Primary Central Nervous System Lymphoma

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Cairo, Egypt
Primary Central Nervous System Lymphoma (PCNSL)

- Epidemiologic data and risk factors
- Underlying molecular mechanisms
- Prognosis
- Current treatment options:
  - High dose methotrexate (HDMTX) polchemotherpay
  - Whole brain radiotherapy (WBRT)
  - High dose sequential therapy (HDS) and auto- SCT
Epidemiology and risk factors

• No gender preference and median age is 60 years

• It accounts for 1% of NHL and 6% of extra-nodal NHL

• A steady rise in incidence was seen during last two decades

• Association with low immunity is a known risk factors
  • In HIV-infected patients it represent 15% of developing NHL → there is decline in incidence with successful anti-HIV therapy
  • In post-transplant lymphomas show rising incidence in CNS form
  • CNS lymphomas is strongly related to Epstein-Barr virus infection in immunocompromised patients

• Risk factors in immunocompetent patients are still not known
Underlying molecular mechanisms

DLBCL

The Hans Classifier

Hans et al., Blood 2003
Underlying molecular mechanisms
Primary Central Nervous System Lymphoma (PCNSL)

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- Underlying molecular mechanisms
- Prognosis
- Current treatment options:
  - HDMTX polchemotherpay
  - WBRT
  - HDS and autologous SCT
Historic progress in the treatment of CNS lymphoma and prognosis

<table>
<thead>
<tr>
<th>Modality</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery/untreated</td>
<td>2</td>
</tr>
<tr>
<td>RT</td>
<td>16</td>
</tr>
<tr>
<td>CTH</td>
<td>13</td>
</tr>
<tr>
<td>CTM</td>
<td>27</td>
</tr>
<tr>
<td>TOTAL (676 ptsns)</td>
<td>14</td>
</tr>
</tbody>
</table>

Reni et al, Ann Onc 1997
Prognostic Scoring System for Primary CNS Lymphomas: the IELSG scoring system

OS according to IELSG prognostic score
All patients

Risk factors:
1. Age
   (≤ 60 v > 60 yrs),
2. PS
   (0-1 v 2-4),
3. LDH
   (normal v H),
4. protein CSF
   (normal v H),
5. → deep brain
   (no v yes).

Ferreri et al. JCO 2003
Prognostic Scoring System for Primary CNS Lymphomas: the IELSG scoring system

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>Entire Series (N = 370)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Age</td>
<td>Continuous variable</td>
<td>1.02</td>
</tr>
<tr>
<td>Sex</td>
<td>Female/male</td>
<td>1.24</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>0-1/2-4</td>
<td>1.64</td>
</tr>
<tr>
<td>Histotype</td>
<td>A-C/D-K</td>
<td>0.97</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>A/B</td>
<td>2.31</td>
</tr>
<tr>
<td>LDH serum level</td>
<td>Normal/elevated</td>
<td>1.41</td>
</tr>
<tr>
<td>CSF protein level</td>
<td>Normal/elevated</td>
<td>1.71</td>
</tr>
<tr>
<td>No. of lesions</td>
<td>Single/multiple</td>
<td>0.98</td>
</tr>
<tr>
<td>Meningeal disease</td>
<td>No/yes</td>
<td>1.28</td>
</tr>
<tr>
<td>Ocular disease</td>
<td>No/yes</td>
<td>0.81</td>
</tr>
<tr>
<td>Deep lesions</td>
<td>No/yes</td>
<td>1.45</td>
</tr>
<tr>
<td>Planned treatment</td>
<td>RT/RT-CHT/CHT/CHT-RT</td>
<td>0.91</td>
</tr>
<tr>
<td>HD-MTX</td>
<td>Yes/no</td>
<td>1.32</td>
</tr>
<tr>
<td>HD cytarabine</td>
<td>Yes/no</td>
<td>1.15</td>
</tr>
<tr>
<td>Anthraclyine</td>
<td>Yes/no</td>
<td>1.01</td>
</tr>
<tr>
<td>Alkyiating agents</td>
<td>Yes/no</td>
<td>1.27</td>
</tr>
<tr>
<td>Intrathecal CHT</td>
<td>Yes/no</td>
<td>1.21</td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td>Continuous variable</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Ferreri et al. JCO 2003
IELSG 20: a randomised phase II trial of HD MTX alone vs HD Ara-C plus HD MTX in patients with primary CNS lymphoma

