Welcome & Introductions

Update on Aggressive Non-Hodgkin Lymphoma (NHL): Diagnosis and Treatment

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Disclosure

David C. Fisher, MD, has affiliations with Genetics Institute and Celgene (Consultant).

An Overview and Management of High Grade Lymphoma

February 24, 2016
David C. Fisher, MD
Agenda

• Classification of lymphoma
• Diffuse large B-cell lymphoma subtypes:
  – Germinal center subtype
  – Activated B-cell subtype
  – Primary mediastinal large B-cell lymphoma
  – “double-hit” lymphoma
  – Double protein expresser
• Novel therapeutic approaches

Classification of lymphoma

• Malignancies of normal lymphoid cells which reside predominantly in lymphoid tissues (nodes, spleen, marrow)
• WHO classification based on morphology, immunophenotype, cytogenetics and clinical factors
• Non-Hodgkin’s lymphoma
  – B-cell
    • Precursor
    • Mature
  – T and NK-cell
    • Precursor
    • Mature
• Hodgkin lymphoma
### Pathogenesis of B-cell lymphomas

Subsets of lymphoma identified by corresponding normal counterpart in B-cell development.
Non-Hodgkin's Lymphoma

- Most common hematologic malignancy
- 72,000 cases/year in the US
- 5th most common cause of cancer deaths
- 2nd fastest growing malignancy in terms of mortality
- 85% are of B-cell origin

Presentation

- Lymphadenopathy (2/3)
- B symptoms - fever (>38), drenching night sweats, weight loss > 10% in 6 months
- Extra nodal sites - GI tract, skin, bone
- Rare - kidney, bladder, adrenal, heart, lungs, breast, testes, thyroid
**Biopsy**

- Supraclavicular > cervical/axillary > inguinal
- Excisional biopsy when possible
- CT guided core needle
- Send for pathology, immunohistochemistry/flow cytometry

**Staging system**

A – asymptomatic; B- fever, night sweats, 10% wt loss
Infectious associations

**EBV:**
- Burkitt lymphoma
- DLBCL
- NK-T cell lymphoma
- Hodgkin lymphoma
- Plasmablastic lymphoma

**HTLV-1:**
- Adult T-cell leukemia/lymphoma

**HHV-8:**
- Primary effusion lymphoma
- Large B cell lymphoma associated with Castleman's

Marginal zone lymphoma:
- *H. pylori*
- *B. burgdorferi*
- *C. jejuni*
- *Hepatitis C*

Risk factors

**Exposures:**
- Occupational
- Environmental
- Prior RT, chemotherapy

**Immune dysfunction:**
- Autoimmune disease
- Immunodeficiency
- Immune suppression

**Genetics:**
Clinical behavior of non-Hodgkin’s lymphoma

<table>
<thead>
<tr>
<th>Survival untreated</th>
<th>Indolent</th>
<th>Aggressive</th>
<th>Highly aggressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>Months</td>
<td>Weeks</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response to chemotherapy</th>
<th>Indolent</th>
<th>Aggressive</th>
<th>Highly aggressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not curable</td>
<td>Curable</td>
<td>Curable</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Example</th>
<th>Indolent</th>
<th>Aggressive</th>
<th>Highly aggressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular lymphoma</td>
<td>Diffuse large B-cell lymphoma</td>
<td>Burkitt lymphoma</td>
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</table>

High grade lymphoma

Highly aggressive lymphoma

- **B-cell:**
  - Burkitt lymphoma
  - Precursor B Lymphoblastic lymphoma

- **T-cell:**
  - Precursor T Lymphoblastic lymphoma
  - Adult T-cell leukemia lymphoma
Aggressive lymphoma

B-cell:
Diffuse large B-cell lymphoma
Follicular lymphoma grade 3 (A+B)

T-cell:
Peripheral T-cell lymphoma, NOS
Anaplastic large cell lymphoma
Angioimmunoblastic T-cell lymphoma
NK/T cell lymphoma

Diffuse large B-cell lymphoma
• Most common subtype NHL – 25%
  • Median age 65
  • Male predominance
Therapy for DLBCL

- **1970’s** - CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
- **1980’s** – 2nd and 3rd generation regimens (addition of other active agents, modification of doses and schedules) with improved CR rates and survivals in pilot studies
- **1990’s** – prospective randomized trials demonstrate 2nd and 3rd generation regimens are no better than CHOP

