Diffuse Large B-cell Lymphoma

- Most common NHL, peak incidence in 6th decade
- Large cells with loss of follicular architecture of node
- May present as extranodal disease (stomach, CNS, testis, skin)
- Curable in >50% of the cases since the advent of rituximab
- Median survival: short if not treated
Clinical predictive factors: Stratification of risk by IPI in aggressive NHL

**Prognostic factors (APLES)**
- Age >60 years
- Performance status >1
- LDH >1 normal
- Extranodal sites >1
- Stage III or IV

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (L)</td>
<td>0 or 1</td>
</tr>
<tr>
<td>Low-intermediate (LI)</td>
<td>2</td>
</tr>
<tr>
<td>High-intermediate (HI)</td>
<td>3</td>
</tr>
<tr>
<td>High (H)</td>
<td>4 or 5</td>
</tr>
</tbody>
</table>

![Graph showing survival (OS) by IPI categories](image)


---

Treatment for aggressive B-cell NHL

**New therapeutic approaches**

- R-CHOP-21 (old, but still gold standard)
- Dose density (e.g. R-CHOP-14)
- Dose intensification (e.g. Auto SCT in 1st CR)
- Other chemorx regimens + R (e.g. CHOEP; ACVBP; ICE)
- Infusional therapy + R (e.g. CODBLAM, DA-EPOCH, VIPER)
- Monoclonal antibodies (e.g. anti-CD22, RIT, CMC-544, etc)
- Modifiers of drug resistance (e.g. proteasome inhibition, Bcl-2 inhibitors, etc.)
- Risk-adapted Therapy (e.g. gene profile, PET, etc)
- Novel agents (e.g. IMiDs, HDAC inhibition, CAL-101, etc.)
A phase III trial comparing R-CHOP 14 and R-CHOP 21 for the treatment of newly diagnosed diffuse large B cell lymphoma

Results from a trial by the UK NCRI Lymphoma Clinical Study Group (CRUKE/03/019)

D. Cunningham, P. Smith, P. Mouncey, W. Qian, C. Pocock, K. M. Ardesha, J. Radford, J. Davies, A. McMillan, D. Linch on behalf of the NCRI trial collaborators

Trial design: R-CHOP-14 vs 21

Newly diagnosed CD20+ve DLBCL

Stratified by
• IPI (0-1, 2, 3, 4-5)
• Age ≤60 vs. >60
• Treatment centre

R

n=540

R-CHOP21

CHOP21 × 8 cycles
Rituximab × 8 cycles

n=540

R-CHOP14

CHOP14 × 6 cycles
Rituximab × 8 cycles
Lenograstim Day 4-12

1080 patients; 119 sites
Recruitment March 2005 - Nov 2008
Overall response rates and F/U

<table>
<thead>
<tr>
<th>Based on end of treatment scan</th>
<th>R-CHOP-21 %</th>
<th>R-CHOP-14 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>49</td>
<td>41</td>
</tr>
<tr>
<td>CRu</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>PR</td>
<td>25</td>
<td>32</td>
</tr>
<tr>
<td>SD</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>PD/relapse</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>CR/CRu, p=0.15</td>
<td>63</td>
<td>58</td>
</tr>
<tr>
<td>CR/CRu/PR, p= 0.11</td>
<td>88</td>
<td>90</td>
</tr>
</tbody>
</table>

- Median F/U of 39 months: 70% of pts alive without progression in both arms!

Failure-free survival

Events, n (%)
- R-CHOP21: 155 (29)
- R-CHOP14: 153 (28)
- 2-yr FFS: 75% (R-CHOP21) vs 75% (R-CHOP14), p=0.94
- Log-rank test: p=0.94
- HR (95% CI): 0.99 (0.79–1.24)

Patients at Risk
- R-CHOP21: 534
- R-CHOP14: 533
Overall survival

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Years from randomisation</th>
<th>R-CHOP21</th>
<th>R-CHOP14</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP21</td>
<td>0</td>
<td>540</td>
<td>476</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>474</td>
<td>393</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>392</td>
<td>242</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>234</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>120</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Events, n (%) | R-CHOP21: 123 (23) | R-CHOP14: 117 (22)

2-yr OS | R-CHOP21: 81% | R-CHOP14: 83%

Log-rank test | p = 0.70

HR (95% CI) | 0.95 (0.74–1.23)

