How should we treat double hit and double expressor lymphomas?

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Consulting Advice

AstraZeneca, Celgene, Juno Therapeutics, Janssen, Verastem
Outline

Diagnosis

Treatment

CNS prophylaxis

Role of stem cell transplant

Novel therapeutic strategies
Diffuse large B-cell lymphoma, NOS
- Germinal center B-cell type (GCB)
- Activated B-cell (ABC)/non-GCB
  
  Co-expression of MYC and BCL2 (double expressor lymphoma) as prognostic marker

High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 translocations

  Double hit lymphoma

High grade B-cell lymphoma, NOS
Double and triple hit lymphoma (DHL/THL)

Defined by **chromosomal translocations** involving MYC, BCL2 and/or **BCL6** genes

- **DHL** – 60-80% MYC / BCL2, 10-18% MYC / BCL6
- **THL** – MYC / BCL2 / BCL6

Characterized by **refractoriness to standard chemotherapy**

OS 5-24 months when treated with R-CHOP

**Extranodal involvement** more common than in non-DHL/THL

Incidence estimated as **5-10% (DHL) and 1% (THL) of DLBCL**
Double protein expressor lymphoma (DEL)

Increased expression of MYC and BCL2 by IHC (without gene rearrangements)

MYC \geq 40\% and BCL2 \geq 50\%

More common than DHL

34\% in a study of 466 DLBCL patients

Indicator of less favorable prognosis than standard DLBCL but not separate category in WHO 2016

Double protein expressors have intermediate prognosis compared to classical DLBCL and DHL.

Most DHL are GCB and DEL are ABC DLBCL

Friedberg J. Blood. 2017, 130:590-596.
MYC, BCL2, and BCL6 rearrangements by molecular subtype

A) Image of cells

B) Pie chart showing percentages of different subtypes:
- ABC/non GCB: 6.5%
- GCB: 17.7%
- Unclassified: 5%

C) Summary:
- MYC-R = 12.2% of 1228 biopsies with DLBCL morphology
- MYC: 5.3%
- MYC/BCL2: 4.8%
- MYC/BCL6: 1.2%
- MYC/BCL2/BCL6: 1.7%
- HGBL-DH/TH = ~8% with DLBCL morphology

R-CHOP vs DA-EPOCH-R (Alliance 50303)

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP</th>
<th>DA-EPOCH-R</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>89%</td>
<td>89%</td>
<td>0.983</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>62%</td>
<td>61%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>27%</td>
<td>27%</td>
<td></td>
</tr>
</tbody>
</table>

Event Free Survival

Overall Survival

Median follow-up 5.0 y
HR=1.14 (0.82-1.61)
p = 0.4386

Slide courtesy of John P. Leonard
R-CHOP vs DA-EPOCH Treatment Regimen

**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-EPOCH-R**

- Rituximab 375 mg/m² d1
- Etoposide 50 mg/m²/d CI d1-4*
- Doxorubicin 10 mg/m²/d CI d1-4*
- Vincristine 0.4 mg/m²/d CI d1-4
- Cyclophosphamide 750 mg/m² d5*
- Prednisone 60 mg/m² bid d1-4
- G-CSF 5 µg/kg d6-ANC recovery

q3w × 6

**Double expressor Lymphomas (DEL)**

**Double and triple hit Lymphomas (DHL/THL)**

*Slide courtesy of John P. Leonard*
DA-EPOCH-R is the accepted front line regimen in DHL/THL but outcomes remain suboptimal

Best Response

Progression Free Survival

PFS 21.6 versus 7.8 mos

Event Free Survival

Overall Survival

CNS relapse in DHL/THL/DEL

Incidence in all DLBCL: 4-7%

Incidence in DEL/DHL: 10-13%

Timing: usually within 2 years from initial diagnosis

Median survival: 4 months after CNS relapse detected

CNS IPI:

- Kidney and/or adrenal gland involvement
- Age > 60 years
- Elevated LDH
- ECOG PS > 1
- Stage III/IV
- >1 extranodal site

High risk sites: testes, breast, paranasal sinuses, paraspinal, bone marrow

Pfreundschuh et al. Lancet Onc;2008;9:105-116
Oki Y et al. BJH. 2014;166:891-901.
Savage Blood 2016;127:2182-2188.
CNS prophylaxis in DHL is associated with improved OS in pts without baseline CNS disease

Median overall survival:

CNS- w/ MTX = 45 months
CNS- w/o MTX = 14 months
CNS+ = 6 months

DHL/THL patients should undergo MRI/LP at baseline; those with high risk sites should receive methotrexate-based prophylaxis

