Therapeutic Strategies for Elderly Patients with DLBCL

Michael Pfreundschuh

German High-Grade Non-Hodgkin Lymphoma Study Group
Internal Medicine I, Saarland University Medical School
Homburg (Saar), Germany
Aggressive Lymphomas in the Elderly

- Clinical relevance
- Definition of „elderly“ patients
- Specific features of elderly patients
- Treatment options
- Perspectives
Aggressive Lymphomas in the Elderly

Clinical Relevance:

• ~ 40% of all lymphomas
• > 50% diagnosed > 65 years
• > 15% diagnosed > 80 years
• Octa- and nona-generians: fast-growing population
• Under- or no presentation in studies
Patients recruited for prospective trials*

* Prospective population based KML Study (Saarland 2000-2003)
Aggressive Lymphomas in the Elderly

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Aggressive Lymphomas in the Elderly

Age groups analyzed*:

• 61 – 65 years
• 66 – 70 years
• 71 – 75 years
• 76 – 81 years
• >80 years [?]

Ricover-60 Trial of the DSHNHL
RICOVER-60 Trial
Course of leukocytes

Day of CHOP-14 cycle

leucocytes x 10^9/mm^3 (median)

- 61 – 70 y
- 71 – 75 y
- 76 – 80 y

DSHNHL 19.05.2003
Grade 3&4 Infections*

* RICOVER-60 Trial (Pats. # 001-500)
Therapy-associated deaths*

* RICOVER-60 Trial (Pats. # 501-1000)
RICOVER60 Trial
Treatment duration – 6 cycles CHOP-14 ± rituximab

proportion of patients

median

Days

61 – 70 y: 76 days
71 – 75 y: 73 days
76 – 80 y: 81 days

DSHNHL 19.05.2003
RICOVER60 Trial

Event-free Survival

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Event-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>61–70 y</td>
<td>0.315</td>
</tr>
<tr>
<td>71–75 y</td>
<td>0.002</td>
</tr>
<tr>
<td>76–80 y</td>
<td>0.076</td>
</tr>
</tbody>
</table>

DShNHL 19.05.2003
RICOVER60 Trial

**Overall Survival**

**Probability vs. Months**

- **61 – 70 y**
- **71 – 75 y**
- **76 – 80 y**

*p* values:
- *p*₁,₂ = 0.004
- *p*₁,₃ < 0.001
- *p*₂,₃ = 0.032
IPI according to age groups*

* RICOVER-60 Trial (Pats. # 001-500)
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Aggressive Lymphomas in the Elderly

Specific features of „elderly“ DLBCL:

- prognosis worsening with age
- hardly explained by protocol adherence
- partially explained by:
  - different biology
  - poorer risk profile
  - higher death rate
Specific features of "elderly" DLBCL:

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Specific features of “elderly“ DLBCL:

- prognosis worsening with age
- hardly explained by protocol adherence
- partially explained by:
  - different biology
  - poorer risk profile
  - higher death rate
Outcome Prediction: Molecular vs. Cytological

Ott et al., *Blood* 2010 (in press)
Aggressive Lymphomas in the Elderly

**DLBCL biology in the elderly:**

- immunoblastic subtype ↑
- ABC type ↑
- BCL2/MYC double expressors ↑
Aggressive Lymphomas in the Elderly

Specific Measures:

1. Prephase Treatment
2. Anti-infective Prophylaxis
3. Hydrocortison Substitution
Aggressive Lymphomas in the Elderly

Prephase treatment:

- Vincristin 1 mg i.v. day –7
- Prednisone 100 mg p.o. days –7 to –1

Effects:

- Improvement of performance state
- Ameliorization of 1st-cycle effect
Aggressive Lymphomas in the Elderly

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Aggressive Lymphomas in the Elderly

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- Vincristin 1 mg i.v. day –7
- Prednisone 100 mg p.o. days –7 to –1

Effects:

- Improvement of performance state
- Ameliorization of 1st-cycle effect
Therapy-associated Deaths before and after Introduction of Prephase Therapy*

* DSHNHL NHL-B2 Trial
**Specific Measures:**

1. Prephase Treatment
2. Anti-infective Prophylaxis (Cotrimoxazole & Aciclovir)
Effect of Prophylaxis on Grade 3&4 Infections

Grade 3&4 Infections per Cycle
Grade 3&4 Infections per Cycle

- 12.7% of patients had Grade 3&4 infections with prophylaxis.