OS by IPI score

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Years from randomisation</th>
<th>Events</th>
<th>Totals</th>
<th>p &lt; 0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84</td>
<td>83</td>
<td>69</td>
<td>42</td>
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<tr>
<td>1</td>
<td>231</td>
<td>215</td>
<td>181</td>
<td>105</td>
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<tr>
<td>2</td>
<td>356</td>
<td>275</td>
<td>228</td>
<td>144</td>
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<tr>
<td>3</td>
<td>280</td>
<td>233</td>
<td>195</td>
<td>120</td>
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<td>4</td>
<td>154</td>
<td>125</td>
<td>96</td>
<td>56</td>
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<tr>
<td>5</td>
<td>25</td>
<td>19</td>
<td>18</td>
<td>9</td>
</tr>
</tbody>
</table>
Conclusions

- R-CHOP-14 for 6 cycles is not superior to R-CHOP-21 for 8 cycles

- No obvious subgroup appears to derive a greater benefit from R-CHOP14, including: age > 60, high IPI, high MIB1 or non-GC phenotype

- As expected a higher frequency of neutropenia was observed in R-CHOP21 (which reflects the primary prophylaxis with G-CSF in R-CHOP14)

- Question: Are 6 cycles R-CHOP-21 similar to 8 cycles of R-CHOP-21?

Randomized phase III US / Canadian Intergroup trial (SWOG S9704) comparing CHOP □ R x 8 vs CHOP □ R x 6 followed by high dose therapy and auto transplant for patients with diffuse aggressive non-Hodgkin lymphoma (NHL) in high-intermediate (H-Int) or high IPI risk groups


1Loyola University Medical Center, Maywood, IL; 2SWOG Statistical Center, Seattle, WA; 3Cleveland Clinic Foundation, Cleveland, OH; 4University of Rochester, Rochester, NY; 5Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, CAN; 6University of North Carolina at Chapel Hill, Chapel Hill, NC; 7Northwestern University, Chicago, IL; 8University of Arizona, Tucson, AZ; 9Margaret and Charles Juravinski Cancer Centre, Hamilton, Ontario, CAN; 10Louisiana State University Medical Center, Shreveport, LA; 11City of Hope Medical Center, Duarte, CA
Background

1. High dose therapy and ASCT is considered the standard of care for relapsed chemosensitive, diffuse intermediate and high grade NHL

2. In first CR, the GELA first found an improvement PFS/OS for patients with high risk (High-Intermediate and High IPI) disease in a retrospective analysis: LNH 87 (Haioun; JCO 2000;18:3025)

3. Numerous subsequent prospective trials have been performed in high-risk patients comparing standard therapy to high-dose Rx and have yielded conflicting results

HDT/ASCT as part of 1st-line therapy in aggressive lymphoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Risk group</th>
<th>Included</th>
<th>EFS1</th>
<th>OS1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haioun et al.</td>
<td>1994</td>
<td>(\geq 1) RF, Bulk</td>
<td>CR</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>(\geq 2) RF</td>
<td>CR</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>Verdonck et al.</td>
<td>1994</td>
<td>II-IV</td>
<td>&lt;CR</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gianni et al.</td>
<td>1997</td>
<td>II/III&lt;bulky,III/IV</td>
<td>all</td>
<td>0.004</td>
<td>n.s.</td>
</tr>
<tr>
<td>Santini et al.</td>
<td>1998</td>
<td>II&lt;bulky,III/IV</td>
<td>all</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\geq 2) RF</td>
<td></td>
<td>0.008</td>
<td>n.s.</td>
</tr>
<tr>
<td>Kluin-N. et al.</td>
<td>2001</td>
<td>all</td>
<td>CR</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Kaiser et al.</td>
<td>2002</td>
<td>LDH &gt;UNV</td>
<td>CR, PR</td>
<td>n.s.</td>
<td>n.s.</td>
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<tr>
<td>Gisselbrecht et al.</td>
<td>2002</td>
<td>(\geq 1) RF</td>
<td>all</td>
<td>0.01</td>
<td>0.009</td>
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<tr>
<td>Martelli et al.</td>
<td>2003</td>
<td>(\geq 2) RF</td>
<td>CR, PR</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sertoli et al.</td>
<td>2003</td>
<td>II&lt;bulky,III/IV</td>
<td>all</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Milpied et al.</td>
<td>2004</td>
<td>(&lt;3) RF</td>
<td>all</td>
<td>0.03</td>
<td>n.s.</td>
</tr>
<tr>
<td>Betticher et al.</td>
<td>2006</td>
<td>aalIPI&gt;2</td>
<td>all</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

1) n.s. = non-significant; otherwise p-values are given
Background

4. Patients with diffuse aggressive NHL with high risk disease still have only about a 50% long term survival (Sehn et al Blood 2007;109:1857)… even with addition of rituximab

