DLBCL: Conventional therapy. Lessons to be learned from molecular analysis

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Hospital Universitario de Salamanca

EBMT LWP 9th Educational Course Lymphomas and Stem Cell Transplantation, 11th October 2013
# Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
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<tbody>
<tr>
<td>Research Support/P.I.</td>
<td>NA</td>
</tr>
<tr>
<td>Employee</td>
<td>NA</td>
</tr>
<tr>
<td>Adv Board</td>
<td>Roche, Celgene, Janssen, Mundipharma</td>
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<tr>
<td>Major Stockholder</td>
<td>NA</td>
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<td>Speakers Bureau</td>
<td>Roche, Janssen, J&amp;J, Mundipharma,Celgene</td>
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<td>Scientific Advisory Board</td>
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</table>
Germinal center

NCCN Guidelines Version 2.2013
Diffuse Large B-Cell Lymphoma

STAGE

Nonbulky (<10 cm)

Stage I, II

Adverse risk factors present:
- Elevated LDH
- Stage II
- Age >60 y
- Performance status ≥2

RCHOP\(^m\) x 3 cycles + RT\(^n\)
or
RCHOP\(^m\) x 6 cycles ± RT\(^n\)

RCHOP\(^m\) x 3 cycles + RT\(^n\)
or
RCHOP\(^m\) x 6 cycles ± RT\(^n\)
(category 2B for RT)

Bulky (≥10 cm)

RCHOP\(^m\) x 6 cycles ± RT\(^n\)
(category 1)

RCHOP\(^m\) x 6 cycles ± RT\(^n\)
(category 1)

Stage III, IV

Clinical trial\(^o\)
or
RCHOP x 6 cycles\(^p,q\) (category 1)

See Pre RT Evaluation (BCEL-4)

See Interim Restaging (BCEL-5)

\(^m\)For systemic disease with concurrent CNS disease, see BCEL-C
\(^n\)Recommendations are for HIV-negative lymphoma only.
For HIV-positive DLBCL, see AIDS-2.
\(^q\)For patients who cannot tolerate anthracyclines, see BCEL-C for regimens for patients with poor left ventricular function.
\(^o\)See Principles of Radiation Therapy (NHODG-D).
\(^p\)May include high-dose therapy.
\(^q\)Based on current clinical trials, CHOP is preferable due to reduced toxicities, but other comparable anthracycline-based regimens are acceptable.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
First line therapy in DLBCL

Coiffier et al, Blood 2010

Pfreundschuh et al, Lancet Oncol 2006
R-CHOP -21 remains as the Standard Therapy in DLBCL for most of the patients.

Cunninham et al, Lancet 2013, 25:1817
ASCT as first line therapy

Negative randomized trials

185 young untreated DLBCL aa-IPI 2-3.
R-CHOEP vs R-MegaCHOEP

286 young untreated DLBCL aa-IPI 0-1-2-3.
R-HDT vs R-CHOP14

Study Limitation
- IPI 2-3 only 57%, 163 pts (unpowered?)
- Too short pre-HDT therapy
- Endpoint PET after 4 courses with change of tx

Schmitz N et al. 11th International Conference on Malignant Lymphoma 2011

Milpied et al ASH 2010
ASCT as first line therapy

Negative randomized trials

399 untreated DLBCL de novo or Follicular gIIb or PMBCL with extrathoracic localization; age 18-65 years; aa-IPI 2-3; CNS negative.

R-HDC+ASCT 70%
R-dose-dense 59%

Vitolo U et al, 11th International Conference on Malignant Lymphoma 2011
DLBCL is a curable disease

40% failure at 2 years

Prof. Coiffier
IPI in the Rituximab Era

Age $\geq 60$, PS $>1$, LDH $>1$
ES, II/III/IV stage

Ziepert et al, J Clin Oncol 2010
## Diffuse Large B-Cell Lymphoma in the New WHO Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Centroblastic</td>
<td>EBV-positive in elderly</td>
</tr>
<tr>
<td>Immunoblastic</td>
<td>With chronic inflammation</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>Lymphomatoid granulomatosis</td>
</tr>
<tr>
<td>Plasmablastic</td>
<td>In HHV-8 associated Castleman disease</td>
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<tr>
<td>T-cell rich</td>
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<tr>
<td>ALK-positive</td>
<td></td>
</tr>
<tr>
<td>CD5-positive</td>
<td></td>
</tr>
<tr>
<td>GCB</td>
<td></td>
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<tr>
<td>Non-GCB</td>
<td></td>
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<tr>
<td>Primary CNS</td>
<td></td>
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<tr>
<td>Primary cutaneous, leg type</td>
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<tr>
<td>Mediastinal</td>
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<tr>
<td>Intravascular</td>
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<tr>
<td>Primary effusion</td>
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**Notes:**