Supported by DSHNHL
Effect of Prophylaxis on Grade 3&4 Infections

Grade 3&4 Infections per Cycle

- # <=20 Patients: 12.7%
- # >20 Patients: 5.7%
DENSE-R-CHOP-14

Effect of Prophylaxis on Grade 3&4 Infections

Grade 3&4 Infections per Cycle

- # <=20 Patients: 12.7%
- # >20 Patients: 5.7%

p=0.007

Supported by DSHNHL
Effect of Prophylaxis on Grade 3&4 Infections

Grade 3&4 Infections per Cycle

Grade 3&4 Infections per Patient

- # <=20 Patients: 12.7%
- # >20 Patients: 5.7%

Supported by p=0.007
Effect of Prophylaxis on Grade 3&4 Infections

Grade 3&4 Infections per Cycle

- # <=20 Patients: 12.7%
- # >20 Patients: 5.7%

Grade 3&4 Infections per Patient

- # <=20 Patients: 35.0%
- # >20 Patients: (no data shown)

**Supported by p=0.007**

**DENSE-R-CHOP-14**
Specific Measures:

1. Prephase Treatment
2. Anti-infective Prophylaxis
3. Hydrocortisone Substitution for intercycle fatigue
Aggressive Lymphomas in the Elderly

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• Specific features of elderly patients
• Treatment options
Aggressive Lymphomas in the Elderly

• Clinical relevance
• Definition of „elderly“ patients
• Specific features of elderly patients
• Treatment options
  • fit elderly
  • unfit elderly / very old
**Study Design**

RICOVER-60

CD20+ DLBCL
Stages I-IV
61 to 80 years

Random 2x2 Factorial Design

- 6 x CHOP-14 + 30-40 Gy (Bulk, E)
- 8 x CHOP-14 + 30-40 Gy (Bulk, E)
- 6 x CHOP-14 + 36 Gy (Bulk, E) + 8 x Rituximab
- 8 x CHOP-14 + 36 Gy (Bulk, E) + 8 x Rituximab
Overall Survival

1: 6 x CHOP -14 (n=307)
2: 8 x CHOP -14 (n=305)
3: 6 x R-CHOP- 14 + 2R (n=306)
4: 8 x R-CHOP- 14 (n=304)

1, 2: p=0.836
1, 3: p=0.018
1, 4: p=0.260
3, 4: p=0.200

Pfreundschuh et al., Lancet Oncol. (2008)
III. Elderly Patients:

*Do we still need Dose Densification / Interval Reduction?*

[R-CHOP-14 vs. R-CHOP-21]
Primary endpoint: EFS
Expected improvement: 10% at 3 years with R-CHOP 14 (55 to 65%)
600 patients required (over 4 years)
LNH-03 6B
The French Learning Curve (I) …
Toxic Deaths with R-CHOP-14

Delarue et al., ASH 2009 / Lancet Oncology 2013
Delarue et al., ASH 2009 / Lancet Oncology 2013

LNH-03 6B
The French Learning Curve (I) …
Toxic Deaths with R-CHOP-14

% patients

4.6%

total
pt. # 1-100
pt. # 101-304
LNH-03 6B
The French Learning Curve (I) …
Toxic Deaths with R-CHOP-14

Delarue et al., ASH 2009 / Lancet Oncology 2013
The French Learning Curve (I) ... Toxic Deaths with R-CHOP-14

Delarue et al., ASH 2009 / Lancet Oncology 2013
GELA LNH03-6B: The French CHOP-14 Learning Curve (II)

OS Pts. #1-200

- 2-year OS: 67% (R-CHOP14) vs 70% (R-CHOP21)

OS Pts. #1-600

- 3y-OS: 70% vs 73%
  - HR: 0.98 (95%CI: 0.74-1.30); p=0.89

Delarue et al., ASH 2009 / Lancet Oncology 2013
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 x CHOP-14</td>
<td>99%</td>
</tr>
<tr>
<td>6 x R-CHOP-14</td>
<td>99%</td>
</tr>
<tr>
<td>8 x CHOP-14</td>
<td>96%</td>
</tr>
<tr>
<td>8 x R-CHOP-14</td>
<td>96%</td>
</tr>
<tr>
<td>GELA 8xR-CHOP-14</td>
<td>83%</td>
</tr>
</tbody>
</table>
Adherence to Protocol

