DLBCL and Double Hit Lymphoma: Diagnosis and Treatment (First Line and Relapsed Disease)

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Disclosures for Burhan Ferhanoğlu

Participated in an advisory board: Roche / Janssen and Janssen / Takeda Pharmaceutical / ABBVIE
Learning Objectives

• Evaluate de-novo DLBCL patients; determine their risk scores and management.

• Select patients to administer CNS prophylaxis

• Manage the treatment of relapsed DLBCL patients

• Diagnose and evaluate patients with DHL and DEL and their management
Introduction

Treatment of early stage DLBCL

Treatment of advanced stage disease

CNS prophylaxis strategy

Treatment of extranodal DLBCL

Trials & New approaches

Objectives

What should be emphasized in the pathology report?

Treatment of early stage DLBCL

Treatment of advanced stage disease

Double Hit, Double Expressor Lymphoma

Treatment of extranodal DLBCL

CNS prophylaxis strategy

Treatment of relapsed/refractory DLBCL

Trials & New approaches
Introduction

DLBCL is the most common lymphoid malignancy in adults
Almost 35% to 40% of lymphomas in Western countries
32% of lymphomas in Turkey

The estimated incidence is 7 to 8 cases per 100,000/year

The peak incidence of DLBCL is in the sixth decade.

Sant et al. Blood 2010
Fisher et al. Oncogene 2004
DLBCL, NOS and other Large B-cell Disorders: WHO 2008

DLBCL is a heterogenous group of disorders with varied natural history, genetic abnormalities, and response to therapy.

Diffuse large B-cell lymphoma (DLBCL), NOS 30%

Primary mediastinal large B-cell lymphoma 3%

Variants: ~5%

✓ T-cell/histiocyte rich large B-cell lymphoma
✓ Primary cutaneous DLBCL, leg type
✓ EBV positive DLBCL
✓ DLBCL associated with chronic inflammation
✓ Lymphomatoid granulomatosis (EBV)
✓ Intravascular large B-cell lymphoma
✓ ALK positive large B-cell lymphoma
✓ Primary CNS large B cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)

*Germinal-centre B-cell-like (GCB)*

*Activated B-cell-like (ABC)*

**DLBCL subtypes**

T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the CNS
Primary cutaneous DLBCL, leg type

**Epstein-Barr virus–positive DLBCL, NOS of the elderly**

*EBV+ mucocutaneous ulcer*

**Primary mediastinal (thymic) large B-cell lymphoma**

Intravascular large B-cell lymphoma
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
ALK-positive DLBCL
Plasmablastic lymphoma
Primary effusion lymphoma

*HHV8-positive, DLBCL, NOS*

B-cell lymphoma, with features intermediate between DLBCL and classical Hodgkin Lym.

B-cell lymphoma, with features intermediate between DLBCL and Burkitt lymphoma

*High grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements, NOS*
Large B cells lymphoma: a long road before a revolution...

Integrative Genetic and Clinical Analysis through Whole Exome Sequencing in 1001 Diffuse Large B Cell Lymphoma (DLBCL) Patients Reveals Novel Disease Drivers and Risk Groups

Anupama Reddy & Jenny Zhang et al Cell 2017
Genomic Lanscape of DLBCL

A better understanding of the genomic markers, associated with a response, will directly allow the development of patients-selection strategies that only treat patients who are most likely to respond
What should be emphasized in the pathology report?
What should be emphasized in the pathology report?

Excisional biopsy remains the optimal method for diagnosis.

Immunohistochemical panel should be planned to confirm B-cell lineage and, must be comprehensive enough to highlight possible variant forms such as:

- Immunoblastic lymphoma
- PMLBCL
- EBV positive DLBCL
- T cell/histiocyte rich B cell lymphoma
- Primary cutaneous DLBCL, leg type
What should be emphasized in the pathology report?

All cases of DLBCL should be tested for MYC rearrangement by FISH, and if it is positive, it should be confirmed by FISH analysis.

The presence of MYC, BCL2, and Bcl6 rearrangements is also important. The correlation between MYC protein expression and MYC rearrangement and MYC protein expression is less clear, as approximately one-third of rearranged cases show negative or low expression by immunohistochemistry.

NEW APPROACH

Valera A. Mod Pathol. 2016
Prognostic parameters
Molecular subtypes of DLBCL

# Clinical predictors of outcome

<table>
<thead>
<tr>
<th></th>
<th>IPI</th>
<th>R-IPI</th>
<th>NCCN-IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&gt;40 to ≤60</td>
<td>1</td>
<td>1</td>
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<tr>
<td>&gt;60 to ≤75</td>
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<tr>
<td>&gt;75</td>
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<tr>
<td><strong>LDH normalized</strong></td>
<td></td>
<td></td>
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<tr>
<td>&gt;1 to ≤3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt;3</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>Ann Arbor stage III-IV</strong></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Extranodal disease</strong></td>
<td></td>
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<tr>
<td>&gt;1 site</td>
<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>Any if BM, CNS, liver/GI tract or lung</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Performance status ≥2</strong></td>
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<tr>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0-1</td>
<td>0</td>
<td>0-1</td>
</tr>
<tr>
<td>Low-intermediate</td>
<td>2</td>
<td>1-2</td>
<td>2-3</td>
</tr>
<tr>
<td>High-intermediate</td>
<td>3</td>
<td></td>
<td>4-5</td>
</tr>
<tr>
<td>High</td>
<td>4-5</td>
<td>≥3</td>
<td>≥6</td>
</tr>
</tbody>
</table>
Outcome of DLBCL with R-CHOP

Sehn et al. Blood 2007

Coiffier et al. Blood 2010

Age +16
Newly diagnosed DLBCL
Treated with R-CHOP

Age 60-80
Newly diagnosed DLBCL
Treated with CHOP vs R-CHOP
IPI vs NCCN-IPI in High Risk DLBCL

Overall Survival according to IPI (p<0.001)

- Low Risk
- Low-Intermediate Risk
- High-Intermediate Risk
- High Risk

Overall Survival according to NCCN-IPI (p<0.001)

- Low Risk
- Low-Intermediate Risk
- High-Intermediate Risk
- High Risk

Ozturk & Ferhanoğlu. Leukemia & Lymphoma 2015

67% vs 44%

64% vs 29%
Treatment of early stage DLBCL
Treatment of early stage disease

Early stage disease is commonly defined as stage I or non-bulky stage II disease.

