Update on the Management of Aggressive Non-Hodgkin Lymphoma

Suzanne R. Fanning, DO
Director, Blood and Marrow Transplant Program
Greenville Health System - Cancer Institute
August 8, 2015
Outline

- DLBCL: GBC vs. non-GBC
- Double-hit lymphoma (DHL)
- Mantle cell NHL
- Transformed NHL
- Emerging methods in the detection of recurrent disease
Diffuse Large B-cell NHL
DLBCL

- Most common NHL: 30-40%

- Heterogenous disease:
  - clinical presentation
  - pathologic/molecular characteristics
  - response to therapy

- IPI: age, stage, LDH, PS, extranodal
Overall survival in DLBCL – stage
**Burkitt**
- CD10 +
- BCL6 +
- BCL2 -
- Sox 11 +/-
- MIB-1 > 98%
- MYC simple
- EBV +/-

**B-UNC/BL/DLBCL**
- CD10 +
- BCL6 +/-
- BCL2 +
- Sox 11 ND
- MIB-1 < 90%
- MYC complex
- EBV -

**DLBCL GCB**
- CD10 +
- BCL6 +
- BCL2 +/-
- Sox 11 -
- MIB-1 Variable
- MYC rare +
- EBV -
DLBCL: GBC vs. non-GBC

- Hans algorithm - immunohistochemistry
- CD10/BCL-6/MUM1
- Independent predictor of OS in multivariate analysis
Shimin Hu et al. Blood 2013;121:4021-4031
DLBCL – RCHOP as initial therapy

- All patients:
  - CR – 76%
  - 10-yr OS – 44%
R-CHOP is inadequate in many DLBCL subsets and high-risk groups

<table>
<thead>
<tr>
<th>Subsets</th>
<th>Freq</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC DLBCL</td>
<td>30-50%</td>
<td>2-yr 28%</td>
<td>2-yr 46%</td>
</tr>
<tr>
<td>DHL</td>
<td>5-7%</td>
<td>1-yr 33%</td>
<td>&lt;1 yr</td>
</tr>
<tr>
<td>DPL (MYC+BCL2)</td>
<td>34%</td>
<td>5-yr 27%</td>
<td>5-yr 30%</td>
</tr>
<tr>
<td>Elderly DLBCL &gt;60 yr</td>
<td>50%</td>
<td>5-yr 50%</td>
<td>5-yr 58%</td>
</tr>
<tr>
<td>High IPI</td>
<td>45%</td>
<td>4-yr 53%</td>
<td>4-yr 55%</td>
</tr>
</tbody>
</table>

NCI CTPM: Recommendations of the DLBCL Subcommittee
November 21, 214
Sonali Smith, Kristie Blum, David Maloney, Greg Nowakowski, Laurie Sehn, Michael Williams, Wyndham Wilson
DLBCL: R2CHOP – previously untreated

- Nonrandomized, Phase II, N= 55
- OS (2yr): GC 83%, ABC 75%
- PFS (2yr): GC 60%, ABC 50%
- Case-matched historical analysis (RCHOP) -
  PFS (2yr): GC 64%, ABC 28%
RCHOP + bortezomib: previously untreated

- Ph I/II, multicenter, n=40 (additional 36 w/ MCL)
- Bortezomib 1.3mg/m2 d1, d4 q 21d
- VCR – full dose
- ORR 88%
- CR/Cru 75%
- PFS at 2 yrs – 64%
DLBCL: RCHOP +/- bortezomib
DLBCL: RCHOP +/- bortezomib
Clinical trials: initial therapy

- Phase III trial of R2CHOP, non-GBC patients
- Randomized Phase II of RCHOP +/- bortezomib, non-GBC
  - no longer accruing, info expected Fall 2015
- SWOG: RCHOP + bortezomib followed by bortezomib maintenance
B-cell signaling pathway
DLBCL: RCHOP + Ibrutinib

- Phase Ib, n=33
- Phase II dosing – 560mg
- DLBCL, n=22, ORR 100%
  - CR 64%
  - PR 36%
- PHOENIX: phase III, RCHOP +/- ibrutinib, non-GCB patients
Relapsed DLBCL
Relapsed DLBCL

- Bendamustine + Rituxan
- R-ICE/R-ESHAP
- R-DHAP: significantly improved PFS in GCB-relapsed disease
- Revlimid + Rituxan: non-FDA approved
- Ibrutinib +/- Rituxan: non-FDA-approved
  - monotherapy – ORR 41%, non-GCB (ASH 2012)
- Clinical trial
## Novel therapies in relapsed DLBCL