Relative Dose Cyclophosphamide (median)

- 6 x CHOP-14: 99%
- 6 x R-CHOP-14: 99%
- 8 x CHOP-14: 96%
- 8 x R-CHOP-14: 96%
- GELA 8xR-CHOP-14: 83%

Are German patients tougher?
### Relative Dose Intensity Cyclophosphamide (median)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 x CHOP-14</td>
<td>99%</td>
</tr>
<tr>
<td>6 x R-CHOP-14</td>
<td>99%</td>
</tr>
<tr>
<td>8 x CHOP-14</td>
<td>96%</td>
</tr>
<tr>
<td>8 x R-CHOP-14</td>
<td>96%</td>
</tr>
</tbody>
</table>

- Supportive measures as discussed
- No dose reductions unless delay > 7 days
- Strict adherence to G-CSF schedule
Unresolved Issues in DLBCL

*R-CHOP-14 vs R-CHOP-21 in Elderly*
Unresolved Issues in DLBCL

*R-CHOP-14 vs R-CHOP-21 in Elderly:*

- Equal efficacy
Unresolved Issues in DLBCL

R-CHOP-14 vs R-CHOP-21 in Elderly:

- Equal efficacy
- Equal acute toxicity
Recommendation Elderly DLBCL:

- 6 cycles R-CHOP-14 + 2 R

- 8 cycles R-CHOP-21
Unresolved Issues in DLBCL

R-CHOP-14 vs R-CHOP-21 in Elderly:

- Equal efficacy
- Equal acute toxicity

What about long-term toxicity?
R-CHOP: Reduction of EF

![Graph showing ejection fraction (Teichholz) in different groups: 6xCHOP pre, 6xCHOP post, 8xCHOP pre, 8xCHOP post. The graph indicates a significant reduction in ejection fraction post-treatment, with a p-value less than 0.01.](image)
Unresolved Issues in DLBCL

*R-CHOP-14 vs R-CHOP-21 in Elderly:

- Equal efficacy
- Equal acute toxicity
- Less long-term toxicity (cardiac: yes; second neoplasms: probably)
R-CHOP-14 vs R-CHOP-21 in Elderly:

- Equal efficacy
- Equal acute toxicity
- Less long-term toxicity (cardiac: yes; second neoplasms: probably)
- Shorter time under chemo (10 vs. 21 weeks)
Aggressive Lymphomas in the Elderly

- Clinical relevance
- Definition of „elderly“ patients
- Specific features of elderly patients
- Treatment options
  - fit elderly
  - unfit elderly / very old (>80 years?)
Rituximab and reduced dose R-miniCHOP for patients aged over 80 with DLBCL

Groupe d’Etude Des Lymphomes De l’Adulte (GELA) Study LNH03-7B

Frédéric Peyrade, Fabrice Jardin, Christian Gisselbrecht, Antoine Thyss, Jean François Emile, Sylvie Castaigne, Bertrand Coiffier, Corinne Haioun, Serge Bologna, Olivier Fitoussi, Gérard Lepeu, Christophe Fruchart, Dominique Bordessoule, Michel Blanc, Richard Delarue, Maud Janvier, Bruno Salles, Andre Bosly, and Hervé Tilly.
## Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>40 mg/m²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m²</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>25 mg/m²</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>400 mg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1 mg DT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inclusion:

- C1
- C2
- C3
- C4
- C5
- C6

Follow-up:

- FU0
- FU1
- FU2

**Primary endpoint: overall survival**
Primary endpoint: Overall survival
Intent-to-treat population

Median: 29 months
At two years: 59%

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>149</td>
<td>39% (58)</td>
<td>61% (91)</td>
<td>29.14 (21.22 NA)</td>
</tr>
</tbody>
</table>
Conclusions

- R-miniCHOP: adapted regimen for DLBCL patients older 80 years
- Acceptable toxicity, but first treatment cycles represent a crucial period
- 59% patients are alive at two years
- Less toxicity with perphase treatment*

* ASH 2014
Specific evaluation:

- Comprehensive geriatric assessment (CGA)
- Activities of daily life (ADL)
- Instrumental activities of daily living (IADL)
- Cumulative illness rating score (CIRS)
**Aggressive Lymphomas in the Elderly**

**Basic geriatric evaluation:**

- Gait speed
- Timed up and go
- Hand grip
- Tinetti gait and balance test
- Hurria Self Assessment Test
Geriatric Assessment-modified Strategy

Comorbidities

No

RCHOP/CHOP

Yes

Mild Cardiopathy

CEOP or R-CEOP

Severe Cardiopathy

CVP or R-CVP

Diabetes

CHO or R-CHO

Neuropathy

CHP or R-CHP

Step 2: Dosage of chemotherapy

<table>
<thead>
<tr>
<th>ADL</th>
<th>6</th>
<th>5</th>
<th>&lt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td>or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IADL</td>
<td>7-8</td>
<td>5-6</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

100%  75%  50%

Spina et al. 2012
Geriatric Assessment-modified Strategy

Spina et al. 2012
Patients >60 Years of Age with Diffuse Large B-Cell Lymphoma (DLBCL) Treated with Standard or Liposomal Chemotherapies

Romega et al. ASH 2015
Median follow-up: 23 months (range 1-39)

Median OS: 23 months
Median PFS: 13 months

2-years OS: 49%
2-years PFS: 38%

Follow-up, months

PFS 49 36 30 26 23 19 19 15 8 6 4 3 2
OS 49 40 35 30 28 25 25 20 11 6 5 5 4

R-BENDA Frail, Sergio Storti, Campobasso -Italy
Aggressive Lymphomas in the Elderly

• Clinical relevance
• Definition of „elderly“ patients
• Specific features of elderly patients
• Treatment options
• Perspectives
1. Intensified chemotherapy?

2. Intensified rituximab?
Improvement Strategies In Elderly DLBCL

1. Intensified chemotherapy ?

2. Intensified rituximab ?
RICOVER-60 Trial: Rituximab Clearance

Müller et al., Blood 2012
RICOVER-60

Trough Serum Levels

- females
- males
RICOVER-60 Trial (n=1222)

PFS according to Sex and Rituximab

Müller et al, Blood 2012
RICOVER-60 Trial (n=1222)

PFS according to Sex and Rituximab

Müller et al, Blood 2012
### RICOVER-60 Trial (n=1222)

**Multivariate Analysis PFS Without Rituximab**

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH</td>
<td>1.526</td>
<td>0.002</td>
</tr>
<tr>
<td>ECOG</td>
<td>1.672</td>
<td>0.001</td>
</tr>
<tr>
<td>Stage</td>
<td>1.957</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ex&gt;1</td>
<td>1.650</td>
<td>0.001</td>
</tr>
<tr>
<td>Male vs. Female</td>
<td>1.127</td>
<td>0.348</td>
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*Müller et al, Blood 2012*
### RICOVER-60 Trial (n=1222) Multivariate Analysis PFS

#### Without Rituximab

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#### With Rituximab

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<tr>
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</thead>
<tbody>
<tr>
<td>LDH</td>
<td>2.210</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECOG</td>
<td>1.743</td>
<td>0.004</td>
</tr>
<tr>
<td>Stage</td>
<td>1.450</td>
<td>0.045</td>
</tr>
<tr>
<td>Ex&gt;1</td>
<td>1.075</td>
<td>0.724</td>
</tr>
<tr>
<td>Male vs. Female</td>
<td>1.592</td>
<td>0.004</td>
</tr>
</tbody>
</table>

* Müller et al, Blood 2012*
Outcome of Young Females and Males with DLBCL in the MInT Study

**Event-free survival (%)**

- **Male without R** (n=221)
- **Male with R** (n=257)
- **Female without R** (n=189)
- **Female with R** (n=156)

**Progression-free survival (%)**

- **Male without R** (n=221)
- **Male with R** (n=257)
- **Female without R** (n=189)
- **Female with R** (n=156)

**Overall survival (%)**

- **Male without R** (n=221)
- **Male with R** (n=257)
- **Female without R** (n=189)
- **Female with R** (n=156)

