CNS Lymphoma

Las Vegas-- March 10-12, 2016
Frequency

- 3% of primary cerebral tumors
- 1% of NHLs
Recent developments and controversies in PCNSL Hottinger et al

Current Opinion in Oncology

• Vol 27 No. 6 November 2015

• Molecular genetics
• Diagnostic biomarkers
• Prognostic factors
• Neuroimaging
• Surgery
• Radiotherapy
• Chemotherapy
• Auto SCTx
• Elderly patients
• Rituximab and other targeted therapies
• Influence of rituxan on CNS relapse in DLBCL and role of prophylaxis—a systematic review of prospective studies. Clinical Lymphoma, Myeloma & Leukemia August 2015
Molecular genetics

• 3 genome wide analyses using whole genome sequencing
• Identify alterations of NF-κB pathways, especially through somatic mutations of MYD88 and CD79B
  – Bruno et al Oncotarget 2014;5:5065-5075
  – Vater et al Leukemia 2014
• MYD88 mutations were identified in 20/29 vitrectomy specimens from a primary and secondary ocular lymphoma.

• Also elevated in CSF, and reported to be of value in distinguishing PCNSL from other brain tumors and CNS inflammatory disease:
  – Neopterine
  – CXCL13
  – Interleukin 10
Lugano updates
2015

Jasmine Zain
ABSTRACT 131
CNS RELAPSE

• Validation of the German High Grade NHL study group prognostic model for CNS relapse in PET/CT staged patients: El. Galaly et al
• Retrospective, multi-center study 1290 patients
• Staged with PET/CT
• Treated with R-CHOP
• Denmark, Australia, British Columbia
Who should receive CNS directed prophylactic therapy in DLBCL

• Incidence is about 5%
• Outcome is usually fatal
• Who is at risk
• What is the best strategy to prevent CNS relapse
Identification of risk factors

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>2 year risk of CNS relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>0.6%</td>
</tr>
<tr>
<td>2-3</td>
<td>3.45</td>
</tr>
<tr>
<td>4-6</td>
<td>Risk factors</td>
</tr>
</tbody>
</table>

- German High Grade NHL Study group (DSHNHL)- 2164 patients (80% DLBCL) R-CHO(E)P  
- BCCA- Savage et al, 1597 patients , DLBCL,R-CHOP
Methods

• All staged with PET/CT
• R-CHOP, high risk patients got CNS prophylaxis as per treating physicians assessment
• Median fu 43 months
• Risk factors
  – >60 yrs – 65%
  – Elevated LDH- 49%
  – Stage III/IV- 23%
  – EN >1- 23%
  – PS>1- 13%
  – kidney./renal – 4%
  0-1 risk factors- Low risk--- 34%
  2-3– intermediate risk, 48%
  >3- high risk, 18%
Abstract 137
Lenalidomide is highly active in recurrent CNS lymphoma

- Lenalidomide active in aggressive NHL esp ABC subtype
- Case report in 2011- efficacy of lenalidomide in ocular lymphoma
- Phase 1 trial of Lenalidomide in CNS NHL

Rubenstein et al
Methods

• Determine safety and efficacy of 3 dose levels of Lenalidomide in refractory CD20+ CNS lymphoma
• Determine CSF penetration of Lenalidomide
• Feasibility of combined IT and IV rituximab
• Effect of lenalidomide on tumor microenvironment
Results

- 9 patients on phase 1 (7 PCNSL, 2 SCNSL)
- 8 evaluable
- 6/8 had response at 1 month of therapy, 2 CRs, 1 PR in brain NHL, 1 CR of CSF NHL and 1 CR and 2 PR of intraocular lymphoma
- 3 maintain response to mono therapy at > 6 months and 2 beyond 1 year.
Results

• Independent cohort of 10 patients received lenalidomide maintainance after initial salvage therapy
• Median fu is 18 months
• 5 pts have durable response after 2 years
• Lenalidomide levels detected in ventricular CSF in 4 patients, 12-15 hours after a 20 mg dose
• Metabolomic profiling suggested CSF lactate correlated with response
Abstract 136
Phase 1/11 study of TEDDI-R in PCNSL

- Temazolomide, etoposdie, doxil, dex, ibrutinib and rituxin with IT cytarabine
- MTX excluded due to interaction with ibrutinib in vivo
Methods

- Untreated or R/R PCNSL
- Ibrutinib 560 mg PO daily for 14 days
- followed by brain MRI/PET
- Followed by DA-TEDDI-R every 21 days x 6 cycles
- Plasma and CSF PKs of Ibrutinib and its metabolite PCI-45227
Results

