Overview of Aggressive Lymphomas

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DISCLOSURES

Sonali M. Smith, MD

• I have the following relevant financial relationships to disclose:
  – Consultant for: Genentech, Bayer, TGTX, Kite, Seattle Genetics, Gilead
  – Speaker’s Bureau for: none
  – Stockholder in: none
  – Honoraria from: none
  – Employee of: none

• I will discuss the following off label use and/or investigational use in my presentation: lenalidomide, ibrutinib, acalabrutinib, venetoclax. I will disclose when they are being discussed in an off-label manner.
OBJECTIVES

• To discuss the historical and current treatment of diffuse large B-cell lymphoma

• To distinguish “double hit lymphoma” from aggressive lymphomas with “double protein expression”

• To understand risk stratification in diffuse large B-cell lymphoma

• To describe the treatment options for patients with relapsed disease
There are nearly 100 types of lymphoma.

Goals of therapy vary by histology and expected clinical behavior:
- Curative intent
- Palliative intent
Most common NHL, peak incidence 6th decade
Large cells with loss of follicular architecture of node
May present as extranodal disease (stomach, CNS, testis, skin)
Median survival, weeks to months if not treated
Immunophenotype: CD19+, CD20+, CD22+, CD79a+
Cytogenetics: t(14;18) in 20-30%; 3q27 in 30%
Curable in 30-90%
2002+: Rituximab plus CHOP-like regimens improves overall survival

Habermann et al., JCO. 2006; 24: 3121. Feugier et al., JCO. 2005; 23: 4117.
CAN WE MOVE BEYOND R-CHOP?
Challenging R-CHOP

DA-EPOCH-R

Add biologic agents

Obinutuzumab

GA101: Mechanisms of action

Increased Direct Cell Death
Type II versus Type I antibody

Enhanced ADCC
Glycoengineering for increased affinity to FcγRⅢa

Lower CDC
Type II versus Type I antibody

Consolidation
DLBCL: a study in clinical and biologic heterogeneity

Clinicopathologic subtypes (PMBL, PCNSL, 10 testicular lymphoma, IVL, PEL)

Genomic variants

Gene expression profiling subtypes

Morphologic variants

Neoplasm of large B lymphoid cells with a diffuse growth pattern

Altered protein expression
Clinical impact of heterogeneity on curative potential

Low IPI
Low stage
GC phenotype

R-CHOP remains the standard of care in 2019 (except for DHL)

High IPI
Elderly
Non-GC phenotype
Double hit lymphoma
Double protein lymphoma
HETEROGENEITY AND RISK STRATIFICATION IN AGGRESSIVE B-NHL
Identifying high-risk subsets: 4 key approaches

1. Histopathology
2. Clinical features/IPI
3. Cell-of-origin
4. DHL, DEL, other

Clinical features/IPI

- Very Good
- Good
- Poor

Probability of Progression-Free Survival (%)

- Germinal-center B-cell-like
- Activated B-cell-like

P < .001

OS (%)

All others (n=260)

MYC+BCL2+ (n=124)

p < .0001

Months

OS (%)

All others (n=384)

MYC/BCL2 DH (n=10)

p < .0001

Months
FOCUS ON HGBL-DHL/THL
Co-rearrangement of **MYC and BCL2**- in DLBCL

A

**OS**

- **MYC/BCL2 DH** (n=10)
- All others (n=384)
- p<.0001

B

**PFS**

- **MYC/BCL2 DH** (n=10)
- All others (n=384)
- p<.0001

**MYC** + **BCL2** = **“DOUBLE HIT LYMPHOMA”**

proliferation  Anti-apoptosis

Approximately 25-30% of DLBCL have dual protein expression:

<table>
<thead>
<tr>
<th>Condition</th>
<th>BCL2</th>
<th>MYC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse large B-cell lymphoma, NOS</td>
<td>&gt;50%</td>
<td>≥40%</td>
</tr>
<tr>
<td>EBV⁺ DLBCL, NOS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV⁺ mucocutaneous T-cell lymphoma</td>
<td></td>
<td></td>
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<tr>
<td>Burkitt lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burkitt-like lymphoma with 11q deletions</td>
<td></td>
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</tr>
<tr>
<td>High-grade B-cell lymphoma, and/or BCL6 translocations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-grade B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BCLU)</td>
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</tr>
</tbody>
</table>

