Primary CNS Lymphoma: diagnosis and treatment

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Even if it exhibits one of the worst prognoses among NHL, it is a curable brain tumor.
### Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Positive cases</th>
<th>Assessed cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median: 61 ys.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>range: 14 - 85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>220</td>
<td>378</td>
<td>58%</td>
</tr>
<tr>
<td><strong>ECOG-PS 0 - 1</strong></td>
<td>117</td>
<td>339</td>
<td>35%</td>
</tr>
<tr>
<td>2 - 3</td>
<td>175</td>
<td></td>
<td>52%</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td><strong>Prior cancers</strong></td>
<td>16</td>
<td>378</td>
<td>4%</td>
</tr>
<tr>
<td><strong>B-symptoms</strong></td>
<td>7</td>
<td>378</td>
<td>2%</td>
</tr>
<tr>
<td><strong>LDH ratio &gt;1</strong></td>
<td>69</td>
<td>195</td>
<td>35%</td>
</tr>
</tbody>
</table>

Ferreri AJM, et al., Neurology, 2002
Clinical Presentation

- Motor and sensory focal deficits 50%
- Personality changes 30%
- Headaches 55%
- Intracranial hypertension
  - Nausea 35%
  - Vomiting 10%
- Uveitis 20%
- Floaters or campimeter deficits 10%
- Seizures, brain stem or cerebellum symptoms 5%
- Extrapyramidal syndrome 5%
Multiple lesions: 34%
Deep lesions: 40%
Multiple lesions: 34%
Management difficulties

- High proportion of elderly pts
- Poor PS at presentation
- Biopsy not performed
- Palliative treatment
- Therapeutic consensus is lacking
- A few centers with adequate expertise
- Many pts can not be referred to other centers
Early Diagnosis is the Best Therapy

• Several patients receive steroids for months before biopsy:
  – Confounding effect on neuroimaging
  – Delayed and unsuitable biopsy (52% inter-observer variability)
  – Diabetes and other metabolic disorders
  – Immunodepression (severe infections)
  – Half of cases of early PD are related to interruptions due to toxicity

• CNS tissues exposed to lymphoma infiltration by months:
  – Tissue damage results in poor PS and disabling symptoms
  – Loss of autonomy and poor treatment tolerability
  – CR and cure do not result in neurological and PS improvement
  – Therapeutic interruptions due to poor, irreversible conditions
  – Negative effects on trials accrual
PCNSL suspicion

Current strategy= low diagnosis sensitivity

- **Neuroimaging:** T1, T2, flair, DWI, enhancement, spectroscopy

- **Site:** corpus callosum, basal ganglia, periventricular areas, ...

- **Response to steroids**
Neuroimaging
Response to Corticosteroids

Is a “vanishing tumor” always a lymphoma?

**Abstract**—The authors report clinical and radiologic characteristics and ultimate diagnosis in 12 patients with a regressing cerebral mass lesion. Primary CNS lymphoma (PCNL) was found in only half of the patients with such a lesion. In patients showing a complete resolution of the enhancing lesion the probability of finding a PCNL is smaller and survival is longer.

*NEUROLOGY* 2002;59:762-764

J.E.C. Bromberg, MD; M.D. Siemers, MD; and M.J.B. Taphoorn, MD

- Multiple sclerosis
- Acute disseminated encephalomyelitis
- Cerebral infarction
- Neurosarcoidosis
- Germinoma
- Renal cell carcinoma metastases
- Prolactinoma
- Hemangioma
Response to Steroids

Lymphoma
Bp: no tumor

Response to steroids
Bp: Glioblastoma multiforme
Early Reliable Suspicion

✓ Reliable molecular and biological parameters that can be easily incorporated in routine practice.

✓ Some chemokines (CXCL13) can be used as diagnostic & prognostic tools.

✓ IL-10 concentration in the CSF is a useful diagnostic and prognostic biomarker.

✓ Some miRNA (21, 19b, 92a) are expressed in the CSF of PCNSL patients, with a diagnosis sensitivity and specificity >95%

✓ Recurrent mutations of CD79B (83%) and MYD88 (76%) in tissue samples.

✓ MYD88 mutations can be detected in the vitreous and plasma (CSF?).

✓ The combined use of ADC, CSF CXCL13, and IL-10 results in increased diagnostic performance in CNSL.

Diagnostic Sampling

- Stereotactic biopsy
- Total resection
- Partial resection
- CSF cytology examination
- Vitrectomy
PCNSL: Surgery

Resected

Biopsied
Histopathological Features

CD20

CD3

DLBCL
Bcl-6 +
Bcl-2 +
MUM-1 +
CD10 –
MIB-1: 70%
Table 14.2. Staging work-up and pre-treatment evaluations in PCNSL.