5. Based on the lack of an optimal approach for high risk disease, the SWOG in conjunction with the ECOG, CALGB and the NCIC Clinical Trials Group undertook a prospective randomized Phase III trial comparing CHOP(R) x 6 followed by ASCT vs CHOP(R) x 8 for patients with diffuse aggressive NHL in the High-Int and High IPI groups

- 68% H-I risk; 32% High-risk
- B-cell NHL: 40% CHOP; 48% R-CHOP

Schema

Register (n=397)

- CHOP/CHOP-R x 5 (n=370)
  - PR or CR (n=253)
  - <PR (n=66)

Randomize

- Off Protocol therapy

- CHOP/CHOP-R x 1 + Auto transplant
- CHOP/CHOP-R x 3

- Patients were permitted to have 1 cycle of CHOP(R) prior to protocol registration
- Transplant regimens: SWOG TBI (12Gy / 8 Fx) or BCNU (150mg/m² x 3d) + VP16 (60mg/kg) + Cyclophosphamide (100mg / kg)
Overall Outcome: PFS

Overall Outcome: Survival

Note: 18% of control pts were salvaged by auto-SCT
Conclusions from SWOG S9704

• Pts with high-risk diffuse aggressive NHL have a better 2-yr PFS (69%) with auto SCT c/w standard Rx (2-yr PFS = 56%)

• No survival advantage in the upfront auto SCT arm

• Exploratory analyses: Majority of ASCT benefit seen in high-risk IPI group (i.e. 2-yr PFS = 75% vs. 41%; 2-yr OS: 82% vs. 64%)
  – Further subset analyses would have been helpful (e.g. look at R-CHOP arm alone; benefit of CR prior to ASCT?; ABC vs. GCB?; value of PET-negativity?)
  – Many high-risk IPI did not get ASCT!

Conventional chemoimmunotherapy (R-CHOEP-14) or high-dose therapy (R-MegaCHOEP) for young, high-risk patients with aggressive B-cell lymphoma:

Final results of the randomized MegaCHOEP trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL)

**R-MegaCHOEP**

**DESIGN OF THE RANDOMIZED STUDY**

**GERMAN HIGH-GRADE NHL STUDY GROUP (DSHNHL)**

www.lymphome.de/en/Groups/DSHNHL

---

**PBSC**

**mCHOEP II**
- CYC 1500
- ADR 70
- VCR 2
- ETO 600
- PRD 500

**mCHOEP III**
- CYC 4500
- ADR 70
- VCR 2
- ETO 960
- PRD 500

**mCHOEP IV**
- CYC 6000
- ADR 70
- VCR 2
- ETO 1480
- PRD 500

**mCHOEP I**
- CYC 1500
- ADR 50
- VCR 2
- ETO 300
- PRD 500

---

**Rituximab**
- (6 x 375 mg/m²)

---

**R-MegaCHOEP Study**

**COURSE OF THERAPY**

**GERMAN HIGH-GRADE NHL STUDY GROUP (DSHNHL)**

www.lymphome.de/en/Groups/DSHNHL

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<table>
<thead>
<tr>
<th></th>
<th>R-CHOEP-14 (n=130)</th>
<th>R-MegaCHOEP (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy as per protocol</td>
<td>87.7%</td>
<td>57.5%</td>
</tr>
<tr>
<td>Early termination of chemotherapy</td>
<td>2.3%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Early termination of rituximab</td>
<td>0.0%</td>
<td>14.2%</td>
</tr>
<tr>
<td>Early termination of both</td>
<td>9.2%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.8%</td>
<td>3.1%</td>
</tr>
</tbody>
</table>
### R-MegaCHOEP Study

#### FREQUENT ADVERSE EVENTS

<table>
<thead>
<tr>
<th>Event</th>
<th>R-CHOEP-14 (n=130)</th>
<th>R-MegaCHOEP (n=132)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>31.3%</td>
<td>75.0%</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>8.3%</td>
<td>64.8%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>0.8%</td>
<td>17.1%</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.3%</td>
<td>11.5%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.7%</td>
<td>10.6%</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>1.7%</td>
<td>5.7%</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0.0%</td>
<td>4.1%</td>
<td></td>
</tr>
<tr>
<td>Sensory</td>
<td>8.1%</td>
<td>1.7%</td>
<td></td>
</tr>
</tbody>
</table>