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-199</td>
<td>Platelet-sparing BCL2 inhibitor (BH₃-mimetic)</td>
<td>28, 63</td>
</tr>
<tr>
<td>BET bromodomain inhibitors (JQ1, I-BET 151, OTX015)</td>
<td>Down-regulation of MYC-associated transcription; Decreased cell proliferation and inhibition of MYC-driven neoplasms</td>
<td>64-66</td>
</tr>
<tr>
<td>CAR-T cells</td>
<td>Autologous T-cell-mediated killing of CD19-positive lymphoid neoplasms</td>
<td>67, 68</td>
</tr>
<tr>
<td>Aurora kinase inhibitors (alisertib)</td>
<td>Aurora kinase function is required for tumor maintenance of MYC-driven lymphoma</td>
<td>69, 70</td>
</tr>
<tr>
<td>mTor inhibition</td>
<td>mTOR may play an important role in tumor maintenance by MYC in B lymphocytes</td>
<td>71, 72</td>
</tr>
<tr>
<td>MLN9708/Ixazomib (second generation proteasome inhibitor)</td>
<td>Preclinical model; Degraded MYC and can induce lymphoma cell death at nanomolar concentrations</td>
<td>73</td>
</tr>
<tr>
<td>PI3K inhibition</td>
<td>High percent GCB-DLBCL cases: loss of PTEN → activation of PI3K/AKT pathway → MYC upregulation</td>
<td>74</td>
</tr>
<tr>
<td>Inhibition of human mitochondrial peptide deformylase</td>
<td>Causes apoptosis in MYC-overexpressing hematopoietic neoplasms</td>
<td>75</td>
</tr>
<tr>
<td>SIRT4 protein</td>
<td>Suppresses tumor formation in MYC-induced B-cell lymphoma models</td>
<td>76</td>
</tr>
</tbody>
</table>

Abbreviations: mTOR, mammalian target of rapamycin; GCB, germinal B cell; DLBCL, diffuse large B-cell lymphoma.
Relapsed DLBCL

- Standard of care for patients with chemo-sensitive disease:
  - consolidation with ASCT
- UK study: 5-yr EFS 72% (BJH 2012;156:142)
Double-hit lymphoma
Double hit lymphoma

- Phenotype: clinically aggressive B-cell malignancies
- MYC partnered with BCL2 or BCL6
- 5-10% of DLBCL by FISH
- Approx 30% by immunohistochemistry (IHC)
- 30-40% are MYC+/BCL2+
- MYC: proto-oncogene
- Diffuse large B-cell lymphoma
- MYC/BCL2 co-expressing diffuse large B-cell lymphoma
- Cytogenetic double hit lymphomas
- B-cell lymphoma, unclassifiable
- Burkitt lymphoma
DHL

- Aggressive
- Chemo-refractory
- Short survival – median OS <2yrs
- Poor prognosis at relapse
DHL – Patient characteristics

- Median age 60
- Male:female 2:1
- Transformed NHL = 20%
- Ki67 median of 80%
- Advanced stage, B symptoms, BM involvement, high LDH, and extranodal involvement – all common

BJH 2015, 168, 784-795
Myc+ staining in DLBCL
Gene expression signature of DLBCL with MYC/BCL2 coexpression.

Shimin Hu et al. Blood 2013;121:4021-4031
Overall survival (proportion)

Time (years)

Other (n = 236)
MYC+/BCL2+ (n = 55)
DHIT (n = 14)

\[ P < 0.001 \]
\[ *P = 0.014 \text{ (MYC+/BCL2+ vs other)} \]
Difference in OS

- Frontline therapy:
  - 60% for DLBCL s/p first line RCHOP
  - 33% w/ DHL s/p RCHOP
DHL

- MYC–associated lymphomas
  - rearrangements
  - chromosomal abnormalities
  - mutations
  - increased copy numbers
  - increased protein expression
DHL – pathology algorithm

- **DLBCL**
  - IHC: MYC, BCL2, BCL6
  - MYC-IHC positive – then FISH for MYC
  - MYC-FISH positive – then FISH for BCL2 and BCL6

- **B-cell NHL unclassified, transformed NHL, immunoblastic** – FISH for MYC
DHL: Initial therapy – MDACC experience

- **RCHOP:**
  - CR 40%/ PFS 25%/ OS 41%

- **DA (dose adjusted)-EPOCH –R:**
  - superior EFS
  - trend toward improved OS

- **R-HyperCVAD:**
  - CR 68%
DHL: Initial therapy

- US multicenter study:
  - intensive regimens > RCHOP
  - exploratory multivariate analysis – improved OS

- Meta-analysis:
  - n=401
  - improved PFS w/ DA –EPOCH-R vs. RCHOP
  - no OS advantage
DHL: Initial therapy

- ASCT consolidation – data limited
  - consider in CR

- Allo-SCT consolidation – improved outcome
  ? Better PS, younger, ....