Patients with non-bulky stage 1A disease (IPI=0) presenting at sites associated with low morbidity for RT (i.e. Axilla, neck, groin)

Patients who do not tolerate full course CT due to comorbidities or advanced age

6 R-CHOP is an alternative to combined therapy

Miller TP. NEJM, 1998
Shenkier TN. JCO, 2002
Bonnet C. JCO, 2007
Treatment of limited stage Diffuse Large B Cell Lymphoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Age (median)</th>
<th>Number</th>
<th>Risk factors</th>
<th>Treatment arms</th>
<th>PFS (% years)</th>
<th>OS (% years)</th>
<th>In-field relapse (%)</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG 8736</td>
<td>59</td>
<td>200</td>
<td>68% stage I, 3% bulky</td>
<td>CHOP x 4 + IRRT</td>
<td>76(5), 40(15)</td>
<td>82(5), 46(15)</td>
<td>87(5), 74(15)</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>201</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Kumar et al. Curr Treat Options in Oncol 2016
SWOG S8736 PFS and OS Final & Long-Term Analysis

PFS (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5-year PFS (%, 95% CI)</th>
<th>10-year PFS (%, 95% CI)</th>
<th>15-year PFS (%, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP8</td>
<td>69 (60.6 to 75.4)</td>
<td>55 (46.9 to 62.8)</td>
<td>40 (32.3 to 48.1)</td>
</tr>
<tr>
<td>CHOP3RT</td>
<td>76 (68.6 to 82.1)</td>
<td>55 (46.5 to 62.3)</td>
<td>41 (33.2 to 49.1)</td>
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</tbody>
</table>

P = .73*

OS (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5-year OS (%, 95% CI)</th>
<th>10-year OS (%, 95% CI)</th>
<th>15-year OS (%, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP8</td>
<td>76 (68.3 to 82.1)</td>
<td>61 (53.0 to 68.5)</td>
<td>43 (35.2 to 51.3)</td>
</tr>
<tr>
<td>CHOP3RT</td>
<td>84 (77.0 to 88.8)</td>
<td>63 (55.0 to 70.3)</td>
<td>47 (38.8 to 54.8)</td>
</tr>
</tbody>
</table>

P = .38*

Stephens et al. JCO 2016
Introduction

What should be emphasized in the pathology report?

Treatment of early stage DLBCL

Treatment of advanced stage disease

Double Hit, Double Expressor Lymphoma

Treatment of extranodal DLBCL

CNS prophylaxis strategy

Treatment of relapsed/refractory DLBCL

Trials & New approaches

Treatment of advanced stage disease
NHL in elderly: Rituximab era
LNH 98.5 study: Design

- DLBCL
- Age 60–80 years
- No prior treatment
- PS 0–2
- Stage II–IV

Rituximab: 375 mg/m² on day 1
Cyclophosphamide: 750 mg/m² on day 1
Doxorubicin: 50 mg/m² on day 1
Vincristine: 1.4 mg/m² (up to 2 mg/m²) on day 1
Prednisolone: 40 mg/m²/d days 1–5

Rituximab + CHOP q3wk x 8

CHOP q3wk x 8
Treatment of advanced stage disease

R-CHOP is the standard treatment for patients with advanced stage DLBCL based on GELA (LNH98-5) study.

Coiffier B.Blood.2010
Held G.JCO.2014
Wilson WH:Haematologica 2012

<table>
<thead>
<tr>
<th></th>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A: CHOP</td>
<td>120</td>
<td>79% (95)</td>
<td>21% (26)</td>
<td>1.791 (1.142 - 3.723)</td>
</tr>
<tr>
<td>Arm B: CHOP + Rituximab</td>
<td>121</td>
<td>66% (89)</td>
<td>34% (41)</td>
<td>2.883 (1.807 - 7.065)</td>
</tr>
</tbody>
</table>
R-CHOP: a consistent clinical benefit

2) Sehn et al. JCO 2005
3) Habermann et al. JCO 2006
Even in Rituximab era, more than one third of DLBCL are not cured …

Outcome for all patients with DLBCL treated with R-CHOP in British Columbia between 2001 and 2013

Salvage Regimens With Autologous Transplantation for Relapsed Large B-Cell Lymphoma in the Rituximab Era

N=1660

N=187

Sehn & Gascogne Blood 2015

Gisselbrecht et al JCO 2010
DLBCL: Strategies to improve beyond R-CHOP-21

Optimization of the use of Anti CD 20

Rituximab / Obinutuzumab

HOVON R2 CHOP no difference

R-ACVBP > R-CHOP

(in subsets of pts: aalPl 1, ABC ++)

R-CHOP vs R-CHOP / Alliance P

ASH 2016

DA-R-EPOCH

No difference ASH 2016

Pfreundschuh, Lancet Oncol, Feb 2008
Delarue, Lancet Oncol May 2013
Cunningham, Lancet Oncol May 2013
Wilson, Haematologica, May 2013
Molina, JCO Dec 2014
Smith, NEJM, Oct 2013

Molina, JCO Dec 2014
Wilson, Haematologica, May 2013
Smith, NEJM, Oct 2013

Cunningham, Lancet Oncol May 2013
Delarue, Lancet Oncol May 2013
Wilson, Haematologica, May 2013
Molina, JCO Dec 2014
Smith, NEJM, Oct 2013
DLBCL: Strategies to improve beyond R-CHOP-21

Intensification of R-CHOP-21?

Better predict / evaluate quality of response?