**Staging**
- Physical examination
- Routine blood studies
- Whole-brain MRI
- Contrast total-body CT scan
- Ophthalmologic evaluation (including slit-lamp examination)
- Cerebrospinal-fluid cytology
- Cerebrospinal-fluid biochemical examination
- Bone-marrow biopsy
- Testicular ultrasonography (older men)
- FDG-PET (investigational role)
- Suspicion of vitreal infiltration may require confirmation by vitrectomy

**Prognostic factors**
- Age
- Performance status (PS)
- Lactate dehydrogenase (LDH) serum level
- Cerebrospinal-fluid protein concentration
- Involvement of deep regions of the brain

**Pre-treatment assessment**
- Neurological examination
- Biochemical serum profile
- Baseline neuropsychiatric tests
- Renal and hepatic functionality tests (creatinine clearance)
- Cardiac function tests
- HIV, hepatitis B & C virus evaluation

Ferreri AJM & DeAngelis LM. The Lymphoma. Cambridge 2007
Intraocular Lymphoma

- 5-20% of PCNSL
- Ophthalmologic examination, fluorescein angiography, color photography
- IOL precedes brain lesions (95%)
- bilateral disease in 80% of cases
- floaters and burred vision (uveitis)
- several diagnostic difficulties
- molecular analysis & cytokine assay useful in diagnosis

CSF alterations

✓ All PCNSL patients should have a lumbar puncture for CSF cytology unless medically contraindicated.

✓ CSF should be assessed on 3-10 mL collected by lumbar puncture (lower pCSF levels in ventricules). It should be sampled before or 1 week after biopsy (false positive).

✓ CSF studies: cytology examination, cell count, biochemical profile, ICC, β2-microglobulin, IgH, and flow cytometry.

✓ Not specific, but useful for diagnostic orientation. Positive cytology in 15% of cases (underestimated?).

✓ Increased protein concentration (>60% of PCNSL).

✓ Normal glucose concentration.
<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>( \leq 60 \text{ ys.} )</td>
<td>&gt; 60 \text{ ys.}</td>
</tr>
<tr>
<td>ECOG-PS</td>
<td>0 - 1</td>
<td>2 - 4</td>
</tr>
<tr>
<td>LDH</td>
<td>normal</td>
<td>elevated</td>
</tr>
<tr>
<td>CSF protein</td>
<td>normal</td>
<td>elevated</td>
</tr>
<tr>
<td>Deep lesions</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>

I.E.L.S.G. Prognostic Score

Modern Approach

- Age & PS
- Comorbidity
- Prognostic score
- Histotype (DLBCL)

INDUCTION

- HD-MTX poly
- WBRT
- Others

CONSOLIDATION

Updated from Ferreri AJM, ASCO 2012
the dilemma posed by PCNSL treatment is the choice between strategies designed to intensify therapy to improve cure rate and treatment de-escalation strategies to avoid neurotoxicity.
Chemotherapy

Its efficacy is limited by several factors including the biology and microenvironment of this malignancy, which is “protected” by the BBB.

<table>
<thead>
<tr>
<th>BBB penetration</th>
<th>Doses</th>
<th>CNS availability</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>conventional</td>
<td>good</td>
<td>steroids, alkylating ag.</td>
</tr>
<tr>
<td>Low to moderate</td>
<td>high</td>
<td>good</td>
<td>MTX, araC</td>
</tr>
<tr>
<td>Poor</td>
<td>conventional(-limiting tox)</td>
<td>low</td>
<td>anthracyclines, vinca-alkaloids</td>
</tr>
</tbody>
</table>
CHOP regimen


- WBRT 40 + 14 Gy; n=15
- WBRT + CHOP; n=38

Survival Rate vs. Months from randomization
| **Pharmacokinetics** | Triphasic plasmatic clearance  
<table>
<thead>
<tr>
<th></th>
<th>Good BBB penetration at HD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Schedule</strong></td>
<td>Infusion duration 3 hours</td>
</tr>
<tr>
<td></td>
<td>Infusion timing every 2 wks = 3 wks</td>
</tr>
<tr>
<td></td>
<td>Dose ≥ 3 g/m²</td>
</tr>
<tr>
<td><strong>CNS availability</strong></td>
<td>≥ 1 g/m² tumoricidal levels in the brain</td>
</tr>
<tr>
<td></td>
<td>≥ 3 g/m² tumoricidal levels in the CSF</td>
</tr>
<tr>
<td></td>
<td>24-hr inf. tumoricidal levels in the CSF</td>
</tr>
<tr>
<td><strong>Tolerability</strong></td>
<td>8 g/m² 45% dose reductions</td>
</tr>
<tr>
<td></td>
<td>3.5 g/m² good compromise</td>
</tr>
</tbody>
</table>

Ferreri AJM. Blood 2011
High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial

Andrés J M Ferreri, Michele Reni, Marco Foppoli, Maurizio Martelli, Gerasimus A Pangalis, Maurizio Frezzato, Maria Giuseppina Cabras, Alberto Fabbri, Gaetano Corazzelli, Fiorella Iarucci, Giuseppe Rossi, Riccardo Soffiatti, Caterina Stelitano, Daniele Vallisa, Francesco Zaja, Lucia Zoppengo, Gian Marco Aondio, Giuseppe Avvisati, Monica Balzarotti, Alba A Brandes, José Fajardo, Henry Gomez, Attilio Guarini, Graziella Pinotti, Luigi Rigacci, Catrina Uhlmann, Piero Picozzi, Paolo Vezzulli, Maurilio Ponzoni, Emanuele Zucca, Federico Caligaris-Cappio, Franco Cavalli, on behalf of the International Extranodal Lymphoma Study Group

<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>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>
<td>0.35</td>
</tr>
</tbody>
</table>

<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>0.002</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>Gl/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>0.002</td>
</tr>
</tbody>
</table>

Lancet 2009; 374: 1512–20
# MTX + Alkylator + Rituximab

<table>
<thead>
<tr>
<th>INDUCTION</th>
<th>CONSOLIDATION</th>
<th>N°</th>
<th>ORR</th>
<th>2-year PFS</th>
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</thead>
<tbody>
<tr>
<td>Rituximab Methotrexate Procarbazine Vincristine&lt;sup&gt;1&lt;/sup&gt;</td>
<td>low-dose WBRT</td>
<td>52</td>
<td>79%</td>
<td>57%</td>
</tr>
<tr>
<td>Rituximab Methotrexate Procarbazine Vincristine&lt;sup&gt;2&lt;/sup&gt;</td>
<td>TBC - ASCT</td>
<td>33</td>
<td>94%</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>(&lt;≤ 65 ys)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab Methotrexate Temozolomide&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Non-myeloablative HD-cytarabine</td>
<td>44</td>
<td>77%</td>
<td>59%</td>
</tr>
<tr>
<td></td>
<td>HD-etoposide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab Methotrexate Temozolomide&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Hyperfract WBRT + TMZ maintenance</td>
<td>53</td>
<td>57%</td>
<td>64%</td>
</tr>
<tr>
<td></td>
<td>(&lt;≤ 60 yo: 62%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The IELSG #32 trial

**PCNSL [≤ 65 ys. + PS 0-3] or [65-70 ys. + PS ≤2]**

**Response assessment**

- **CR – PR - SD**
  - WBRT 36 Gy ± boost 9 Gy
  - BCNU 400 mg/m² d.1
  - Thiotepa 5 mg/Kg x 2/d; d.2-3 + APBSCT

- **PD – tox**
  - SC harvest
  - WBRT 40 Gy ± boost 9 Gy

**WBRT 40 Gy** ± boost 9 Gy

**4 c. MTX 3.5 g/m² d.1**

- araC 2 g/m² x 2/d, d. 2-3 every 3 weeks

**4 c. rituximab 375 mg/m² d-5 & 0**

- MTX 3.5 g/m² d.1
- araC 2 g/m² x 2/d, d. 2-3 every 3 weeks

**4 c. rituximab 375 mg/m² d-5 & 0**

- MTX 3.5 g/m² d.1
- araC 2 g/m² x 2/d, d. 2-3
- Thiotepa 30 mg/m² d.4 every 3 weeks
Arms Activity

Activity: Arm and IELSG risk

<table>
<thead>
<tr>
<th>Logit</th>
<th>CR</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IELSG risk score</td>
<td>0.13</td>
<td>0.09</td>
</tr>
<tr>
<td>Arm</td>
<td>0.0004</td>
<td>0.000004</td>
</tr>
</tbody>
</table>

**Overall Response Rate**

- Low risk: Arm A 14, Arm B 12, Arm C 13
- Intermediate risk: Arm A 47, Arm B 44, Arm C 87
- High risk: Arm A 14, Arm B 13, Arm C 15

**Complete Remission Rate**

- Low risk: Arm A 12, Arm B 13, Arm C 47
- Intermediate risk: Arm A 47, Arm B 44, Arm C 47
- High risk: Arm A 14, Arm B 13, Arm C 15
**MATRIX: Efficacy**

**Median follow-up: 40 months (24-76)**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>A vs. B</td>
<td>0.68</td>
<td>0.45 - 1.02</td>
<td>0.06</td>
</tr>
<tr>
<td>A vs. C</td>
<td>0.66</td>
<td>0.53 - 0.81</td>
<td>0.0001</td>
</tr>
<tr>
<td>B vs. C</td>
<td>0.63</td>
<td>0.40 - 0.99</td>
<td>0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>A vs. B</td>
<td>0.73</td>
<td>0.48 - 1.11</td>
<td>0.14</td>
</tr>
<tr>
<td>A vs. C</td>
<td>0.65</td>
<td>0.52 - 0.83</td>
<td>0.0004</td>
</tr>
<tr>
<td>B vs. C</td>
<td>0.57</td>
<td>0.35 - 0.93</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Chemotherapy: Elderly Patients

- HD-MTX improved outcome in selected pts (biased results).

