Stem Cell Transplantation in Primary CNS Lymphoma

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Epidemiology:

- 0.5 / 100,000 / year
- 1 - 2% of all extranodal NHL
- 4 to 7% of newly diagnosed primary CNS tumors
- Increasing incidence - more than ten-fold over the past three decades
- Median age: 61 ys.
Clinical Presentation:

- History of 3 - 7 months
- Personality changes
- Neurocognitive impairment (dementia...)
- Focal neurologic deficits
- Intracranial pressure, headache, nausea...
Background

Stereotactic biopsy:
Background

> 90% DLBCL; T-NHL, low grade B-NHL < 5%
Background

Inflammation vs. lymphoma

Micro-RNA in CSF
Background

**Inflammation vs. lymphoma**

**Micro-RNA in CSF**

Sens. and Spec. > 95%

Baraniskin et al, Blood 2011

Figure 3. CSF miRNA expression classification tree correctly diagnosing 95.7% of patients with PCNSL and 96.7% of control patients. Relative expression cutoff levels of ≥ 8.0 REL for miR-21, ≥ 1.4 REL for miR-19b, and ≥ 2.5 REL for miR-92a, respectively, were applied for diagnostic placements as depicted.
Special issues in PCNSL:

- aggressive lymphoma entity with a unique localisation
Background

Special issues in PCNSL:

- aggressive lymphoma entity with a unique localisation
- the surrounding brain tissue is highly vulnerable
  → risk of leukencephalopathy (from disease / from therapy)
Special issues in PCNSL:

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- aggressive lymphoma is a systemic disease
  → need for systemic therapy
Special issues in PCNSL:

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  → risk of leukencephalopathy (from disease / from therapy)
- aggressive lymphoma is a systemic disease
  → need for systemic therapy
- effective regimens for systemic lymphoma (i.e. CHOP) do not work in PCNSL
Special issues in PCNSL II:

- Local therapy without (long-term) benefit
- Whole brain radiotherapy – highly effective, med OS appr. 18mo
- MTX alone effective - but most patients relapse
- Polychemotherapy more effective - more toxic

→ not always more effective
Risk Factors I

- Age > 60
- ECOG > 0
- LDH > n
- CSF-protein > n
- deep brain lesions
- N = 105

(Ferreri et al., Journal of Clin Onc 2003)
Risk Factors II

- Age > 50 years
- KPS < 70 and age > 50
- N=338

(Abrey et al., Journal of Clin Onc 2006)
MTX Monotherapy
## Treatment Strategies – MTX Monotherapy

### Hochberg et al., J Neuroonc, 1999
- MTX 8g/m² q 2w
- n=31: 20(65%) CR; 11(35%) PR
- 9/20 relapse;
- median OS: 30 mo
- 2 yrs OS: 63%
- 2 yrs OS 90% in CR pat)

### Herrlinger et al., Ann Neur 2002
- MTX 8/m² q2w
- n=37
- CR appr. 30%
- Median OS: 25 mo

MTX + AraC
IELSG #20: Trial Design Randomization

IELSG score: 0 - 1 / 2 - 3 / 4 - 5

Intention to irradiate pts > 60 ys. in CR after CHT

MTX 3.5 g/m², d1
every 3 weeks

MTX 3.5 g/m², d1
araC 2 g/m² x 2, d2-3
every 3 weeks

MTX +/- AraC
### Tolerability

<table>
<thead>
<tr>
<th></th>
<th>Methotrexate (n=40)</th>
<th>Methotrexate+cytarabine (n=39)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic deaths</td>
<td>1 (3%)</td>
<td>3 (8%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (15%)</td>
<td>35 (90%)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (8%)</td>
<td>36 (92%)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Anaemia</td>
<td>4 (10%)</td>
<td>18 (46%)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Infective complications</td>
<td>1 (3%)</td>
<td>9 (23%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>1 (3%)</td>
<td>4 (10%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>2 (5%)</td>
<td>1 (3%)</td>
<td>0.31</td>
</tr>
<tr>
<td>GI/mucositis</td>
<td>2 (5%)</td>
<td>1 (3%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Cardiotoxicity</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>0</td>
<td>1 (3%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Coagulation/DVT</td>
<td>4 (10%)</td>
<td>1 (3%)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

The worst toxicity per organ, per patient was considered for analyses. GI=gastrointestinal. DVT=deep venous thrombosis.