### R-MegaCHOEP Study

#### RESPONSE

<table>
<thead>
<tr>
<th></th>
<th>R-CHOEP-14 n=127</th>
<th>R-MegaCHOEP n=126</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR / CRu</td>
<td>78.7%</td>
<td>71.4%</td>
<td>75.1%</td>
</tr>
<tr>
<td>PR</td>
<td>1.6%</td>
<td>4.0%</td>
<td>2.8%</td>
</tr>
<tr>
<td>NC</td>
<td>1.6%</td>
<td>1.6%</td>
<td>1.6%</td>
</tr>
<tr>
<td>PRO</td>
<td>10.2%</td>
<td>11.9%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Treatment-related death(^1)</td>
<td>3.1%</td>
<td>5.6%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Unknown</td>
<td>3.9%</td>
<td>4.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td>CR/ CRu and additional treatment</td>
<td>0.8%</td>
<td>1.6%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

\(^1\) deaths on study only
### Event-free Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Event-free (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOEP-14</td>
<td>69.5%</td>
<td>(61.3%; 77.7%)</td>
</tr>
<tr>
<td>R-MegaCHOEP</td>
<td>61.4%</td>
<td>(52.8%; 70.0%)</td>
</tr>
</tbody>
</table>

### Progression-free Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Progression-free (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOEP-14</td>
<td>73.7%</td>
<td>(65.9%; 81.5%)</td>
</tr>
<tr>
<td>R-MegaCHOEP</td>
<td>69.8%</td>
<td>(61.6%; 78.0%)</td>
</tr>
</tbody>
</table>

### Overall Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Overall (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOEP-14</td>
<td>84.6%</td>
<td>(78.3%; 90.9%)</td>
</tr>
<tr>
<td>R-MegaCHOEP</td>
<td>77.0%</td>
<td>(69.6%; 84.4%)</td>
</tr>
</tbody>
</table>

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### EFS: Effect of Rituximab

- **R-MegaCHOEP or R-CHOEP-14 (n=262)**: 65.5%
- **MegaCHOEP or CHOEP-14 (n=31)**: 37.0%

*p = 0.001*
First-line treatment with high-dose therapy and rituximab (R-MegaCHOEP) is not superior to conventional chemotherapy and rituximab (R-CHOEP-14) in young, high-risk patients.

- EFS, PFS, and OS after R-CHOEP-14 represent the best treatment results ever reported for young, high-risk patients with aggressive CD20-positive B-cell lymphoma.

- Addition of rituximab (6 infusions only!) to 8 x CHOEP-14 improved EFS by 28.5% at 3 years. Optimization of rituximab administration may further improve outcome.

- The role of etoposide needs to be determined.

No Benefit of Rituximab High Dose Therapy Over Rituximab-CHOP for Newly Dx’ed DLBCL in Young Adults

Preliminary results of the GOELAMS 075 prospective multicenter randomized trial

N. J. Milipied for the group
Randomized between ‘intensive’ CHOP-R 14 for 8 cycles versus an ‘intensive, modified’ CHOP-like regimen plus MTX/ARA-C followed by BEAM ASCT (only for those PET negative in both arms after 4 cycles).

‘chop-like’: higher dose CTX, epirubicin, vindesine

PET positive patients after 4 cycles were all given DHAP and transplanted with BEAM

**PROTOCOL (CD20-positive DLBCL); n=340**

- **Stratification:**
  - Center
  - aa IPI: 0-1/II/II

- **Diagnosis**
  - Randomization
  - PET negative
  - PET positive
  - PET negative

- **Day 1:**
  - CHOP
  - PET

- **Day 15:**
  - CHOP
  - PET

- **Day 29:**
  - CHOP
  - PET

- **Day 43:**
  - CHOP
  - PET

- **Day 57:**
  - CHOP
  - PET

- **Day 71:**
  - CHOP
  - PET

- **Day 85:**
  - CHOP
  - PET

- **Day 99:**
  - CHOP
  - PET

- **CHOP:** Cyclophosphamide (750 mg/m² on day 1)
  - Doxorubicin (50 mg/m² N on day 1)
  - Vincristine (1.4 mg/m² IV on day 1)
  - Prednisone (100 mg/m² orally on days 1–5)

- **CEP:** Cyclophosphamide (1200 mg/m² IV on day 1)
  - Epirubicin (100 mg/m² IV on day 1)
  - Vindesine (1 mg/m² IV on day 1)
  - Prednisone (80 mg/m² N or orally on days 1–5)

- **DHAP X 3:**
  - Methotrexate (1 g/m² IV on day 1)
  - Cytarabine (100 mg/m² by continuous infusion on days 1–5)

- **BEAM:**
  - Carmustine (100 mg/m² N on day 1)
  - Etoposide (150 mg/m² IV on days 2–5)
  - Cytarabine (140 mg/m² IV on day 6)