<table>
<thead>
<tr>
<th>Ref.</th>
<th>N</th>
<th>Median age, y (range)</th>
<th>MTX, g/m²</th>
<th>Other drugs</th>
<th>IT</th>
<th>WBRT</th>
<th>PFS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>23</td>
<td>68 (60-79)</td>
<td>3</td>
<td>Te</td>
<td>No</td>
<td>No</td>
<td>8</td>
</tr>
<tr>
<td>66</td>
<td>10</td>
<td>73 (66-75)</td>
<td>8</td>
<td>—</td>
<td>No</td>
<td>No</td>
<td>18</td>
</tr>
<tr>
<td>22</td>
<td>12</td>
<td>70 (54-89)</td>
<td>3.5</td>
<td>O, P</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>79</td>
<td>12</td>
<td>67 (60-72)</td>
<td>3.5</td>
<td>O, P</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>93</td>
<td>13</td>
<td>76 (54-89)</td>
<td>1-3.5</td>
<td>A, O, P, T</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>94</td>
<td>50</td>
<td>72 (60-81)</td>
<td>1</td>
<td>CN, P, S</td>
<td>Yes</td>
<td>No</td>
<td>7</td>
</tr>
<tr>
<td>95</td>
<td>30</td>
<td>70 (57-79)</td>
<td>3</td>
<td>CN, P</td>
<td>No</td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>96</td>
<td>17</td>
<td>67 (58-78)</td>
<td>1</td>
<td>MCN, P, S</td>
<td>Yes</td>
<td>No</td>
<td>20</td>
</tr>
</tbody>
</table>

The age upper limit to define elderly pts remains uncertain.

Ferreri AJM. Blood 2011
AGE ≥ 60 YEARS

Elderly Pts: PHRC 2006 Trial

**Arm A**  M-PVA

3 cycles/ 28 d

- Procarbazine 100 mg/m²/d D1-
- Vincristine 1.4 mg/m² D1
- MTX 3.5 g/m² d1

<table>
<thead>
<tr>
<th>D1</th>
<th>D7</th>
<th>D14</th>
<th>D21</th>
<th>D28</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Methylprednisolone 60 mg/d D1-5

**Arm B**  M-TMZ

3 cycles/28 d

- TMZ 150 mg/m²/d D1-5
- MTX 3.5 g/m² d1

<table>
<thead>
<tr>
<th>D1</th>
<th>D7</th>
<th>D14</th>
<th>D21</th>
<th>D28</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Methylprednisolone 60 mg/d D1-5

Cytarabine 3 g/m²/d1-2

After 3rd Cycle

If no tox= TMZ 150 mg/m²/d D15-19, cycle 2 & 3

Methylprednisolone 60 mg/d D1-5

AGE ≥ 60 YEARS

PHRC 2006 Trial

<table>
<thead>
<tr>
<th></th>
<th>Methotrexate with temozolomide (n=48)</th>
<th>Methotrexate, procarbazine, vincristine, and cytarabine (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or 4 toxicities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-haematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>21 (44%)</td>
<td>18 (38%)</td>
</tr>
<tr>
<td>Infection</td>
<td>6 (13%)</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td>2 (4%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Venous thrombosis or pulmonary embolism</td>
<td>0</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>4 (8%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Hyponatraemia</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Hyperatraemia</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Haematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>6 (13%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5 (10%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>7 (15%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (10%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>14 (29%)</td>
<td>14 (30%)</td>
</tr>
<tr>
<td>All grades 3 and 4 toxicities</td>
<td>34 (71%)</td>
<td>34 (72%)</td>
</tr>
<tr>
<td>Deaths due to toxicity*</td>
<td>5 (10%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Methotrexate dose reductions</td>
<td>12 (25%)</td>
<td>14 (30%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MPV-A (n= 47)</th>
<th>M-TMZ (n= 48)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>62%</td>
<td>45%</td>
<td>0.11</td>
</tr>
<tr>
<td>PR</td>
<td>20%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>2%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>16%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>82%</td>
<td>71%</td>
<td>0.23</td>
</tr>
</tbody>
</table>

*Deaths due to toxicity excludes one death from infection.
AGE ≥ 65 YEARS

Elderly pts: PRIMAIN Trial (n= 108)