- 6 enrolled so far
- 6 completed ibrutinib
- 4 completed at least 2 cycles of chemo
- Pk in 4 patients have shown CSF penetration of Ibrutinib and its emtabolite
- Tumor improvement seen in 5/6 patients with Ibrutinib alone
Results and conclusions

- 51 (4%) developed CNS relapse at a median time of 9 months
- CI of CNS relapse at 2 years was
  - Low risk - 0.5%
  - Intermediate risk - 2.5%
  - High risk – 12.3% - (85/235 of high risk received CNS prophylaxis, IT alone 22%, systemic 31%, both 47%). Number of CNS events was the same with or without prophylaxis i.e 12%
Figure 1 Survival of all patients (A) and survival according to HSCT (B).

Jeeyun Lee, Wing-Yan Au, Min Jae Park, Junji Suzumiya, Shigeo Nakamura, Jun-Ichi Kameoka, Chikara Sakai, K...

**Autologous Hematopoietic Stem Cell Transplantation in Extranodal Natural Killer/T Cell Lymphoma: A Multinational, Multicenter, Matched Controlled Study**

Biology of Blood and Marrow Transplantation, Volume 14, Issue 12, 2008, 1356 - 1364

http://dx.doi.org/10.1016/j.bbmt.2008.09.014
Figure 2 A) OS according to HSCT in CR patients, B) Impact of HSCT on survival of the low NKIPI group (CR), C) Impact of HSCT on survival of the high NKIPI group (non-CR).

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http://dx.doi.org/10.1016/j.bbmt.2008.09.014
Figure 3 A) OS according to HSCT in non-CR patients, B) Impact of HSCT on survival of the low NKIPI group (non-CR), C) Impact of HSCT on survival of the high NKIPI group (non-CR).

Jeeyun Lee, Wing-Yan Au, Min Jae Park, Junji Suzumiya, Shigeo Nakamura, Jun-Ichi Kameoka, Chikara Sakai, K...

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(A) Therapy scheme of study I  (B) Therapy scheme of study II

**Abbreviations:** AraC, cytarabine; BCNU, carmustine; MTX, methotrexate; PBSCT, peripheral blood stem cell transplantation; TT, thiotepa; WBRT, whole brain radiotherapy
Overall survival entire cohort

- All patients (N=43)
- Received HCT-ASCT (N=34)
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>No of Pts</th>
<th>Induction treatment</th>
<th>ASCT conditioning</th>
<th>WBRT</th>
<th>Neurotoxicity</th>
<th>Median FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrey (2003)</td>
<td>28</td>
<td>MTX+AraC</td>
<td>BEAM</td>
<td>no</td>
<td>0%</td>
<td>28 mo</td>
</tr>
<tr>
<td>Cheng (2003)</td>
<td>7</td>
<td>MTX+AraC</td>
<td>TT/Bu/Cy</td>
<td>no</td>
<td>0%</td>
<td>24 mo</td>
</tr>
<tr>
<td>Brevet (2005)</td>
<td>6</td>
<td>MBVP+Ifo/AraC</td>
<td>BEAM</td>
<td>yes</td>
<td>30%</td>
<td>42 mo</td>
</tr>
<tr>
<td>Colombat (2006)</td>
<td>25</td>
<td>MBVP+Ifo/AraC</td>
<td>BEAM</td>
<td>yes</td>
<td>12%</td>
<td>34 mo</td>
</tr>
<tr>
<td>Illerhaus (2006)*</td>
<td>30</td>
<td>MTX+AraC/TT</td>
<td>BCNU/TT</td>
<td>yes</td>
<td>17%</td>
<td>140 mo</td>
</tr>
<tr>
<td>Montemurro (2007)</td>
<td>23</td>
<td>MTX</td>
<td>Bu/TT</td>
<td>no</td>
<td>40%</td>
<td>15 mo</td>
</tr>
<tr>
<td>Illerhaus (2008)*</td>
<td>13</td>
<td>MTX+AraC/TT</td>
<td>BCNU/TT</td>
<td>no</td>
<td>8%</td>
<td>72 mo</td>
</tr>
<tr>
<td>Yoon (2011)</td>
<td>11</td>
<td>MTX+AraC</td>
<td>BU/Cy/Eto</td>
<td>no</td>
<td>27%</td>
<td>10 mo</td>
</tr>
</tbody>
</table>

Abbreviations: ASCT, autologous stem cell transplantation; AraC, cytarabine; BCNU, carmustine; Bu, busulfan; Cy, cyclophosphamide; Eto, etoposide; Ifo, ifosfamide; MBVP, melphalan/busulfan/etoposide; MTX, melphalan; TT, total body irradiation; WBRT, whole brain radiotherapy.
Overall survival study I (N = 30).


