Aggressive lymphomas ASH 2015

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A.Z. St.Jan, Brugge-Oostende AV
LNH-84 Regimen: A Multicenter Study of Intensive Chemotherapy in 737 Patients With Aggressive Malignant Lymphoma

By Bertrand Coiffier, Christian Gisselbrecht, Raoul Herbrecht, Hervé Tilly, André Bosly, and Nicole Brousse

Table 1. Distribution of Patients According to Working Formulation Histologic Types of Phenotypes

<table>
<thead>
<tr>
<th>Histologic Subtypes</th>
<th>Immunophenotype</th>
<th>N</th>
<th>(%)</th>
<th>B</th>
<th>T</th>
<th>Nontyped</th>
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<tbody>
<tr>
<td>Intermediate-grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular large-cell</td>
<td></td>
<td>25</td>
<td>(3)</td>
<td>8</td>
<td>—</td>
<td>17</td>
</tr>
<tr>
<td>Diffuse small-cleaved-cell</td>
<td></td>
<td>17</td>
<td>(2)</td>
<td>7</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Diffuse mixed</td>
<td></td>
<td>122</td>
<td>(17)</td>
<td>25</td>
<td>37</td>
<td>60</td>
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<tr>
<td>Diffuse large-cell</td>
<td></td>
<td>278</td>
<td>(38)</td>
<td>110</td>
<td>16</td>
<td>152</td>
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<tr>
<td>High-grade</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Immunoblastic</td>
<td></td>
<td>160</td>
<td>(22)</td>
<td>35</td>
<td>37</td>
<td>88</td>
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<tr>
<td>Lymphoblastic</td>
<td></td>
<td>25</td>
<td>(3)</td>
<td>2</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Small-noncleaved-cell</td>
<td></td>
<td>36</td>
<td>(5)</td>
<td>19</td>
<td>—</td>
<td>17</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
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<tr>
<td>Ki-1+</td>
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<td>16</td>
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<td>—</td>
<td>8</td>
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<tr>
<td>Unclassified</td>
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<td>41</td>
<td>(6)</td>
<td>6</td>
<td>4</td>
<td>31</td>
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<tr>
<td>Unclassifiable</td>
<td></td>
<td>17</td>
<td>(2)</td>
<td>5</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>737</td>
<td></td>
<td>217</td>
<td>123</td>
<td>397</td>
</tr>
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</table>

Fig 2. Overall survival (S), time to failure (TTF) survival, and time to relapse (TTR) survival of the 737 patients with aggressive lymphoma included in the LNH-84 protocol.
CHOP
1992

R-CHOP
For DLBCL

High dose chemo
With PBSCT
Aggressive lymphomas

1. DLBCL
2. Primary Mediastinal Lymphoma
3. CNS lymphoma
4. Burkitt lymphoma
5. Mantle cell lymphoma
6. Take home message
Not all lymphomas are equal

Treating all DLBCL with RCHOP is no longer appropriate.
We are moving quickly to “precision medicine” approach to treatment of DLBCL.

Jonathan Friedberg, ASH 2015

1. Diagnostic accuracy and prognosis
2. New treatments for subgroups?
Double Hit and Double Expression lymphomas (DHL/DEL)

- **DHL:** studies show these are very aggressive with median survivals of < 1 year
  - MYC-R in combination with either BCL2-R or BCL6-R
  - Immunophenotype is usually of GCB (80-90 %)
  - MYC/BCL6 DHL may differ from MYC/BCL2

- **DEL:** IHC positive for MYC and BCL-2 more ABC than GCB
DHL or DEL

DHL : FISH

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Percentage</th>
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<tr>
<td>DLBCL</td>
<td>50 %</td>
</tr>
<tr>
<td>BCLu</td>
<td>48 %</td>
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Partner

<table>
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<tr>
<th>Protein</th>
<th>Percentage</th>
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<tr>
<td>BCL2</td>
<td>87 %</td>
</tr>
<tr>
<td>BCL6</td>
<td>8 %</td>
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</table>

COO

<table>
<thead>
<tr>
<th>COO</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCB</td>
<td>90 %</td>
</tr>
<tr>
<td>ABC</td>
<td>9 %</td>
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</table>

DEL : IHC

<table>
<thead>
<tr>
<th>COO</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCB</td>
<td>35 %</td>
</tr>
<tr>
<td>ABC</td>
<td>65 %</td>
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</tbody>
</table>