- ALK = anaplastic lymphoma kinase
- CNS = central nervous system
- EBV = Epstein-Barr virus
- GCB = germinal center B-cell
- HHV-8 = human herpesvirus 8
Characteristics of Morphological variants. Different approach?

<table>
<thead>
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<th>Characteristics</th>
<th>Details</th>
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<tr>
<td>Plasmablastic</td>
<td>Usually CD20-negative, so rituximab is not useful</td>
</tr>
<tr>
<td>DLBCL arising from lymphomatoid granulomatosis</td>
<td>Sometimes relapses as low-grade lymphomatoid granulomatosis and can be treated with interferon or rituximab</td>
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<table>
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<tr>
<th>Specific sites of involvement</th>
<th>Details</th>
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<tbody>
<tr>
<td>Testes</td>
<td>Frequent CNS metastasis and recurrence in the opposite testicle necessitate CNS prophylaxis and scrotal irradiation</td>
</tr>
<tr>
<td>CNS</td>
<td>Does not benefit from CHOP-R and requires high-dose intravenous methotrexate-based regimen</td>
</tr>
<tr>
<td>Skin</td>
<td>Must distinguish between cutaneous DLBCL, leg type, which requires systemic treatment such as CHOP-R, and other tumors (termed cutaneous follicle center cell lymphoma) that need only local treatment</td>
</tr>
</tbody>
</table>

Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling

Ash A. Alizadeh, Michael B. Eisen, H. Eric Davis, Chi Ma, Judah S. Lerner, Andreas Rosenthal, Jennifer G. Oldrick, Haji A. Vidal, R. Eric Davis, and Lewis M. Staudt

Figure 3: Discovery of DLBCL subtypes by gene expression profiling. The samples used in this clustering analysis are shown at the bottom. a. Hierarchical clustering of DLBCL cases (blue and orange) and germinal center B cells (black) based on the genes of the germinal center B-cell gene expression signature shown in Figs. 1 and 2. Two DLBCL subgroups, GC-like DLBCL (orange) and activated B-like DLBCL (blue) were defined by this process. b. Discovery of genes that are selectively expressed in GC-like DLBCL and activated B-like DLBCL. All genes from Fig. 1, with the exception of the genes in the proliferation, T-cell, and lymph-node gene expression signatures, were ordered by hierarchical clustering while maintaining the order of samples determined in Fig. 3a. Genes selectively expressed in GC-like DLBCL (orange) and activated B-like DLBCL (blue) are indicated. c. Hierarchical clustering of the genes selectively expressed in GC-like DLBCL and activated B-like DLBCL, which was determined from Fig. 3a.
Influence of GEP on survival (ABC vs GCB)

A Gene-Expression Signatures and Survival

<table>
<thead>
<tr>
<th>Signature Averages</th>
<th>ABC</th>
<th>GCB</th>
<th>Undescribed DLBCL</th>
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<tr>
<td>Germinal-center B cell</td>
<td></td>
<td></td>
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<tr>
<td>Stromal-1</td>
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<td></td>
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<tr>
<td>Stromal-2</td>
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<tr>
<td>Survival Predictor Score</td>
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Biopsy Specimens (N = 233)

Representative Signature Genes

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<tr>
<th>Gene</th>
<th>Signature Source</th>
<th>Biologic Correlate</th>
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<tr>
<td>BCL6</td>
<td>Malignant cells</td>
<td>Germinal-center B cell origin</td>
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<tr>
<td>MYBL1</td>
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<tr>
<td>SERPINA9</td>
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<td>MME</td>
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<td>LRMP</td>
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<td>LMO2</td>
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<td>COL5A2</td>
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<td>FN1</td>
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<td>THBS2</td>
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<td>PECAM1</td>
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<td>GRB10</td>
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<td>ROBO4</td>
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B Survival after R-CHOP