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Overall survival study II (N = 3).


All patients (N=13)

Received HCT-ASCT (N=11)
Cumulative incidence rates of death due to primary central nervous system lymphoma with death due to other cause as competing risk in the per-protocol population (N = 34).


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Abstract 472 Phase I Study of Dose-Adjusted-Teddi-R with Ibrutinib in Untreated and Relapsed/Refractory Primary CNS Lymphoma
ASH 2015 abstracts PCNSL

• Abstract 472 Phase I Study of Dose-Adjusted-Teddi-R with Ibrutinib in Untreated and Relapsed/Refractory Primary CNS Lymphoma

  1. Paper: Phase II Study of Rituximab Given in Conjunction with Standard Chemotherapy in Primary Central Nervous System Lymphoma (PCNSL)[E1F05] [Annual Meeting Program including Abstracts] [Annual Meeting Abstracts]
  Type: Poster
  Date: Saturday, December 5, 2015
  Abstract Number: 1530
  Category: 624
  ... of Rituximab Given in Conjunction with Standard Chemotherapy in Primary Central Nervous System Lymphoma (PCNSL)[E1F05] Annual Meeting Program Information Saturday, December 5, 2015 ...
  Terms matched: 1

• 2. Paper: Genetic Basis of Primary Central Nervous System Lymphoma [Annual Meeting Program including Abstracts] [Annual Meeting Abstracts]
  Type: Poster
  Date: Sunday, December 6, 2015
  Abstract Number: 2687
  Category: 622
  ... Prefectural University of Medicine, Kyoto, Japan Introduction Primary central nervous system lymphoma (PCNSL) is a rare subtype of non-Hodgkin lymphoma, of which approximately 95% ...
  Terms matched: 1

• 3. Paper: Very High Efficiency of ICE (Ifosfamide-Carboplatin-Etoposide) in Relapse/Refractory (R/R) Primary Central Nervous System (PCNSL) and Vitreo-Retinal (VRL) Non Hodgkin Lymphoma. a LOC Network Multicenter Retrospective Study on 58 Cases [Annual Meeting Program including Abstracts] [Annual Meeting Abstracts]
  Type: Poster
  Date: Saturday, December 5, 2015
  Abstract Number: 1524
  Category: 623
  ... ) in Relapse/Refractory (R /R) Primary Central Nervous System (PCNSL) and Vitreo-Retinal (VRL) Non Hodgkin Lymphoma. a LOC Network Multicenter ...
  Terms matched: 1

• 4. Paper: Long Term Outcomes of Rituximab, Temozolamide, and High-Dose Methotrexate for Lymphoma Involving the Central Nervous System [Annual Meeting Program including Abstracts] [Annual Meeting Abstracts]
  Type: Poster
  Date: Sunday, December 6, 2015
  Abstract Number: 2701
  Category: 623
  Abstract 2701: Category 623. Lymphoma: Chemotherapy, excluding Pre-Clinical Models: Poster II - Sunday, December 6, 2015, 6:00 PM-8:00 PM: Oral and Poster Abstracts; 623. Lymphoma: Chemotherapy, excluding Pre-Clinical Models: Poster II
  ... PA Background Management of patients (pts) with primary central nervous system lymphoma (PCNSL) and those with secondary CNS involvement by diffuse large B cell lymphoma ( ... Terms matched: 1

• 5. Paper: Combination of Rituximab with Chemotherapy Improved Outcome of Newly Diagnosed Primary CNS Lymphoma: A Retrospective Study of 209 Unselected Patients Referred to a Single Institution [Annual Meeting Program including Abstracts] [Annual Meeting Abstracts]
  Type: Poster
11. Paper: Expression of B and T Lymphocyte Attenuator (BTLA) Correlates with CNS Metastasis and Adverse Prognosis in Activated B-Cell Lymphoma and Acute Lymphoblastic Leukemia

Paper: Expression of B and T Lymphocyte Attenuator (BTLA) Correlates with CNS Metastasis and Adverse Prognosis in Activated B-Cell Lymphoma and Acute Lymphoblastic Leukemia

Type: Poster
Date: Monday, December 7, 2015
Abstract Number: 3900
Category: 622
... types of lymphoid neoplasms: large B-cell lymphoma, primary central nervous system lymphoma (PCNSL, DLBCL) and ALL. Methods. We used a variety of approaches ...
Terms matched: 1

12. Paper: To Dose or Not to Dose: Are IL-10 and IL-6 Accurate Biomarkers to Detect Leptomeningeal Involvement in Small B-Cell Lymphoproliferation

Paper: To Dose or Not to Dose: Are IL-10 and IL-6 Accurate Biomarkers to Detect Leptomeningeal Involvement in Small B-Cell Lymphoproliferation?