- Distinction of GCB vs ABC/non-GC type required with use of immunohistochemical algorithm acceptable, may affect therapy.
- Coexpression of MYC and BCL2 considered new prognostic marker (double-expressor lymphoma).
- Mutational landscape better understood but clinical impact remains to be determined.
Double-hit lymphoma

- High grade B-cell lymphoma with translocations of MYC, BCL2, +/- BCL6
- Accounts for 5-7% of all DLBCL
- New category:
  - 2016 WHO category: “High grade B-cell lymphoma, with rearrangements of MYC and BCL2 and/or BCL6”
- Outcome poor with standard therapies

Double-expressing lymphomas

- DLBCL with immunohistochemical expression of MYC (≥40%) and BCL2 (≥50% recommended in 2016 WHO revision) in the absence of translocations
- Accounts for 20-30% of all DLBCL
- Not a distinct entity but an adverse prognostic factor
- Outcome inferior to other DLBCLs treated with R-CHOP, but not as poor as DHL

Majority are germinal center DLBCL

Majority are non-germinal center DLBCL

Slide modified from Jeremy Abramson
TREATMENT OF DHL
Management considerations

• All data to date is retrospective
• All data to date is on DHL and not DLBCL, NOS with DEL
• Role of intensified treatment
• Does achievement of CR matter?
• Impact of consolidative stem cell transplant
• Management of relapsed/refractory disease
• Need for CNS prophylaxis
R-CHOP is inferior to intensive therapy

C

Relapse-Free Survival (%)

0 12 24 36 48 60 72 84

Time (months)

R-CHOP

Intensive

P = .002

D

Overall Survival (%)

0 12 24 36 48 60 72 84

Time (months)

R-CHOP

Intensive

P = .13

No. at risk

R-CHOP 35 25 21 18 17 9 8 7 5 1 0 0 0 0 0

Intensive 124 96 79 67 52 38 32 26 22 16 13 12 11 9 3

DA-EPOCH-R in MYC-R NHL (n=43)
MANAGEMENT OF RELAPSED DLBCL
Autologous transplant in modern era: outcome by prior rituximab exposure and time to relapse

Outcome by prior rituximab AND relapse < 12 months

Outcome by prior rituximab AND relapse > 12 months

Expected survival for rel/ref DLBCL

Patients unable to undergo autologous stem cell transplant have median survivals < 1 year

Chimeric Antigen Receptor (CAR) T-cells

- Uses patients own cells
- Tumor specific
- Can be applied to multiple malignancies

Courtesy N. Frey

Slide courtesy of Dr. Michael Bishop, University of Chicago
Patient Characteristics in CAR-T trials

Patient characteristics in the three largest anti-CD19 multicenter studies CAR T-cells in aggressive B-cell NHLs.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>No of patients enrolled</td>
<td>111 (101)</td>
<td>141 (85)</td>
<td>91 (67)</td>
</tr>
<tr>
<td>Median age, range</td>
<td>58 (23–76)</td>
<td>56 (24–75)</td>
<td>61 (29–82)</td>
</tr>
<tr>
<td>Age ≥ 65</td>
<td>24%</td>
<td>21%</td>
<td>17%</td>
</tr>
<tr>
<td>Lymphoma subtypes</td>
<td>DLBCL, TFL, PMBCL</td>
<td>DLBCL, TFL</td>
<td>DLBCL, TFL (CORE)</td>
</tr>
<tr>
<td>Double hit lymphomas</td>
<td>NR</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>≥3 lines of therapy</td>
<td>69%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Primary refractoriness</td>
<td>26%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Refractory to &gt; 2nd line</td>
<td>77%</td>
<td>NR</td>
<td>76%</td>
</tr>
<tr>
<td>Relapse post ASCT</td>
<td>21%</td>
<td>51%</td>
<td>44%</td>
</tr>
</tbody>
</table>
## Initial results of CAR-T trials