C Survival Predictor Scores after R-CHOP

<table>
<thead>
<tr>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
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<tbody>
<tr>
<td>Survival Predictor Score</td>
<td>89</td>
<td>69</td>
<td>62</td>
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</tbody>
</table>
Should DLBCL patients be treated based on their molecular characteristics?
PFS and OS of 52 patients according to GEP molecular subtype (GCB vs ABC)

Immunophenotypic Algorithms for Diffuse Large B-cell Lymphomas

- **Hans**
  - CD10
  - BCL6
  - MUM1
  - GCB
  - Non-GCB

- **Choi**
  - ABC
  - GCB
  - FoxP1
  - ABC

- **Muris**
  - BCL2 (50%)
  - CD10
  - MUM1
  - Group1 (GCB)
  - Group2 (ABC)

- **Nyman**
  - MUM1
  - FoxP1
  - ABC
  - Other

- **Tally**
  - "+" = 1, "-" = 0
  - LMO2 ≥ 30% → GCB
  - LMO2 < 30% → ABC

- **Natkunam**
  - CD10 (+ or -)
  - GCET1 (+ or -)
  - Score (0, 1, 2)

- **ABC**
  - Mum1 (+ or -)
  - FoxP1 (+ or -)
  - Score (0, 1, 2)

- **Score**
  - GCB > ABC or ABC > GCB

- **If GCB Score = ABC Score**
  - LMO2 ≥ 30% → GCB
  - LMO2 < 30% → ABC

Meyer J Clin Oncol 2011
GEP and Not IHQ algorithms predicts prognosis in patients treated with R-QT

(A) Colomo
(B) Hans
(C) Muris
(D) Choi
(E) Tally.

N=287

Gutierrez-García, Blood 2011
<table>
<thead>
<tr>
<th>Author</th>
<th>treatment</th>
<th>Algorithm</th>
<th>GCBvsABC</th>
<th>Concordance</th>
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</thead>
<tbody>
<tr>
<td>Choi et CCR 2009</td>
<td>84 (CHOP) + 63 (R-CHOP)</td>
<td>Hans y Choi</td>
<td>OS at 3 y (87% vs 44%) p &lt; 0.001</td>
<td>with GEP 93%</td>
</tr>
<tr>
<td>Meyer JCO 2011</td>
<td>262 RCHOP, CHOPi-</td>
<td>Hans, Choi, Hans*, Choi*, Muris, Nyman, Natkunam,</td>
<td>All had impact</td>
<td>Choi &amp; Tally with GEP (87 y 93%).</td>
</tr>
<tr>
<td>Ott, Blood 2010</td>
<td>179, 173 (CHOP)+/-R RICOVER 60</td>
<td>Hans</td>
<td>No impact</td>
<td>IB morphology</td>
</tr>
<tr>
<td>Gutierrez-García Blood 2011</td>
<td>157 (R-CHOP)</td>
<td>Hans, Choi, Muris, Colomo, Tally</td>
<td>No impact</td>
<td>GEP impact</td>
</tr>
<tr>
<td>Montes-Moreno dBlood 2011</td>
<td>240 (R-CHOP, R-CHOP-like)</td>
<td>Choi</td>
<td>At 2 y (81% vs 69%) p &lt; 0.05</td>
<td>miRNAs and IPI</td>
</tr>
<tr>
<td>Salles Blood 2011</td>
<td>1514 (RCHOP, CHOP) Clinical trials</td>
<td>Hans, BCL2, Ki67, HLA-DR, CD5</td>
<td>No impact, only on early CHOP</td>
<td>BCL2+Ki67+IPI</td>
</tr>
<tr>
<td>Visco Leuk 2012</td>
<td>1049 RCHOP</td>
<td>Hans, Choi, Visco-Young</td>
<td>OS, PFS</td>
<td>GEP Visco-Young, 92.6% with GEP</td>
</tr>
</tbody>
</table>
Diffuse large B-cell lymphomas with *CDKN2A* deletion have a distinct gene expression signature and a poor prognosis under R-CHOP treatment: a GELA study