Type: Poster
Date: Monday, December 7, 2015
Abstract Number: 3878
Category: 622
... described in primary vitreoretinal lymphomas and more recently in primary central nervous system lymphoma (PCNSL). Two patients displayed a ratio >1; one had WM transformed ...
Terms matched: 1


Paper: Outcomes of Pharmacokinetically (PK) Directed Busulfan in Combination with Thiotepa & Cyclophosphamide (TBC) Conditioning with HDT-ASCT in Patients with Primary & Secondary CNS Lymphoma

Type: Poster
Date: Saturday, December 5, 2015
Abstract Number: 1994
Category: 731
... conditioning is effective consolidation for patients with newly diagnosed& relapsed/refractory primary (PCNSL) or secondary CNS (SCNSL) lymphoma. A prospective study by Omuro ...
Terms matched: 1

14. Paper: Inhibition of Hedgehog Signaling for the Treatment of Lymphoma and CLL: A Phase II Study from the Lysa

Paper: Inhibition of Hedgehog Signaling for the Treatment of Lymphoma and CLL: A Phase II Study from the Lysa

Type: Poster
Date: Monday, December 7, 2015
Abstract Number: 3970
Category: 624
Abstract 3970: Category 624. Lymphoma: Therapy with Biologic Agents, excluding Pre-Clinical Models: Poster III - Monday, December 7, 2015, 6:00 PM-8:00 PM: Oral and Poster Abstracts; 624. Lymphoma: Therapy with Biologic Agents, excluding Pre-Clinical Models: Poster III
... , indolent lymphoma (iNHL, N=6 ), primary CNS lymphoma (PCNSL, N=10) and chronic lymphocytic leukemia (CLL, N= ...
Terms matched: 1

15. Author Index G

Author Index G

... ) in Relapse/Refractory (R /R) Primary Central Nervous System (PCNSL) and Vitreo-Retinal (VRL) Non Hodgkin Lymphoma. a LOC Network Multicenter ...
Terms matched: 1

