THE 11TH ANNUAL

CHC 2021

CANADIAN HEMATOLOGY CONFERENCE 2021

Presented by: CARE
Central Nervous System prophylaxis in DLBCL

Dr Chris Fox
MBChB(Hons) PhD FRCP FRCPath

Consultant Haematologist & Honorary Associate Professor
Nottingham University Hospitals, UK

Chair, UK NCRI aggressive lymphoma study group
Abbvie: Consultancy, advisory board honorarium, research funding, travel to scientific conferences
Acerta Pharma/AstraZeneca: Advisory Board honorarium
Atarabio: advisory board honorarium
BeiGene: Research funding
Celgene/BMS: Consultancy, advisory board honorarium, research funding, travel to scientific conferences
GenMab: Consultancy, advisory board honorarium
Gilead/Kite: Advisory Board honorarium, research funding
Incyte: Advisory board honorarium
Janssen: Advisory board honorarium, research funding, travel to scientific conferences
Morphosys: Consultancy, advisory board honorarium
Roche: Consultancy, advisory board honorarium, research funding, travel to scientific conferences
Takeda: Advisory Boards; Honorarium; research funding, travel to scientific conferences
Why worry so much about CNS prophylaxis?

1. CNS relapse is a devastating event with poor outcomes for the majority

2. Accurately identifying patients at risk of a CNS event is difficult

3. It remains unclear how best to mitigate against the risk of CNS relapse

4. Prophylactic interventions confer risks of additional toxicity
What are the unanswered questions on CNS prophylaxis?

1. Who?
2. When?
3. How?
Concepts & patterns of CNS relapse

CNS seeded at diagnosis or early during therapy

Influenced by disease burden/late presentation?

Biological predilection: postcode or microenvironment?

Sub-clones destined or selected to invade CNS at relapse

Driver or acquired mutations?

Early events

Late events

Isolated CNS relapse

Concurrent CNS and systemic disease

Parenchymal

Leptomeningeal

Patients destined for a CNS event

High risk CNS-IPI

Intermediate risk IPI

Low risk CNS-IPI
Concepts & patterns of CNS relapse

Patients destined for a CNS event

- High risk CNS-IPI
- Intermediate risk IPI
- Low risk CNS-IPI

Pattern of relapse

- Isolated CNS
- Systemic & CNS

~33% of patients who experience a CNS event will have high-risk CNS-IPI at baseline and experience isolated CNS relapse.
Who? Utility and limitations of the CNS-IPI

CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP

Norbert Schmitz, Samira Zeynalova, Maike Nickelsen, Roopesh Kansara, Diego Villa, Laurie H. Sehn, Bertram Glass, David W. Scott, Randy D. Gascoyne, Joseph M. Connors, Marita Ziepert, Michael Pfundtshuh, Markus Loeffler, and Kerry J. Savage

J Clin Oncol 34:3150-3156. © 2016 by American Society of Clinical Oncology

Table 1. Major Clinical Characteristics of Patients Representing the Training Set (German High-Grade Non-Hodgkin Lymphoma Study Group, MabThera International Trial) and the Validation Set (British Columbia Cancer Agency)

<table>
<thead>
<tr>
<th>Cohort Characteristic</th>
<th>DSHNHL/Mnt, n = 2,164 (%)</th>
<th>BCCA, n = 1,597 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>58 (18-80)</td>
<td>65 (16-84)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>974 (45)</td>
<td>1,035 (65)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Male</td>
<td>1,244 (59)</td>
<td>915 (57)</td>
<td>.907</td>
</tr>
<tr>
<td>LDH &gt; normal*</td>
<td>1,147 (53)</td>
<td>737 (49)</td>
<td>.017</td>
</tr>
<tr>
<td>ECOG PS &gt; 1</td>
<td>247 (11)</td>
<td>594 (37)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Stage III/IV disease</td>
<td>1,148 (53)</td>
<td>916 (57)</td>
<td>.009</td>
</tr>
<tr>
<td>Extramedial site &gt; 1</td>
<td>479 (22)</td>
<td>396 (25)</td>
<td>.057</td>
</tr>
<tr>
<td>Bulky disease, &gt; 7 cm*</td>
<td>1,027 (49)</td>
<td>636 (41)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Kidney/adrenal glands</td>
<td>90 (4)</td>
<td>56 (4)</td>
<td>.536</td>
</tr>
</tbody>
</table>

CNS-IPI score 4-6 263 (12.3%) 344 (23%)

Therefore, ~1 in 5 patients with DLBCL may fall into the high-risk group by CNS-IPI.

