Diffuse Large B-cell Lymphoma
Research to Practice
ASH 2016 Satellite Symposium

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- Data Safety Monitoring Committee:
  - Celgene, Takeda

- Consultant:
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- ABIM:
  - Chair, Hematology Subspecialty Board
  - Member, ABIM Council
DLBCL 2016

• Should cell-of-origin guide therapy?
• Implications of CMYC, BCL2 and BCL6 translocation and expression
• Therapeutic roles for Immune Checkpoint Inhibitors and CAR-T cells
• When to use CNS prophylaxis?
Cell of Origin in DLBCL: PFS and Survival after R-CHOP
Gene expression profiling (GEP) using frozen tissue

Dave, NEJM 2005; Lenz, NEJM 2008
DLBCL- Overall survival according to cell of origin by immunostaining vs gene expression profiling

Difficulties with reproducibility and interpretation limit reliability for risk-adapted therapy

Patient outcomes following R-CHOP induction according to COO: Lymph2Cx (paraffin-embedded tissue) vs Gold Standard GEP (frozen tissue)

**A** PFS
- Proportion PFS
- Time (years)
- $P < 0.001$ RR = 3.6 (1.6-8.4)

**B** OS
- Proportion OS
- Time (years)
- $P = 0.01$ RR = 2.8 (1.1-7.3)

**C** GEP
- Proportion PFS
- Time (years)
- $P = 0.01$ RR = 2.6 (1.1-6.3)

**D** GEP
- Proportion OS
- Time (years)
- $P = 0.04$ RR = 2.3 (0.8-6.3)

Germinal-Center B-cell-like DLBCL
Unclassified DLBCL
Activated B-cell-like DLBCL

Scott et al. Blood 2014;123:1214; Scott et al. JCO 2015;33:2848
Therapeutic implications: GCB vs non-GCB

• 5-year PFS after R-CHOP
  - 73% for GCB versus 48-54% for non-GCB
• Non-GCB characterized by NF-kB activation
• Lenalidomide, bortezomib and ibrutinib have single-agent activity in relapsed non-GCB DLBCL
  - Limited activity in GCB
• Phase II trial adding Lenalidomide to front-line therapy (R2-CHOP) overcame negative prognosis of non-GCB (Nowakowski et al, JCO 2015; 33:251)
• Phase Ib trial of ibrutinib plus R-CHOP in DLBCL
  - 5/7 GCB and 4/4 non-GCB achieved CR (Younes et al, Lancet Oncol 2014;15:1019)
Selected DLBCL Phase 2-3 Trials:
COO-Driven

- **R-CHOP vs R2-CHOP**
  - ECOG E1412
  - ROBUST

- **R-CHOP vs IR-CHOP**
  - PHOENIX (accretion complete)

- **R-CHOP vs Bortezomib-R-CHOP**
  - REMoDLB, PYRAMID, LYM2034
  - Accruals complete, to date show no clear benefit for addition of bortezomib
Double/Triple Hit DLBCL

- CMYC plus BCL2 and/or BCL6 translocations by interphase FISH
  - CMYC translocation alone in 6-14%
  - BCL2 with CMYC in 2-11%: Almost all are GCB subtype

- BCL6 translocations
  - Present in 33% of DLBCL
  - BCL2 and BCL6 often occur together, do not alter prognosis
  - CMYC plus BCL6 translocations less clear regarding prognosis

- **Recommendation:** test all newly-diagnosed DLBCL for translocations
**Double Expresser DLBCL**

- **Co-expression** of MYC and BCL2 by IHC in ~40% of DLBCL: More frequent in non-GCB subtype
  - Associated with poorer outcome vs no co-expression

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*R-CHOP front-line therapy*

*Johnson et al, JCO 2012*

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![Graph showing overall survival comparison between Double Expresser, Double Hit, and No DH or Co-Expr.](image)
• R-EPOCH may have better outcomes in retrospective reviews

• SCT consolidation in CR1 unproven, but often considered in younger/fit patients