Take into consideration biological diversity of DLBCL
Focus on: GCB / non GCB
### Prospectives Study of First Line Consolidation HDT in the Rituximab Era

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy</th>
<th>Patients</th>
<th>n</th>
<th>HDT vs Std</th>
<th>OS HDT vs Std</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG 9704*</td>
<td>CHOP (+/-)R +/- HDT</td>
<td>aalPl 2,3 &gt; PR to Induction</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>2 yrs</td>
<td>2 yrs OS 74% vs 71%</td>
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<td></td>
<td></td>
<td>69% vs 55%</td>
<td></td>
</tr>
<tr>
<td>DSHNHL 2002-1**</td>
<td>R-CHOEP vs R-MegaCHOEP</td>
<td>aalPl 2,3</td>
<td>75</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>3 yrs</td>
<td>3 yrs 77% vs 85%</td>
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<td>70% vs 74%</td>
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<td>77% vs 85%</td>
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<tr>
<td>GOELAMS 075***</td>
<td>RCHOP 14 vs RCHOP 14, MTX + AraC, HDT</td>
<td>aalPl 2,3</td>
<td>286</td>
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<td></td>
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<td></td>
<td>3 yrs</td>
<td>3 yrs 80% vs 88%</td>
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<td>92% vs 80%</td>
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<td></td>
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<td></td>
<td></td>
<td>80% vs 88%</td>
<td></td>
</tr>
<tr>
<td>DLCL04**</td>
<td>RCHOP 14 +/- HDT</td>
<td>aalPl 2,3</td>
<td>399</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 yrs</td>
<td>3 yrs 81% vs 78%</td>
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<td></td>
<td></td>
<td></td>
<td>70% vs 59%</td>
<td></td>
</tr>
</tbody>
</table>

*PFS advantage in 2 studies
No OS advantage in any study

*Stiff et al. NEJM 2013
**Schmitz et al. Lancel Oncol 2012
***LeGouille et al. JCO 2011
****Chiappella et al. Lancet Oncol 2017
DLBCL: Strategies to improve beyond R-CHOP-21

Better predict / evaluate quality of response?

Take into consideration biological diversity of DLBCL
Focus on: GCB / non GCB
Primary end point is EFS

Mamot et al JCO 2015
Early treatment intensification with R-ICE and 90Y-ibritumomab tiuxetan (Zevalin)-BEAM stem cell transplantation in patients with high-risk diffuse large B-cell lymphoma patients and positive interim PET after 4 cycles of R-CHOP-14

Mark Hertzberg,1 Maher K. Gandhi,2,3 Judith Trotman,4 Belinda Butcher,5 John Taper,6 Amanda Johnston,7 Devinder Gill,8 Shir-Jing Ho,8 Gavin Cull,9 Keith Fay,10 Geoff Chong,11 Andrew Grigg,12 Ian D. Lewis,13 Sam Milliken,14 William Renwick,15 Uwe Hahn,16 Robin Filshie,17 George Kannourakis,18 Anne-Marie Watson,19 Pauline Warburton,20 Andrew Wirth,21 John F. Seymour,22 Michael S. Hofman23 and Rodney J. Hicks,23 on behalf of the Australasian Leukaemia Lymphoma Group (ALLG)
Enrolled = 162
Excluded = 11
did not fulfill I/E criteria
Failed to reach iPET = 8
PD = 1
Toxicity = 5 (bowel perforation = 2, hepatic failure = 1, cardiac = 2)
Dose-delays = 2

Eligible = 151

R-CHOP-14 x 4

iPET status = 143

29%
iPET-neg = 101
R-CHOP x 2 + R x 2: n= 96
PD = 3; toxicity = 1; R x 1 omitted=1

iPET-pos = 42
R-ICE x 3 + Z-BEAM: n = 32
PD = 6; consent w/drawn = 3; 2nd cancer = 1

DLBCL: IPI = L-I to H, L + bulk (≥ 7.5 cm)
Age ≤ 70 yrs; fit for HDT

*1. Delay #5 R-CHOP-14 x 7 days: iPET d17-20 of cycle #4.
2. Central PET consensus reporting by 2 PET physicians: IHP criteria
PFS is equivalent: iPET- vs iPET+

n=143: Median follow up = 35 m

iPET- 74% 2-yr

iPET+ 67% 2-yr

tzberg et al. Haematologica 2017
IPI 3-5: PFS and OS are equivalent

**PFS:**

iPET- vs. iPET+

**OS:**

iPET- vs. iPET+

**PFS:**

\[ P = 0.79 \]

**OS:**

\[ P = 0.98 \]
iPET-positive
Deauville Score 4 vs. 5

**PFS**

Score 4: 88% 2-yr

Score 5: 33% 2-yr

\[ P = 0.0002 \]

**OS**

Number at risk:
- Deauville = 4: 27
- Deauville = 5: 15

Number of patients:
- Deauville = 4: 22, 22, 17, 9, 6
- Deauville = 5: 7, 5, 5, 2, 1

\[ \text{Deauville } = 4 \quad - - - - - \quad \text{Deauville } = 5 \]
DLBCL: Strategies to improve beyond R-CHOP-21

Take into consideration biological diversity of DLBCL
Focus on: GCB / non GCB

Intensification of

quality of response?
Frontline rituximab, cyclophosphamide, doxorubicin, and prednisone with bortezomib (VR-CAP) or vincristine (R-CHOP) for non-GCB DLBCL

Fritz Offner, Olga Samoilova, Evgenii Osmanov, Hyeon-Seok Eom, Max S. Topp, João Raposo, Viacheslav Pavlov, Deborah Ricci, Shalini Chaturvedi, Eugene Zhu, Helgi van de Velde, Christopher Enny, Aleksandra Rizo and Burhan Forhanoglu
Phase 2 Randomized Trial Comparing 6 Cycles of Standard Brcap (bortezomib, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) Treatment in Young Patients with DLBCL: Analysis

Adding Bortezomibe to R-CHOP Backbone, did not targeting NF-κB pathway, did not show any improvement in non-GCB DLBCL

Gonzalez-Barca et al. ASH 2015 Abstract#1514
Introduction

Objectives

What should be emphasized in the pathology report?

Treatment

- Treatment of early stage DLBCL
- Treatment of advanced stage DLBCL
- Treatment of extranodal DLBCL
- Treatment of CNS disease
- Treatment of refractory DLBCL
- Treatment of relapsed DLBCL

Double Hit, Double Expressor Lymphoma

High grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements, NOS (WHO 2016)

Trials & New approaches
Double Hit and Double Expressor Lymphomas

Double Hit Lymphoma is defined as rearrangement of MYC with BCL2 or BCL6
It constitutes 10% of GCB-like DLBCL
DLBCL with high MYC >40% , plus BCL2 (50-70%) protein expression by IHC without genetic rearrangements is called DEL
Majority of DHL = GCB like
Majority of DEL = ABC like
Data from the Mitelman database of chromosomal alterations in cancer;

- 62% of these newly categorized myc rearranged lymphomas involve bcl-2 translocations,
- 18% involve bcl-6 translocations,
- and the remaining cases are triple-hit lymphomas