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>No of patients enrolled (treated)</strong></td>
<td>111 (101)</td>
<td>141 (99)</td>
<td>NR (91)</td>
</tr>
<tr>
<td><strong>Median age, range</strong></td>
<td>58 (23–76)</td>
<td>56 (24–75)</td>
<td>61 (29–82)</td>
</tr>
<tr>
<td><strong>Median follow-up</strong></td>
<td>15.4 months</td>
<td>5.6 months</td>
<td>6.3 months</td>
</tr>
<tr>
<td><strong>Costimulatory domain</strong></td>
<td>CD28</td>
<td>4-1BB</td>
<td>4-1BB</td>
</tr>
<tr>
<td><strong>Bridging chemotherapy</strong></td>
<td>Not allowed</td>
<td>Allowed</td>
<td>Allowed</td>
</tr>
<tr>
<td><strong>CART dose</strong></td>
<td>$2.0 \times 10^6$ cells/kg</td>
<td>Median, $3.1 \times 10^8$</td>
<td>DL1 $5.0 \times 10^7$ cells$^a$</td>
</tr>
<tr>
<td><strong>Conditioning regimen</strong></td>
<td>Flu 30 mg/m² x3d</td>
<td>Flu 25/m² x 3d</td>
<td>Flu 30 mg/m² x3d</td>
</tr>
<tr>
<td></td>
<td>Cy 500 mg/m² x3d</td>
<td>Cy 250 mg/m² x3d or B 90 mg/m² x2d</td>
<td>Cy 300 mg/m² x3d</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%ORR (%CR)</td>
<td>82 (54)</td>
<td>59 (43)</td>
<td>84 (61)</td>
</tr>
<tr>
<td>3-mo %ORR (%CR)</td>
<td>44 (39)</td>
<td>45 (37)</td>
<td>65 (53)</td>
</tr>
<tr>
<td>mDOR</td>
<td>11.1 months</td>
<td>NR</td>
<td>9.2 months</td>
</tr>
</tbody>
</table>
Published CAR-T results

“Axi-cel”

“Tisa-cel”
CAR-T IN DLBCL: ONE YEAR LATER...
“Real-world” Axi-cel

Seventeen US academic
N= 165 with 78% pts completing axi-cel infusion
Grade 3 CRS in 7%
Grade 3 NE in 31%
ORR at Day 30 in 112 evaluable pts was 79% with 50% CR
PFS and OS data to be presented

<table>
<thead>
<tr>
<th>% meeting ZUMA-1 eligibility criteria</th>
<th>ZUMA-1</th>
<th>This Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>N infused pts</td>
<td>108</td>
<td>165</td>
</tr>
<tr>
<td>% meeting ZUMA-1 eligibility criteria</td>
<td>100%</td>
<td>51%</td>
</tr>
<tr>
<td>Age median range</td>
<td>65/27/61</td>
<td>57/41-84%</td>
</tr>
<tr>
<td>ECOG 0 or 1</td>
<td>100%</td>
<td>64%</td>
</tr>
<tr>
<td>Prior autologous transplant</td>
<td>23%</td>
<td>31%</td>
</tr>
<tr>
<td>DLBCL including HGBCL, not FL or PMBCL</td>
<td>78%</td>
<td>61%</td>
</tr>
<tr>
<td>ORR/CR</td>
<td>82%/58% [Best]</td>
<td>79%/50% [Day 30]</td>
</tr>
<tr>
<td>Grade 3 or higher toxicity</td>
<td>CRS 13%/NEs 31%</td>
<td>CRS 7%/NEs 31%</td>
</tr>
</tbody>
</table>
“Real-world” Axi-cel

- N=73 evaluable patients
- At 4m median f/u, best ORR and CRR was 64% and 41% among those treated.
- Predictors of poor outcome:
  - Poor PS, tumor bulk, high IPI, baseline CRP, prior ibrutinib
  - 96% all-grade CRS, 17% grade 3-4 CRS

**AUTHORS’ CONCLUSION:** “The ORR and CR rate are lower than the 82% and 54% reported on ZUMA-1. This may reflect inclusion of sicker patients with a poorer PS, and/or with different histologies (ie transformation from non-FL). Outcomes were significantly worse in high risk lymphomas, reflected by IPI, PS, tumor bulk, and baseline CRP. Rates of CRS and NT were similar to ZUMA-1”
New relapsed DLBCL algorithm

1st LINE

R/R

SALVAGE #1

CAR T

*R/R

†PR

CR

SALVAGE #2

CAR T

ASCT

CR

RELAPSE < 12 MO.