Ferreri et al. Lancet 2009
IELSG 20: a randomised phase II trial of HD Ara-C plus HD MTX vs HD MTX alone in patients with primary CNS lymphoma

<table>
<thead>
<tr>
<th></th>
<th>HD MTX alone</th>
<th>HD Ara-C plus HD MTX</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong></td>
<td>18% (95% CI 6–30)</td>
<td>46% (95% CI 31–61)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>40% (95% CI 25–55)</td>
<td>69% (95% CI 55–83)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Ferreri et al. Lancet 2009
Conclusion I

High-dose antimetabolites (MTX + AraC) are the backbone of induction chemotherapy.
Primary Central Nervous System Lymphoma (PCNSL)

• Epidemiologic data and risk factors

• Underlying molecular mechanisms

• Prognosis

• Current treatment options:
  • HDMTX polchemotherpay
  • WBRT
  • HDS and autologous SCT
Phase III randomized of HD-MTX with or without WBRT for PCNSL (G-PCNSL-SG-1)

318 patients treated with 4 g/m² HDMTX i every 14 days for six cycles with or without ifosfamide → CR
patients were randomized at consolidation:
- WBRT (45 Gy in 30 fractions for 6 weeks) or
- no further treatment.

Thiel et al. Lancet Oncology 2010
HD-MTX with or without WBRT for primary CNS lymphoma (G-PCNSL-SG-1): Phase III randomised, non-inferiority trial

**Overall survival**

- **C** Patients with complete response, PP population
  - $p=0.56$
  - HR 1.15 (95% CI 0.73–1.80)

- **D** Patients with complete response, ITT population
  - $p=0.43$
  - HR 1.18 (95% CI 0.78–1.78)

- **E** Patients without complete response, PP population
  - $p=0.10$
  - HR 0.74 (95% CI 0.51–1.06)

- **F** Patients without complete response, ITT population
  - $p=0.31$
  - HR 0.85 (95% CI 0.62–1.16)

Thiel et al. Lancet Oncology 2010
Conclusion II

The impact of consolidation WBRT and the optimum dose is still debatable and is currently a subject of prospective studies.
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Current treatment options:
  - HDMTX polchemotherpay
  - WBRT
  - HDS and autologous SCT
High-dose chemotherapy and auto-SCT in patients with systemic B-cell lymphoma and secondary CNS involvement: final results of a multicenter Phase II Trial

Ferreri et al. JCO 2015
High-dose chemotherapy and auto-SCT in patients with systemic B-cell lymphoma and secondary CNS involvement: final results of a multicenter Phase II Trial

Median FU 48 months

5-yr EFS (A) whole series

B

Event-Free Survival (probability)

Time (months)

40%

(B) Auto-SCT patients

Event-Free Survival (probability)

Time (months)

63%

5-yr OS (C) whole series

D

Overall Survival (probability)

Time (months)

42%

(D) Auto-SCT patients

Overall Survival (probability)

Time (months)

68%

Ferreri et al. JCO 2015
Expanding our Knowledge

Ferreri et al. JCO 2015
within the Context of other results

<table>
<thead>
<tr>
<th>Type</th>
<th>N°</th>
<th>Upper age</th>
<th>ECOG PS</th>
<th>DLBCL (%)</th>
<th>Toxic deaths (%)</th>
<th>Median f-up (months)</th>
<th>CRR (%)</th>
<th>EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine¹</td>
<td>R</td>
<td>92</td>
<td>23-88</td>
<td>~</td>
<td>76</td>
<td>15-32</td>
<td>51</td>
<td>36</td>
<td>NR</td>
</tr>
<tr>
<td>German²</td>
<td>P</td>
<td>30</td>
<td>65</td>
<td>≤2</td>
<td>90</td>
<td>3</td>
<td>21</td>
<td>50</td>
<td>2-y: 44%</td>
</tr>
<tr>
<td>HOVON³</td>
<td>P</td>
<td>36</td>
<td>65</td>
<td>≤2</td>
<td>100</td>
<td>14</td>
<td>20</td>
<td>28</td>
<td>1-y: 21%</td>
</tr>
<tr>
<td>SCNSL⁴</td>
<td>P</td>
<td>38</td>
<td>70</td>
<td>≤3</td>
<td>84</td>
<td>11</td>
<td>48</td>
<td>63</td>
<td>2-y: 73%</td>
</tr>
</tbody>
</table>

³Doorduijn J, et al. ASCO 2013  
⁴Ferreri AJM, et al. JCO 2015
Conclusion III

HDS/ASCT can be a valid alternative to WBRT as consolidative treatment.
PCNSL: open questions in treatment

✓ New drugs and combinations are needed to improve outcome.