**Rituximab** – anti CD20 monoclonal antibody

- CDC
- ADCC
- direct killing
International Prognostic Index

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>5 yr OS</th>
<th>4 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>73%</td>
<td>94%</td>
</tr>
<tr>
<td>2</td>
<td>51%</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>42%</td>
<td>53%</td>
</tr>
<tr>
<td>4-5</td>
<td>26%</td>
<td>55%</td>
</tr>
</tbody>
</table>

Risk factors: age > 60, stage III/IV, >1 EN site, PS, LDH

Gene expression profiling in DLBCL

Figure 1: Differentiating Diffuse Large B-Cell Lymphoma (DLBCL) into Molecularly and Clinically Distinct Subgroups by Gene Expression Profiling—The heat map shows differential expression of genes in activated B-cell–like (ABC), germinal center B-cell–like (GCB), and primary mediastinal B-cell lymphoma (PMBL) DLBCL subtypes.

Dunleavy and Wilson. Oncology. 2014

Lenz et al. NEJM. 2008
B-cell receptor signaling

Lenz et al. NEJM 2010

Novel targets in ABC DLBCL

Lenz et al. NEJM 2010
Can we improve on RCHOP?

**R-CHOP**
- Rituximab 375 mg/m² d1
- Cyclophosphamide 750 mg/m² d1
- Doxorubicin 50 mg/m² d1
- Vincristine 1.4 mg/m² (2 mg cap) d1
- Prednisone 40 mg/m² d1-5
  
  q3w × 6

**DA*-R-EPOCH**
- Rituximab 375 mg/m² d1
- Etoposide 50 mg/m²/d Cl d1-4*
- Doxorubicin 10 mg/m²/d Cl d1-4*
- Vincristine 0.4 mg/m²/d Cl d1-4
- Cyclophosphamide 750 mg/m² d5*
- Prednisone 60 mg/m² bid d1-4
- G-CSF 5 µg/kg d6-ANC recovery
  
  q3w × 6

*Doses increased or decreased based on degree of neutropenia.

U.S. intergroup study

**Treatment flow chart CALGB 50303**

**ARM A: R-CHOP**
- C1
- Biopsy
- C2
- PET/CT
- C3
- Stage
- C4
- Stage/PET/CT
- C5
- C6
- Treatment completed

**ARM B: DA-EPOCH-R**
- C1
- Randomization
- C2
- C3
- C4
- C5
- C6
- Treatment completed

Correlatives include gene expression profiling
Ibrutinib in relapsed/refractory DLBCL

Younes et al. Lancet Oncology 2015

Definition of double hit lymphoma (DHL)
MYC rearrangement with other specified chromosomal rearrangements
- BCL-2 mostly common (60%)
- BCL-6 rearrangement (<10%)
- BCL-2 and bcl-6 (up to 20%)

Histologically:

Diffuse large B-cell lymphoma
B-cell lymphoma unclassifiable with features intermediate between DLBCL/BL (Gray zone lymphoma)
DHL has poor prognosis

No overall survival benefit of transplant

Oki et al. BJH. 2014
Intensive chemotherapy associated with improved PFS

Table 2. Treatment patterns (N = 311)

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-COPA</td>
<td>108 (35%)</td>
</tr>
<tr>
<td>R-CHOEP</td>
<td>86 (27%)</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>86 (27%)</td>
</tr>
<tr>
<td>R-CHOP MVAC</td>
<td>42 (14%)</td>
</tr>
<tr>
<td>PEX</td>
<td>7 (2%)</td>
</tr>
</tbody>
</table>


No clear benefit to upfront transplantation

Prognostic factors

Table 3. Prognostic factors with associated hazard ratios and P-values, by both univariate and multivariate analyses