Abramson JS. Cancer. 2010;4283-4290.
The role and timing of SCT in DHL/THL is not clear

Any time N=83 (27%)
In CR1 N=53 (17%)
39 auto, 14 allo

Any time N=26 (20%)
In CR1 N=23 (18%)
24 auto, 2 allo

In CR2 4Y OS
Not DHL = 67%
DHL = 25%

Oki Y et al. BJH. 2014;166:891-901.
Novel therapeutic strategies in DHL/DEL/THL

1. Target BCL2, MYC or BCL6

2. Target alternate proteins involved in multiple oncogene networks (XPO1, eIF4E)
Venetoclax + DA-EPOCH-R in Newly Diagnosed DLBCL

Phase 1 investigator-initiated trial (NCT03036904)

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Venetoclax dose</th>
<th>Cycle 1 Schedule</th>
<th>Cycles 2-6 Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>400mg PO QD</td>
<td>Days 3-7</td>
<td>Days 1-5</td>
</tr>
<tr>
<td>0</td>
<td>400 mg PO QD</td>
<td>Days 3-12</td>
<td>Days 1-10</td>
</tr>
<tr>
<td>1</td>
<td>600 mg PO QD</td>
<td>Days 3-12</td>
<td>Days 1-10</td>
</tr>
<tr>
<td>2</td>
<td>800 mg PO QD</td>
<td>Days 3-12</td>
<td>Days 1-10</td>
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**Primary objective:**
Determine MTD, R2P2 dose, and DLTs of venetoclax in combination with DA-EPOCH-R

**Secondary objectives:**
Evaluate toxicities
Evaluate response rate and EFS12

**Current status:** 18 patients enrolled. Expansion cohort planned. Follow up phase 2 study planned.
Exportin 1 (XPO1)

XPO1 is the major nuclear export protein of

- Tumor Suppressor Proteins (TSPs)
- Oncogenic mRNAs (e.g., c-Myc, Bcl-2, Bcl-6)

XPO1 acts in cancer cells to

- Inactivate TSPs by extruding them from nucleus
- Contribute to cell proliferation

**XPO1 Expression in DLBCL Tissues (by IHC)**

<table>
<thead>
<tr>
<th>XPO1 Expression</th>
<th>% of XPO1-positive cells</th>
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<tbody>
<tr>
<td></td>
<td>&gt;5% &lt;30%</td>
</tr>
<tr>
<td>n=58</td>
<td>46.5%</td>
</tr>
</tbody>
</table>

**XPO1 Expression in Chemo-sensitive and Chemo-refractory DLBCL Patient Cells**

| Sustained Response (CR 2 years) | n=23 | 36.3 | 18.1% |
| Relapsed/Refractory             | n=20 | 60%  | 40%   |

**XPO1 is inhibited by selinexor**

Marullo, AACR 2015
Selinexor + RICE in Relapsed/Refractory Aggressive B-cell lymphomas

Phase 1 investigator-initiated trial (NCT02471911)

RICE

Dexamethasone

Selinexor

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>20</td>
</tr>
<tr>
<td>-1</td>
<td>40</td>
</tr>
<tr>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
</tr>
</tbody>
</table>

Cycle 1, D1

D1, 2, 3, 4, 5, D7

D3, D5, D7

= Drug administration day

= Tumor biopsy

= Peripheral blood

Weeks

-2 -1 1 2

Tumor Biopsy/Peripheral Blood for Correlative Studies

Within 2 months and prior to first dose of selinexor

D3 of cycle 1

D8 +/- 3 days of cycle 1

Weill Cornell Medicine
Eukaryotic translation initiation factor 4E (eIF4E)

- Facilitates translation of mRNAs (MYC, BCL2, BCL6)
- Preferentially exports mRNAs (MYC, BCL2, BCL6)

Laboratories of Leandro Cerchietti and Kathy Borden
eIF4E is overexpressed in DHL/THL and is inhibited by ribavirin

**eIF4E Expression**

- eIF4E positivity:
  - 0
  - 10%
  - 25%
  - 32%
  - 33%
  - 3 (6 pts. with double or triple-hit lymphomas (p > 0.001)

**Triple Hit Patient-Derived Xenograft Model**

Pilot IIT of Ribavirin in B-cell lymphomas (NCT03585725) currently enrolling at WCM

Treatment Summary

Double and triple hit lymphomas – DA-EPOCH-R x 6

Double expressor lymphomas – R-CHOP x 6

High risk sites for CNS relapse – IT methotrexate during DA-EPOCH-R, consider high dose methotrexate after completion

Stem cell transplant – insufficient evidence to support in CR1

➢ Enroll on clinical trials with novel agents when possible