Mutational analysis vs cell of origin in diffuse large B-cell lymphoma, one or both?

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Aggressive Mature B-cell Lymphoma
A heterogeneous Category

Topographic site
Microenvironment

Clinical setting

Cell differentiation stage

Molecular Pathogenesis
Large B-cell lymphoma in the 2016 WHO classification

Diffuse large B-cell lymphoma, not otherwise specified (NOS)
- Germinal center B-cell subtype
- Activated B-cell subtype

DLBCL, topographic site/ microenvironment

DLBCL, EBV-related

LBCL Terminal B-cell differentiation

High grade B-cell lymphomas

Gene Expression Profiling Identifies two Molecular Subtypes of DLBCL


Molecular Subtypes of DLBCL Have Different Molecular Pathogenesis

DLBCL COO in the Clinics

• Distinction of **GCB vs ABC/non-GC type** now required (2016 WHO update)
• RNA vs IHC algorithms? (IHC acceptable)

• Limitation to translate complex signatures into restricted immunophenotypic panels
• Alternative techniques to apply GEP in routinely processed tissues
NanoString: New technique for molecular classification of DLBCL

Molecular Subtypes of DLBCL May Respond to Different Therapies (Lenalidomide)

Nowakowski GS et al J Clin Oncol. 2015 20;33:251-7
Molecular Subtypes of DLBCL May Respond to Different Therapies (Ibrutinib)

**Therapeutic opportunities in ABC-DLBCL**

- **ABC-DLBCL:**
  - Constitutive activation of NFkB
  - Poor outcome with R-CHOP

- **Bortezomib**
  - ↑ PFS when combined with E-EPOCH in ABC\(^1\)
  - However: no differences in two phase 2 randomized trials\(^2,3\)
  - Other studies going on

- **Lenalidomide**
  - Active in non-GCB in monotherapy\(^4,5\)
  - R-CHOP + lena feasible and differentially active in non-GCB\(^6,7\)
  - Trials on going (ROBUST)

- **Ibrutinib**
  - More active in ABC\(^8\)
  - R-CHOP + ibru feasible\(^9\)
  - Trials going on

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1) Dunleavy K, Blood 2009;113:6069
2) Offner F, Blood 2015;126:1893
3) Leonard JP, ASH 2015
4) Hernandez-Illizalitur FJ, Cancer 2011;117:5058
5) Czuczman MS, ASH 2014
7) Nowakowski GS, J Clin Oncol 2015;33:251
9) Younes A, Lancet Oncol 2014;15:1019
No survival benefit with bortezomib, ibrutinib or lenalidomide plus R-CHOP versus R-CHOP in 1L DLBCL

No significant difference in PFS between bortezomib-R-CHOP and R-CHOP

No significant difference in EFS between ibrutinib-R-CHOP versus R-CHOP

No significant difference in EFS between lenalidomide-R-CHOP versus R-CHOP

These data are from different studies with different study designs; they are not intended to be directly compared.

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone;
EFS, event-free survival; ITT, intent-to-treat; len, lenalidomide; R, rituximab
Outcome of Patients with ABC-DLBCL Treated with Ibrutinib May Be Related to Age

< 65 yr

≥ 65 yr

Note: All p values for the table and figure are nominal.

Younes A, ASH 2018 #784
Primary Mediastinal (Thymic) Large B-cell Lymphoma

- **Clinical Characteristics**
  - Young female
  - Bulky mediastinal mass
  - Frequent extrathoracic relapses

- **Phenotype**
  - B-cell markers, Discordant CD79+ Ig-
  - CD30, IRF4, CD23 +; CD10-, MAL+

- **Specific Gene Expression Signature**
  - Detected in non-mediastinal LBCL

- **Molecular Genetic Alterations**
  - Immunoscape (CIITA inactivation)
  - JAK/STAT pathway activation
  - NFKB activation (REL, A20)

Lymph3Cx Assay for the Diagnosis of Primary Mediastinal large B-cell lymphoma

Mottok A et al Blood 2018
Molecular Primary Mediastinal Large B-cell lymphoma without Mediastinal Involvement