Cancer 2014
DHL – emerging treatment options

- Tandem ASCT followed by NMA allo
- Stanford Univ, 2007-2012
- N=34, only 12 completed planned tandem
- Median f/u 10 months:
  - 2 patients died from relapse
  - EFS 37.7 months
  - OS not reached
Increase risk of CNS disease in DHL
DHL: CNS disease

- 4-7% w/ CNS+ at initial diagnosis
- MDACC: 3-yr cumulative risk – 13%
  - correlated with DHIPI
- Retrospective evaluation of IT MTX:
  - improved OS
  - decreased risk of CNS involvement
DHL: CNS disease

- Savage, et al 2014:
  - N=447 DLBCL, n=131 (29%) DHL
  - DHL w/ increased risk of CNS disease
    - HR 3.76
    - p=0.007
- Significantly higher CNS disease in DHL c/w other DLBCL
Relapsed DHL
DHL: Relapsed/refractory disease

- Novel therapy
  - SINE: Selinexor (KPT-330)
  - BH3-mimetic: ABT-199
  - BET bromodomain inhibitors: GSK525762 / CPI-0610
  - BTK: ibrutinib
  - iMID: lenalinomide
  - antibody-drug conjugate: brentuximab vedotin
DHL: Relapsed/refractory disease

- Novel therapy
  - antibody-drug conjugate: brentuximab vedotin
  - Alisertib – selective Aurora A kinase inhibitor
  - MLNM9708 – NF-kB pathway inhibitor

Cancer 2014
Mantle cell NHL
Mantle cell NHL

- Median age: 60’s
- Male 2:1
- Stage III/IV
- LA, +BM, splenomegaly
Mantle cell NHL

- CD20+/ CD5+
- CD10-/bcl6-
- Cyclin D1+
- t(11;14)(q13;32)
Mantle cell NHL

- Prognosis: median survival 4-5 years

- Simplified MIPI (age, PS, LDH, WBC)
  - low-risk: median OS not-reached (5-yr OS 60%)
  - intermediate risk: median OS 51 months
  - high risk: median OS 29 months
Mantle cell NHL: Induction

- Elderly patients:
  - RCHOP vs. BR — similar ORR 95% vs. 89%
  - RV-CAP vs. RCHOP — ORR 88 vs. 85% (improved PFS, OS not reached)
  - RCHOP vs. R-FC — 4yr OS 65% vs. 50%
  - RCHOP w/ rituxan maintenance — 4yr OS 87%
MCL: Clinical trials - induction

- SHINE: Phase III - BR +/- ibrutinib, untreated, elderly patients
Mantle cell NHL: induction

- Transplant eligible:
  - Hyper CVAD – multicenter data: ORR 88%, CR 58%
    - high-dose cytarabine containing regimens superior
  - HyperCVAD + ASCT vs. RCHOP + ASCT – (JCO 2006;24:424a)
  - RCHOP x 3 + RDHAP x 3 + ASCT – 5yr OS 75%
Institutional variability in the selection of first-line therapy for MCL patients (n = 167).


©2012 by American Society of Hematology
KM estimates of PFS from diagnosis by therapy group.

Mantle cell NHL: role of ASCT

- Retrospective – supports use in front-line setting
- JCO 2006;24:424a
- Blood 2012;119:2093-2099
Mantle cell NHL: clinical trials for induction

- Bortezomib + R-HyperCVAD – 90% CR
- Bortezomib + RCHOP – 72% CR/Cru

Campo E. Blood 2015; 125:48-55
Relapsed MCL
Relapsed MCL: ibrutinib

- FDA approval 11/2013
- Phase II, relapsed or refractory
- N=111
- ORR 68%
- Median PFS – 13.9 months
- Estimated 18-month OS was 58%
Relapsed MCL

- Ibrutinib – ORR 68%/CR 21%/DOR 17.5/PFS 13.9/OS not reached
- Bortezomib – ORR 33%/CR 8%/DOR 9.2/PFS 6.5/OS 23.5
- Lenalinomide – ORR 28%/CR 8%/DOR 16.6/PFS 4/OS 19
Wang, et al. ASH 2014. Ibrutinib + rituxan: ORR 87%
Transformed NHL
Transformed NHL – addition of rituxan

All 118 patients
2 year OS 68%
Kaplan-Meier curves for progression-free survival and overall survival for autologous HCT.
ASCT in t-NHL

- NRM at 1-yr – 8%
- 5-yr PFS 35%
- 5-yr OS 50%
ASCT in t-NHL

- No statistically significant difference with regard to number of prior therapies
PFS vs. TTNT

- PFS post ASCT
- TTNT post 1st CT

Time (years)
Circulating tumor DNA
Circulating tumor DNA

- Biomarker for patients with DLBCL
- NIH, n=126, retrospective 1993-2013
- Rate of progression at 5 yrs was 41.7% vs. 80.2% in patients with detectable ctDNA after 2 cycles of EPOCH/REPOCH
Circulating tumor DNA

- Kurtz et al, Blood 2015
- high-throughput sequencing of tumor-specific immunoglobulin genes (Ig-HTS) in the blood
- noninvasive test to monitor disease response and recurrence in DLBCL
Ig-HTS for disease progression or relapse in DLBCL in 2 patients.

John W. Sweetenham Blood 2015;125:3673-3674
Thank you!

sfanning@ghs.org
GHS Cancer Institute
65 International Dr., Greenville, SC 29615
Office: 864-679-4064
Cell: 864-404-8244