- **Rituximab (375 mg/m²):**

- **TDM & PET-SCAN**

- **Evaluation**

- **Splenocyte transplantation (56–48 h after melphalan)**
INTERMEDIATE EVALUATION

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP n=156</th>
<th>R-HDT n=156</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET⁻ n (%)</td>
<td>104 (67)</td>
<td>88 (56)</td>
<td>0.07</td>
</tr>
<tr>
<td>PET⁺ n (%)</td>
<td>48 (31)</td>
<td>63 (40)</td>
<td></td>
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</tbody>
</table>

Patients disposition after interim evaluation

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>Interim evaluation</th>
<th>Final treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP 14 x 4 156</td>
<td>PET neg 104</td>
<td>R-CHOP 14 x 4 104 (+ 5)</td>
</tr>
<tr>
<td>RDZ</td>
<td>PET pos 48</td>
<td>R-DHAP x 3 96</td>
</tr>
<tr>
<td>R-HDT 156</td>
<td>PET pos 63</td>
<td>BEAM 73</td>
</tr>
<tr>
<td></td>
<td>PET neg 88</td>
<td>BEAM 86 (+ 10)</td>
</tr>
</tbody>
</table>
### Overall Response

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP (N=156)</th>
<th>R-HDT (N=156)</th>
<th>All Pts (N=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR n (%)</td>
<td>110 (71%)</td>
<td>112 (72%)</td>
<td>222 (71%)</td>
</tr>
<tr>
<td>CRu</td>
<td>18 (12%)</td>
<td>12 (8%)</td>
<td>40 (10%)</td>
</tr>
<tr>
<td>PR</td>
<td>9 (5%)</td>
<td>12 (8%)</td>
<td>21 (7%)</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fail/PD</td>
<td>13 (8%)</td>
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</tr>
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<td>Death</td>
<td>3 (2%)</td>
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</tr>
<tr>
<td>NP</td>
<td>3 (2%)</td>
<td>5 (3%)</td>
<td>8 (2%)</td>
</tr>
</tbody>
</table>

### PFS according to Tx arm (intent to treat)

- 3y PFS R-CHOP 81 % (+/- 3 %)
- 3y PFS R-HDT 79 % (+/- 4 %)

P= 0.9
BOTTOM LINE:
In those patients with a negative PET after 4 cycles, there was no benefit from ASCT over continued CHOP-R (for a full 8 cycles) in response, PFS, or survival.
There was no difference in response between the ‘modified’ CHOP-R-like regimen with MTX/ARA-C and the standard CHOP-R after 4 cycles.

Summary of the CORAL (Collaborative trial in Relapsed Aggressive Lymphoma) results reported at ASH, ASCO, EHA, & Lugano
CORAL trial: Study design

Which salvage regimen is the best?

R-ICE

R-ICE

R-DHAP

ASCT

RANDOMISE

CR

PR,

RANDOMISE

R-DHAP

x 3

x 3

ASCT

BEAM

q2mo x 6

Observation only

Place of immunotherapy

Post-transplantation?

Relapsed/ refractory DLBCL
n = 396

R-DHAP = rituximab, dexamethasone, high-dose cytarabine, cisplatin

R-ICE = rituximab, ifosfamide, carboplatin, etoposide

• There was essentially no difference overall between R-ICE and R-DHAP for re-induction (salvage therapy pre-ASCT).
• There was no benefit from rituximab maintenance.
• Relapse from a rituximab-containing regimen carries with it a poorer prognosis of benefit from salvage chemorx and ASCT.
• Prognostic factors (early relapse, sIPI, response) may predict outcome.
• In subgroup analysis, some differences emerged regarding salvage rx, maintenance and gender.
CORAL maintenance: OS by gender

Summary of reports on PET scanning in diffuse, large, cell lymphoma from various meetings:
PET in DLBCL

- A negative PET scan, whether interim or at the end of treatment is highly predictive of an excellent outcome with usually less than a 15% chance of relapse.
- The use of interim PET scans for prediction of outcome or therapy change remains controversial, particularly with regard to positive scans.
- Rituximab may be responsible for some false positive scans.
- Timing of the scan after the treatment cycle, and after how many cycles, 'standards' of negativity, etc. may play a role in results.
- The depth of response may play a role in prediction with interim PET scans.
- PET at the end of therapy is still considered more accurate in terms of prediction of outcome.