Jardin, Blood 2010 (GELA)

A new biologic prognostic model based on immunohistochemistry predicts survival in patients with diffuse large B-cell lymphoma

NGCB, *SPARC* (secreted protein, acidic, and rich in cysteine (<5%), and microvascular density quartile 4)

Perry et al, Blood 2012 ( multicentric)

BCL2 Predicts Survival in Germinal Center B-cell–like Diffuse Large B-cell Lymphoma Treated with CHOP-like Therapy and Rituximab

Iqbal, CLCR 2011
Should DLBCL patients be treated based on their molecular characteristics?

NO: technical limitations of IHQ; GEP only in frozen samples and....

Do we have demonstrated alternatives for this poor prognostic patterns?
A Microarray Platform-Independent Classification Tool for Cell of Origin Class Allows Comparative Analysis of Gene Expression in Diffuse Large B-cell Lymphoma
LARGE B CELL LYMPHOMA: FROM BL TO ACTIVATED B CELL TYPE DLBCL. BIOLOGY

- Complexity
- mBL Index
- Core group
- Gene Expression
- mBL Index
- mBL
- Intermediate
- Extranodal
- myc Partner
- Histologic Diagnosis

- ID3
- VPREB1
- CD10
- SOX11
- SMARC4
- LEF1
- STAT3
- CD44
- NFkB1A

Characteristics of Morphological variants. Different approach?

<table>
<thead>
<tr>
<th>Highly proliferative variants</th>
<th>Other subtype</th>
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</thead>
<tbody>
<tr>
<td>Lymphoma with features intermediate between DLBCL and Burkitt lymphoma</td>
<td>Mediastinal gray zone lymphoma</td>
</tr>
<tr>
<td>Double-hit lymphoma (MYC and BCL-2)</td>
<td>The best treatment is uncertain. The most common treatment is CHOP-R followed by radiotherapy</td>
</tr>
<tr>
<td>MYC-positive</td>
<td>(CNS – central nervous system; DLBCL – diffuse large B-cell lymphoma)</td>
</tr>
</tbody>
</table>

Immunohistochemical Double-Hit Score Is a Strong Predictor of Outcome in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP

Green et al; J clin Oncol 2012
Concurrent Expression of MYC and BCL2 in Diffuse Large B-Cell Lymphoma Treated With R-CHOP

Johnson et al.; J Clin Oncol 2012
MYC status in concert with BCL2 and BCL6 expression predicts outcome in DLBCL

Horn et al. Blood 2013
MYC, BCL2, BCL6 in DLBCL: impact for clinics in the future?

**GC DLBCL**
- MYC translocation: 8.8%
- BCL2 translocation: 13.5%
- MYC protein high: 30%
- BCL2 protein high: 70%
- BCL6 protein high: 73%

**Non-GC DLBCL**
- BCL6 translocation: 29%
- BCL2 protein high: 87%
- BCL6 protein high: 95%

**Poor independent prognosis on EFS and OS in patients treated by R-CHOP**
- MYC protein overexpression
- BCL2 protein overexpression
- BCL6 protein overexpression
- Pattern: MYC translocation, MYC high, BCL2 high and BCL6 low protein expressions

Catherine Thieblemont

Comment on Horn et al, page 2253

Blood 2013
Long term survival in DLBCL

Courtesy from Prof Coiffier
“The Hallmarks of Cancer”

Hanahan & Weinberg, Cell 2000
Genetic heterogeneity of diffuse large B-cell lymphoma

Zhang, PNAS 2013

Mutaciones en LBDCG
Overlaps in genes discovered in multiple cancer studies

Zhang, PNAS 2013; Morin, Nature 2011; Lohr Proc Natl Acad Sc USA 2012; Pasqualacci Nat Genet 2011
Oncogenically active MYD88 mutations in human lymphoma

Ngo, Nature 2013
Should DLBCL patients be treated based on their molecular characteristics?

