Lymphoma

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Disclosures

• Honoraria from Astra-Zeneca and Gilead
AGENDA

- Overview
- Key News This Year
- Key News out of ASH 2020
- Canadian Perspective
Overview

• Review background, key publications and abstracts this yr in 2 key areas:
  • Frontline aggressive lymphomas – CNS prophylaxis
  • Early stage Hodgkin lymphoma

• Observations from a Canadian perspective
Aggressive lymphomas – DLBCL – CNS prophylaxis etc.
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>.006</td>
</tr>
<tr>
<td>Stage III/IV disease</td>
<td>2.2</td>
<td>1.1 to 3.5</td>
<td>.035</td>
</tr>
<tr>
<td>Extranodal involvement &gt; 1</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.
A systematic review of the efficacy of CNS prophylaxis with stand-alone intrathecal chemotherapy in diffuse large B cell lymphoma patients treated with anthracycline-based chemotherapy in the rituximab era

by Toby A. Eyre, Faouzi Djebbari, Amy A. Kirkwood, and Graham P. Collins

Haematologica 2019 [Epub ahead of print]

There is no strong evidence to support the use of stand-alone IT chemotherapy prophylaxis for patients treated with anthracycline-based chemotherapy in the rituximab era. Conversely, the strength of evidence suggesting a genuine lack of evidence is also weak. The majority (70%) of CNS relapses occurring in anti-CD20 antibody-exposed patients treated in our systematic review involved parenchymal tissue. No study within the systematic review reported a toxicity analysis of intrathecal chemotherapy and as such few meaningful conclusions can be made regarding the morbidity of IT prophylaxis from these series.

The quality of the data is relatively weak to poor. Although some of the studies included relatively large numbers of patients, the absolute number of CNS relapse events limits the power to perform high-quality multivariable analysis or adjusted analysis. As such, we conclude that there is little evidence for the benefit of stand-alone IT CNS prophylaxis in preventing CNS relapse in DLBCL-treated patients using anthracycline-based immunochemotherapy.
<table>
<thead>
<tr>
<th>Study</th>
<th>Systemic regimen</th>
<th>CNS Px</th>
<th>Criteria</th>
<th>CNS relapse rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abramson’10 Retrospective</td>
<td>R-CHOP-21</td>
<td>IV MTX 3.5g/m2 X 3 cycles</td>
<td>&gt;1EN with ↑LDH, BM, sinus, testes, epidural, liver, adrenal, renal, orbit</td>
<td>3% (2/65)</td>
</tr>
<tr>
<td>Holte ‘13</td>
<td>R-CHOEP-14</td>
<td>Ara-C 3g/m2 q12 X 2d, MTX 3g/m2 X 1</td>
<td>All in trial: aaIPI 2-3 97% ↑LDH, stg 3-4, 57% &gt;1EN</td>
<td>4.5%</td>
</tr>
<tr>
<td>Guirguis ’12 Retrospective</td>
<td>R-CHOP</td>
<td>27/214 (12.6%): IT 10, HD2, IT and HDMTX</td>
<td>↑LDH, &gt;1EN (esp BM, testicular, epidural, sinus)</td>
<td>3.7%</td>
</tr>
<tr>
<td>Kumar ’11 NCCN database</td>
<td>R-CHOP</td>
<td>72% IT MTX/Ara-C, 28% HDMTX</td>
<td>↑LDH, &gt;1EN (esp BM, testicular, epidural, sinus)</td>
<td>2%</td>
</tr>
<tr>
<td>Ferreri ‘15 Retrospective</td>
<td>R-CHOP</td>
<td>40/200 83% HDMTX 17% IT Ara-C</td>
<td>adv stage and incr. LDH (cns-IPI), testis, spine, skull, paranasal sinuses, orbit, nasopharynx, kidney/adrenal, and/or breast</td>
<td>0% vs 12% (in HR pts)</td>
</tr>
<tr>
<td>Leppa ‘20</td>
<td>R-CHOED-14</td>
<td>Ara-C 3g/m2 q12 X 2d, MTX 3g/m2 X 1</td>
<td>All in trial: aaIPI 2-3 91% ↑LDH, stg 3-4, 45% high-risk CNS IPI</td>
<td>2.3%</td>
</tr>
</tbody>
</table>
Lack of Effectiveness of Intravenous High-Dose Methotrexate for Prevention of CNS Relapse in Patients with High-Risk DLBCL: A Retrospective Analysis from Alberta, Canada

