PRIMARY CNS LYMPHOMA

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Oxford
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Potential conflicts of interest

- Roche
  - Advisory/consultancy/speaker fees, research and travel funding

- Janssen
  - Advisory board and speaker fees, travel funding

- Celgene
  - Consultancy/speaker fees and travel funding

- Adienne
  - Speaker fees, travel funding and research support
Overview

- Pathobiology

- First-line therapy
  - Remission induction
  - Consolidation and HDT-ASCT

- Older patients

- Relapsed/refractory disease
PCNSL - epidemiology

- 2-5% of all primary brain tumours
- 2% of all extra-nodal NHL
- Vast majority are DLBCL in immunocompetent patients
- Most patients >60yrs
  - Median age at diagnosis in East Midlands = 70 years
- Rising incidence
  - 3-4 per million/year in Europe
  - 4.8 per million/year in US
  - Not solely explained by improved diagnostics
Particular considerations in PCNSL

- Unique localisation of this aggressive lymphoma entity
- Challenges with drug delivery to CNS
- Surrounding brain tissue is highly vulnerable
Stereotactic biopsy remains standard-of-care for PCNSL diagnosis

- Emerging data on soluble factors as diagnostic tools; CSF cytokines (IL-10 & CXCL13) and miRNAs. cfDNA?
  Rubenstein et al Blood 2013

- Advanced MRI imaging
PCNSL, a whole brain disease

…… but presents challenges to diagnostic and biological studies

Thanks to Manuel Montesinos-Rongen, Cologne

Thanks to James Lowe, Nottingham
PCNSL - PHENOTYPE

- CD20
- CD79a
- MIB1
- BCL2
- BCL6
- MHC II
- IRF4/MUM1
- PAX5
- CD3
MYC and BCL2 protein co-expression in PCNSL

<table>
<thead>
<tr>
<th>PCNSL</th>
<th>Breakpoints (FISH)</th>
<th>Protein expression (IHC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYC</td>
<td>MYC-IGH-fusion</td>
<td>MYC high/BCL2 high</td>
</tr>
<tr>
<td>BCL2</td>
<td>BCL2</td>
<td>MYC low/BCL2 low</td>
</tr>
<tr>
<td>BCL6</td>
<td></td>
<td>MYC high/BCL6 high</td>
</tr>
<tr>
<td>Ki67</td>
<td></td>
<td>MYC low/BCL6 low</td>
</tr>
<tr>
<td>Number / cases evaluated</td>
<td>4/49</td>
<td>0/49</td>
</tr>
<tr>
<td>Frequency</td>
<td>8%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Acta Neuropathol, 2013
PCNSL – cell of origin

- Highly mutated IG genes
- Ongoing SHM
- IgM+/IgD+ => No CSR

‘GC exit phenotype’
Pathobiology

- Genomically, primary DLBCL of the CNS appears to be a relatively uniform disease
  - High mutation rate for \textit{MYD88} (~70-80%)
    - Coexistent CD79b mutations in ~50% of MYD88mut cases
  - PIM1, BTG2 frequently mutated

- Uniform negativity for \textit{BCL2} rearrangement

- NFKB pathway genes frequently mutated, multiple points within same tumour

- Clustering analysis according to gene mutation profile showed that PCNSL forms a branch distinct to systemic DLBCL
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Two drugs are better than one……IELSG20

Median f-up: 46 months

MTX
MTX-araC +/- WBRT

Ferreri et al, Lancet 2009 UPDATED FU
<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>OR</td>
<td>40 (53%)</td>
<td>51 (74%)</td>
<td>65 (87%)</td>
<td>B vs. C= 0.05</td>
</tr>
<tr>
<td></td>
<td>(95%CI= 42-64%)</td>
<td>(95%CI= 64-84%)</td>
<td>(95%CI= 80-94%)</td>
<td></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>
Response: treatment arm and IELSG risk

- Age
- ECOG PS
- LDH
- Deep lesions
- CSF protein

**ORR**

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

**CR**

- Low risk: Arm A = 12, Arm B = 13, Arm C = 11
- Intermediate risk: Arm A = 47, Arm B = 44, Arm C = 47
- High risk: Arm A = 14, Arm B = 13, Arm C = 11
Outcomes (intention to treat) by induction arm