*Table 2: Grade 3–4 toxic effects per treatment group*
## Activity

<table>
<thead>
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<th>Methotrexate+cytarabine (n=39)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>7 (18%)</td>
<td>18 (46%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Partial response</td>
<td>9 (23%)</td>
<td>9 (23%)</td>
<td>..</td>
</tr>
<tr>
<td>Overall response</td>
<td>16 (40%)</td>
<td>27 (69%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1 (3%)</td>
<td>2 (5%)</td>
<td>..</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>22 (55%)</td>
<td>7 (18%)</td>
<td>..</td>
</tr>
<tr>
<td>Toxic deaths</td>
<td>1 (3%)</td>
<td>3 (8%)</td>
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</tr>
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Ferreri et al. Lancet 2009
IELSG #20: Survival Curves

MTX +/- AraC

Ferreri et al. Lancet 2009
MTX +/- AraC

IELSG #20: Survival Curves

Median f-up: 46 months

MTX-araC

24 ± 8%

45 ± 8%

p= 0.05

Failure free survival (%)

Probability OS
Take-Home-Message:

MTX in combination with AraC may be the new standard for induction treatment
Induction - Consolidation
Induction - Consolidation

- HD-MTX
- AraC
- Ifosfamid
- Temozolomide
- Thiotepa
- Rituximab
Induction - Consolidation

- HD-MTX
- AraC
- Ifosfamid
- Temozolomide
- Thiotepa
- Rituximab

- WBRT
- High-dose CHT/auto PBSCT
High-Dose Chemotherapy in PCNSL
Background

- High-dose-MTX (>3g / ≤4h) + AraC +/- WBRT old / new
  "gold-standard" for PCNSL → long-term survival appr. 40-50%

- Intensive chemotherapy (BCNU / thiotepa / busulfan / melphalan....) is expected to deliver adequate cytotoxic levels CSF / brain

- Objective: to eradicate residual lymphoma cells systemically and behind the BBB → HDT as CONSOLIDSATION
Rationale for 1st line High-Dose Chemotherapy
HDT and ASCT - "Freiburg I" (1998-2003)
High-Dose Chemotherapy in PCNSL

n=30, median age: 54 y (22-64), median KI 70% (30-100%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Off Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>after 2. MTX</td>
<td>6</td>
<td>15</td>
<td>5</td>
<td>10</td>
<td>2 pts in CR no WBRT</td>
</tr>
<tr>
<td>after AraC/TT</td>
<td>10</td>
<td>14</td>
<td>4</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>after HD</td>
<td>15</td>
<td>8</td>
<td>7</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>

HD (n=23)
High-Dose Chemotherapy in PCNSL


n=30, median age: 54 y (22-64), median KI 70% (30-100%)

Overall-Survival

- HD, n=23, med OS: 121 mo
- all, n=30, med OS: 104 mo

No of patients [n]

- 0: 2 pts in CR no WBRT
- 48: HD (n=23)
- 72: Neurotoxicity n=5
- 96: Kasenda et al., AnnOnc 2012 (update)
- 120: Illerhaus et al JCO 2006
- 144: Ilerhaus et al., JCO 2006

Time (months)

- 0: CR
- 12: PR
- 18: SD
- 24: PD

Illerhaus et al., JCO 2006
What did we learn from this pilot trial (Freiburg II)?

- High-Dose Chemotherapy in PCNSL is feasible and safe
What did we learn from this pilot trial (Freiburg II)?