RELAPSE > 12 MO.

CR

CAR T

CAR T

STANDARD RX

CR

‡R/R

CHOW BLOOD 2018
If CAR-T doesn’t work...

- N=51
- Initial progression did worse than delayed progression
  - Med OS 5.1 m vs. 13.6m

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=51)</th>
<th>Initial PD (N=27)</th>
<th>Delayed PD (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17 (33.3%)</td>
<td>8 (29.6%)</td>
<td>9 (37.5%)</td>
</tr>
<tr>
<td>Male</td>
<td>34 (66.7%)</td>
<td>19 (70.4%)</td>
<td>15 (62.5%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HGBCL</td>
<td>11 (21.6%)</td>
<td>3 (11.1%)</td>
<td>8 (33.3%)</td>
</tr>
<tr>
<td>DLBCL</td>
<td>29 (56.9%)</td>
<td>18 (66.7%)</td>
<td>11 (45.8%)</td>
</tr>
<tr>
<td>PMBCL</td>
<td>3 (5.9%)</td>
<td>2 (7.4%)</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>MCL</td>
<td>8 (15.7%)</td>
<td>4 (14.8%)</td>
<td>4 (16.7%)</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>60 (26-75)</td>
<td>60 (29-70)</td>
<td>59 (26-75)</td>
</tr>
<tr>
<td>Additional therapy after progression</td>
<td>39 (76.5%)</td>
<td>17 (63.0%)</td>
<td>22 (91.7%)</td>
</tr>
<tr>
<td>Next line of therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allogeneic Transplant</td>
<td>1 (2.6%)</td>
<td>0 (0.0%)</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>CAR T</td>
<td>14 (35.9%)</td>
<td>6 (35.3%)</td>
<td>8 (36.4%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>7 (17.9%)</td>
<td>5 (29.4%)</td>
<td>2 (9.1%)</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>3 (7.7%)</td>
<td>1 (5.9%)</td>
<td>2 (9.1%)</td>
</tr>
<tr>
<td>Intrathecal</td>
<td>1 (2.6%)</td>
<td>0 (0.0%)</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Radiation</td>
<td>3 (7.7%)</td>
<td>1 (5.9%)</td>
<td>2 (9.1%)</td>
</tr>
<tr>
<td>Targeted</td>
<td>10 (25.6%)</td>
<td>4 (23.5%)</td>
<td>6 (27.3%)</td>
</tr>
<tr>
<td>Next treatment on clinical trial</td>
<td>5 (9.8%)</td>
<td>3 (11.1%)</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>Allogeneic transplant after progression</td>
<td>4 (7.8%)</td>
<td>1 (3.7%)</td>
<td>3 (12.5%)</td>
</tr>
</tbody>
</table>
What if transplant and/or CAR-T are not options?

• Chemoimmunotherapy
  – Gemcitabine-based regimens
  – BR

• Non-chemotherapy agents include:
  – Ibrutinib (for non-GCB only and if insurance allows)
  – Len/rituximab

• Best supportive care
Targeting the macrophage checkpoint: 5F9 plus rituximab

- Favorable toxicity profile
- No chemotherapy
Polatuzumab plus BR in rel/ref DLBCL

**Ph Ib safety run-in: Pola + BR or BG**

- **Cohort 1a**
  - R/R DLBCL
  - 1.8mg/kg + BR (n=6)

- **Cohort 1b**
  - R/R DLBCL
  - 1.8mg/kg + BR (n=6)

**Ph II randomization: Pola + BR versus BR**

- R/R DLBCL
- 1:1 randomization
- Pola + BR (n=40)
- BR (n=40)

**Ph II expansion: Pola + BG**

- R/R DLBCL
- Pola + BG (n=20)

---

**Figure 2a. Randomized DLBCL cohort: Kaplan Meier curves for PFS**

- B, bendamustine; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma
- vedotin; R, rituximab

**Figure 2b. Randomized DLBCL cohort: Kaplan Meier curves for OS**

- B, bendamustine; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma
- N, Number of patients at risk
Please join us!!

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