NB EN sites & renal/adrenal disease frequencies may be underestimated by CT staging.
CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP

Norbert Schmitz, Samira Zeynalova, Maike Nickelsen, Roopesh Kansara, Diego Villa, Laurie H. Sehn, Bertram Glass, David W. Scott, Randy D. Gascoyne, Joseph M. Connors, Marita Ziepert, Michael Pfreundschuh, Markus Loefler, and Barry J. Savage

J Clin Oncol 34:3150-3156. © 2016 by American Society of Clinical Oncology

Table 2. Factors Defining the CNS International Prognostic Index: Results of Multivariable Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney and/or adrenal glands involved</td>
<td>2.8</td>
<td>1.3 to 5.8</td>
<td>.006</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>2.5</td>
<td>1.3 to 4.5</td>
<td>.001</td>
</tr>
<tr>
<td>LDH &gt; normal</td>
<td>2.4</td>
<td>1.3 to 4.5</td>
<td>.005</td>
</tr>
<tr>
<td>ECOG PS &gt; 1</td>
<td>2.2</td>
<td>1.3 to 3.9</td>
<td>.008</td>
</tr>
<tr>
<td>Stage III/IV disease</td>
<td>2.0</td>
<td>1.0 to 3.8</td>
<td>.039</td>
</tr>
<tr>
<td>Extracranial involvement &gt; 1</td>
<td>1.0</td>
<td>0.5 to 1.8</td>
<td>.935</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.
All DLBCL patients

The positive predictive value (PPV) of the CNS-IPI is ~10-15%

- High risk CNS-IPI
- Intermediate and low risk IPI
All DLBCL patients

- High risk CNS-IPI no event
- High risk CNS-IPI with event
- Intermediate and low risk IPI

Pattern of relapse

- Isolated CNS
- Systemic & CNS

- Thus, it may be only 2% of all DLBCL patients who are identified as ‘high risk’ by the CNS-IPI and subsequently experience an isolated CNS relapse.

- The CNS-IPI did not delineate isolated CNS relapse vs synchronous systemic/CNS.

- Assuming ‘equally predictable’ : the PPV (of the CNS-IPI) for isolated CNS relapse is ~6-9% rather than 10-15%.
• A positive predictive value of 10% equates to a ‘number needed to treat’ (NNT) of 10 patients
• A prophylactic intervention may reduce (but won’t eliminate) risk
• Assume a given intervention may reduce risk by 50%....
• The NNT = 20 patients

• That is, in order to prevent one (isolated) CNS relapse, ~20 patients need to receive CNS prophylaxis

---------we need better tools to identify the ‘who’...
Who? Cell of origin by GEP to inform CNS risk

Table 4. Results of multivariate Cox regression analysis on factors associated with CNS relapse in the COO and BCL2/MYC dual-expression status-available population (n = 688). CNS relapses (n = 22)

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR*</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS-IPI intermediate (v low)</td>
<td>0.75</td>
<td>0.23:2.45</td>
<td>.6378</td>
</tr>
<tr>
<td>CNS-IPI high (v low)</td>
<td>2.76</td>
<td>0.81:9.42</td>
<td>.1042</td>
</tr>
<tr>
<td>ABC COO (v GCB)</td>
<td>4.78</td>
<td>1.49:15.29</td>
<td>.0084</td>
</tr>
<tr>
<td>Unclassified COO (v GCB)</td>
<td>4.24</td>
<td>1.32:13.61</td>
<td>.0151</td>
</tr>
<tr>
<td>BCL2/MYC dual expresser (v non-dual expresser)</td>
<td>0.83</td>
<td>0.34:2.06</td>
<td>.6931</td>
</tr>
</tbody>
</table>

Klanova et al, Blood 2019  Fox CP Blood 2019
• MCD characterised by
  • Enriched at the ‘far ABC end’ of the genetic spectrum
  • frequent co-occurrence of $\text{MYD88}^{L265P}$ & $\text{CD79B}$ mutations
  • prominent immune-editing features $\text{PIM1}$ mutations
  • Frequently involve extra-nodal sites including the testes, breast and CNS

• A very similar subtype termed Cluster 5 (C5) identified in an independent genomic study
  • $\text{MYD88}^{L265P}$ and $\text{CD79B}$ mutations, gain of 18q, and $\text{PIM1}$
  • Propensity for extra-nodal sites, including the CNS and testes

• A recent series (n=26) of patients with SCNSL confirmed a higher prevalence of MCD subtype vs a cohort of rDLBCL without CNS involvement (38% vs. 8%, p=0.003)
  • The majority of other DLBCL cases with CNS involvement were HGBCL-DH/TH or associated with TP53 mutations.