Brentuximab Vedotin (SGN-35) in CD-30 positive disease:

- CD-30 Lymphoma Diseases: Hodgkins Lymphoma and Anaplastic Large Cell Lymphoma (ALCL)
- Reed-Sternberg cells are CD-30+.
- SGN-35: anti-CD 30 antibody conjugated with a potent antimicrotubule agent, MMAE(monomethyl auristatin E).
- SGN-35 is given @ 1.8mgm/kg every 3 wks.
- Thus far has been successful in heavily pre-treated, poor prognosis patients with responses ranging from 75% to 90%. Median duration of response ranges from six months to two years.
- Role in previously untreated disease to be explored, such as alk-negative ALCL.
**Brentuximab Vedotin Mechanism of Action**

Brentuximab vedotin (SGN-35) ADC
monomethyl auristatin E (MMAE), potent antitubulin agent

- protease-cleavable linker
- anti-CD30 monoclonal antibody

ADC binds to CD30
ADC-CD30 complex traffics to lysosome

MMAE is released
MMAE disrupts Microtubule network

Microtubule network

G2/M cell cycle arrest

**Conclusions:**

- CHOP-R 21 Remains the Standard of RX.
- Increasing the Density or Intensity of RX does not appear effective for the average DBLCL.
- Use of interim PET scans for DBLCL remains controversial and experimental.
- Negative PET scans connote a good prognosis.
- Novel therapies or administration still are under exploration in DLBCL.
- DHAP-R and EPOCH-R are essentially equivalent as salvage therapy.
Conclusions

• SGN-35 offers great promise for CD-30 disease
• Large cell lymphoma patients in general are doing better than ever with the advent of antibody therapy, i.e., SGN-35 (ALCL) and rituximab which seems to be the ‘giant equalizer’ with regard to intensity, duration, and addition of therapies in DBLCL.

THANK YOU FOR YOUR ATTENTION
Systemic and intrathecal chemotherapy followed by high-dose chemotherapy with autologous stem cell transplantation (HD-ASCT) for CNS relapse of aggressive lymphomas – A potentially curative approach?

Clinicaltrials.gov: NCT01148173


QUESTION

Does front line R-high-dose therapy with autologous support remain an option as compared to R-CHOP-14?
PROTOCOL (CD20-positive DLBCL); n=340

Stratification:
- aa IPI:0-I/II/III

Day 15
Day 29
Day 43
Day 85
Day 71
Day 57
Day 1
Day 99

PET negative
PET positive
PET negative

Evaluation
TDM & PET-SCAN

R
R
R
R

PET negative
PET negative
PET positive

R
R
R
R

DHAP X 3
BEAM

PET negative
PET negative
PET positive

R
R
R
R

CHOP X 3
BEAM

PET negative
PET negative
PET positive

R
R
R
R

DHAP X 3
BEAM

PET negative
PET negative
PET positive

R
R
R
R

DHAP X 3
BEAM

R-CHOP n=156
R-HDT n=156

PET- n (%) 104 (67) 88 (56) P
PET+ n (%) 48 (31) 63 (40) 0.07

R: Rituximab
CHOP: Cyclophosphamide (750 mg/m² on day 1)
Doxorubicin (50 mg/m² IV on day 1)
Vincristine (1.4 mg/m² IV on day 1)
Prednisone (100 mg/m² orally on days 1–5)

CEP: Cyclophosphamide (1200 mg/m² IV on day 1)
Epirubicin (100 mg/m² IV on day 1)
Vincristine (1 mg/m² IV on day 1)
Prednisone (80 mg/m² IV or orally on days 1–5)

DHAP: Dexamethasone (100 mg/m² IV on day 1)
Etoposide (400 mg/m² IV on day 2–5)
Cytarabine (70 mg/m² IV by continuous infusion on days 3–5)
Methotrexate (140 mg/m² IV on day 6)

INTERMEDIATE EVALUATION

PET- n (%) 104 (67) 88 (56) P
PET+ n (%) 48 (31) 63 (40) 0.07
Patients disposition after interim evaluation

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>Interim evaluation</th>
<th>Final treatment</th>
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<tbody>
<tr>
<td>RDZ</td>
<td>PET neg 104</td>
<td>R-CHOP 14 x 4</td>
</tr>
<tr>
<td>R-HDT 156</td>
<td>PET pos 48</td>
<td>PET pos 63</td>
</tr>
<tr>
<td></td>
<td>PET neg 88</td>
<td>PET neg 88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BEAM 86 (+ 10)</td>
</tr>
<tr>
<td></td>
<td>R-DHAP x 3 96</td>
<td>BEAM 73</td>
</tr>
</tbody>
</table>

Overall Response

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP N= 156</th>
<th>R-HDT N= 156</th>
<th>All Pts</th>
</tr>
</thead>
<tbody>
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**PFS according to Tx arm (intent to treat)**