16. Author Index S

Author Index S

... of Rituximab Given in Conjunction with Standard Chemotherapy in Primary Central Nervous System Lymphoma (PCNSL) [E1F05] Schiffer, Charles Wayne State University, Detroit, MI
Terms matched: 1
Type: Poster
Date: Saturday, December 5, 2015
Category: 624
Saturday, December 5, 2015: 5:30 PM-7:30 PM; Oral and Poster Abstracts; Category 624. Lymphoma: Therapy with Biologic Agents, excluding Pre-Clinical Models
... of Rituximab Given in Conjunction with Standard Chemotherapy in Primary Central Nervous System Lymphoma (PCNSL)[E1F05] Lode J. Swinnen, MBChB1, Anne O'Neill2* ...
Terms matched: 1
... ) in Relapse/Refractory (R /R) Primary Central Nervous System (PCNSL) and Vitreo-Retinal (VRL) Non Hodgkin Lymphoma. a LOC Network Multicenter ...
Terms matched: 1
Type: Poster
Date: Saturday, December 5, 2015
Category: 623
Saturday, December 5, 2015: 5:30 PM-7:30 PM; Oral and Poster Abstracts; Category 623. Lymphoma: Chemotherapy, excluding Pre-Clinical Models
... ) in Relapse/Refractory (R /R) Primary Central Nervous System (PCNSL) and Vitreo-Retinal (VRL) Non Hodgkin Lymphoma. a LOC Network Multicenter ...
Terms matched: 1
24. Author Index L [Annual Meeting Program including Abstracts] [Annual Meeting Abstracts]
... ) in Relapse/Refractory (R /R) Primary Central Nervous System (PCNSL) and Vitreo-Retinal (VRL) Non Hodgkin Lymphoma. a LOC Network Multicenter ...
Terms matched: 1
25. Author Index O [Annual Meeting Program including Abstracts] [Annual Meeting Abstracts]
... of Rituximab Given in Conjunction with Standard Chemotherapy in Primary Central Nervous System Lymphoma (PCNSL)[E1F05] O'Neill, David Fight Against Cancer Innovation Trust, Toronto ...
Terms matched: 1
26. Author Index I [Annual Meeting Program including Abstracts] [Annual Meeting Abstracts]
... of Rituximab Given in Conjunction with Standard Chemotherapy in Primary Central Nervous System Lymphoma (PCNSL)[E1F05] In het Panhuis, Leslie Maastricht University Medical Center, ...
Terms matched: 1
27. Author Index A [Annual Meeting Program including Abstracts] [Annual Meeting Abstracts]
... of Rituximab Given in Conjunction with Standard Chemotherapy in Primary Central Nervous System Lymphoma (PCNSL)[E1F05] 1536- Phase I/II Clinical Trial of CpG-Activated ...
Terms matched: 1
28. Author Index D [Annual Meeting Program including Abstracts] [Annual Meeting Abstracts]
... of Rituximab Given in Conjunction with Standard Chemotherapy in Primary Central Nervous System Lymphoma (PCNSL)[E1F05] Dunbar, Martin AbbVie Inc., North Chicago, ...
Terms matched: 1
29. Author Index K [Annual Meeting Program including Abstracts] [Annual Meeting Abstracts]
... of Rituximab Given in Conjunction with Standard Chemotherapy in Primary Central Nervous System Lymphoma (PCNSL)[E1F05] Kleine, Moritz Hannover Medical School, Hannover, Germany ...
Terms matched: 1
30. Author Index R [Annual Meeting Program including Abstracts] [Annual Meeting Abstracts]
... ) in Relapse/Refractory (R /R) Primary Central Nervous System (PCNSL) and Vitreo-Retinal (VRL) Non Hodgkin Lymphoma. a LOC Network Multicenter ...
Terms matched: 1
Ibrutinib is an inhibitor of BTK that targets BCR signaling and is active in patients with relapsed/refractory (R/R) ABC DLBCL. **Methods:** Ibrutinib was incorporated into a novel regimen called DA-TEDDI-R (temozolomide, etoposide, doxil, dexamethasone, ibrutinib and rituximab) (with intraventricular cytarabine). DA-TEDDI-R was designed around therapeutic principles for systemic DLBCL and CNS penetration. Methotrexate was excluded due to potential antagonism with ibrutinib based on preliminary in vitro experiments. Untreated or R/R PCNSL patients were eligible and received ibrutinib in cohorts (560-1120 mg/day PO) for 14-days in a “window” prior to cycle 1 of DA-TEDDI-R (with pre and post-brain MRI/FDG-PET), followed by DA-TEDDI-R with ibrutinib (days 1-10) q21 days x 6. Plasma and CSF PKs of ibrutinib and its metabolite PCI-45227 were analyzed. CSF penetration (AUC\textsubscript{CSF}: AUC\textsubscript{PLASMA}) was corrected for human plasma protein binding: parent: 97.3%, metabolite: 91%. CSF PKs of TEDDI drugs and molecular analysis of FFPE biopsies are ongoing. **Results:** Eleven patients have enrolled; 6 were R/R (median 3 (1-5) prior treatments) and 5
Protocol schema.

Remission Induction Therapy: MT-R (14-day cycle)
- Day 1: Methotrexate 8 grams/m² IV over 4 hrs
- Day 2: Leucovorin 100 mg/m² every 6 hrs, until methotrexate < 0.05 mM
- Day 3: Rituximab 375 mg/m² IV cycles 1 through 6
- Day 7-11: Temozolomide 150 mg/m² PO (odd cycles only)

Consolidation Therapy: EA
- Day 1-4: Etoposide 40 mg/kg continuous IV over 96 hrs
- Day 1-4: Cytarabine 2 gm/m² IV over 2 hrs every 12 hrs × 8 doses

James L. Rubenstein et al. JCO 2013;31:3061-3068
Outcome for all 50202 study patients; y-axis refers to cumulative probability of event.

James L. Rubenstein et al. JCO 2013;31:3061-3068
Clinical prognostic variables and their relationship to progression-free survival (PFS); median PFS survival was 2.4 years (22 patients who experienced disease progression plus two patients achieving complete response who succumbed to sepsis and lung cancer...
BCL6 expression is associated with short time to progression (TTP) and overall survival (OS) in patients with primary CNS lymphoma (PCNSL) treated in the 50202 study.

James L. Rubenstein et al. JCO 2013;31:3061-3068