<table>
<thead>
<tr>
<th>Primary chemoimmunotherapy (PRIMAIN regimen, 2 courses; every 35 days)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab 375 mg/m² standard infusion</td>
<td>days -5, 0, 15 &amp; 30</td>
</tr>
<tr>
<td>Methotrexate 3 g/m² 0.5 g/m² in 15 min. + 2.5 g/m² in 3-hr inf.</td>
<td>days 1, 15 &amp; 30</td>
</tr>
<tr>
<td>Procarbazine 60 mg/m²/d oral</td>
<td>days 1 to 10</td>
</tr>
</tbody>
</table>

**Procarbazine maintenance (6 courses; every 4 weeks)**

- Procarbazine 100 mg/d oral days 1 to 5

<table>
<thead>
<tr>
<th>Best response</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>46 (42.6%)</td>
</tr>
<tr>
<td>PR</td>
<td>34 (31.5%)</td>
</tr>
<tr>
<td>PD</td>
<td>12 (11.1%)</td>
</tr>
<tr>
<td>SD</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Missing</td>
<td>15 (13.9%)</td>
</tr>
</tbody>
</table>

Sanctuaries

- CSF and eyes (intrathecal and intravitreal chemo).

- IT/IV chemo efficacy has not been prospectively confirmed. Most trials do not include IT/IV drug delivery.

- IT is associated with additional risk of infective complications, neurotoxicity and chemical meningitis.

- HD-MTX (≥ 3 g/m²) treats adequately meninges.

- IVi: is active, but toxic (visual acuity deterioration in 27%).

- Impact on OS???

Ferreri AJM, et al. Neurology 2002
## High-dose Ifosfamide

<table>
<thead>
<tr>
<th></th>
<th>R-IE (n= 22)</th>
<th>VIA (n= 16)</th>
<th>ICE (n= 17)</th>
<th>ICED (n=25)</th>
<th>De-VIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line</td>
<td>Salvage</td>
<td>Salvage</td>
<td>Salvage</td>
<td>Salvage</td>
<td>First</td>
</tr>
<tr>
<td>Other drugs</td>
<td>R, VP16</td>
<td>araC; VP16</td>
<td>CBDCA; VP16</td>
<td>CBDCA; VP16</td>
<td>CBDCA; VP16</td>
</tr>
<tr>
<td>Previous chemo</td>
<td>MA</td>
<td>CHOD, MA</td>
<td>MA</td>
<td>M</td>
<td>-</td>
</tr>
<tr>
<td>Pre-irradiated pts</td>
<td>55%</td>
<td>100%</td>
<td>NR</td>
<td>27%</td>
<td>-</td>
</tr>
<tr>
<td>Median age</td>
<td>60 (39-72)</td>
<td>54 (31-69)</td>
<td>62 (28-84)</td>
<td>58 (20-73)</td>
<td>61 (19-79)</td>
</tr>
<tr>
<td>Refractory (mPFS)</td>
<td>50% (8 mo)</td>
<td>6% (19 mo)</td>
<td>24% (12 mo)</td>
<td>36% (12 mo)</td>
<td>0</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>0%</td>
<td>NR</td>
<td>24%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>NF (TRM)</td>
<td>14% (5%)</td>
<td>50% (0%)</td>
<td>53% (6%)</td>
<td>NR (8%)</td>
<td>10% (0%)</td>
</tr>
<tr>
<td>ASCT</td>
<td>20%</td>
<td>0%</td>
<td>35%</td>
<td>52%</td>
<td>NA</td>
</tr>
<tr>
<td>CRR</td>
<td>27%</td>
<td>37%</td>
<td>76% (ASCT)</td>
<td>48%</td>
<td>62% (2c.)</td>
</tr>
<tr>
<td>mPFS</td>
<td>4.0 mo</td>
<td>4.5 mo</td>
<td>2.6 mo</td>
<td>11 mo</td>
<td>37 mo</td>
</tr>
<tr>
<td>mOS</td>
<td>6.0 mo</td>
<td>6.0</td>
<td>7.3 mo</td>
<td>27 mo</td>
<td>48 mo</td>
</tr>
</tbody>
</table>

Mappa, HemOnc 2013; Arellano-Rodrigo, EJH 2003; Choquet, Lugano 2013 Abs #3664; Motomura, L&L 2011; Choi, IJH 2013
Molecular components of oncogenic survival signalling in PCNSL