**Number at risk**

- **Male without R**
  - 115
  - 82
  - 63
  - 14
  - 0
- **Male with R**
  - 189
  - 130
  - 94
  - 17
  - 0
- **Female without R**
  - 118
  - 81
  - 54
  - 11
  - 0
- **Female with R**
  - 116
  - 84
  - 56
  - 13
  - 0

**Females without rituximab**

**Males without rituximab**

**Females with rituximab**

**Males with rituximab**
Rituximab Clearance in DLBCL according to Age
Rituximab Clearance in DLBCL according to Age

All Patients

\[ p = 0.320 \]

Pfreundschuh et al., *Blood* 2014
Rituximab Clearance in DLBCL according to Age

All Patients

Males

p=0.320  
p=0.168

Pfreundschuh et al., Blood 2014
Rituximab Clearance in DLBCL according to Age

All Patients

Males

Females

p=0.320

p=0.168

Pfreundschuh et al., *Blood* 2014
Rituximab Clearance in DLBCL according to Age

All Patients

Males

Females

p=0.320  

p=0.168  

p=0.004

Pfreundschuh et al., *Blood* 2014
Rituximab Clearance in DLBCL Subgroups

Rituximab Clearance (ml/hr)

- Elderly patients: 25 females, 24 males
- Young patients: 13 females, 20 males
Rituximab Clearance in DLBCL Subgroups

Rituximab clearance (ml/hr)

p=0.005

elderly patients

young patients

n = 25 24 13 20
Rituximab Clearance in DLBCL Subgroups

- Elderly patients: n = 25, p = 0.005
- Young patients: n = 24, p = 0.004

Rituximab clearance (ml/hr)
Rituximab Clearance in DLBCL Subgroups

- Elderly patients: n=25, Clearance: 7.0-11.0 ml/hr, p=0.004
- Young patients: n=24, Clearance: 10.0-14.0 ml/hr, p=0.015
- Young male patients: n=20, Clearance: 13.0-17.0 ml/hr, p=0.005

Graph showing box plots for the distribution of Rituximab clearance in elderly vs. young patients.
Rituximab Pharmacokinetics in DBLC

Clinical Consequences

?
Rituximab Pharmacokinetics in DBLC

Clinical Consequences (I):

SEXIER-CHOP-14
Study Design

SEXIE-R-CHOP-14

CD20+ DLBCL
Stages I-IV
61 to 80 years

Rituximab 375 mg/m²

Rituximab 500 mg/m²

Weeks
SEXIE-R-CHOP-14

Trough Serum Levels

Pfreundschuh et al., ASCO 2014
SEXIE-R-CHOP-14: PFS

SEXIE-R

Pfreundschuh et al., ASCO 2014
SEXIE-R-CHOP-14: PFS

SEXIE-R

RICOVER-60

Pfreundschuh et al., ASCO 2014
Sex as a Risk Factor in Elderly DLBCL Patients
Multivariable Analysis: RICOVER-60 (375mg/m²) vs. SEXIE-R-CHOP-14 (500 mg/m²)

<table>
<thead>
<tr>
<th></th>
<th>EFS (Hazard ratio [95%-CI])</th>
<th>PFS (Hazard ratio [95%-CI])</th>
<th>OS (Hazard ratio [95%-CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>RICOVER (n=610)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>1.8 (p&lt;0.001)</td>
<td>2.2 (p&lt;0.001)</td>
<td>2.1 (p&lt;0.001)</td>
</tr>
<tr>
<td>ECOG&gt;1</td>
<td>1.8 (p=0.001)</td>
<td>1.7 (p=0.873)</td>
<td>1.9 (p=0.001)</td>
</tr>
<tr>
<td>Stages III&amp;IV</td>
<td>1.5 (p=0.011)</td>
<td>1.5 (p=0.045)</td>
<td>1.5 (p=0.047)</td>
</tr>
<tr>
<td>&gt;1 extra-lymphatic site</td>
<td>1.0 (p=0.937)</td>
<td>1.1 (p=0.724)</td>
<td>1.1 (p=0.817)</td>
</tr>
<tr>
<td>Male vs. female</td>
<td>1.4 (p=0.016)</td>
<td>1.6 (p=0.004)</td>
<td>1.4 (p=0.063)</td>
</tr>
</tbody>
</table>