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

A vs. B = 0.06, HR = 0.68, 95% CI = 0.45 - 1.02
A vs. C = 0.0001, HR = 0.66, 95% CI = 0.53 - 0.81
B vs. C = 0.049, HR = 0.63, 95% CI = 0.40 - 0.99

A vs. B = 0.14, HR = 0.73, 95% CI = 0.48 - 1.11
A vs. C = 0.0004, HR = 0.65, 95% CI = 0.52 - 0.83
B vs. C = 0.02, HR = 0.57, 95% CI = 0.35 - 0.93

Ferreri AJM et al ASH 2016, Lancet Haematology 2016
Outcomes (intention to treat) by induction arm

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Ferreri AJM et al ASH 2016, Lancet Haematology 2016
Overview

• Pathobiology

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  • Remission induction
  • Consolidation and HDT-ASCT

• Older patients

• Relapsed/refractory disease
  • New agents
High dose chemotherapy and ASCT in PCNSL

- Broad consensus that consolidation therapy is required for PCNSL patients treated with HD-MTX protocols
  - Very high risk of relapse without consolidation
  - WBRT effective but significant risks of disabling neurocognitive toxicity

- HDT-ASCT addresses key issue of drug delivery to CNS with non-cross resistant agents, active in G0 of cell cycle
High-Dose Chemotherapy in PCNSL

Progression-Free Survival

Median FU 57 months

Median age 56yrs, good PS

5-year PFS 64.8%

Median PFS 74 months.

Illerhaus et al Lancet Haematol 2016

From Gerard Illerhaus
High-Dose Chemotherapy in PCNSL

Overall Survival

Median FU 57 months

5-year OS 79%

From Gerard Illerhaus et al Lancet Haematol 2016
10/79 (13%) patients were irradiated due to “no CR” after PBSCT

5-year OS 79%

Overall Survival
Median FU 57 months

Illerhaus et al Lancet Haematol 2016

CNS-Lymphoma
REGISTERED PATIENTS

Strata: IELSG score

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
ev. 3 wks

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
ev. 3 wks

Response assessment

CR – PR - SD

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

PD – toxicity
Poor mobilizers

WBRT 40 Gy
± boost 9 Gy

WBRT 36 GY
± BOOST 9 GY

BCNU 400 mg/m² d.1
Thiotepa 5 mg/Kg x 2/d; d.2-3
+ APBSCT
Effects on Survival and Neurocognitive Functions of Whole-Brain Radiotherapy (WBRT) and Autologous Stem Cell Transplantation (ASCT) as Consolidation Options After High-Dose Methotrexate-Based Chemoimmunotherapy in Patients with Newly Diagnosed Primary CNS Lymphoma (PCNSL): Results of the Second Randomization of the IELSG32 Trial


On behalf of the International Extranodal Lymphoma Study Group (IELSG)
IELSG32 STUDY - CONSORT

75 assessable patients

- 46 patients with responsive or stable disease
  - Excluded patients (n=11): Poor mobilizers (2), Poor conditions (3), Patient’s refusal (2), Protocol violation (2), Others (2)
  - 35 patients referred to second randomization
    - n=17
      - 59 patients in arm D (WBRT)
        - Actually performed therapy: WBRT=53, ASCT=4, None=2
      - Per protocol: WBRT=55

- 69 assessable patients
  - 55 patients with responsive or stable disease
    - Excluded patients (n=20): Poor mobilizers (1), Poor conditions (6), Patient’s refusal (4), Protocol violation (3), Others (6)
    - 35 patients referred to second randomization
      - n=17
        - 59 patients in arm D (WBRT)
          - Actually performed therapy: WBRT=53, ASCT=4, None=2
      - Per protocol: WBRT=55

- 75 assessable patients
  - 66 patients with responsive or stable disease
    - Excluded patients (n=18): Poor mobilizers (5), Poor conditions (4), Patient’s refusal (3), Protocol violation (1), Others (5)
    - 48 patients referred to second randomization
      - n=25
        - 59 patients in arm E (HDC/ASCT)
          - Actually performed therapy: ASCT=54, WBRT=2, None=3
      - Per protocol: HDC/ASCT = 58