✓ The role of rituximab in improving the outcome is still unclear.

✓ WBRT parameters should be optimized to reduce neurotoxicity.

✓ HDS/ASCT as valid alternative to WBRT as consolidative treatment.
IELSG #32 (n=219): REGISTERED PATIENTS

**Strata: IELSG score**

- 4 c. MTX 3.5 g/m$^2$ d.1
  - araC 2 g/m$^2$ x 2/d, d. 2-3
  - every 3 weeks

- 4 c. rituximab 375 mg/m$^2$ d-5 & 0
  - MTX 3.5 g/m$^2$ d.1
  - araC 2 g/m$^2$ x 2/d, d. 2-3
  - ev. 3 wks

- 4 c. rituximab 375 mg/m$^2$ d-5 & 0
  - MTX 3.5 g/m$^2$ d.1
  - araC 2 g/m$^2$ x 2/d, d. 2-3
  - Thiotepa 30 mg/m$^2$ d.4
  - ev. 3 wks

**Response assessment**

- CR – PR - SD
- PD – toxicity
  - Poor mobilizers
  - WBRT 40 Gy ± boost 9 Gy

**Strata: previous arm & OR (CR vs. PR/SD)**

- WBRT 36 GY ± BOOST 9 GY
- BCNU 400 mg/m$^2$ d.1
  - Thiotepa 5 mg/Kg x 2/d, d.2-3 + APBSCT
**Response assessment**

- **Total Active Centers**: 53
- **Randomized pts**: 227

**Incorrect diagnosis**: 3
- **Treated w/o random**: 2
- **Systemic lymphoma**: 2
- **Second cancer**: 1

**ARM A: 75 pts**
**ARM B: 69 pts**
**ARM C: 75 pts**

**118 pts eligible for 2° random**

**ARM D: 59 pts**
**ARM E: 59 pts**
### Feasibility and Toxicity

<table>
<thead>
<tr>
<th></th>
<th>A (n= 75)</th>
<th>B (n= 69)</th>
<th>C (n= 75)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actually delivered courses</td>
<td>223 (74%)</td>
<td>236 (86%)</td>
<td>274 (91%)</td>
<td></td>
</tr>
<tr>
<td>RDI Methotrexate</td>
<td>92%</td>
<td>84%</td>
<td>85%</td>
<td>NS</td>
</tr>
<tr>
<td>RDI Cytarabine</td>
<td>87%</td>
<td>81%</td>
<td>80%</td>
<td>NS</td>
</tr>
<tr>
<td>RDI Rituximab</td>
<td>-</td>
<td>82%</td>
<td>83%</td>
<td>NS</td>
</tr>
<tr>
<td>RDI Thiotepa</td>
<td>-</td>
<td>-</td>
<td>76%</td>
<td>-</td>
</tr>
<tr>
<td>G4 neutropenia</td>
<td>99 (44%)</td>
<td>119 (50%)</td>
<td>153 (56%)</td>
<td>0.01</td>
</tr>
<tr>
<td>G4 thrombocytopenia</td>
<td>116 (52%)</td>
<td>140 (59%)</td>
<td>200 (73%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>G4 anemia</td>
<td>9 ( 4%)</td>
<td>6 ( 3%)</td>
<td>14 ( 5%)</td>
<td>NS</td>
</tr>
<tr>
<td>G≥3 febrile neutrop./infections</td>
<td>43 (19%)</td>
<td>31 (13%)</td>
<td>45 (16%)</td>
<td>NS</td>
</tr>
<tr>
<td>G4 hepatotoxicity</td>
<td>6 ( 3%)</td>
<td>3 ( 1%)</td>
<td>1 ( 1%)</td>
<td>NS</td>
</tr>
<tr>
<td>G4 nephrotoxicity</td>
<td>0 ( 0%)</td>
<td>0 ( 0%)</td>
<td>1 ( 1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Interruptions x toxicity (/pts)</td>
<td>9 (12%)</td>
<td>5 ( 7%)</td>
<td>4 ( 5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Toxic deaths (/ pts)</td>
<td>7 ( 9%)</td>
<td>3 ( 4%)</td>
<td>3 ( 4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Autologous stem cell collection</td>
<td>48/51 (94%)</td>
<td>44/46 (96%)</td>
<td>60/64 (94%)</td>
<td>NS</td>
</tr>
<tr>
<td>Median APBSC (x 10^6 c/kg bw)</td>
<td>12.3</td>
<td>15</td>
<td>8.2</td>
<td>NS</td>
</tr>
</tbody>
</table>
## Arms Activity