Sunday, December 6, 2020: 2:15 PM R. Puckrin et al.

- Retrospective 2012-2019, 906 pts DLBCL pts with 18-70 yrs of age
- From 2015 - HD-MTX 3.5g/m² IV after cycles 2, 4, and 6 of R-CHOP: CNS-IPI 4-6, double hit lymphoma, or testicular involvement.

**Figure 1: Risk of CNS relapse by CNS-IPI score**

- CNS-IPI 1-3: 12.2%
- CNS-IPI 3-6: 4.9%
- CNS-IPI 4-6: 1.9%
Table 1: Risk of CNS relapse by treatment arm in APLCPG high-risk patients (n=326)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>Risk of CNS relapse with vs. without treatment</th>
<th>Hazard ratio</th>
<th>95% C.I.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD-MTX prophylaxis</td>
<td>115</td>
<td>11.2% vs. 12.2%</td>
<td>0.92</td>
<td>0.44-1.91</td>
<td>0.82</td>
</tr>
<tr>
<td>Higher intensity chemoimmunotherapy</td>
<td>35</td>
<td>5.7% vs. 12.6%</td>
<td>0.64</td>
<td>0.20-1.98</td>
<td>0.43</td>
</tr>
<tr>
<td>Consolidative autotransplant</td>
<td>68</td>
<td>6.0% vs. 13.7%</td>
<td>0.55</td>
<td>0.24-1.25</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Table 2: Multivariate analysis of CNS relapse, progression-free survival, and overall survival by treatment arm in APLCPG high-risk patients, controlling for CNS-IPI score, double hit lymphoma, and testicular involvement (n=326)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CNS relapse</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% C.I.</td>
<td>P value</td>
</tr>
<tr>
<td>HD-MTX prophylaxis</td>
<td>1.61</td>
<td>0.72-3.59</td>
<td>0.25</td>
</tr>
<tr>
<td>Higher intensity chemoimmunotherapy</td>
<td>0.38</td>
<td>0.08-1.95</td>
<td>0.25</td>
</tr>
<tr>
<td>Consolidative autotransplant</td>
<td>0.30</td>
<td>0.09-1.01</td>
<td>0.051</td>
</tr>
</tbody>
</table>
478 CNS Prophylaxis during Front-Line Therapy in Aggressive Non-Hodgkin Lymphomas: Real-World Outcomes and Practice Patterns from 19 US Academic Institutions
Sunday, December 6, 2020: 2:30 PM
Victor M. Orellana-Noia et al.

• Program: Oral and Poster Abstracts
  Type: Oral
  Session: 627. Aggressive Lymphoma (Diffuse Large B-Cell and Other Aggressive B-Cell Non-Hodgkin Lymphomas)—Results from Retrospective/Observational Studies: PCNSL Treatment and Prognosis and CNS Prophylaxis in High-Risk Aggressive Lymphomas
530 Cerebrospinal Fluid (CSF) Analysis of Tumor-Specific Cell-Free DNA (cfDNA) As a Diagnostic and Prognostic Tool for Central Nervous System (CNS) Invasion in Lymphoma