<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>≥70</td>
<td>&lt;70</td>
<td>1.02 (1.17, 2.29)</td>
<td>.90</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>2/4</td>
<td>0/1</td>
<td>1.75 (1.24, 2.49)</td>
<td>.01</td>
</tr>
<tr>
<td>WBC</td>
<td>≥10³</td>
<td>&lt;10³</td>
<td>2.24 (1.34, 3.74)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Albumin</td>
<td>≥4</td>
<td>&lt;4</td>
<td>1.06 (1.01, 1.11)</td>
<td>.01</td>
</tr>
<tr>
<td>LDH</td>
<td>≥3.0 U/L</td>
<td>&lt;3.0 U/L</td>
<td>1.02 (1.05, 2.11)</td>
<td>.19</td>
</tr>
<tr>
<td>B symptoms</td>
<td>Present</td>
<td>Absent</td>
<td>1.50 (0.78, 2.95)</td>
<td>.24</td>
</tr>
<tr>
<td>Extensive disease</td>
<td>&gt;1 site</td>
<td>≤1 site</td>
<td>1.06 (1.03, 2.11)</td>
<td>.01</td>
</tr>
<tr>
<td>Bone marrow infiltration</td>
<td>Positive</td>
<td>Negative</td>
<td>1.06 (1.01, 1.11)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CNS infiltration</td>
<td>Present</td>
<td>Absent</td>
<td>2.5 (1.62, 4.09)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariate analysis</td>
<td></td>
<td></td>
<td>2.45 (1.26, 4.78)</td>
<td>.01</td>
</tr>
</tbody>
</table>


Response to initial chemotherapy predicts outcome

DA-EPOCH-R in MYC-R DLBCL  N=52

**Characteristics** | %
--- | ---
Median (range) age (years) | 61y (29-80y)
Male sex | 71%
Stage III or IV | 73%
High LDH | 59%
CNS disease | 6%
IPI score
- 0-2 | 35%
- 3-5 | 65%
Histology
- DLBCL | 86%
- BCL-U | 14%
MYC + by FISH or cytogenetics | 100%
BCL2 + by FISH | 45%
BCL2 – High by IHC | 56%

* Of 31 cases tested

Dunleavy et al. ASH 2014

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**Progression-free survival – All patients**

![Graph showing progression-free survival](image-url)
Over-expression of MYC and bcl-2 protein associated with inferior outcomes

![Image](image1.png)

Johnson et al. JCO. 2012

Double expresser DLBCL

<table>
<thead>
<tr>
<th>Reference</th>
<th>Frequency (type of lymphoma studied)</th>
<th>% GC based on GEP or phenotype</th>
<th>Therapy</th>
<th>Significant impact on overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al. 2012</td>
<td>19% (DLBCL)</td>
<td>24%</td>
<td>R-CHOP</td>
<td>Adverse</td>
</tr>
<tr>
<td>Griess et al. 2012</td>
<td>20% (DLBCL)</td>
<td>37%</td>
<td>R-CHOP</td>
<td>Adverse</td>
</tr>
<tr>
<td>Hu et al. 2012</td>
<td>54% (DLBCL)</td>
<td>54%</td>
<td>R-CHOP</td>
<td>Adverse</td>
</tr>
<tr>
<td>Dunleavy et al. 2013</td>
<td>20% (DLBCL, includes 33% HIV+)</td>
<td>43%</td>
<td>DA-EPOCH-R or short course EPOCH-RR</td>
<td>None</td>
</tr>
<tr>
<td>Perry et al. 2014</td>
<td>27% (DLBCL)</td>
<td>64%</td>
<td>R-CHOP or CHOP-Bea</td>
<td>Adverse</td>
</tr>
<tr>
<td>Fehlert et al. 2014</td>
<td>27% (advanced stage DLBCL)</td>
<td>N/A</td>
<td>R-CHOP + ibudilast</td>
<td>None</td>
</tr>
</tbody>
</table>

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
DHL/DEL lymphoma summary

- Double hit (<10% of DLBCL) and double expresser (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
Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

- Comprise approximately 7% of DLBCL
- Female predominance
- Median age 30-40’s
- SVC syndrome common
- 50% pts with pleural or pericardial effusion
- Cough, dyspnea, hoarseness and dysphagia
- B symptoms common

Pathology

Savage. Oncologist 2006

Immunohistochemical studies reveal the neoplastic cells to be CD20-positive B cells co-expressing CD10 (weak), Bcl-2, and Bcl-6. Immunostain for CD30 is weakly positive in scattered neoplastic cells.
Possible diagnostic clues: PMBCL

- pericardial or pleural effusion
- elevated LDH
- extranodal sites of disease outside the chest