~50%

Ferreri AJM et al ASH 2016
RESPONSE TO CONSOLIDATION THERAPY:
CR ‘CONVERSION’ RATE

After induction
32 CR (54%)

Arm D
(WBRT)

CR (95%)

After induction
31 CR (53%)

Arm E
(ASCT)

CR (93%)

Ferreri AJM et al ASH 2016
EVENTS

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

<table>
<thead>
<tr>
<th>Events</th>
<th>Arm D (%)</th>
<th>Arm E (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>16 (27%)</td>
<td>18 (31%)</td>
</tr>
<tr>
<td>PD during consolidation</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Toxic death</td>
<td>0 (0%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Death off-therapy (NED)</td>
<td>2 (3%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>
EFFICACY: PFS

Randomization | Primary endpoint | P0* | P1 | α | 1 - β | Estimated sample | Minimum Nº of progression-free survivors at 2 ys.
--- | --- | --- | --- | --- | --- | --- | ---
2nd | 2-yr PFS | 65% | 85% | 5% | 95% | 52/ arm | 40

<table>
<thead>
<tr>
<th>ITT</th>
<th>Arm D</th>
<th>Arm E</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 104 pts (52/arm)</td>
<td>40 (77%)</td>
<td>40 (77%)</td>
</tr>
</tbody>
</table>

Ferreri AJM et al ASH 2016
EFFICACY: OS

102 (47%) pts are alive:
- 44 (75%) in arm D
- 37 (63%) in arm E
- 21 pts excluded from R2.

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Arm D</th>
<th>Arm E</th>
<th>Non R2</th>
</tr>
</thead>
<tbody>
<tr>
<td>lymphoma</td>
<td>11</td>
<td>15</td>
<td>62</td>
</tr>
<tr>
<td>treatment toxicity</td>
<td>0</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>toxicity during salvage therapy</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>neurocognitive decline while NED</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>late infective complications</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>car accident</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>acute erythroid leukaemia</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>sudden death (&gt; 1 year)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>unknown</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Ferreri AJM et al ASH 2016
UK ‘real-world’ experience

High-dose chemotherapy and autologous stem cell transplantation for primary central nervous system lymphoma; a multi-centre retrospective analysis from the United Kingdom

Shireen Kassam¹, Emily Chernucha², Aideen O’Neill³, Claire Hemmaway⁴, Tom Cummins⁵, Silvia Montoto⁶, Anne Lennard⁷, George Adams⁸, Kim Linton⁹, Pam McKay¹⁰, David Davies¹¹, Clare Rowntree¹¹, Sandra Easdale¹², Toby Eyre¹³, Robert Marcus¹, Kate Cwynarski³, Christopher P. Fox².
UK HDT-ASCT cohort: PFS

PFS from date of autograft

Median FU:
20mo from diagnosis
13mo from ASCT
UK HDT-ASCT cohort: OS

Median FU:
- 20mo from diagnosis
- 13mo from ASCT
HDT-ASCT in older PCNSL patients

‘High-dose thiotepa-based chemotherapy with autologous stem cell support in elderly patients with primary central nervous system lymphoma - a European retrospective study’

Elisabeth Schorb*, Christopher P Fox*, Kristina Fritsch, Lisa Isbell, Amelie Neubauer, Asterios Tzalavras, Ruth Witherall, Sylvain Choquet, Outi Kuittinen, Dunnya De-Silva, Kate Cwynarski, Caroline Houillier, Khê Hoang-Xuan, Valérie Touitou, Nathalie Cassoux, Jean-Pierre Marolleau, Jérome Tamburini, Roch Houot, Vincent Delwail, Gerald Illerhaus, Carole Soussain*, and Benjamin Kasenda*
HDT-ASCT in older PCNSL patients: PFS

Median 69 years (65-77)
38% first-line
62% for relapsed disease
2 yr PFS 62%
TRM 3.8%

Schorb E, Fox CP et al BMT 2017
HDT-ASCT in older PCNSL patients: OS

2 yr OS 71.4%

12-month OS 71.4%, 95% CI 59.2% – 86.2%
24-month OS 71.4%, 95% CI 59.2% – 86.2%
HDT-ASCT for PCNSL - summary

- HDT ASCT an effective consolidation treatment in PCNSL and allows most patients to avoid WBRT

- UK data are comparable to international results

- Evidence that HDT-ASCT for older PCNSL patients is a safe and effective treatment option

- Randomised trials in progress comparing HDT-ASCT to non-myeloablative chemotherapy consolidation
Current German-led, IELSG-badge study: **MATRix** trial

**Randomisation**

- **HCT-ASCT** (HD BCNU / TT)
- **2 # DeVIC** (Dexa/Ifo/VP16/Carbopl.)