Monday, December 7, 2020: 7:00 AM *Adam J Olszewski et al*

**A**

<table>
<thead>
<tr>
<th>Study group</th>
<th>CNS invasion status</th>
<th>CSF NGS-MRD assay result</th>
<th>Sensitivity: 100%</th>
<th>Specificity: 53%</th>
<th>Negative predictive value: 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known CNS lymphoma N = 6</td>
<td>Brain parenchyma</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Historical DNA isolate from CSF N = 6</td>
<td>Leptomeningeal</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Newly diagnosed aggressive lymphoma with no CNS invasion N = 19</td>
<td>No known CNS invasion: (negative CSF cytology, flow cytometry, and/or IGH-PCR)</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**E**

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(copies per 10⁷ genomic equivalents)

<table>
<thead>
<tr>
<th>0</th>
<th>0.0</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>P=0.10</td>
<td>29% CSF cfDNA positive</td>
<td>0% CSF cfDNA negative</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
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N = 8, 6, 3, 0, 0; Months since CSF sample collection = 9, 4, 1, 0, 0

- IMPACT cohort: all Ontario, Canada AYA aged 15-21 years diagnosed with one of six common cancers (including NHL) between 1992-2012
- 176 AYA pts, 35% treated at pediatric centres, more pts had Burkitt (42% vs. 18%)

### Table 1. Event-free and overall survival by locus of care among adolescents and young adults with mature B-cell non-Hodgkin lymphoma

<table>
<thead>
<tr>
<th>Category</th>
<th>Pediatric Center</th>
<th>Adult Center</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All mature B-cell non-Hodgkin lymphoma (N=176)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year event-free survival (±standard error)</td>
<td>82.3%±4.9%</td>
<td>66.7%±4.4%</td>
<td>0.02</td>
</tr>
<tr>
<td>5-year overall survival (±standard error)</td>
<td>85.5%±4.5%</td>
<td>71.1%±4.3%</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Diffuse large B-cell lymphoma (N=129)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year event-free survival (±standard error)</td>
<td>83.3%±6.2%</td>
<td>66.7%±4.9%</td>
<td>0.04</td>
</tr>
<tr>
<td>5-year overall survival (±standard error)</td>
<td>88.9%±5.2%</td>
<td>72.0%±4.7%</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Burkitt lymphoma (N=47)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year event-free survival (±standard error)</td>
<td>80.8%±7.7%</td>
<td>66.7%±10.3%</td>
<td>0.20</td>
</tr>
<tr>
<td>5-year overall survival (±standard error)</td>
<td>80.8%±7.7%</td>
<td>66.7%±10.3%</td>
<td>0.25</td>
</tr>
</tbody>
</table>
Early unfavourable Hodgkin lymphoma – first line
EORTC H10 trial design

U-group: 5 year PFS 92.1% vs 89.6%
HR 1.45 CI (0.8 – 2.5) > prespecified non-inferiority margin of 2.1
OS 96.7% vs 98.3%

PET negative

PET positive

5-year PFS 77.4% vs 90.6%
HR 0.42 (0.23 – 0.74)
OS 89.3% vs 96% (p = 0.062)
Dose-Intensification in Early Unfavorable Hodgkin’s Lymphoma: GHSG HD14 Trial

2 escBEACOPP + 2 ABVD vs 4 ABVD (+ 30 Gy IFRT)

G3-4 toxicity: 50.7% vs 87.1%; TRM in arm B (2+2) : 0.52%
Infection: 3.4% vs 7.3%
SPM: 2.2% vs 2.0%
No OS difference 97% in both arms

Von Tresckow et al. JCO 2012
S101: Final Results of the Phase III HD Trial

HD17 Trial Design

Early-stage unfavorable HL

Randomization

Standard CMT arm A
- 2x eBEACOPP + 2x ABVD
- PET/CT
- PET (+/-)
- 30 Gy IF-RT

PET-guided arm B
- 2x eBEACOPP + 2x ABVD
- PET/CT
- PET (+) [DS 3-4]
- PET (-)
- 30 Gy IN-RT

Follow-up

Sunday, December 6, 2020, 7:00 AM-3:30 PM  Michael Fuchs et al
HD17 Trial  Sensitivity analysis in PET-negative patients