- High-Dose Chemotherapy in PCNSL is feasible and safe

Open questions:

- Is WBRT restrictable to pts not in CR after HDT?
- Can we improve the induccion treatment?
- Is there a role for Rituximab?
Rituximab - open questions?
Rituximab - open questions:

- passage through BBB?
- how much is necessary in the CNS compartment?
- efficacy as single drug in PCNSL!
Rituximab - open questions:

→ NEW Study-Protocol:
High-Dose Chemotherapy in PCNSL

Freiburg III (2007 - 2011)

- MTX 8g/m²
- MTX 8g/m²
- MTX 8g/m²
- MTX 8g/m²
- AraC 2x3g/m²
- TT 40mg/m²
- AraC 2x3g/m²
- TT 40mg/m²
- BCNU 400mg/m²
- TT 4x5mg/kg

R: Rituximab 375mg/m²

WBRT only in case of "no CR" after HD
Study design:

- multicentric phase II
- 21 centers, 80 planned patients

Primary end-point:

- CR-rate after PBSCT (d30)

Secondary end-points:

- PFS, OS
- toxicity
Patient Characteristics:

- **81 Patients included, 79 Pts. evaluable**
- **Sex:** f 35, m 44
- **med Age:** 56yrs (20 - 66)
- **med KPS:** 90% (30 – 100%)
# High-Dose Chemotherapy in PCNSL

## Toxicity (Grade 3 -5):

<table>
<thead>
<tr>
<th></th>
<th>Induction</th>
<th></th>
<th></th>
<th>HDT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>[%]</td>
<td>No</td>
<td>[%]</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>62</td>
<td>78.5</td>
<td>68</td>
<td>93.2</td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>61</td>
<td>77.2</td>
<td>71</td>
<td>97.3</td>
<td></td>
</tr>
<tr>
<td>HB</td>
<td>40</td>
<td>50.6</td>
<td>41</td>
<td>56.2</td>
<td></td>
</tr>
<tr>
<td>GPT/ALT</td>
<td>34</td>
<td>43.0</td>
<td>3</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>32</td>
<td>40.5</td>
<td>42</td>
<td>57.5</td>
<td></td>
</tr>
<tr>
<td>Bilirubine</td>
<td>3</td>
<td>3.8</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cardial function</td>
<td>2</td>
<td>2.5</td>
<td>1</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>2</td>
<td>2.5</td>
<td>29</td>
<td>39.7</td>
<td></td>
</tr>
<tr>
<td>Creatinin</td>
<td>2</td>
<td>2.5</td>
<td>0</td>
<td>0</td>
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High-Dose Chemotherapy in PCNSL

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<tr>
<td>Creatinin</td>
<td>2  2.5</td>
<td>0  0</td>
</tr>
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TRM (induction) 2/79 (2.5%, PJP)  Transplant related mortality 1/73 (1.4%)
High-Dose Chemotherapy in PCNSL

Remissions after HDT/PBSCT:

ITT (n=79): 61 CR (77%), 11 PR (14%), 7 n.e. (9%)
→ ORR 91%

PP (n=73): 61 CR (83.6%), 11 PR (15%), 1 n.e. (14%)
→ ORR 98.6%

10/79 patients were irradiated due to “no CR” after PBSCT
High-Dose Chemotherapy in PCNSL

Remission rates after sequential therapy (ITT)

- after 2nd MTX
- after 4th MTX
- after 1st AraC/TT
- after 2nd AraC/TT
- after HD (d30)

(central neuroradiological review)
High-Dose Chemotherapy in PCNSL

Progression-Free Survival

Median follow-up 35 mo

Probabilities at different time points:
- PP, n=73
  - 36 months: 69.8%
- ITT, n=79
  - 36 months: 63.2%
High-Dose Chemotherapy in PCNSL

Overall Survival

Median follow-up 35 mo

Probability [%]

0 12 24 36 48 60 72

0
10
20
30
40
50
60
70
80
90
100

PP, n=73

ITT, n=79

87.1%

77.6%
Conclusion

- Thiotepa based high-dose chemotherapy for PCNSL is highly effective (98% ORR, 3y OS 87%)
- Manageable toxicity
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- Manageable toxicity
- WBRT may not be needed in 1\textsuperscript{st} line treatment in CR patients
Conclusion

- Thiotepa based high-dose chemotherapy for PCNSL is highly effective (98% ORR, 3y OS 87%)
- Manageable toxicity
- WBRT may not be needed in 1st line treatment
- The role of consolidating WBRT vs. HDT and PBSCT has to be determined → IELSG32-Trial
- Induction treatment could be more effective
Alternative induction regimens?
New induction

