III study of R-ICE versus R-DHAP in relapsed patients with DLBCL followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study.

Christian Gisselbrecht et al. JCO 2010;28:4184-4190
(A) Overall survival according to the first random assignment (intent to treat).

Christian Gisselbrecht et al. JCO 2010;28:4184-4190
The impact of pre- and post-transplantation positron emission tomography using 18-fluorodeoxyglucose on poor-prognosis lymphoma patients undergoing autologous stem cell transplantation

Pre-auto SCT

Post auto-SCT

Cancer
Volume 110, Issue 6, pages 1361-1369, 10 JUL 2007 DOI: 10.1002/cncr.22911
http://onlinelibrary.wiley.com/doi/10.1002/cncr.22911/full#fig1
Kaplan-Meier survival estimates based on Deauville responses to ST. (A) PFS. (B) OS.

Craig S. Sauter et al. Blood 2015;125:2579-2581
Novel Agents

- Obinutuzumab
- Polatuzumab (anti-CD 79B antibody conjugated to monomethyl auristation E)
- Bruton’s tyrosine kinase inhibitors
- PI3 kinase inhibitors
- Aurora A kinase inhibitors
- Syk inhibitors
- CAR-T cells direct at CD19
Primary Mediastinal Large B-Cell Lymphoma

• Primary mediastinal large B-cell lymphoma (PMBL) can be defined as a clinical entity presenting with primary site of disease in mediastinum with or without other sites and has histology of DLBCL. PBML overlaps with grey zone lymphomas that have intermediate features between Hodgkin lymphoma and PMBL and have unique diagnostic characteristics. See Grey Zone Lymphoma (BCEL-B 2 of 3).

• Clinical pathologic correlation is required to establish diagnosis.

• Optimal first-line therapy is more controversial than other subtypes of NHL; however, treatment regimens include (in order of preference):
  ➢ Dose-adjusted EPOCH-R ([etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin] + rituximab) x 6 cycles
  ◦ for persistent focal disease, RT can be added.
  ➢ RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) x 6 cycles + RT
  ➢ RCHOP x 4 cycles followed by ICE (ifosfamide, carboplatin, etoposide) x 3 cycles ± RT (category 2B)

• Role of RT is controversial. If PET-CT scan was negative at the end of treatment and initial disease was non-bulky, observation may be considered.

• Residual mediastinal masses are common. PET-CT scan is essential post-treatment. Biopsy of PET-CT scan positive mass is recommended if additional systemic treatment is contemplated.
Relationship of PMBL to Hodgkin lymphoma.

Kieron Dunleavy, and Wyndham H. Wilson Blood
2015;125:33-39
Grey Zone Lymphoma
(intermediate between DLBCL and classical HL)

**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.

**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
Grey Zone Lymphoma
(intermediate between DLBCL and classical HL)

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.
Summary and Conclusion

- The prognosis of patients with DLBCL has improved with the addition of rituximab to CHOP
- R-CHOP remains the standard of care especially for GCB subtype
- Patients with non-GCB type have poorer prognosis and should be enrolled in clinical trial. The new regimen of R(X)CHOP appears promising but must await phase 3 trials due to additional toxicity
- Patients who fail R-CHOP continue to have poor outcome
- Future studies designing treatment based on cell of origin/molecular profile and availability of biomarker will allow the possibility of individualized risk-adapted therapy.
Questions

• Would you recommend CNS prophylaxis in patient with DLBCL who present with epidural mass?
  a. Yes
  b. NO

• Should patients with double-hit DLBCL receive R-CHOP?
  a. Yes
  b. NO