% of DLBCL cases

<table>
<thead>
<tr>
<th>Method</th>
<th>MYC aberrancy</th>
<th>MYC plus BCL2 aberrancy</th>
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</thead>
<tbody>
<tr>
<td>IHC</td>
<td>37%</td>
<td>26%</td>
</tr>
<tr>
<td>FISH</td>
<td>12%</td>
<td>8%</td>
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</table>
DEL: inferior outcome

ALL patients were treated with intensive induction and autologous SCT

Takahashi, ASH 2015
Diagnostic accuracy: pathology

1. Double hit (DHL)?
   • Fish for MYC: all cases? if GCB or if Myc+ on IHC?
   • if positive: FISH for BCL-2 and BCL-6

2. IHC for MYC and BCL-2: Double expression (DEL) or Double Protein Lymphoma (DPL)

3. Cell of origin (COO): GCB or ABC: IHC or GEP?
COO: ABC or GCB: implications for treatment?

Remodl-B-Trial: 1147 patients: classification by GEP
ABC 23 %
GCB 44 %
unclassified 19 %
unsuitable 14 %

Difference in prognosis? Not always confirmed
COO – directed treatment: ?

ABC subtype

BCR/NfκB signalling
  CD79A/B, CARD11, MYD88 mutations

CREBBP mutations

MYC translocations, MYC and BCL2 protein overexpression

JAK/Stat activation

bortezomib
BCRi
Ibrutinib,

lenalidomide
ABC subtype: bortezomib?

3 randomised trials: no effect if bortezomib added to R-CHOP

- LYM-2034 trial, ICH; Offner, Blood 2015
- Remodl-B trial: GEP; Davies, ASH
- Pyramid trial: IHC; Leonard, ASH

R-CHOP for ABC did better as expected reason? IHC vs GEP? selection of good patients?

.............
Excluded due to concerns about delays/risk

Randomised in a selected patient Population (who could wait for evaluation/randomisation)
ABC subtype: BCRi?

ABC subtype: trials running

BCRi: ibrutinib
High Prevalence of *Myd88* L265P Mutation in Extra-nodal DLBCL with an ABC Phenotype
COO – directed treatment?
GCB subtype

**EZH2 mutations**
**MLL2 mutations**
**CREBBP mutations**
**MYC and BCL2 Translocations (DHL)**
**and DEL**
**PTEN deletion**

**TAZEMETOSTAT** (Ribrag)

**DEL/DHL:** downregulation of expression of myc
**CUDC-907** (Younes)
**SEL24** (Jablonska)
Checkpoint inhibitors in DLBCL?

Generally not very effective: ORR 35 %, but response not durable

DLBCL subsets: EBV+ DLBCL, T-Cell Rich LCL: PD-L1 positive?

But: assays differ, dynamic event, mutational load, microenvironment, no good correlation with response (myeloma, FL)…
CAR-T cells in relapsed DLBCL

Modified T Cells against CD-19

overall response in R/R DLBCL  47 %

side effects:
  • cytokine release syndrome: also dependend on lymphodepletion chemotherapy before infusion of CAR T cells
  • Neurotoxicity

All pts in CR remain in CR
Primary mediastinal lymphoma

- First line treatment: DA-EPOCH, no radiotherapy (?)
- Relapsed patients: checkpoint inhibitor?

Genetically related to Hodgkin lymphoma: 9p24 copy gain/amplification in 60 – 70 %
Frequent PDL-1L expression

Phase I pembrolizumab (Zinzani, ASH)

ORR 40 %, mostly partial duration of remission > 1 y

phase 2 study launching
CNS lymphoma: first treatment

For fit patients: autologous transplantation standard of care?
CNS lymphoma: DA-TEDDI

Systemic

- Etoposide
- Prednisone
- Vincristine
- Cyclophosphamide
- Doxorubicin
- Rituximab
- Ibrutinib ?

CNS

- Etoposide
- Dexamethasone
- X
- Temozolomide
- Doxil
- Rituximab
- Ibrutinib
CNS lymphoma: relapse

ibrutinib?

Pre and Post Ibrutinib alone
DHL lymphoma

- Intensive induction? RCHOP not enough
- most important:
  - CR
  - Stage
  - auto SCT

Saksena, ASH 2015
157 pts with DHL
DEL lymphoma

- No good data on best induction therapy; R-CHOP poor outcome
- Role of transplant is not well studied
- Urgent need for better induction treatment
First-line autotransplants in DLBCL?