Aukemia et al 2011
Oliveria et al. 2017
Figure 1. New WHO classification of lymphoma. Regardless of morphology, if myc and bcl-2 rearrangements are present, they are now categorized as high-grade B-cell lymphoma with myc and bcl-2 and/or bcl-6 rearrangements. HGBL, high-grade B-cell lymphoma; NOS, not otherwise specified. Adapted from Swerdlow et al.\textsuperscript{21}
(A) FISH for MYC using MYC break-apart probe in DLBCL. (B) In the study of Scott et al, GCB, ABC, and unclassified DLBCLs represent 50%, 38%, and 12% of all DLBCLs, respectively. MYC-R DLBCL (yellow) accounts for 17.7% of GCB, 6.5% of ABC, and 5% of unclassified DLBCLs. (C) MYC-R was detected in 12.2% of cases with DLBCL morphology, including 5.3% of DLBCLs with MYC sole rearrangement; 4.2% of MYC/BCL2 HGBL-DH; 1.2% of MYC/BCL6 HGBL-DH; and 1.7% of MYC/BCL2/BCL6 HGBL-TH. Overall, HGBL-DH/TH represents ~8% of cases with DLBCL morphology.
Characteristics of DHL at presentation:

- Median age: 7th decade
- Stage III/IV
- HI/H IPI
- LDH > nl
- Extranodal sites (incl. CNS)
Overview: OS in DHL and DEL (DLBCL)

Fig 2. Overall survival of patients with diffuse large B-cell lymphoma and cytogenetic MYC/BCL2 double hit lymphoma (DHL, grey), MYC/BCL2 co-expressing lymphoma (yellow) and all remaining cases (blue). Reprinted with permission. © 2012 American Society of Clinical Oncology. All rights reserved; Johnson et al (2012).
## MYC-R DLBCL: Inferior Outcome with CHOP/R-CHOP

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Treatment</th>
<th>MYC-R %</th>
<th>DHL % (BCL-2-R)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klapper et al.</td>
<td>177</td>
<td>CHOP or CHOEP</td>
<td>8%</td>
<td>ND</td>
<td>OS in MYC-R worse</td>
</tr>
<tr>
<td>Barrans et al.</td>
<td>303</td>
<td>R-CHOP</td>
<td>14%</td>
<td>11%</td>
<td>2 yr OS 35% (MYC-R) vs 61% (MYC-N)</td>
</tr>
<tr>
<td>Savage et al.</td>
<td>135</td>
<td>R-CHOP</td>
<td>9%</td>
<td>2%</td>
<td>5 yr OS 33% (MYC-R) vs 72% (MYC-N)</td>
</tr>
<tr>
<td>Cunningham et al.</td>
<td>1080</td>
<td>R-CHOP-14 or R-CHOP-21</td>
<td>6%</td>
<td>3%</td>
<td>2 yr OS not inferior in MYC-R</td>
</tr>
</tbody>
</table>
Double-hit Lymphoma Results

- **129 patients**
  - Median age 62 (17-84)
  - 65% are male

- **IPI score**
  - 0-1: 13%
  - 2-3: 61%
  - 4-5: 26%

- **DLBCL or BCLU**: 92%

- **Translocations**
  - MYC: 81%
  - BCL2: 84%
  - BCL6: 12%
  - MYC & BCL2: 72%
  - Triple hit: 11%

- **GCB by IHC**: >90%

Oki et al. BJH 2014
EFS improved following intensive therapy
High IPI: Worse EFS – N=129

Oki et al. BJH 2014
Translocation Partner does not influence EFS

Oki et al. BJH 2014
OS is better in patients receiving DA-EPOCH-R

- R-CHOP: 57 (44%)
- R-EPOCH: 28 (22%)
- R-HCVAD/MA: 34 (26%)
- Diğer: 10 (7%)

Oki et al. BJH 2014
CNS involvement / relapse risk is high in DHL

Bone marrow involvement
ECOG ≥2

CNS relapse risk at 3 years decreased from 15% to 5% with IT prophylaxis (p=0.017)

Oki et al. BJH 2014
No improvement in EFS & OS in patients with ASCT in first CR
Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis

- 311 patients
- Median age 60 (19-87)
- 61% are male
- Stage III or IV: 81%
- >2 extranodal site: 28%
- DLBCL or BCLU ratio; 98%
- Partner translocations
  - BCL2: 87%
  - BCL6: 5%
  - Triple hit: 8%
- GCB ratio with IHC >%87

2 y PFS: 40%
OS 49%
Multi-center study– DHL results

There is a small number of DHL patients whose clinical and laboratory parameters point us a better outcome

- DHL prognostic score
  - Leucocytosis
  - Stage 3-4
  - LDH>3x ULN
  - CNS inv

Petrich AM. et al. Blood 2014
CR rates are higher with DA-EPOCH-R

R-CHOP: 33%
R-Hyper CVAD: 21%
DA-EPOCH-R: 21%
R-CODOX-M/IVAC: 15%
Other: 10%
PFS improved after intensive therapy

• >60 yo patients received mostly R-CHOP or DA-EPOCH-R

• No OS advantage of SCT performed in CR

• CNS prophylaxis: OS 14 vs 45 months (p=0.06)
Median follow-up for survivors: 46 months

Outcomes after Allogeneic Stem Cell Transplantation in Patients with Double-Hit and Double-Expressor Lymphoma

Alex F. Herrera 1,*, Scott J. Rodig 2, Joo Y. Song 3, Young Kim 2, Gabriel K. Griffin 2, Dongyun Yang 4, Liana Nikolaenko 1, Matthew Mei 1, Victoria Bedell 3, Paola Dal Cin 2, Christine Pak 2, Edwin P. Alyea 5, Lihua E. Budde 1, Robert Chen 1, Yi-Bin Chen 6, Wing C. Chan 3, Corey S. Cutler 5, Vincent T. Ho 5, John Koredt 5, Amrita Krishnan 1, Joyce L. Murata-Collins 3, Sarah Nikiforow 5, Joycelyne Palmer 4, German A. Pihani 7, Raju Pillai 3, Leslie Popplewell 1, Steven T. Rosen 1, Tanya Siddiqui 1, Aliyah R. Sohani 8, Jasmine Zain 1, Larry W. Kwak 1, Dennis D. Weisenburger 3, David M. Weinstock 5, Robert J. Soiffer 5, Joseph H. Antin 5, Stephen J. Forman 1, Auayporn P. Nademane 1, Philippe Armand 5
summary of Immunohistochemistry and FISH Results and Comparison of Clinical Characteristics between Patients with DEL, DHL, and Neither DEL nor DHL