Table 1. Candidate investigational agents in CNS lymphoma

<table>
<thead>
<tr>
<th>Candidate pathway</th>
<th>Investigational agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell receptor</td>
<td>Ibrutinib, fostamatinib, BKM120, GA101</td>
</tr>
<tr>
<td>JAK/STAT</td>
<td>Ruxolitinib</td>
</tr>
<tr>
<td>IRF4/MUM1</td>
<td>Lenalidomide, pomalidomide</td>
</tr>
<tr>
<td>BCL-6</td>
<td>RI-BPI</td>
</tr>
<tr>
<td>NFkB</td>
<td>MALT1 inhibitors</td>
</tr>
<tr>
<td>CXCL12, CXCL13</td>
<td>Plerixafor (AMD3100), BKM120, GA101</td>
</tr>
<tr>
<td>PIM kinases</td>
<td>SGI-1776</td>
</tr>
<tr>
<td>Mtor</td>
<td>Temsirolimus, everolimus</td>
</tr>
</tbody>
</table>
Ibrutinib at ASH 2016

- 13 PCNSL; 7 SCNSL
- Ibrutinib 560 mg and 840 mg was well tolerated.
- No DLT
- Meaningful concentrations in the CSF.
- ORR= 75%
- Median PFS= 5 months.
- Ongoing MTX-IBT-R trial
Lenalidomide at ASH 2016

- 8 c. LENA 20-25 mg + ritux => 12 c LENA 10 mg
- 50 pts with rrPCNSL
- ORR= 67% (36% after induction) EARLY
- 24% of pts received 1 course
- 50% of pts received 2 courses
- 36% completed induction
- 1-yr PFS: 20%
- Dose reduction in 42%
- Prior vs. LENA median PFS= 4 vs. 8 months
Checkpoint Immune Blockade

Frequent 9p24.1 copy number alterations.

Associated expression of PD-L1 and PD-L2.


Therapeutic target.
Modern Approach

Age & PS
Comorbidity
Prognostic score
Histotype (DLBCL)

Induction
Response
Quality response

INDUCTION
HD-MTX poly
WBRT
Others

CONSOLIDATION
Observation
WBRT
HDC/ASCT
Non-myeloablative
Maintenance

Updated from Ferreri AJM, ASCO 2012
Radiation Field and Doses

RESPONSE

COMPLETE REMISSION

PARTIAL RESPONSE

PROGRESSIVE DISEASE

30 Gy

36 Gy

40-45 Gy

10 Gy

10 Gy

30 Gy
Neurotoxicity


Poor QoL and >50% were not working due to illness
Reducing Neurotoxicity Risk

- To avoid consolidation RT (only CRs).
- To improve radiation parameters.
- To replace RT with other strategies.
Consolidation RT withdrawal?

G-PCNSL-SG-1 trial

551 pts with newly diagnosed PCNSL were enrolled from 75 German Centers and treated between 2000 and 2009

G-PCNSL-SG-1 trial: results
Has the role of WBRT in primary CNS lymphoma been settled?

Lisa M. DeAngelis

The use of whole-brain radiation therapy (WBRT) in the treatment of primary central nervous system lymphoma is controversial. A recent randomized study addressing the use of this therapy was flawed and questions remain about the use of WBRT in these patients.

DeAngelis, L. M. Nat. Rev. Clin. Oncol. 8, 196–198 (2011); published online 8 February 2011;

The trial was inconclusive, but the authors proceeded with further analyses...

answers to these thorny questions. Two large European studies are randomizing patients to high-dose chemotherapy with autologous stem-cell transplant versus WBRT after induction chemotherapy. Although these European studies are necessarily limited to younger patients because of the transplant option, I do not think that either patients or physicians should hesitate to be randomized to a regimen that incorporates WBRT on the basis of this recently published Lancet Oncology article.4

Practice point

Further study is necessary to clarify the true role of whole-brain radiation therapy for patients with primary central nervous system lymphoma.
Low-dose WBRT

C

![Graph showing survival and time since diagnosis with different colored lines for OS and PFS.]

- **Survival (%)**
- **Time Since Diagnosis (years)**

<table>
<thead>
<tr>
<th>RPA Class</th>
<th>Randomize</th>
<th>Arm A (chemo only)</th>
<th>Arm B (chemo + low-dose WBRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1: age ≤ 50</td>
<td>OS</td>
<td>R-MPV Cycle 1</td>
<td>R-MPV Cycle 1</td>
</tr>
<tr>
<td>Class 2: age &gt; 50 and KPS ≥ 70</td>
<td>PFS</td>
<td>R-MPV Cycle 2 (no vincristine)</td>
<td>R-MPV Cycle 2 (no vincristine)</td>
</tr>
<tr>
<td>Class 3: age &gt;50 and KPS &lt; 70</td>
<td>OS</td>
<td>R-MPV Cycle 3 (no vincristine)</td>
<td>R-MPV Cycle 3 (no vincristine)</td>
</tr>
<tr>
<td>Ara-C Cycle 1</td>
<td>Ara-C Cycle 1</td>
<td>Low-Dose WBRT (13 fx)</td>
<td>Ara-C Cycle 2</td>
</tr>
</tbody>
</table>