<table>
<thead>
<tr>
<th></th>
<th>A (n= 75)</th>
<th>B (n= 69)</th>
<th>C (n= 75)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>17 (23%)</td>
<td>21 (30%)</td>
<td>37 (49%)</td>
<td>A vs. B= 0,29</td>
</tr>
<tr>
<td></td>
<td>(95%CI= 14-31%)</td>
<td>(95%CI= 21-42%)</td>
<td>(95%CI= 38-60%)</td>
<td>A vs. C= 0,0007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B vs. C= 0,02</td>
</tr>
<tr>
<td>PR</td>
<td>23 (31%)</td>
<td>30 (43%)</td>
<td>28 (37%)</td>
<td>A vs. B= 0,01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A vs. C= 0,00001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B vs. C= 0,05</td>
</tr>
<tr>
<td>OR</td>
<td>40 (53%)</td>
<td>51 (74%)</td>
<td>65 (87%)</td>
<td>A vs. B= 0,01</td>
</tr>
<tr>
<td></td>
<td>(95%CI= 42-64%)</td>
<td>(95%CI= 64-84%)</td>
<td>(95%CI= 80-94%)</td>
<td>A vs. C= 0,00001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B vs. C= 0,05</td>
</tr>
<tr>
<td>SD</td>
<td>6 ( 8%)</td>
<td>4 ( 6%)</td>
<td>1 ( 1%)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>22 (29%)</td>
<td>11 (16%)</td>
<td>6 ( 8%)</td>
<td></td>
</tr>
<tr>
<td>TD</td>
<td>7 ( 9%)</td>
<td>3 ( 4%)</td>
<td>3 ( 4%)</td>
<td></td>
</tr>
</tbody>
</table>
Activity: Arm and IELSG risk

**Logit**

<table>
<thead>
<tr>
<th>IELSG risk score</th>
<th>CR</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.13</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

**Arm**

<table>
<thead>
<tr>
<th>CR</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0004</td>
<td>0.000004</td>
</tr>
</tbody>
</table>
Progression-Free Survival

median follow-up: 30 months (12-66)

96 (44%) pts remain failure-free
A: 22 (29%)
B: 30 (43%)
C: 44 (60%)

Failure: primary site involvement, usually the brain, in 97% of cases

Extra-CNS relapse in two pts.

No differences in salvage efficacy (65% of failed pts).
Overall Survival

114 (52%) pts are alive
A: 28 (37%)  
B: 36 (52%)  
C: 50 (67%)  

LTF: 5 pts (2%)  
5-17 months

Causes of death (n= 105):
- lymphoma  
- toxicity (1° line)  
- toxicity (salvage)  
- neurotoxicity (rel-free)  
- others while rel-free  
- unknown
IELSG #32 trial: Conclusions

The addition of thiotepa and rituximab to MTX-ARAC (MATRIX) is associated with significantly improved CRR and ORR.

This positive effect was observed in the three IELSG risk groups. Some subgroups are small.

Preliminary results suggest a positive effect of these drugs on PFS and OS.

Follow-up is still short to analyse the effects of the 2nd randomization.
Elderly patients

High dose RT alone $\rightarrow$ median OS of 7.8 mo

The use of at least 1gm MTX $\rightarrow$ median OS 14-37 mo

No formal comparisons between MTX containing regimens
Radnomised phase II:
- MPV-A (MTX, Procarbazine VCR, Ara-C) VS MTX plus Temzolomide
- MPV-A produced better response rates, PFS, OS but not difference was significant

Eldely fit patients $\leq$ 70 years can tolerate HDMTX

Considering complications of leukencephalopathy RT is offered to those who can’t tolerate HDMTX or in relapsed patients
Flow chart of therapy for primary CNS lymphoma in clinical routine

Thank you all!