Notes:
- Elevated LDH: 1.8 (p<0.001), 1.7 (p=0.170), 2.2 (p<0.001), 1.6 (p=0.238), 2.1 (p<0.001), 2.2 (p=0.107)
- ECOG>1: 1.8 (p=0.001), 1.1 (p=0.873), 1.7 (p=0.004), 1.2 (p=0.719), 1.9 (p=0.001), 1.3 (p=0.644)
- Stages III&IV: 1.5 (p=0.011), 1.2 (p=0.755), 1.5 (p=0.045), 1.2 (p=0.686), 1.5 (p=0.047), 1.1 (p=0.791)
- >1 extra-lymphatic site: 1.0 (p=0.937), 1.9 (p=0.121), 1.1 (p=0.724), 2.0 (p=0.103), 1.1 (p=0.817), 1.5 (p=0.420)
- Male vs. female: 1.4 (p=0.016), 0.9 (p=0.708), 1.6 (p=0.004), 0.8 (p=0.613), 1.4 (p=0.063), 0.7 (p=0.252)
Rituximab Pharmacokinetics in DBLC

Clinical Consequences (II):

SMARTE-R-CHOP-14
Simulation for a Maximum Area under the Curve (AUC) with 8 x Rituximab
Rituximab Schedules for DLBCL

SMARTE-R-CHOP-14
(8 x R)

-4 -1 15 29 43 57 71 85 99 155 239
Rituximab Schedules for DLBCL

**SMARTE-R-CHOP-14**
(8 x R)

**RICOVER-60**
R-CHOP-14
(8 x R)

Supported by

**Days**

-4 -1 15 29 43 57 71 85 99 155 239
Overall Survival

SMARTE-R-CHOP-14

Overall Survival

Proportion

Months

median time of observation: 37 / 34 months

78%

SMARTER
(n=189)

RICOVER-60
(n=306)

40
45
50
55
60
Overall Survival

SMARTE-R-CHOP-14

Proportion

Months

0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

84%
78%

p=0.118

median time of observation: 37 / 34 months

SMARTER (n=189)
RICOVER-60 (n=306)
IPI=1,2

Overall Survival
Overall Survival

IPI=1,2

p=0.489

SMARTE-R-CHOP-14

Proportion

Months

SMARTER (n=90)
RICOVER-6 (n=183)
Overall Survival

IPI=1,2

IPI>2

p=0.489

Proportion

0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

Months

0 5 10 15 20 25 30 35 40 45 50 55 60

SMARTE-R-CHOP-14

SMARTER (n=90)

RICOVER-6 (n=183)
Overall Survival

IPI=1,2

- SMARTER (n=90)
- RICOVER-60 (n=183)

IPI>2

- SMARTER (n=99)
- RICOVER-60 (n=123)

p=0.489

67%
Overall Survival

IPI=1,2

IPI>2

p=0.489

SMARTE-R-CHOP-14

RICOVER-60 (n=183)

SMARTER (n=123)

80%

67%
Overall Survival

IPI=1,2

- RICOVER-60 (n=183)
- SMARTER (n=90)

\[ p=0.489 \]

IPI>2

- RICOVER-60 (n=123)
- SMARTER (n=99)

\[ p=0.034 \]
SMARTe-R vs. RICOVER
Sex-differential Improvement

Pfreundschuh et al., J Clin Oncol 2014
SMARTER-R vs. RICOVER
Sex-differential Improvement

OS of Females (IPI=3-5)

- Female SMARTER (n=48)
- Female RICOVER (n=57)

80% at 35 months
76% at 40 months

Pfreundschuh et al., J Clin Oncol 2014
SMARTE-R vs. RICOVER
Sex-differential Improvement

OS of Females (IPI=3-5)

OS of Males (IPI=3-5)

Pfreundschuh et al., J Clin Oncol 2014
Adherence to Protocol

Relative Dose Cyclophosphamide (median)