---

## Consolidative HDC/ASCT

<table>
<thead>
<tr>
<th>N°</th>
<th>Age m(r)</th>
<th>PS m(r)</th>
<th>Induction</th>
<th>CRR (%)</th>
<th>Conditioning</th>
<th>ASCT (%)</th>
<th>F-up (mo)</th>
<th>2-yr PFS (%)</th>
<th>TRM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>51 (21-60)</td>
<td>PS3-4: 32%</td>
<td>MVpBP + itx/araC</td>
<td>44</td>
<td>BEAM + RT</td>
<td>68</td>
<td>34</td>
<td>60</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>52 (33-65)</td>
<td>PS1: 91%</td>
<td>MTX araC</td>
<td>18</td>
<td>BEAM</td>
<td>50</td>
<td>28</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>28</td>
<td>55 (18-70)</td>
<td>70 (30-100)</td>
<td>MTX araC</td>
<td>73</td>
<td>Bus, CTX VP16 ± RT</td>
<td>100</td>
<td>25</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>54 (27-64)</td>
<td>70 (30-100)</td>
<td>MTX araC, TTP</td>
<td>37</td>
<td>Thiotepa BCNU + RT</td>
<td>77</td>
<td>140</td>
<td>81</td>
<td>3</td>
</tr>
<tr>
<td>79</td>
<td>56 (51-62)</td>
<td>90 (70-90)</td>
<td>MTX araC, TTP</td>
<td>23</td>
<td>Thiotepa BCNU ± RT</td>
<td>92</td>
<td>57</td>
<td>75</td>
<td>5</td>
</tr>
</tbody>
</table>

- MVpBP: Melphalan, VP16, and Busulfan
- BEAM: Busulfan, Etoposide, Ara-C, Melphalan
- BCNU: Lomustine
- TRM: Treatment-Related Mortality

- Colombat P, et al. BMT 2006
- Abrey L, et al. JCO 2003
- Yoon DH, et al. BMT 2011
## ASCT vs. Alternatives

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>IELSG32:</td>
<td>WBRT vs. ASCT</td>
</tr>
<tr>
<td>PRECIS:</td>
<td>WBRT vs. ASCT</td>
</tr>
<tr>
<td>IELSG43 (MATRix):</td>
<td>ASCT vs. NMC</td>
</tr>
<tr>
<td>ALLIANCE:</td>
<td>ASCT vs. NMC</td>
</tr>
</tbody>
</table>
The IELSG #32 trial

PCNSL [≤ 65 ys. + PS 0-3] or [65-70 ys. + PS ≤2]

Response assessment

CR – PR - SD

PD – tox

SC harvest

WBRT 40 Gy ± boost 9 Gy

BCNU 400 mg/m² d.1
Thiotepa 5 mg/Kg x 2/d; d.2-3 + APBSCT

WBRT 36 Gy ± boost 9 Gy

4 c. MTX 3.5 g/m² d.1
araC 2 g/m² x 2/d, d. 2-3
every 3 weeks

4 c. rituximab 375 mg/m² d-5 & 0
MTX 3.5 g/m² d.1
araC 2 g/m² x 2/d, d. 2-3
every 3 weeks

4 c. rituximab 375 mg/m² d-5 & 0
MTX 3.5 g/m² d.1
araC 2 g/m² x 2/d, d. 2-3
Thiotepa 30 mg/m² d.4
every 3 weeks

Ferreri AJM, et al. 13-ICML, Lugano 2015
ACTIVITY AND EFFICACY

After induction
32 CR (54%)

Arm D (WBRT)
CR (95%)

Arm E (ASCT)
CR (93%)

MEDIAN FOLLOW-UP: 40 MONTHS (24-76)

COGNITIVE FUNCTIONS AT 2 YEARS
PCNSL [≤ 65 yrs. + PS 0-3] or [65-70 yrs. + PS ≤2]

- **Rituximab 375 mg/m² d -5 & 0**
- **MTX 3.5 g/m² d 1**
- **AraC 2 g/m² x 2/d, d 2-3**
- **Thiotepa 30 mg/m² d 4**

2 x stem cell harvest

**PD: off study**

- **Response Assessment**

- **Rituximab 375 mg/m² d -5 & 0**
- **MTX 3.5 g/m² d 1**
- **AraC 2 g/m² x 2/d, d 2-3**
- **Thiotepa 30 mg/m² d 4**

2 x

**PD/SD: off study**

- **Response Assessment**

- **Randomization**

**High-dose Consolidation:**

- **BCNU 400 mg/m² d 1**
- **Thiotepa 5 mg/Kg x 2/d; d 2-3**
  + PBSCT d0

**Conventional Consolidation:**

- **Dexamethasone 40 mg (d1-3)**
- **VP-16 (Etoposid) 100 mg/m²/d(d1-3)**
- **Ifosfamide 1500 mg/m² (d 1-3)**
- **Carboplatin 300 mg/m² (d1) 2 x**
Non-Myeloablative Chemo

Alliance/CALGB 50202 trial

44 pts (age: 12-76)

MTX (8)
Rituximab
TMZ x 8 c.