- R-CHOP
- R-HDT

3y PFS R-CHOP 81% (+/- 3%)
3y PFS R-HDT 79% (+/- 4%)

**Survival according to the Tx Arm**

- R-CHOP
- R-HDT

3y OS R-CHOP: 85% (+/- 3%)
3y OS R-HDT: 82% (+/- 4%)
Conclusions

• R-HDT as proposed here is not superior to R-CHOP 14 in any aaIPI strata

• R-HDT as proposed here is not superior to R-CHOP-14 for patients with intermediate negative PET scan

• R-CHOP 14 x 8 courses could be regarded as a standard treatment for young adults with CD20+ DLBCL responding to the first 4 courses

• Salvage with R-DHAP followed by BEAM and PBSCT for PET + pts (biopsies not done) was not harmful

CORAL: COllaborative trial in Relapsed Aggressive Lymphoma

Maintenance with rituximab after autologous stem cell transplantation (ASCT) in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) analysis

**CORAL trial: Study design**

Which salvage regimen is the best?

- Relapsed/refractory DLBCL \( n = 396 \)
- R-ICE x 3
  - CR, PR
  - ASCT
  - BEAM
- R-DHAP x 3
  - SD, PD
- Observation only

R-DHAP = rituximab, dexamethasone, high-dose cytarabine, cisplatin

R-ICE = rituximab, ifosfamide, carboplatin, etoposide

**CORAL maintenance: PFS/OS by treatment arm**

**PFS**
- Observation: 120, Event: 43% (52), Censored: 57% (68), Median: 58.22
- Rituximab: 122, Event: 46% (55), Censored: 54% (67), Median: 57.89

**OS**
- Observation: 120, Event: 33% (40), Censored: 67% (80), Median: 62.92
- Rituximab: 122, Event: 36% (44), Censored: 64% (78), Median: NA
**CORAL maintenance: OS by gender**

![Graph showing OS by gender](image)

**Analysis of maximum likelihood estimates**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Parameter estimate</th>
<th>Standard error</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Hazard ratio</th>
<th>95% Hazard ratio confidence limits</th>
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<tbody>
<tr>
<td>brasrand2 RITUXIMAB</td>
<td>1</td>
<td>0.19196</td>
<td>0.22723</td>
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<td>0.776 - 1.891</td>
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<td>0.22754</td>
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<td>&lt;.0001</td>
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<td>SEX MALE</td>
<td>1</td>
<td>0.63522</td>
<td>0.25860</td>
<td>6.0341</td>
<td>0.0140</td>
<td>1.887</td>
<td>1.13 - 3.133</td>
</tr>
</tbody>
</table>

**CORAL maintenance phase: Efficacy**

- No difference in EFS at 3 years: 54% in both arms ($p = 0.74$)
- No difference in 3 year PFS: 54% rituximab vs 57% observation ($p = 0.82$)
- No difference in 3 year overall survival: 66% rituximab vs 69% observation ($p = 0.91$)
- Same results for patients in CR/CRu or PR after induction treatment or according to type of chemotherapy (R-ICE or R-DHAP)
- The main prognostic factor after ASCT is secondary IPI
Systemic and intrathecal chemotherapy followed by high-dose chemotherapy with autologous stem cell transplantation (HD-ASCT) for CNS relapse of aggressive lymphomas – A potentially curative approach?

Clinicaltrials.gov: NCT01148173


Background I

- CNS relapse in DLBCL approx. 5%
- Median OS < 6 months
- No standard therapy
- Radiotherapy / ith. therapy usually palliative
- Frequent simultaneous systemic relapse/progression
Background II

- HD-MTX beneficial
  \[(Doolittle\ 2008,\ Glantz\ 1998)\]
- HD-MTX + Ifosfamide feasible
  \[(Fischer\ 2008)\]
- Retrospective SCT data in CNS relapse
  \[(Williams\ 1994,\ Alvarnas\ 2000,\ Kasamon\ 2005,\ Jahnke\ 2005)\]

CORAL maintenance phase:

**Efficacy**

- No difference in EFS at 3 years: 54% in both arms \( (p = 0.74) \)
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- HD-MTX beneficial
  (Doolittle 2008, Glantz 1998)
- HD-MTX + Ifosfamide feasible
  (Fischer 2008)
- Retrospective SCT data in CNS relapse

Study Design

- Aim: Feasibility and efficacy of a CNS-directed protocol incl. HD-ASCT (explorative analysis)
- Eligibility criteria:
  CNS relapse of aggressive systemic NHL
  18 - 65 years, ECOG PS ≤ 2
  Creatinine clearance ≥ 50ml/min
  No previous CNS directed therapy
- Primary endpoint: progression-free survival
- Secondary endpoints: remission rate, toxicity, overall survival
**Induction chemotherapy**