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N = 78)</th>
<th>Non-DHL/Non-DEL Patients (n = 37)</th>
<th>DEL (Non-DHL) Patients (n = 31)</th>
<th>DHL Patients (n = 10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MYC median (range)</td>
<td>40 (0-90)</td>
<td>33 (89)</td>
<td>24 (77)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>BCL2 median (range)</td>
<td>90 (0-100)</td>
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<tr>
<td>DEL</td>
<td>37 (47)</td>
<td></td>
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<td></td>
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<tr>
<td>FISH</td>
<td></td>
<td></td>
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<tr>
<td>MYC not rearranged</td>
<td>57 (73)</td>
<td>33 (89)</td>
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<td>4 (11)</td>
<td>7 (23)</td>
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<td>MYC only</td>
<td>11 (14)</td>
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<td>0 (0)</td>
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<td>Atypical DHL</td>
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<td>9 (24)</td>
<td>8 (26)</td>
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<td>Median age, yr (range)</td>
<td>54 (24-69)</td>
<td>55 (24-69)</td>
<td>54 (32-69)</td>
<td>47 (34-62)</td>
<td>.4</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.11</td>
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<tr>
<td>Male</td>
<td>53 (68)</td>
<td>28 (76)</td>
<td>21 (68)</td>
<td>4 (40)</td>
<td></td>
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<tr>
<td>Female</td>
<td>25 (32)</td>
<td>9 (24)</td>
<td>10 (32)</td>
<td>6 (60)</td>
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<td>Histology</td>
<td></td>
<td></td>
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<td></td>
<td>.089</td>
</tr>
<tr>
<td>DLBCL/BCLU</td>
<td>53 (68)</td>
<td>25 (68)</td>
<td>24 (77)</td>
<td>4 (40)</td>
<td></td>
</tr>
<tr>
<td>TIL</td>
<td>25 (32)</td>
<td>12 (32)</td>
<td>7 (23)</td>
<td>6 (60)</td>
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<tr>
<td>Median no. prior lines of therapy (range)</td>
<td>4 (2-9)</td>
<td>4 (2-8)</td>
<td>4 (2-6)</td>
<td>5 (2-9)</td>
<td>.16</td>
</tr>
<tr>
<td>Prior autoSCT</td>
<td>45 (58)</td>
<td>21 (57)</td>
<td>17 (55)</td>
<td>7 (70)</td>
<td>.8</td>
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<tr>
<td>Disease status at SCT</td>
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<td></td>
<td></td>
<td></td>
<td>.8</td>
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<tr>
<td>Remission</td>
<td>58 (74)</td>
<td>27 (73)</td>
<td>23 (74)</td>
<td>8 (80)</td>
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<td>CR</td>
<td>33 (42)</td>
<td>18 (49)</td>
<td>11 (35)</td>
<td>4 (40)</td>
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<tr>
<td>PR</td>
<td>25 (32)</td>
<td>9 (24)</td>
<td>12 (39)</td>
<td>4 (40)</td>
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<tr>
<td>Not in remission</td>
<td>19 (24)</td>
<td>10 (27)</td>
<td>7 (23)</td>
<td>2 (20)</td>
<td></td>
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<td>SD</td>
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<td>5 (14)</td>
<td>4 (13)</td>
<td>1 (10)</td>
<td></td>
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<tr>
<td>PD</td>
<td>9 (12)</td>
<td>5 (14)</td>
<td>3 (10)</td>
<td>1 (10)</td>
<td></td>
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<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>Primary refractory disease</td>
<td>38 (49)</td>
<td>15 (41)</td>
<td>17 (55)</td>
<td>6 (60)</td>
<td>.4</td>
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</table>
Figure 1. PFS (A) and OS (B) after alloSCT in patients with DEL compared with non-DEL patients.
Figure 2. PFS (A) and OS (B) after alloSCT in patients with DHL compared with non-DHL patients. (C) PFS in patients with DHL compared with patients with DEL without DHL and patients with neither DEL nor DHL.
Introduction

Objectives

Introduction

What should be emphasized in the pathology report?

Treatment of advanced stage disease

CNS prophylaxis strategy

Treatment of early stage DLBCL

Treatment of extranodal DLBCL

Treatment of extranodal DLBCL

Trials & New approaches

Treatment of advanced stage DLBCL

Double Hit, Double Expressor Lymphoma

Treatment of extranodal DLBCL

CNS prophylaxis strategy

Treatment of advanced stage disease

CNS prophylaxis strategy

Treatment of advanced stage disease
### Table 7. Recommended first-line treatment strategies in extranodal diffuse large B-cell lymphoma (DLBCL)

<table>
<thead>
<tr>
<th>Primary sites</th>
<th>Treatment</th>
<th>Consolidation</th>
<th>CNS prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary testicular lymphoma</td>
<td>R-CHOP21X6-8</td>
<td>RT to contralateral testis (25-30 Gy)</td>
<td>IT MTX or i.v. systemic MTX</td>
</tr>
<tr>
<td>Primary central nervous lymphoma</td>
<td>HD-MTX (MTX ≥3 g/m²) plus HD-ara-C</td>
<td>WBRT is not routinely recommended</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>HD-MTX-based (adjusted dose on ECOG PS, renal function, etc.) in elderly patients (clinical trial)</td>
<td>HDCT/ASCT suggested in young patients</td>
<td>N/A</td>
</tr>
<tr>
<td>Primary mediastinal lymphoma</td>
<td>R-CHOP or R-V/MACOP-B or R-CHOP14 or DA-EPOCH-R</td>
<td>Mediastinal RT (30 Gy) in responding patients; RT could be omitted in CMR only after DA-EPOCH-R</td>
<td>Not recommended in CR1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Primary breast lymphoma</td>
<td>R-CHOP1X6</td>
<td></td>
<td>To be considered in all patients</td>
</tr>
<tr>
<td>Primary bone lymphoma</td>
<td>R-CHOP21X6-8</td>
<td>RT (30-40 Gy) to involved bone</td>
<td>Only if involvement of the skull and/or spine</td>
</tr>
</tbody>
</table>

CNS, central nervous system; R-CHOP21, cyclophosphamide, doxorubicin, vincristine and prednisone treatment combined with rituximab given every 21 days; RT, radiotherapy; IT, intrathecal; MTX, methotrexate; i.v., intravenous; HD-MTX, high-dose methotrexate; HD-ara-C, high-dose cytarabine; ECOG PS, Eastern Cooperative Oncology Group performance status; WBRT, whole-brain radiotherapy; HDCT/ASCT, high-dose chemotherapy followed by autologous stem cell transplantation; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-V/MACOP-B, rituximab, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, bleomycin/rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone, bleomycin; R-CHOP14, cyclophosphamide, doxorubicin, vincristine and prednisone treatment combined with rituximab given every 14 days; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine cyclophosphamide, doxorubicin and rituximab; CMR, complete metabolic response; CR1, first complete remission.
Objectives

Introduction

Treatment of advanced stage disease

CNS prophylaxis strategy

What should be emphasized in the pathology report?