Non-inferiority can be confirmed in PET-negative patients

5-year PFS
Arm A: 97.7%  [93.6 - 99.2]
Arm B: 95.9%  [92.4 - 97.9]

Diff. in 5-year PFS
1.7%  [-5.3 – 1.8]
• Deauville 1-2: 67%, 3: 24%, 4: 9%

• When Deauville cutoff changed from 3-4: HR 10.2 [4.16-25]

• On MV analysis, bulky disease at dx associated with D4 at end of treatment
Probability of resumption of menses is dependent on age and chemotherapy

Likelihood of amenorrhea at 4 y increases with use of escBEACOPP vs ABVD

Conclusions from a Canadian Perspective

- We can reliably identify aggressive B-cell lymphoma patients at higher risk of CNS relapse.
- However, it doesn’t seem like CNS directed prophylaxis, even systemic, necessarily changes that risk.
- Better systemic disease control and diagnosis of minimal involvement of CSF is needed to decrease the risk in high risk patients, including novel regimens for pts with CNS involvement.
- Similar to ALL, intriguing to consider that AYA DLBCL pts (up to 21 yrs of age) have worse outcomes with adult protocols (mostly RCHOP), should we be considering pediatric protocols.
- For early stage unfavourable HL pts, 2escBEACOPP + 2 ABVD with radiation omission if PET negative is very attractive, esp in young patients with large radiation fields – likely individualized choice for each patient, and multidisciplinary discussion required from the start with radonc colleagues for best approach.
Thank you!

Enjoy CARE at ASH 2020
(Virtual Edition)
Hodgkin lymphoma – first line – elderly patients
PVAG Regimen (Prednisone, Vinblastine, Doxorubicin, Gemcitabine) Used in Real-Life Setting in First Line Therapy for Elderly Classical Hodgkin Lymphoma Patients: A Retrospective Study of Lysa Centers

Saturday, December 5, 2020, 7:00 AM-3:30 PM **Guillaume Aussedat et al.**

- PVAG (Prednisone 40 mg/m², Vinblastine 6 mg/m², Doxorubicin 50 mg/m², Gemcitabine 1000 mg/m²) – developed for older pts
- 49 pts – median age 76 yrs (61-87)
- Median # of cycles: 6, feb neut 12%, one toxic death
- ORR 65%, CR 53%
- 3yr PFS 49%
- 3yr OS 74%

Figure 1. Overall survival (OS) and progression-free survival (PFS) in patients treated with PVAG
471 Frontline Brentuximab Vedotin As Monotherapy or in Combination for Older Hodgkin Lymphoma Patients


Christopher A. Yasenchak et al.

• Phase 2, open-label study, efficacy and tolerability of Brentuximab vedotin alone or combined with single-agents in treatment-naive cHL patients ≥60 yr.
• Part A: BV monotherapy on Day 1 of every 3-week cycle (n=26)
• Part B: BV+dacarbazine (DTIC; 375 mg/m²; n=19);
• Part C: BV+bendamustine (benda; 70 mg/m²; n=20);
• Part D: BV+nivolumab (nivo; 3 mg/kg; n=20).
• Median age 78, 69, 75, and 72 yr respectively
• Most patients had stg III-IV disease
## Outcomes

<table>
<thead>
<tr>
<th></th>
<th>BV alone</th>
<th>BV + DTIC</th>
<th>BV + benda</th>
<th>BV + Nivo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>92%</td>
<td>100%</td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Med PFS</strong></td>
<td>10.5 mo</td>
<td>46.8</td>
<td>40.3</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Med OS</strong></td>
<td>77.5 mo</td>
<td>64 mo</td>
<td>46.9 mo</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Med treatment cycles</strong></td>
<td>8</td>
<td>12</td>
<td>5</td>
<td>14.5</td>
</tr>
<tr>
<td><strong>Treatment-related SAEs</strong></td>
<td>12%</td>
<td>11%</td>
<td>40%</td>
<td>30%</td>
</tr>
</tbody>
</table>