• Common genomic aberrations associated with CNS relapse in a study of primary testicular DLBCL (n=82) include BCL6 and/or PDL1 or PDL2 rearrangements

Emerging data on utility of cell free circulating tumour (ct) DNA in CSF and plasma
- Potential prognostic and diagnostic value in PCNSL
- Potential utility as a dynamic biomarker to predict CNS relapse

Bobillo et al, (n=19) 6 SCNSL, 1 PCNSL, 12 systemic DLBCL
- Tumour-specific somatic mutations (WES/targeted sequencing)
- Variant-specific ddPCR detected CSF ctDNA in one patient with systemic lymphoma, 8 months before CNS relapse was manifest

CSF ctDNA as a potential tool to identify occult CNS disease at baseline and/or as an early predictor of CNS relapse

Bobillo et al, Haematologica 106; 2021
• The weaker the evidence….the more contentious the debate!
Majority of CNS relapses involve the brain parenchyma
  - Intrathecal prophylaxis insufficient
  - HD-MTX at doses >3g/m² infused over 2-4 hours should deliver adequate levels in parenchyma and CSF

No good evidence to support IT prophylaxis
  - Retrospective studies (including RICOVER-60)
  - Systematic review of >7000 patients

Intravenous HD-MTX commonly used but not supported by strong evidence – no RCT data
  - May reduce (but does not eliminate) risk of isolated CNS relapse
  - Confers toxicity risks and many will be over-treated.

Publications within the last 6 months:

High-dose methotrexate is **effective** for prevention of isolated CNS relapse in diffuse large B cell lymphoma.
Ong SY et al. Blood Cancer J. 2021 PMID: 34385415

**Ineffectiveness** of high-dose methotrexate for prevention of CNS relapse in diffuse large B-cell lymphoma.

Prophylaxis with intrathecal or high-dose methotrexate in diffuse large B-cell lymphoma and high risk of CNS relapse. ("**prevents early CNS events**")
Bobillo S et al Blood Cancer J. 2021 PMID: 34135307

Efficacy and safety of prophylactic high-dose MTX in high-risk DLBCL: a treatment intent-based analysis. ("**HD-MTX ineffective**")
Why such uncertainty and lack of clarity?

• Sample sizes too small - insufficient power for rare events

• Selection bias a major problem

• No distinction between isolated CNS relapse and concurrent systemic relapse

• Timing and nature of prophylactic interventions are variable

• The high-risk CNS-IPI group is heterogeneous
409 Cycles HD-MTX intercalated with R-CHOP

82 (20%) associated with delay in next R-CHOP
Median delay 7 days (range 2-150)

56 (14%) delays directly attributed to MTX (clinician judgement)

Wilson M et al, Blood Advances 2020

Multivariable analysis: factors influencing delay of R-CHOP after intercalated HD-MTX
## When? Toxicity of intercalated HD-MTX vs EOT HD-MTX

<table>
<thead>
<tr>
<th></th>
<th>All (n=729)</th>
<th>Intercalated (n=409)</th>
<th>End of treatment (n=320)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number inpatient days (median, range)</strong></td>
<td>5 (2-60)</td>
<td>5 (2-60)</td>
<td>4 (3-80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Toxicity:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal (any)</td>
<td>38 (5%)</td>
<td>21 (5%)</td>
<td>17 (5%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Grade 1 (Creat 1.5-1.9 x baseline)</td>
<td>22 (3%)</td>
<td>12 (3%)</td>
<td>10 (3%)</td>
<td></td>
</tr>
<tr>
<td>Grade 2 (Creat 2-2.9 x baseline)</td>
<td>6 (1%)</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
<td></td>
</tr>
<tr>
<td>Grade 3 (Creat &gt;3 x baseline)</td>
<td>10 (1%)</td>
<td>6 (1%)</td>
<td>4 (1%)</td>
<td></td>
</tr>
<tr>
<td>Liver (grade 2 or worse)</td>
<td>17 (2%)</td>
<td>7 (2%)</td>
<td>10 (3%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Mucositis</td>
<td>54 (7%)</td>
<td>42 (10%)</td>
<td>12 (4%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>49 (7%)</td>
<td>42 (10%)</td>
<td>7 (2%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Wilson M et al, Blood Advances 2020
When? Intercalated HD-MTX vs EOT HD-MTX

Wilson M et al, Blood Advances 2020
How do I discuss CNS prophylaxis with my patients?