Do we have demonstrated alternatives for this poor prognostic patterns
Abstract 686 The Bruton’s Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765), Has Preferential Activity in the ABC Subtype of Relapsed/Refractory De Novo Diffuse Large B-Cell Lymphoma (DLBCL): Interim Results of a Multicenter, Open-Label, Phase 2 Study. Wyndham H. Wilson et al. ASH 2012

Abstract 3720 Spleen Tyrosine Kinase Inhibitor Fostamatinib Blocks B-Cell Receptor Signaling and Reduces Viability of BCR Subtype Diffuse Large B Cell Lymphoma. Yue Zhang et al. ASH 2012.

Inhibition of NF-κB by bortezomib
Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma

A

Relapsed/Refractory DLBCL (N=49)

Biopsy

Gene expression profiling

Immunohistochemistry

CD10
BCL6
IRF4/MUM1

ABC DLBCL (N=5)
GCB DLBCL (N=10)
ABC DLBCL (N=12)
GCB DLBCL (N=12)

Part A
Bortezomib (N=23)

Treat until disease progression or maximum allowable cycles

Part B
Bortezomib + DA-EPOCH (N=44)

Treat until disease progression or maximum allowable cycles

DLBCL subtype classification by gene expression profiling or IHC

ABC DLBCL (N=12)
GCB DLBCL (N=15)

Dunleavy et al Blood 2009
Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma

Dunleavy et al Blood 2009
First line therapy with R-CHOP + Bortezomib in DLBCL and MCL

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<tr>
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<td>Rituximab</td>
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Total 6 ciclos

E. Progression-Free Survival by Subtypes

- GC
- Non-GC

Ruan J et al. JCO 2010.
RCHOP +/- Bortezomib as first line Therapy in DLBCL (Phase II Trial)

http://www.clinicaltrials.gov/ct2/show/NCT00931918?term=BORTEZOMIB+AND+DLBCL&rank=1
RCHOP +/- Bortezomib as first line Therapy in DLBCLLYYM 2034

A

Fase II; N=164, Multinacional
Objetivo primario: CR
Cerrado. Pendiente de presentación de resultados.

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<td>Bortezomib</td>
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<td>100 mg/m² po x 5d</td>
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B

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<td>750 mg/m² iv</td>
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<td>CHOP: CFM</td>
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<td>50 mg/m² iv</td>
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<td>CHOP: Doxo</td>
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<td>*1.4 mg/m² (2 mg max) iv</td>
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<td>CHOP: VCR</td>
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<td>100 mg/m² po x 5d</td>
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<td>CHOP: PRED</td>
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http://www.clinicaltrials.gov/ct2/show/NCT01040871?term=LYM+2034&rank=1
Estudio fase II aleatorizado de tratamiento de los pacientes jóvenes diagnosticados de linfoma B difuso de célula grande con IPI de alto riesgo con R-CHOP vs Bortezomib-R-CAP

- Reclutamiento: junio 2013 a junio 2015
  - 20 centros del GELTAMO
  - Objetivo: SLE 5 años
  - 127 pac

Diagrama:

- PET/CT/1 positive
  - R
  - RB-CAP21 x 2
    - PET/CT/2 exploratory
      - RB-CAP21 x 2
        - Less than CR
          - Out off
        - R-CHOP21 x 2
          - PET/CT/3 Evaluation
            - RB-CAP21 x 2
              - PET/CT/4 Evaluation
                - Less than CR
B cell receptor signaling pathway

BCR-associated kinases

Syk
*(spleen tyrosine kinase)*

Btk
*(Bruton’s tyrosine kinase)*

**PI3Kδ**
*(Phosphatidylinositol 3-kinases)*
B-Cell Receptor Pathways

- Plays an important role in proliferation and survival in B-NHL
- Targets in this pathway includes: Splenic tyrosin kinase, (SyK) y BTK (Bruton’s tyrosine kinase).
- SyK is important in survival
- BTK is important in BCR signaling and maduration
- BCR is sobreexpressed in B neoplasia.
New Strategies in Diffuse Large B-cell Lymphoma
Ibrutinib: A First-in-Class Inhibitor of BTK

- Forms covalent bond with cysteine-481 in BTK
- High BTK specificity
- IC$_{50}$ = 0.5 nM
- Daily oral dosing produces 24-hr BTK inhibition
- Blocks NF-κB activation in ABC-DLBCL cell lines$^{1,2}$