Treatment of early stage DLBCL

Treatment of extranodal DLBCL

CNS prophylaxis strategy

Treatment of advanced stage DLBCL

Trials & New approaches

Double Hit, Double Expressor Lymphoma

Treatments of relapsed/refractory DLBCL

CNS prophylaxis strategy
CNS prophylaxis strategy

CNS-IPI includes
- age > 60
- LDH > UNL
- stage: III or IV
- ECOG > 1
- Extranodal inv. > 1
- renal or adrenal involvement

Low (0,1): < %1
Intermediate: (2,3) : %2-10
High: (4-6): %17; perform LP!
CNS prophylaxis strategy

CNS prophylaxis should be performed for:
- Double Hit lymphoma,
- HIV lymphoma
- Testicular lymphoma,
- Breast involvement

At least 2 IT MTX for elderly patients on D15th of first and second cycle of CT
At least 2 High dose MTX for young high risk patients
Objectives

Introduction

What should be emphasized in the pathology report?

Treatment of advanced stage disease

Double Hit, Double Expressor Lymphoma

Treatment of extranodal DLBCL

CNS prophylaxis strategy

Treatment of relapsed/refractory DLBCL

Treatment of early stage DLBCL

Treatment of relapsed/refractory DLBCL

Trials & New approaches
Confirm relapse by biopsy

Re-stage the patient

Is patient transplant eligible?

Intensive salvage chemoimmunotherapy with non-cross resistant regimen
But Cell of origin?

GCB → R-DHAP
Non-GCB → R-ICE

Follow renal function closely especially for R-DHAP!
CORAL study: Autologous Stem Cell Transplantation for DLBCL in R/R disease

Which salvage regimen is better?

Gisselbrecht C et al. JCO 2010;28:4184-4190
Response After Induction Treatment (including death) for All Patients

<table>
<thead>
<tr>
<th>Response (including death)</th>
<th>R-ICE</th>
<th>R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>63.5%</td>
<td>62.8%</td>
</tr>
<tr>
<td>Unconfirmed complete response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>52.3</td>
<td>54.5</td>
</tr>
<tr>
<td>Stable disease</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>38</td>
<td>35</td>
</tr>
<tr>
<td>Death</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Premature withdrawal, not evaluated</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>197</td>
<td>191</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>n</th>
<th>Mobilization adjusted response</th>
<th>MARR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ICE</td>
<td>197</td>
<td>103</td>
<td>52.3</td>
</tr>
<tr>
<td>R-DHAP</td>
<td>191</td>
<td>104</td>
<td>54.5</td>
</tr>
</tbody>
</table>

Gisselbrecht C et al. JCO 2010;28:4184-4190
Multivariate Analysis to Evaluate Survival - p values

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior rituximab administration</td>
<td>0.003</td>
<td>0.0007</td>
<td>0.01</td>
</tr>
<tr>
<td>Relapse &lt; 12 ay</td>
<td>&lt; 0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>sIPI &gt; 1</td>
<td>&lt; 0.0001</td>
<td>&lt;0.0004</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment arm</td>
<td>0.1</td>
<td>0.3</td>
<td>0.07</td>
</tr>
</tbody>
</table>

➢ Relapses are more severe following rituximab administration.

➢ Early relapse and treatment failure are poor prognostic factors.

Gisselbrecht C et al. JCO 2010;28:4184-4190
R-DHAP for GCB subtype and R-ICE for non-GCB subtype
Median follow-up: 53 months

Randomized Comparison of Gemcitabine, Dexamethasone, and Cisplatin Versus Dexamethasone, Cytarabine, and Cisplatin Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed and Refractory Aggressive Lymphomas: NCIC-CTG LY.12


See accompanying editorial on page 3472
Fig 2. (A) Progression-free survival for patients randomly assigned to gemcitabine, dexamethasone, and cisplatin (GDP; gold line) or dexamethasone, cytarabine, and cisplatin (DHAP; blue dashed line). (B) Overall survival for patients randomly assigned to GDP (gold line) or DHAP (blue dashed line). HR, hazard ratio.
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N = 203</th>
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<tbody>
<tr>
<td>Age at CORAL inclusion (years)</td>
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<tr>
<td>Median</td>
<td>55.0</td>
</tr>
<tr>
<td>Min-max</td>
<td>19.0–65.0</td>
</tr>
<tr>
<td>Sex M/F (%)</td>
<td>61.1/38.9</td>
</tr>
<tr>
<td>CORAL arm of treatment, n patients (%)</td>
<td></td>
</tr>
<tr>
<td>R-DHAP</td>
<td>94 (46.3)</td>
</tr>
<tr>
<td>R-ICE</td>
<td>109 (53.7)</td>
</tr>
</tbody>
</table>

Type of salvage (n = 166) (%)

- ICE-like: 31 (18.5)
- DHAP-like: 30 (18)
- Gemcitabine-containing: 23 (13.8)
- Dexa-BEAM: 15 (9)
- CHOP-like: 14 (8.4)
- Miscellaneous: 53 (31.9)

Randomly assigned in maintenance (n = 122)

- Dexa-BEAM: 15 (9)
- CHOP-like: 14 (8.4)
- Miscellaneous: 53 (31.9)

Transplantation, n patients (%)

- ASCT: 56 (27.6)
- Allo-SCT: 8 (4.0)
- No transplantation: 139 (68.5)

Abbreviations: allo-SCT = allogeneic SCT; ASCT = autologous stem cell transplantation; F = female; GC = germinal center; IPI = International Prognosis Index; M = male. *Number of patients for whom information was available.