• Estimate their risk of a CNS event
  • Compare to an ‘average’ DLBCL patient

• Explain the consequences of CNS relapse
  • Recognising whether potentially fit for intensive SCNSL therapy

• Re-cap the prognosis of their systemic DLBCL
  • Relapse risk may be as high as 50% for high-risk patients

• Explain the rationale of CNS prophylaxis and emphasise the uncertainty regarding efficacy
  • Aim to reduce not eliminate risk of CNS relapse
  • No impact on risk of systemic disease recurrence

• Discuss the practicalities and toxicities of CNS prophylaxis
1. **Who?**
Focus on ‘highest risk’ patients – testicular/renal/adrenal/CNS-IPI (4),5-6 and/or ≥3 EN sites.

*Careful and balanced discussion regarding the uncertainties*

2. **When?**
Typically EOT (PET CMR)
Consider CSF and MRI at baseline to ‘exclude’ occult CNS disease

3. **How?**
HD-MTX 3.5g/m2 over 3 hours, 2x infusions q14-21
1. Who?
- A large (retrospective) dataset anticipated at ASH 2021 – will this be sufficient to inform practice?
- Efforts must focus on validating biomarkers to accurately characterise a very high risk group

2. When?
- A (separate) large (retrospective) study anticipated at ASH 2021 (EOT vs intercalated HD-MTX)
- CSF biomarkers +/- neuroimaging studies may inform the question on who and when

3. How?
- Impact of more effective systemic DLBCL regimens deserves attention
- CNS-active agents beyond HD-MTX warrant investigation as prophylaxis
When prophylaxis fails...
**RATIONALE:** Dose intensive, non-cross resistant regimens, active in DLBCL with good CNS bioavailability

(Start with R-CHOP in the case of life-threatening systemic disease)

Strong data in PCNSL with HD-MTX, HD-ARAC and thiotepa (MATRIX)

R-ICE is standard in R/R DLBCL, and active in R/R PCNSL

Deliver WBRT in patients with PD during induction and patients with residual CNS disease after ASCT

Ferreri AJMF et al, Lancet Haematology 2021
MARIETTA study - patient characteristics (n=75)

- Age 18 - 70 years
- ECOG PS 0 – 3
- No prior HD-MTX or WBRT or ASCT

<table>
<thead>
<tr>
<th>Disease site at registration</th>
<th>CNS involvement at presentation</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS involvement at presentation</td>
<td>32 (43%)</td>
<td></td>
</tr>
<tr>
<td>Concomitant CNS/systemic relapse</td>
<td>28 (37%)</td>
<td></td>
</tr>
<tr>
<td>Isolated CNS relapse</td>
<td>15 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

Ferreri AJMF et al, Lancet Haematology 2021
Treatment-naïve patients & those with disease limited to a single CNS compartment had improved outcomes.

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>PFS (probability)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>0.8</td>
</tr>
<tr>
<td>24</td>
<td>0.6</td>
</tr>
<tr>
<td>36</td>
<td>0.4</td>
</tr>
<tr>
<td>48</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Patients with CNS disease at presentation had the best outcome.

CSF/meningeal disease was associated with poor outcome.

Ferreri AJMF et al, Lancet Haematology 2021
Patients undergoing ASCT had improved survival outcomes

The International Extranodal Lymphoma Study Group-42 Phase II (MARIETTA) Trial (N=75)

2-yr PFS: 46%\(^1\)

2-yr PFS: 83%\(^1\)

MATRIX-RICE followed by ASCT achieved the primary endpoint (1-year PFS) in this very-poor-prognosis population, without major safety concerns

Ferreri AJM, et al. Lancet Haematology 2021
Conclusions from IELSG42/MARIETTA

• MATRIX-RICE followed by ASCT achieved the primary endpoint without major safety concerns

• Response to 2x MATRIX was a strong prognostic factor.

• Patients with SCNSL refractory to MATRIX did not benefit from RICE + ASCT.

• The best survival outcomes were achieved in chemo-naïve patients and in patients with disease limited to a single CNS compartment (parenchyma or CSF/meninges)
Thank you for your attention