- 6 x CHOP-14: 99%
- 6 x R-CHOP-14: 99%
- 8 x CHOP-14: 96%
- 8 x R-CHOP-14: 96%
<table>
<thead>
<tr>
<th>Dosage [mg]</th>
<th>cycle 1</th>
<th>cycle 2</th>
<th>cycle 3</th>
<th>cycle 4</th>
<th>cycle 5</th>
<th>cycle 6</th>
<th>cycle 7</th>
<th>cycle 8</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.5%</td>
<td>2.4%</td>
<td>5.3%</td>
<td>9.8%</td>
<td>16.4%</td>
<td>22.0%</td>
<td>30.4%</td>
<td>35.5%</td>
<td>11.8%</td>
</tr>
<tr>
<td>0.1 - 1.9</td>
<td>10.9%</td>
<td>12.5%</td>
<td>14.7%</td>
<td>17.0%</td>
<td>17.6%</td>
<td>17.4%</td>
<td>17.3%</td>
<td>15.2%</td>
<td>15.0%</td>
</tr>
<tr>
<td>2</td>
<td>86.5%</td>
<td>84.9%</td>
<td>79.5%</td>
<td>72.6%</td>
<td>65.3%</td>
<td>59.0%</td>
<td>51.0%</td>
<td>47.9%</td>
<td>72.5%</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>-</td>
<td>0.1%</td>
<td>0.2%</td>
<td>-</td>
<td>-</td>
<td>0.2%</td>
<td>-</td>
<td>0.3%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.3%</td>
<td>0.6%</td>
<td>0.8%</td>
<td>1.4%</td>
<td>1.3%</td>
<td>1.1%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>
Towards the Cure of DLBCL

Vincristine polyneuropathy:
an unmet medical need
Random 2x2 Factorial Design

CD20⁺ DLBCL
IPI 2-4
IPI 1 Bulk
61 to 80 years

Except PET-neg.

§ conventional vincristine 2 mg (absol.)
& liposomal vincristine 2 mg/m²

R-CHOP-14§
+ 36 Gy BULK-IN-RT*

Opti-R-CHOP-14§
+ 36 Gy BULK-INRT*

R-CHLIP-14&
+ 36 Gy BULK-IN-RT*

Opti-R-CHLIP-14&
+ 36 Gy BULK-IN-RT*
# Towards the Cure of DLBCL

**CHOP:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Day(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/m²</td>
<td>i.v.</td>
<td>day 1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>50 mg/m²</td>
<td>i.v.</td>
<td>day 1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4 mg/m²</td>
<td>i.v. (max. 2mg)</td>
<td>day 1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>100 mg</td>
<td>p.o.</td>
<td>days 1-5</td>
</tr>
</tbody>
</table>

**CHLIP:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Day(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/m²</td>
<td>i.v.</td>
<td>day 1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>50 mg/m²</td>
<td>i.v.</td>
<td>day 1</td>
</tr>
<tr>
<td>liposomal Vincristine</td>
<td>2.0 mg/m²</td>
<td>i.v.</td>
<td>day 1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>100 mg</td>
<td>p.o.</td>
<td>days 1-5</td>
</tr>
</tbody>
</table>
OPTIMAL >60

Study Design

OPTIMAL
R-CHOP-14
R-CHLIP-14
(12 x R)

2-week
R-CHOP-14
R-CHLIP-14
(8 x R)

Supported by DSHNHL
OPTIMAL>60: Further Improvement?

Overall Survival

- OPTIMAL>60 (n=245)
- RICOVER-60: 6xR-CHOP-14 (n=306)
Beyond Rituximab
Pharmacokinetics ...
Vitamin D Deficiency: Not a Problem in „Sunny Rimini“?
RICOVER-60:
Vitamin D serum levels (n=359)

Median: 9.2 ng/ml

Bittenbring et al., J Clin Oncol 2014
RICOVER-60: Event-free Survival

CHOP

Bittenbring et al., J Clin Oncol 2014
RICOVER-60: Event-free Survival

**CHOP**

- ≥ 8 ng/ml 25-OH Vitamin D
- < 8 ng/ml 25-OH Vitamin D

**R-CHOP**

- ≥ 8 ng/ml 25-OH Vitamin D (p=0.001)
- < 8 ng/ml 25-OH Vitamin D

Bittenbring et al., *J Clin Oncol* 2014
Rituximab-mediated Cellular Cytotoxicity in Vitamin-D Deficient Individuals before and after Substitution

Bittenbring et al., *J Clin Oncol* 2014
Rituximab-mediated Cellular Cytotoxicity before and after Vitamin-D-Substitution