• High rate of CNS dissemination, consider HD MTX or IT chemo

• US Intergroup trial in development

Oki et al, BJH 2015
Therapy of DH DLBCL

- R-EPOCH may have better outcomes in retrospective reviews

Treatment and outcomes in Double/Triple Hit Lymphomas

Habermann et al, ASH 2016, abstract #155

Clinical impact of cell-of-origin and MYC+/BCL2+ double expresser status in DLBCL

Staiger et al, ASH 2016, abstract #151

- US Intergroup trial in development

Oki et al, BJH 2015
Second-generation anti-CD19 CAR-T-cell

CTL, cytotoxic T lymphocyte; MHC, major histocompatibility complex

Anti-CD19-CAR-T Therapy of R/R DLBCL

- Kochenderfer et al. JCO 2015;33:540
  - ORR 36% (n = 5): 2 CR, 2 PR, 1 NE
- Schuster et al. ASH 2015, abst. #183
  - ORR 54% (n = 13)

Neelapu et al, ASH 2016 LBA-6
ZUMA-1 Phase 2 Multicenter trial
n = 111: ORR 76%
Immune Checkpoint Inhibitors in R/R DLBCL

• Several small studies show activity in NHL, including DLBCL

• Nivolumab in R/R DLBCL
  \(\text{(Lesokhin et al, JCO 2016;34:2698)}\)
  - ORR 36\% (n=11): 2 CR, 2 PR
Primary Mediastinal B-cell Lymphoma (PMBL)

- Subtype of DLBCL
- Most common in young women
- Highly curable with DA-R-EPOCH (No RT)
  - or with other intensive R-chemo + RT
- Extranodal sites (kidney, adrenal or liver) may be present at Dx or relapse
- Molecularly similar to NS Hodgkin lymphoma
  - Frequent 9p24.1 copy number alterations and rearrangements → PD-L1 and PD-L2 expression
Relationship of PMBL to Hodgkin lymphoma

PMBL: Response to Immune Checkpoint Inhibitors

Pembrolizumab in R/R PMBL
Zinzani et al, ASH 2016, abstract #619

- KEYNOTE-013 Trial, phase 1b
Predicting risk of CNS involvement in aggressive B-cell NHL

- German High-grade NHL Study Group prognostic model (Schmitz et al, JCO 2016)
- **6 Factors:** Age >60, LDH> nl, stage III - IV, PS >1, EN sites >1, and kidney or adrenal involvement
- **3 Risk Groups → 2 yr CNS relapse risk**
  - Low risk (0-1 factor) → 0.6%
  - Int. risk (2-3 factors) → 3.4%
  - High risk (4-6 factors) → 10.2%
Validation of DLBCL CNS prognostic risk model

Schmitz et al, JCO 2016

- Retrospective review of 2164 German Group and 1597 Vancouver Group DLBCL pts who rec’d at least one cycle of R-CHOP

- Vancouver population-based analysis confirmed the German risk model

- Median time to CNS relapse 6.7 mo

- Kidney/adrenal involvement highly associated with CNS risk
Risk of CNS Progression by CNS IPI

Schmitz et al, JCO 2016;34:3150

[Graph showing the risk of CNS progression by CNS IPI over time with data points for different IPI stages and corresponding numbers at risk.]
Risk of CNS Progression by Kidney/Adrenal Involvement

Schmitz et al, JCO 2016;34:3150

![Graph showing the risk of CNS progression by kidney/adrenal involvement.](image)

- **Kidney/adrenal glands involved (n = 90)**
- **Kidney/adrenal glands not involved (n = 2,074)**

**Time to Relapse (months)**

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*P < .001*
How should we manage DLBCL patients at high risk of CNS disease?

- No prospective data, no standard of care
- For fit patients, < 65-70 yr, normal renal function, consider:
  - R-CHOP-21 with high-dose MTX at day 10-14 of 2 - 3 cycles (Abramson et al, Cancer 2010)
  - Relapses occur early, so don’t delay MTX until after R-CHOP x 6 completed
  - Use a 28 day cycle when MTX given, don’t give G-CSF after CHOP in MTX cycles
- For less fit pts, consider IT chemo with each cycle of R-CHOP