Clinical and pathologic distinction between NSHL and PMBCL

<table>
<thead>
<tr>
<th>Feature</th>
<th>PMBCL</th>
<th>NScHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age distribution</td>
<td>Third to fourth decade</td>
<td>Peak at 15–35 years</td>
</tr>
<tr>
<td>Gender</td>
<td>Female predominance</td>
<td>Slight female predominance</td>
</tr>
<tr>
<td>Site of disease</td>
<td>Anterior mediastinum</td>
<td>Anterior mediastinum most common</td>
</tr>
<tr>
<td>Pathology</td>
<td>Sclerosis</td>
<td>Sclerosis</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>CD30 variable and weak; surface Ig absent in ~70%</td>
<td>CD30 usually strong; surface Ig absent in all</td>
</tr>
<tr>
<td>Genetics</td>
<td>2p (REL) and 9p (JAK-2) amplification</td>
<td>2p (REL) and 9p (JAK-2) amplification</td>
</tr>
</tbody>
</table>

Savage. Oncologist 2006
EFS PMBCL approximately 80% with RCHOP +/- RT

Extremely high PFS and OS with DA-REPOCH
What about precision medicine in DLBCL?

MLL2, B2M, CD58, MEF2B, FOXO1, TP53, PIM1, SOCS1, MYC, GNA13, SGK1, TNFAIP3, MYD88, PRDM1, CDKN2A, EZH2 and CIITA.

102 potential “driver” mutations

Wise et al, ASH 2015, abstract 110
Evolution of trials in DLBCL

When to consider MCL?

Pathology

- Intermediate size monomorphic infiltrate
- CD5+ CD10- CD20+ CD23- Bcl-2+ Bcl6- CyclinD1+
- Cytogenetics=t(11;14)
- FISH=IGH-CCND1 rearrangement

DDx
Prognosis

- Pathological variants
- Prognostic factors
  - MIPI and derivatives
  - Ki67 (Mib-1) index
  - MIPI/Ki67 widely applied
    - At diagnosis with different therapies
    - At relapse?

First-Line Therapy

- The Basics
  - R improves EFS in meta-analysis
  - RCHOP PFS 1.5y
  - RCHOP + Autologous SCT
    - European MCL network RCT
      - (R)CHOP + ASCT versus Interferon maintenance
      - 3y PFS 54% versus 25%
First-Line Therapy

The Basics
- RCHOP PFS 1.5y
- RCHOP + ASCT PFS 4y

The role of Cytarabine
- R-HCVAD
  - OR 97% CR 87%;
  - mFFS ~5y (5.9y in <65yo, 4y >65yo)
  - Outside MDACC mPFS ~5y, 5.5y <65yo
  - 39% could not complete for toxicity...

First-Line Therapy

The role of Cytarabine
- R-HCVAD PFS 5.5y
- R-CHOP + ASCT ~ R-HCVAD PFS 4y
- RHCVAD + ASCT
  - Good single arm results, PFS>5y
  - Unclear benefit in comparative studies
  - Toxicity clear
First-Line Therapy

- The role of Cytarabine
  - R-HCVAD PFS 5.5y
  - R-CHOP + ASCT ~ R-HCVAD PFS 4y
  - RHCVAD + ASCT PFS>5y
  - R-MegaCHOP/RHIDAC + ASCT PFS 7.5y
  - RCHOP/RDHAP + ASCT PFS 7y
    - Benefit in all MIPI groups
    - If CR before ASCT no difference

First-Line Therapy

- The role of Cytarabine
- The wonders of bendamustine
  - R-Benda versus R-CHOP
    - R-Benda superior
    - PFS 35 v 22m
    - Less toxic
First-Line Therapy

- **Current concepts**
  - R-Benda + Ara-C 2y PFS 95%
  - DFCI protocol 12-168: BRAC
    - Transplant eligible; R-Benda x3 + R-HIDAC x 3
    - OR 96% CR 96%

Salvage

- **Available agents**
  - “Targeted Therapy”
    | Agent               | OR/CR | PFS     |
    |---------------------|-------|---------|
    | Y90-Ibritumomab     | 30/15 | 6m      |
    | Lenalidomide*       | 30-50/10 | 6-12m  |
    | Temsirolimus*       | 40/5  | 6m      |
    | Bortezomib*         | 50/10-40 | 12m    |
    | Idelalisib          | 40/5  | 4m      |
    | Ibrutinib           | 70/20 | 14m     |
    | ABT-199             | 100/0 | 7       |