$^1$Staudt et al, Blood 2011; 118:2716
$^2$Balasubramanian et al, Blood 2011;118:4969
In B-Cell Malignancies, PI3K Delta Is at the Crossroads of Critical Signaling Pathways
“The Hallmarks of Cancer”

Hanahan & Weinberg, Cell 2000

- (+) death receptors
- (-) antiapopt. proteins
- (-) angiogenesis
- Microambiente
- (-) Tyrosin-K receptors
- (-) proliferative pathways
- Proteasome inhibitors
- Epigenetics (Demethylating agents, H-D inhibitors)
Abstract 903
Rituximab-CHOP21 Plus Lenalidomide (LR-CHOP21) is Effective and Feasible in Elderly Untreated Diffuse Large B-cell Lymphoma (DLBCL): Results of Phase II REAL07 Study of the Fondazione Italiana Linfomi (FIL)

Annalisa Chiappella, Silvia Franceschetti, Alessia Castellino, Angelo Michele Carella, Ileana Baldi, Manuela Zanni, Anna Marina Liberati, Michele Spina, Chiara Bottelli, Vincenzo Pavone, Anna Lia Molinari, Pier Luigi Zinzani, Flavia Salvi, Pier Paolo Fattori, Alfonso Zaccaria, Barbara Botto, Angela Congiu, Marco Ladetto, Martin Dreyling, Gianluca Gaidano, Giuseppe Rossi, Umberto Vitolo

Fondazione Italiana Linfomi, Torino, Italy

Oral Presentation:
Tuesday, Dec. 11
8:00 AM
B405–B407, Level 4, Building B, Georgia World Congress Center
Abstract 689
Combination of Lenalidomide with R-CHOP (R2CHOP) is Well Tolerated and Effective as Initial Therapy for Aggressive B-cell Lymphomas – A Phase II Study


Mayo Clinic, Rochester, MN, USA

Oral Presentation:
Monday, Dec. 10
5:30 PM
Sidney Marcus Auditorium, Level 4, Building A, Georgia World Congress Center

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.
Nowakowski GS, LaPlant BR, Reeder C, et al. Combination of Lenalidomide with R-CHOP (R2CHOP) is Well Tolerated and Effective as Initial Therapy for Aggressive B-cell Lymphomas – A Phase II Study. Oral presentation at: Annual Meeting and Exposition of the American Society of Hematology 2012; December 8-11; Atlanta, GA.
• For CD30 expression, histological analyses performed by immunohistochemistry (IHC) using the anti-CD30 BerH2 antibody on biopsy of most recent relapsed or refractory disease
• Brentuximab vedotin, 1.8 mg/kg, administered IV every 3 weeks until disease progression or unacceptable toxicity
• Restage at Cycles 2, 4, and every 3 cycles thereafter
• Disease response assessed by investigator according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007)
The rationale for combining targeted and biological anti-lymphoma drugs

Anas Younes, Hematological Oncology
Hematol Oncol 2013; 31 (Suppl. 1): 81–83
Strategies on combination

- PI3K and mTOR inhibitors
- PI3k and BTK inhibitors (ABC)
- BTK and Syk inhibitors (ABC)
- PI3K/AKT/mTOR inhibitors
- Blocking “feedback loop negative” (mTOR + HDAC) or de JAK 2+MAP Kinase inhibitors

Staudt, Lugano 2013
Gene expression profiling studies have provided prognostic relevant information with a better division on the basis of cell origin.

Concordance between GEP and IHQ algorithms is discrepant. The IPI remains the best available index but we need:

- More reliable IHC markers
- Cytogenetic markers
- Molecular markers are needed before they could be incorporated in clinical practice
• Personalised medicine is getting closer
• Genetic studies have demonstrated the DLBCL heterogeneity
• Molecular aberrations are non exclusive and are non constant in any DLBCL type
• Retrospective studies have demonstrated poorer outcome of ABC and Double Hit lymphomas
• Perhaps these differences are secondary to other characteristics: age, etc
• We need robust technology and robust molecular markers
Comments

• New molecules will be soon incorporated in first line therapy in order to increases CR rate and decrease early relapse after first line therapy

• Best combinations will exist....we need to find them
Which are the ideal combinations?
Which are the ideal combinations?