<table>
<thead>
<tr>
<th>Consensus Diagnosis</th>
<th>Age/Sex</th>
<th>Stage</th>
<th>Abnormal LDH</th>
<th>Extranodal Sites</th>
<th>Primary Site</th>
<th>Treatment</th>
<th>Response</th>
<th>Outcome (Follow-up [mo])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 DLBCL, c/w gray-zone lymphoma</td>
<td>31/F</td>
<td>IV</td>
<td>+</td>
<td>2</td>
<td>Pelvic mass</td>
<td>CHOP-RT</td>
<td>CR</td>
<td>Dead (9) (COD: lymphoma)</td>
</tr>
<tr>
<td>2 PMBL</td>
<td>53/M</td>
<td>I</td>
<td>-</td>
<td>0</td>
<td>Cervical LN</td>
<td>R-CHOP-21</td>
<td>CR</td>
<td>Alive (100)</td>
</tr>
<tr>
<td>3 DLBCL, c/w PMBL</td>
<td>85/F</td>
<td>II</td>
<td>+</td>
<td>0</td>
<td>Periaortic, inguinal LN</td>
<td>R-CHOP-21</td>
<td>PR</td>
<td>Dead (66) (COD: lymphoma)</td>
</tr>
<tr>
<td>4 DLBCL, c/w PMBL</td>
<td>39/F</td>
<td>IV</td>
<td>+</td>
<td>4</td>
<td>Kidney, adrenal gland, pancreas, small intestine</td>
<td>R-EPOCH</td>
<td>CR</td>
<td>Dead (34) (COD: lymphoma)</td>
</tr>
<tr>
<td>5 DLBCL, c/w PMBL</td>
<td>19/M</td>
<td>I</td>
<td>-</td>
<td>1</td>
<td>Parotid gland</td>
<td>R-CHOP-21</td>
<td>CR</td>
<td>Alive (93)</td>
</tr>
<tr>
<td>6 DLBCL</td>
<td>82/M</td>
<td>III</td>
<td>+</td>
<td>0</td>
<td>Axillary LN</td>
<td>R-CHOP-21</td>
<td>CR</td>
<td>Dead (64) (COD: lymphoma)</td>
</tr>
</tbody>
</table>

CHOP indicates cyclophosphamide, doxorubicin, vincristine, prednisone; COD, cause of death; CR, complete remission; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; LN, lymph node; PR, partial response; R, rituximab; RT, radiation therapy.

SOCS1 NFKBIE Amp 2p16

MYC / BCL2 Genetic vs Protein Double Expressors

Johnson NA et al J Clin Oncol 2012
High grade B-cell lymphoma

- High-grade B-cell lymphomas with \textit{MYC and BCL2 or BCL6 rearrangements} (double-hit)
  - Specify whether DLBCL, blastoid or BCLU morphology
  - Cases with previous FL are to be designated “HGBL-DH transformed from follicular lymphoma”

- High-grade B-cell lymphoma, NOS
  - Cases with BCLU or blastoid morphology but no DH
  - DLBCL with high proliferation are not included
Burkit and DLBCL Mutational profile in HGBL Double-hit, and DLBCL with MYC translocations

- Mut BL: \( \text{ID3, TCF3, CCND3, MYC} \)
- Mut DLBCL-GC: \( \text{BCL2, EZH2, CREBBP, MEF2B, SGK1} \)

Momose S et al Leukemia 2015
Molecular Expression Signature of High Grade B-cell lymphomas. A subset of GCB-DLBCL

- **High expression**
  - Proliferation
  - MYC, E2F, TCF3 target genes
  - FOXP1
- **Low Expression**
  - Immunoresponse (HLA, T-cells)

_Ennish D et al J Clin Oncol 2018_  
_Sha Ch et al J Clin Oncol 2018_
Molecular High Grade B-cell lymphomas are enriched in Double-Hit (but not exclusively)

Ennishi D et al J Clin Oncol 2018
Sha Ch et al J Clin Oncol 2018
Molecular High Grade B-cell lymphoma seems a particular biological Subtype of DLBCL/HGBCL

- GCB subtype
- CD10+/IRF4-
- Enriched in centroblast expression signature (GC Dark zone)
- Share some mutations with GCB-DLBCL but not others
Molecular High Grade B-cell Lymphomas Have Adverse Outcome

Ennishi D et al J Clin Oncol 2018

Sha Ch et al J Clin Oncol 2018
Molecular Subtypes of DLBCL Have Different Mutational Profile in Individual Genes and Pathways

Karube K et al Leukemia 2018; Reddy A et al Cell 2017
BTK/TLR pathway in large B-cell lymphomas

Specific subtypes and response to BTK inhibitors

- Primary CNS
- Cutaneous LBCL Leg type
- Primary Breast LBCL
- IVLCL

Ibrutinib combination chemotherapy

Subgroups of DLBCL Based on Mutational Profile

- 574 DLBCL
- Classifier Algorithm based on 4 “seeds”
- 53.5% cases not included in any subgroup

Subgroups of DLBCL Based on Mutational Profile

- 304 DLBCL
- Clustering method
- 4% cases no alterations

Chapuy B et al Nat Med 2018; 24:679-690
Different Clinical Impact of DLBCL Mutational Subgroups

Different Clinical Impact of DLBCL Mutational Subgroups

Chapuy B et al Nat Med 2018; 24:679-690
Subgroups of DLBCL Based on Mutational Profile

Targeted Therapies

Gene expression subgroups

ABC
Unclass.
GCB

Genetic subtypes

MCD
BN2
N1
EZB

Summary

- Aggressive LBCL are a heterogeneous group of entities with different gene expression signatures and mutational profiles.
- COO expression signatures identify subsets of DLBCL with different pathogenic mechanisms and molecular alterations, but do not seem to capture the biological complexity of these tumors.
- Other gene expression signatures identify specific entities (e.g. PMBL) or categories (mHGBCL) that have clinical and biological relevance.
- Mutational profiles recognize different genetic subgroups of DLBCL, some of them related to particular clinico-pathological entities, that may have important relevance in guiding therapeutic options in the near future.