Death (n = 13)
Voluntary patient withdrawal (n = 6)

E Van Den Neste et al. Bone Marrow Transplantation 2016
<table>
<thead>
<tr>
<th>Tertiary IPI score</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>10.3 months (HR=3.2)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>3.2 months</td>
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</table>

**Transplantation**

Median OS

Not performed: 3.2 months
Performed: 11.1 months

E Van Den Neste et al. Bone Marrow Transplantation 2016
Treatment of relapsed-refractory patients

- The results of studies from GEL-TAMO group and ABMTR suggested that HDT/ASCR should be considered for patients who do not experience CR but who have chemosensitive disease.

- About a third of patients achieving PR also experience long term DFS with ASCT.

Rodriguez J. Annals of Oncol. 2004

Vose JM. JCO. 2001

Derenzini E. Cancer. 2008
Treatment of relapsed-refractory patients

Pretransplant PET scans have been identified as predictive factors following HDT/ASCR

**FIGURE 3.** Progression-free survival curve of 48 patients who had negative positron emission tomography (PET) scans (PET−) compared with 24 patients who had positive pretransplantation PET scans (PET+).

**FIGURE 4.** Overall survival curve of 48 patients who had negative positron emission tomography (PET) scans (PET−) compared with 24 patients who had positive pretransplantation PET scans (PET+).
What does AutoSCT achieve as second line therapy in the rituximab era?*

- **100 Relapsed or Refractory DLBCL**
  - **50 Transplant Ineligible**
    - **25 Patients Fail**
      - Potential Deaths from Lymphoma
  - **50 Transplant Eligible**
    - **25 Respond to Salvage Therapy and ASCT**
      - **10 Patients Cured**

*Assumes all patients received rituximab as part of primary therapy
Allo-transplantation for patients relapsing following ASCT

• There is no clearly defined group where allo-SCT is preferable to ASCT, but it may be an option for some younger patients (age <40-50 years) with high-risk disease.

• The prognosis of the patients relapsing after ASCT is poor.

• Patients who respond to salvage therapy can be considered for alloSCT.

Freytes CO. Biol of Blood and Marrow Trans. 2012
Bacher U. Blood, 120, 2012
IBMTR data between 2008-2013

N=987 pts

254 DLBCL pts

HLA-Matched Sibling Donor
N=807

189 DLBCL pts

Haploidentical related donor
N=180

65 DLBCL pts
### Progression-Free Survival (PFS)

<table>
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<tr>
<th></th>
<th>Haplo</th>
<th>HLA-matched</th>
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<tbody>
<tr>
<td>1 yr</td>
<td>59%</td>
<td>61%</td>
<td>0,55</td>
</tr>
<tr>
<td>2 yrs</td>
<td>51%</td>
<td>52%</td>
<td>0,78</td>
</tr>
<tr>
<td>3 yrs</td>
<td>48%</td>
<td>48%</td>
<td>0,96</td>
</tr>
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</table>

### Overall Survival (OS)

<table>
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<th>Haplo</th>
<th>HLA-matched</th>
<th>p</th>
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<tbody>
<tr>
<td>1 yr</td>
<td>77%</td>
<td>78%</td>
<td>0,64</td>
</tr>
<tr>
<td>2 yrs</td>
<td>65%</td>
<td>68%</td>
<td>0,39</td>
</tr>
<tr>
<td>3 yrs</td>
<td>61%</td>
<td>62%</td>
<td>0,82</td>
</tr>
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</table>
Follow-up

• Patients who achieve a CR following treatment should be followed up on a 3-4 monthly basis for up to 2 years. The risk of relapse beyond 2 years is <10%.

• Outside a clinical trial, there is no role for routine surveillance scans during post-treatment follow-up and patients should be assessed clinically.

Vose JM.BJH.2010
El-Galaly TC.JCO.2015
Objectives

Introduction

What should be emphasized in the pathology report?

Treatment of early stage DLBCL

Treatment of advanced stage disease

CNS prophylaxis strategy

Treatment of extranodal DLBCL

Trials & New approaches

Treatment of refractory DLBCL

Trials & New approaches
Second-generation anti-CD19 CAR-T-cell

CTL, cytotoxic T lymphocyte; MHC, major histocompatibility complex

CD19 Directed CAR-T Cells

- **Yescarta**
  - KTE-C19: axicabtagene ciloleucel
  - Hinge/Transmembrane
  - Signal 2: CD28
  - Yescarta (CD3ζ)
  - Kite Pharma
  - scFv = anti-CD19
  - CD28-CD3ζ

- **Kymriah**
  - CTL019: tisagenlecleucel
  - V_L
  - V_H
  - CD8-alpha hinge and transmembrane
  - 4-1BB Costimulatory domain
  - CD3-zeta signaling domain
  - JCAR017: ?-leucel
  - Transmembrane domain
  - Intraacellular costimulatory domain
  - Signaling sequence
  - Juno Therapeutics
  - scFv = anti-CD19
  - 4-1BB-CD3ζ
# Summary of Pivotal CAR-T Trials in R/R DLBCL

<table>
<thead>
<tr>
<th></th>
<th>JULIET (N=93)</th>
<th>TRANSCEND-NHL-001 (N=102)</th>
<th>ZUMA-1 (N=108)</th>
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</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Tisagenlecleucel</td>
<td>Lisocabtagene maraleucel</td>
<td>Axicabtagene ciloleucel</td>
</tr>
<tr>
<td>Median prior therapies (range)</td>
<td>3 (1-6)</td>
<td>3 (1-8)</td>
<td>NR (1-5+)</td>
</tr>
<tr>
<td>ORR</td>
<td>52%</td>
<td>75%</td>
<td>82%</td>
</tr>
<tr>
<td>CR</td>
<td>40%</td>
<td>55%</td>
<td>58%</td>
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Borchmann et al. EHA 2018 Abstracts S799
Abramson et al. ASCO 2018 Abstract 7505
Locke et al. ASCO 2018 Abstract 3003
Locke et al. ASCO 2018 Abstract 3039
Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial


update 2 years follow up

Figure 3: Kaplan–Meier estimates of investigator-assessed duration of response (A), progression-free survival (B), and overall survival (C). All 107 patients assessable for activity in phase 2 are shown. The x-axis shows time from infusion of chimeric antigen receptor T cells. NE, not estimable.
Proposed Schema for Use of anti-CD19 CAR-T Cell Therapy in Clinical Practice
New Treatment-Targeted Modalities
Targets of Signaling Pathways