CR (66%)

araC (8)
96-hr VP16

TRM (sepsis) 2%
No neurotox

Median f-up: 4.9 ys
21 failures

17 deaths

Rubenstein J, et al. JCO 2013
Nordic Trial: TMZ maintenance

All PCNSL pts ≥ 70 years old

Trial registration

Eligible for therapy (PS ≤3 – Not eligible for ASCT)

Elegible for HD-MTX

PART A (randomized)

RIT-MTX-PCZ x 2 c. (PRIMAIN trial)

CR/PR/SD

PCZ x 6 mo

Lenalidomide x 24 mo

Ineligible for HD-MTX

PART B (Single-Arm)

WBRT 2340 cGy + Temozolomide + Rituximab

Temozolomide x 12 mo

Ineligible for therapy

ONLY DATA COLLECTION
Strategies for Future Studies

- To potentiate early diagnosis
- To identify new active drugs
- To amply our biological and molecular knowledge
- To establish reliable prognostic factors & potential targets
- To enhance drug bioavailability
- To improve radiation therapy
- To reduce neurotoxicity and improve patients’ QoL
- To improve international cooperation
International Collaborative Group Against Primary CNS Lymphomas

To the Editor: Current therapeutic knowledge in primary CNS lymphoma (PCNSL) has come from nonrandomized phase II trials, meta-analyses of published series, and large, retrospective, multicenter series. Despite the fact that literature on PCNSL has been increasing, several fundamental therapeutic questions remain unanswered. The evaluation of new first-line chemotherapy combinations in nonrandomized phase II trials, even in large series with adequate follow-up, has produced some therapeutic progress, but the 5-year progression-free survival for patients with PCNSL remains approximately 25%.1 In a recent editorial written by Dr H.A. Fine in the Journal of Clinical Oncology, several important issues with respect to PCNSL research and treatment were enumerated. In this editorial, Dr Fine concluded that further single-arm phase II trials will not add significant, new information and that it is time to proceed with cooperative group, multi-institutional randomized trials to address the most pressing clinical questions in PCNSL.

To date, only one randomized trial for patients with PCNSL has been published.3 Some authorities contend that the rarity of PCNSL is a major obstacle for the development and execution of randomized trials. However, recent advances in treatment modeling have allowed the design of phase III trials.2

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Milan, Italy

Tracy Batchelor
Harvard Medical School
Massachusetts General Hospital
Boston, MA

Emanuele Zucca

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Journal of Clinical Oncology

Ten Years of International Primary CNS Lymphoma Collaborative Group Studies

To the Editor: Ten years ago, we announced in Journal of Clinical Oncology the formation of a multidisciplinary scientific group focused on primary CNS lymphomas (PCNSL) called the International PCNSL Collaborative Group (IPCG). Since then, more than 100 researchers and clinicians working on PCNSL from 19 countries have been actively involved in this group, established under the sponsorship of the International Extranodal Lymphoma Study Group with conference grant support from the National Cancer Institute (Grant No. R13CA124293). Since 2003, this multidisciplinary group has met annually or biannually, in Europe or the United States, and meetings

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Massachusetts General Hospital Cancer Center, Boston, MA

Authors’ Disclosures of Potential Conflicts of Interest
Although all authors completed the disclosure declaration, the following author(s) and/or an author’s immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked

Ferreri AJM, et al. JCO 2003; Ferreri AJM, et al. JCO 2013
Trend in Survival

Fig 3. Age-standardized 5-year survival estimates for HIV-uninfected PCNSLs by 3-year categories of calendar year of diagnosis in 10 SEER registries during 1992-2005. Points represent estimates and dashed lines represent 95% confidence intervals.
European PCNSL Collaborative Group

IELSG #32 trial

IELSG #43 (MATRIX) trial

IELSG #XX (FIORELLA) trial

IELSG #42 (MARIETTA) trial

PCNSL
Young pts
First line

PCNSL
Young pts
Salvage

PCNSL
Elderly pts
First line

PCNSL
Elderly pts
Salvage

SCNSL
Young pts
First line

SCNSL
Young pts
Salvage

TIER trial

From SHARED IDEAS to FACTS
Acknowledgments

• Our patients and their families

• Colleagues, data managers, co-chairs and friends of the International Extranodal Lymphoma Study Group (IELSG)

• National Coordinators and DMSC Offices

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• Colleagues and friends of the International PCNSL Collaborative Group (IPCG)

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