Cooperative Study Group
CNS-Lymphoma

Klinikum Stuttgart
Consolidating strategies
Whole Brain Radiotherapy
Impact of High-Dose-Chemotherapy and autologous stem-cell transplantation as consolidation

- vs whole brain radiotherapy (WBRT)

→ IELSG-Trial
IELSG32 Trial (Ferreri / Illerhaus)

PCNSL \[≤ 65 \text{ ys.} + \text{PS 0-3}\] or \[65-70 \text{ ys.} + \text{PS ≤2}\]

- \(\text{WBRT 36 Gy boost 9 Gy}\
- \(\text{BCNU 400 mg/m}^2 \text{ d.1}\
- \(\text{Thiotepa 5 mg/Kg x 2/d; d.2-3 + APBSCT}\
- \(\text{4 # MTX 3.5 g/m}^2 \text{ d.1 araC 2 g/m}^2 \times 2/\text{d, d. 2-3 every 3 weeks}\
- \(\text{4 # Rituximab 375 mg/m}^2 \text{ d-5 & 0 MTX 3.5 g/m}^2 \text{ d.1 araC 2 g/m}^2 \times 2/\text{d, d. 2-3 every 3 weeks}\
- \(\text{4 # Rituximab 375 mg/m}^2 \text{ d-5 & 0 MTX 3.5 g/m}^2 \text{ d.1 araC 2 g/m}^2 \times 2/\text{d, d. 2-3 Thiotepa 30 mg/m}^2 \text{ d.4 every 3 weeks}\

Response assessment

- \(\text{CR – PR - SD}\
- \(\text{WBRT 36 Gy ± boost 9 Gy}\
- \(\text{PD – tox SC harvest}\
- \(\text{BCNU 400 mg/m}^2 \text{ d.1 Thiotepa 5 mg/Kg x 2/d; d.2-3 + APBSCT}\

Cooperative Study Group
CNS-Lymphoma

Klinikum Stuttgart
Primary endpoint at first randomization
- CR rate after primary chemotherapy.

Primary endpoint at second randomization
- 2-year failure-free survival (2-yr FFS).

Secondary endpoints
- Toxicity
- Overall survival
- Relapse rates and patterns
- Early and late neurotoxicity
IELSG32 Trial (Ferreri / Illerhaus)

Parameters

- multicentric, phase-II randomised
- n = 200
- open (since 7/2010)
- > 40 centres

n = > 180
Impact of High-Dose-Chemotherapy and autologous stem-cell transplantation as consolidation

- vs whole brain radiotherapy (WBRT)

→ IELSG-Trial

- vs conventional chemotherapy

→ MATRix-Trial
High-dose chemotherapy and autologous stem cell transplant or consolidating conventional chemotherapy in primary CNS lymphoma - a randomized phase III trial

MATRix - Trial
Non-cross-resistant protocol
Non-cross-resistant protocol

Long-term survival in patients with newly diagnosed primary central nervous system lymphoma treated with dexamethasone, etoposide, ifosfamide and carboplatin chemotherapy and whole-brain radiation therapy

Leukemia & Lymphoma, November 2011; 52(11): 2069–2075

- N=21
- 62% CR, 33% PR (after 2#)
- Med OS 47.8 mo
MATRix-Trial

SC Harvest → Randomisation

1. MATRix 2 x
2. MATRix 2 x

CR, PR

→ SD/PD - off study*
→ SD/PD - off study*

Hochdosistherapie
(HD BCNU / TT)

2 # DeVIC
(Dexa/Ifo/VP16/Carbopl.)

CR, PR

→ PD - off study*
* DeVIC + auto-PBSCT

Cooperative Study Group
CNS-Lymphoma
Klinikum Stuttgart
PCNSL must be treated “as hard as possible“

- Early intensive induction with MTX / AraC + R?
- Consolidation with Thiotepa based Conditioning
  → may produce long term survival in most patients

Current and future trials try to answer the role of

HDT vs. WBRT

HDT vs. conventional consolidation
Thank you for your attention