No benefit for consolidative autotransplants in low, intermediate or high-intermediate risk

Potential benefit for early autotransplant in PFS/OS for high risk/DHL/DEL

Pts with PET positive responsive disease after routine induction: biopsy and if not in CR: appropriate candidates for autologous transplant (after salvage chemotherapy?)
R-CHOP PET/Ct after 4 cycles

- Negative
- Positive

R-ICE

Z-BEAM

Herzberg, ASH 2015
Mantle cell lymphoma

Rituximab maintenance after chemo/autoSCT: effective on PFS
(LYMA, ASH 2015; Toronto, ASH 2015)

Bortezomib maintenance after chemo/autoSCT: no effect
(HOVON, ASH 2015)

Ibrutinib maintenance after chemo/autoSCT: study starting
(TRIANGLE)
Mantle cell lymphoma: MCL3001 (RAY):

- Randomized, open-label phase III trial
  - Primary endpoint: PFS
  - Secondary endpoints: ORR, OS, DoR, time to next treatment, and safety

**Stratified by sMIPI and prior lines of therapy**

- Previously treated pts with MCL (N = 280)
  - **Ibrutinib** 560 mg QD PO (n = 139)

- Crossover to ibrutinib arm if progressive disease (n = 32)
  - Temsirolimus IV
    - Cycle 1: 175 mg Days 1, 8, 15
    - Subsequent cycles: 75 mg Days 1, 8, 15 (n = 141)

- Median drug exposure: 14 mos of ibrutinib vs 3 mos of temsirolimus.
### MCL3001 (RAY): Survival Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ibrutinib (n = 139)</th>
<th>Temsirolimus (n =141)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>14.6</td>
<td>6.2</td>
<td>0.43 (0.32-0.58)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>2-year PFS rate, %</td>
<td>41</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS2,* mos</td>
<td>19.1</td>
<td>11.3</td>
<td>0.49 (0.36-0.69)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>Not reached</td>
<td>21.3</td>
<td>0.76 (0.53-1.09)</td>
<td>.1324</td>
</tr>
</tbody>
</table>

*After 1 subsequent line of therapy
Burkitt lymphoma: DA-R-EPOCH

<table>
<thead>
<tr>
<th></th>
<th>TTP</th>
<th>PFS</th>
<th>OS</th>
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<tbody>
<tr>
<td>Patients</td>
<td>N=77 92%</td>
<td>87%</td>
<td>88%</td>
</tr>
<tr>
<td>LR</td>
<td>11</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>HR</td>
<td>66</td>
<td>91%</td>
<td>85%</td>
</tr>
<tr>
<td>( p )</td>
<td>0.35</td>
<td>0.22</td>
<td>0.24</td>
</tr>
<tr>
<td>HIV -</td>
<td>57</td>
<td>96%</td>
<td>88%</td>
</tr>
<tr>
<td>HIV +</td>
<td>20</td>
<td>84%</td>
<td>84%</td>
</tr>
<tr>
<td>( p )</td>
<td>0.1</td>
<td>0.66</td>
<td>0.53</td>
</tr>
<tr>
<td>Age under 40</td>
<td>35</td>
<td>94%</td>
<td>90%</td>
</tr>
<tr>
<td>Age over 40</td>
<td>42</td>
<td>91%</td>
<td>84%</td>
</tr>
<tr>
<td>( p )</td>
<td>0.83</td>
<td>0.45</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Low-risk (LR) patients (normal LDH, ECOG P.S. 0-1, stage I or II disease and a maximum tumor size < 7cm)

Dunleavy, ASH 2015
1. Pathology report for DLBCL should include
   COO (IHC or GEP)
   DEL (IHC)
   DHL (FISH)
2. COO has yet no impact on choice of treatment: wait for trials
3. DHL: DA- R-EPOCH and autoSCT
4. DEL: R-CHOP, autoSCT but new ideas needed (high number of pts)
Take home messages 2

5. Primary mediastinal lymphoma: DA-R-EPOCH (RT ?) relapse: checkpoint inhibitor
6. Primary CNS lymphoma: CNS directed chemo and autologous SCT
7. Mantle cell lymphoma: Rituximab maintenance after auto