**MATRix** x2 → SD/PD - off study

**MATRix** x2 → SD/PD - off study
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  • Consolidation and **HDT-ASCT**

• Older patients

• Relapsed/refractory disease
  • New agents
Older patients with PCNSL

• Age at PCNSL diagnosis rising

• Age an independent prognostic factor in most series
  • Probably a continuous variable and PS arguably more predictive

• Age >60 a particular issue for WBRT-neurocognitive dysfunction

• HDT-eligibility up to 70-75 years

• Improved immunochemotherapy approaches promising
German PRIMAIN protocol (older, HDT-ineligible patients)

From Gerard Illerhaus

Median age 75yrs (65-83)
6-month PFS: 65.7%, 95%CI 57.2–75.5
12-month PFS: 49.5%, 95%CI 40.8–60.1
18-month PFS: 42.8%, 95%CI 34.3–53.4

Median PFS 11.9 months

Median FU 35 months
6-month OS: 72.4%, 95%CI 64.3–81.5
12-month OS: 59%, 95%CI 50.4–69.2
24-month OS: 55.2%, 95%CI 46.4–65.6

Median OS 22.6 months

Median FU 35 months
Potential algorithm for PCNSL (UK 2017)

Age, PS and comorbidity assessment

Potentially fit for HDT-ASCT?

NO
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Management and outcome of Primary CNS Lymphoma at first relapse/progression: Analysis of 256 patients from the French LOC Network


Thanks to Carole Soussain, Paris
SURVIVAL AT FIRST RELAPSE / PROGRESSION

Survival Time (Months)
Survival probability
PFS2: 2.2 months [0-29.6]
OS2: 3.5 months [0-29.6]
OS2 ACCORDING TO SECOND LINE STRATEGIES

Median OS2 = NR [0-29.6] vs 6.7 mo [0-29.5] vs 0.6 mo [0-4.8]
A Phase I/II Study of Thiotepa, Ifosfamide, Etoposide and Rituximab for the treatment of relapsed and refractory PCNSL

Chief Investigator Dr Chris Fox
Louise Hopkins, UoB CRCTU
TIER@trals.bham.ac.uk
Overview

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New agents in development for PCNSL

• BTK inhibitors
  • MYD88 and CD79 mutations very common in PCNSL
  • Ibrutinib crosses BBB in meaningful concentrations
  • High responses to ibrutinib in 3 different studies but short-lived

• IMIDs/PPMs
  • Evidence of Lenalidomide activity in PCNSL in small phase I/II series
    • Parenchymal and CSF responses
    • Role in the maintenance setting under evaluation

• Checkpoint inhibition
  • PD1 disruption common in PCNSL (copy number gain or rearrangement)
  • (very) preliminary evidence of clinical activity with Nivolumab
  • Global phase 2 trial in progress
How should we treat PCNSL in 2017?

- MATRix should be considered standard induction treatment for ‘fit’ patients

- HDT-ASCT in first response should be considered for all suitable patients

- Elderly patients should be offered Rituximab + HD-MTX + oral alkylating agent where possible

- Relapsed/refractory PCNSL should be offered a clinical trial where possible
  - Ifosfamide-regimens + HDT-ASCT offer a chance of long-term PFS/OS
  - Novel agents promising but short-lived responses as single-agent
    - Combinations needed
Research priorities

- Older patients (HDT-ineligible)
- Relapsed/refractory
  - Getting patients to HDT
- HDT-failures
  - Novel agents
- Imaging
  - Prognostication, response evaluation and definitions
- Pathobiology
  - Targeted therapies
Thank you for your attention