BCR signature:
- SYK inh
- PI3K inh
- PKC-β inh
- BTK: ibrutinib
- mTOR inh

Apoptosis:
- BH3 mimetic

Epigenetic
- HDAC inhibitors
- EZH2 inhibitors

Nuclear export
- Selinexor
<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Status</th>
<th>Overall Response</th>
<th>Subtype DLBCL</th>
<th>References</th>
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<tbody>
<tr>
<td>Ibrutinib</td>
<td>BTK</td>
<td>Phase I/II</td>
<td>37%</td>
<td>ABC</td>
<td>(Wilson et al.; 2015)</td>
</tr>
<tr>
<td>Fostamatinib</td>
<td>SYK</td>
<td>Phase II</td>
<td>3%</td>
<td>DLBCL</td>
<td>(Flinn et al., 2016)</td>
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<tr>
<td>Lenalidomide</td>
<td>immunomodulator</td>
<td>Phase II</td>
<td>42%</td>
<td>DLBCL</td>
<td>(Zinzani et al., 2015)</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Hernandez-Illuzaliturri et al., 2011)</td>
</tr>
<tr>
<td>Bortezomib + chemo</td>
<td>NF kB</td>
<td>Phase II</td>
<td>83%</td>
<td>ABC</td>
<td>(Dunleavy et al., 2009)</td>
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<tr>
<td>Tazemetostat</td>
<td>EZH2</td>
<td>Phase II</td>
<td>60%</td>
<td>DLBCL</td>
<td>(Italiano et al., 2018)</td>
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<tr>
<td>Everolimus</td>
<td>m TOR</td>
<td>Phase II</td>
<td>30%</td>
<td>GCB</td>
<td>(Witzig et al., 2011)</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>mTOR</td>
<td>Phase II</td>
<td>28%</td>
<td>DLBCL</td>
<td>(Smith et al., 2010)</td>
</tr>
<tr>
<td>CUDC 907</td>
<td>PI3K delta +HDAC</td>
<td>Phase II</td>
<td>37%</td>
<td>GCB/Myc</td>
<td>(Oki et al., 2017)</td>
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<tr>
<td>Obinutuzumab</td>
<td>CD20</td>
<td>Phase II</td>
<td>32%</td>
<td>DLBCL</td>
<td>(Morschhauser et al., 2013)</td>
</tr>
<tr>
<td>MOR00208</td>
<td>CD 19</td>
<td>Phase II</td>
<td>29%</td>
<td>DLBCL</td>
<td>(Jurczak et al., 2016)</td>
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<td>Blinatumumab</td>
<td>B specific CD19/CD3</td>
<td>Phase II</td>
<td>43%</td>
<td>DLBCL</td>
<td>(Viadrot et al., 2016)</td>
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<td>Polatuzumab vedotin</td>
<td>CD79b</td>
<td>Phase I</td>
<td>25%</td>
<td>DLBCL</td>
<td>(Palanca et al., 2015)</td>
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<tr>
<td>Nivolumab</td>
<td>Anti PD1</td>
<td>Phase I</td>
<td>36%</td>
<td>DLBCL</td>
<td>(Lesokhin et al., 2016)</td>
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<tr>
<td>Selinexor</td>
<td>Exportin XPO1</td>
<td>Phase I/IIb</td>
<td>32%</td>
<td>DLBCL</td>
<td>(Kuruvilla et al., 2017)</td>
</tr>
<tr>
<td>Ublituximab + 1202+ benda</td>
<td>CD20</td>
<td>Phase II/III</td>
<td>32%</td>
<td>DLBCL</td>
<td>(Lunning et al., 2017)</td>
</tr>
</tbody>
</table>

References:
Heavily pretreated DLBCL (n = 80)
- Patients could have had prior autoSCT, but not alloSCT
- Transplant-eligible patients were excluded

<table>
<thead>
<tr>
<th></th>
<th>Polatuzumab + BR [n = 40)]</th>
<th>BR [n = 40]</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>70.0%</td>
<td>32.5%</td>
</tr>
<tr>
<td>CR</td>
<td>57.5%</td>
<td>20.0%</td>
</tr>
<tr>
<td>OS</td>
<td>11.8 months</td>
<td>4.7</td>
</tr>
<tr>
<td>HR = 0.31 (0.19–0.67); P&lt;.0008</td>
<td></td>
<td></td>
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<tr>
<td>PFS</td>
<td>6.7 months</td>
<td>2.0 months</td>
</tr>
<tr>
<td>HR = .31; (0.18–0.55); P&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOR</td>
<td>8.8 months</td>
<td>3.7 months</td>
</tr>
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GO29365: Updates Phase II Trial Results of Polatuzumab Vedotin in Combination with BR for R/R DLBCL or FL

- CR rate for pola+BR and BR were 45% and 18%, respectively.

- Updated follow-up suggests that durable responses could be possible; responses of >20 months have been observed with pola + BR or pola + BD.

- Updated safety results are similar to those previously described with no new safety signals identified.
Autologous Transplant Algorithm

Diffuse Large B Cell Lymphoma

Chemotherapy ± R

PR+ with:
- Primary CNS DLBCL
- Aggressive B in PR
- High Risk B-cell
  - C-myc +
  - Double protein/hit
  - High IPI

Induction Failure

Salvage

CR: all others

Relapse(s)

Chemosensitive

Refractory

CAR-T

Clinical trial and/or Allograft

Landsburg et al. JCO 2017
Conclusions

Outcome in DLBCL has improved dramatically over the last decade with the addition of rituximab to CHOP, which remained the current standard of care.

However, patients who fail R-CHOP continue to have a poor outcome, highlighting the limits of standard chemotherapy in the setting of chemo-resistant disease.
Conclusions

Currently, patients with double hit-lymphoma, as well as DEL, represent poor risk subsets in which alternative strategies should be explored.

To optimize future management, it is necessary to know the molecular heterogeneity of DLBCL and to investigate novel targeted agents within biological subsets that will most likely benefit.
DLBCL and Double Hit Lymphoma: Diagnosis and Treatment (First Line and Relapsed Disease)

Burhan Ferhanoglu M.D.
Professor of Hematology
Koç University Medical School

İzmir, April 7th, 2019