% Lysis of CD20+ Daudi Cells

Vitamin D Serum Level (ng/ml)

11.2, 30.4, 68.5, 100.5

Bittenbring et al., ASH 2015
3-Year EFS Improvement by Rituximab in RICOVER-60

Bittenbring et al., *J Clin Oncol* 2014
Towards the Cure of DLBCL

The future:

- [ Vitamin D substitution: „DR.CHOP“ ]
- Lenalidomide
- BTK inhibitors (Ibrutinib)
- PI3K inhibitors
- Bcl-2 inhibitors
- Combos (PPM + BTK-I + mTor-I)
REAL07 phase II R2-CHOP21 in elderly high risk untreated DLBCL

**Progression-free survival (%)**

- **2-year PFS**
  - All patients: 80%

**Overall survival (%)**

- **2-year OS**
  - All patients: 92%

Towards the Cure of DLBCL

The future:

- Vitamin D substitution: „DR.CHOP“
- Lenalidomide
- BTK inhibitors (Ibrutinib)
- PI3K inhibitors
- Bcl-2 inhibitors
- Combos (PPM + BTK-I + mTor-I)
- BARs
Towards the Cure of DLBCL

The future:

- [ Vitamin D substitution: „DR.CHOP“ ]
- BTK inhibitors (Ibrutinib)
- PI3K inhibitors
- Bcl-2 inhibitors
- Combos (PPM + BTK-I + mTor-I)
- BCR-Antigens for Reverse Targeting
Forward vs. Reverse Targeting

Forward Targeting

Antibody binds to Antigen, e.g. CD20

Complement dependent cytotoxicity (ICD)

Antibody dependent cellular cytotoxicity (ADCC)

Target cell

Effector cell (NK cells)

Programmed cell death (PCD) (apoptosis)
- Binding assay
- Apoptosis assay

Membrane attack complex
Forward vs. Reverse Targeting

**Forward Targeting**
Antibody binds to Antigen, e.g. CD20

- Complement dependent cytotoxicity (CDC)
- Antibody dependent cellular cytotoxicity (ADCC)
- Membrane attack complex
- Programmed cell death (PCD) (apoptosis)
  - Binding assay
  - Apoptosis assay

**Reverse Targeting**
B-Cell Receptor Antigen binds to B-Cell Receptor

B Cell , BCR
Forward vs. Reverse Targeting

**Forward Targeting**
Antibody binds to Antigen, e.g. CD20

**Reverse Targeting**
B-Cell Receptor Antigen binds to B-Cell Receptor

Diagram:
- Forward Targeting:
  - Antibody binds to target cell (NK cells)
  - Membrane attack complex
  - Programmed cell death (PCD) (apoptosis)
  - Binding assay
  - Apoptosis assay

- Reverse Targeting:
  - B-Cell Receptor (BCR)
  - BAR
Forward vs. Reverse Targeting

**Forward Targeting**
Antibody binds to Antigen, e.g. CD20

**Reverse Targeting**
B-Cell Receptor Antigen (with Toxin)
binds to B-Cell Receptor

BAR Toxin
Forward vs. Reverse Targeting

**Forward Targeting**
Antibody binds to Antigen, e.g. CD20

**Reverse Targeting**
B-Cell Receptor Antigen (with Toxin)
binds to B-Cell Receptor
Clinical Relevance of BCR Antigens

*Homburg BARs identified (25.03.15):*

- 30-50% of MGUS/MM (2 antigens, 1 epitope)
- 30% of CLL (diverse, ≥2 epitopes each)
- 25% of FL (1 antigen, 1 epitope)
- 66% of all PCNSL (1 antigen, 1 epitope)
- 60% all ABC-DLBCL (1 antigen, 1 epitope)
- 45% of all MCL (1 antigen, 1 epitope)
- 90% of IgD-NLPHL (Moraxella catarrhalis)
Specific Killing of ARS2-pos ABC-DLBCL by BAR-Toxins (Pseudomonas Exotoxin)
Growth of heterotransplanted ARS2-pos. OCI-LY3 in SCID mice

15 µg PE toxin-conjugated BAR i.v.
BARs: A new dimension in the treatment for a broad spectrum of various B-cell malignancies

or:

„Personalized and Precision Medicine at the Limits“
Thank you!