- MTX 4 g/m²  d1
  - IFO 2 g/m²  d3-5
  - Liposomal AraC 50mg ith.  d6
    + Dexamethasone

- AraC  3 g/m²  d1-2
  - TT 40 mg/m²  d2
  - Liposomal AraC 50mg ith.  d6
    + Dexamethasone

**High-dose chemotherapy**

- BCNU 400 mg/m²  d -5
- TT 2 x 5 mg/kg  d -4 to -3
- Eto 150 mg/m²  d -5 to -3
- ASCT  d0
Patients – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>n=30</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>26</td>
<td>87</td>
</tr>
<tr>
<td>Transformed B-NHL</td>
<td>1</td>
<td>3</td>
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<tr>
<td>T-NHL</td>
<td>3</td>
<td>10</td>
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<tr>
<td><strong>Initial Presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-IV</td>
<td>20</td>
<td>67</td>
</tr>
<tr>
<td>Extranodal involvement</td>
<td>18</td>
<td>60</td>
</tr>
<tr>
<td>B-symptoms</td>
<td>11</td>
<td>37</td>
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<tr>
<td>LDH elevation</td>
<td>16</td>
<td>53</td>
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<tr>
<td><strong>Pretreatment</strong></td>
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<td></td>
</tr>
<tr>
<td>CHOP</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>R-CHO(E)P</td>
<td>26</td>
<td>87</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>CNS prophylaxis</td>
<td>5</td>
<td>17</td>
</tr>
</tbody>
</table>

Progression-free survival (median FU 12.6 mo.)

All patients (n=30) HD-ASCT (n=23)

median PFS 12.2 mo. median n.r.
Overall survival

All patients (n=30) | HD-ASCT (n=23)
---|---
median OS 27.4 mo. | median OS 27.4 mo.

Conclusions

• First prospective evaluation of potentially curative HD-ASCT in this setting
• Emphasis on CNS-directed systemic + intrathecal chemotherapy
• Protocol is feasible and highly active with manageable toxicity
• Progression-free and overall survival promising
Brentuximab Vedotin Mechanism of Action

Brentuximab vedotin (SGN-35) ADC

monomethyl auristatin E (MMAE), potent antitubulin agent
protease-cleavable linker
anti-CD30 monoclonal antibody

ADC binds to CD30
ADC-CD30 complex traffics to lysosome

MMAE disrupts Microtubule network
MMAE is released

Apoptosis
G2/M cell cycle arrest
**Brentuximab Vedotin (SGN-35) in rel/ref HL**

- A pivotal, phase II, single-arm, multicenter study of brentuximab vedotin in 102 pts (54F/48M) with rel/ref HL after HDC-ASCT

- Median of 3.5 (range 1–13) prior systemic therapies (excluding HDC-ASCT)

- Pts received brentuximab vedotin @ 1.8 mg/kg q3 weeks (wks) IV for up to 16 cycles

- The primary endpoint was ORR (as per an independent review facility [IRF] according to the revised Cheson criteria)

---

**Brentuximab Vedotin (SGN-35) in rel/ref HL**

<table>
<thead>
<tr>
<th>All patients (N=102)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>76 (75%)</td>
</tr>
<tr>
<td>CR</td>
<td>35 (34%)</td>
</tr>
<tr>
<td>PR</td>
<td>41 (41%)</td>
</tr>
</tbody>
</table>

- Median duration of response for all responding pts 6.7 months
- Median duration of response for pts with CR (as per IRF) was 20.5 months
- Estimated 12 month OS for all pts was 89%

71% of pts had primary refractory disease and 42% had not responded to their most recent prior therapy.

Chen W. et al, ASCO 2011, abstract 8031
Overall Conclusions

- **DLBCL**
  - R-CHOP-21 for 6 cycles is still standard-of-care!
    - Alternatives: R-CHOP-14 or R-CHOEP-14 (Germany)
  - In young high-risk "IPI pts
    - R-CHOP x 6 followed by autologous SCT should be considered
    - Need to improve induction Rx
  - R-CHOP-21 x 8 = R-CHOP-14 x 6 + 2 R
    - More is not better; Better is better!
- **Secondary CNS relapse of aggressive lymphoma**
  - CNS-directed chemotherapy + HDT-ASCT may be beneficial
- **Relapsed/refractory Hodgkin lymphoma (HL)**
  - Brentuximab vedotin to HL ~ rituximab to B-cell NHL?
- **Future**
  - Personalized regimes + increase utilization of targeted agents