Pediatric Lymphoma
Role of Targeted Therapy??

Piti Techavichit, MD
Division of Hematology and Oncology
Department of Pediatrics
Faculty of Medicine
Chulalongkorn University
Outline

• Introduction: Pediatric lymphoma
  • Classification and current standard of care
• Targeted therapy in Pediatric lymphoma
  • Targeting CD20
  • Targeting CD30
  • Inhibition of the Anaplastic Lymphoma Kinase (ALK)
Age-adjusted incidence rates for childhood cancer by ICCC Group, 2003-2005

NHL=199, HD 67 (3:1)

Total 2,792 cases  Age<15 yrs, Both Sexes

## Pediatric Non-Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Adult</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Low-or intermediate grade disease</td>
<td>• High-grade tumors</td>
</tr>
<tr>
<td>• Usually present with lymph node disease</td>
<td>• Present with extranodal diseases</td>
</tr>
<tr>
<td></td>
<td>• Most common sites of disease: abdomen, mediastinum, and neck</td>
</tr>
</tbody>
</table>
NHL Cellular Classifications:

Age 0-14 yr.

- Burkitt: 38%
- Follicular: 1%
- DLBCL: 20%
- ALCL: 10%
- Lymphoblastic: 29%
- Other: 2%

Age 15-19 yr.

- Burkitt’s: 21%
- DLBCL: 37%
- Other: 6%
- Lymphoblastic: 19%
- ALCL: 17%

ThaiPOG treatment schema for NHL

NHL

Mature B cell lymphoma
- DLBCL
- Burkitt lymphoma

Anaplastic large cell lymphoma

Lymphoblastic lymphoma

Treated as ALL

LR
ThaiPOG-NHL-13-BL-LR
SR
ThaiPOG-NHL-13-BL-SR
HR
ThaiPOG-NHL-13-BL-HR

LR
ThaiPOG-NHL-13-ALCL-LR
SR
ThaiPOG-NHL-13-ALCL-SR
HR
ThaiPOG-NHL-13-ALCL-HR
Mature B cell lymphoma

• Burkitt Lymphoma (BL)
  • Express surface Ig
  • Translocation \textit{cMYC} oncogene 8q24; t(8;14) t(2;8) t(8;22)
  • Ki-67 fraction $>$ 99%

• Diffuse Large B-Cell Lymphoma (DLBCL)
  • Germinal center phenotype is more common
  • Presents with a rapidly enlarging mass and usually an advanced stage
  • Treatment in children is identical to BL

• LNs below diaphragm, abdominal mass, ascites or head/neck (jaw mass, orbital swelling), CNS involvement, tumor lysis syndrome.
Mature B cell lymphoma
ThaiPOG protocol 2013

Risk stratification

| Low Risk | Completely resected stage I or completely resected abdominal stage II lesions. |
| Standard Risk | All cases not eligible for low or high risk. (Murphy Stage III and non-CNS Stage IV) |
| High Risk | Any CNS involvement and/or bone marrow involvement. |
| | CNS involvement is defined by one or more of the following: |
| | (1) Any L3 blasts in CSF |
| | (2) Cranial nerve palsy (if not explained by extracranial tumor) |
| | (3) Clinical spinal cord compression |
| | (4) Isolated intracerebral mass |
| | (5) Parameningeal extension: cranial and/or spinal |

- Treatment of nonlocalized disease involves
  - Short, intense blocks of chemotherapy and CNS prophylaxis
### Treatment plan

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Pre-Phase</th>
<th>Induction X2</th>
<th>Consolidation X2</th>
<th>Continuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>-</td>
<td>COPAD</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Standard risk</td>
<td>COP</td>
<td>COPAD-M3</td>
<td>CYM</td>
<td>-</td>
</tr>
<tr>
<td>High risk</td>
<td>COP</td>
<td>COPAD-M8</td>
<td>CYVE</td>
<td>Seq. No 1, 2, 3, 4</td>
</tr>
</tbody>
</table>

- **COP;** CTX/ VCR/ Pred + IT MHA
- **COPAD;** CTX/ VCR/ Pred/ Doxo
- **COPAD-M3;** CTX/ VCR/ Pred/ ADR/ MTX3 + IT MH
- **COPAD-M8;** CTX/ VCR/ Pred/ ADR/ MTX8 + IT MHA
- **CYM;** Cytarabine/ MTX3 + IT MHA
- **CYVE;** Cytarabine/ HC-AraC/ Eto
- **SR and HR;** + **Rituximab for CD20** during induction and consolidation

### Continuation

1. **COPAD-M8 = CTX/ VCR/ Pred/ ADR/ MTX8 + IT MHA**
2. **CYE = Cytarabine/ Eto + IT MHA**
3. **COPAD = CTX/ VCR/ Pred/ Doxo + IT MHA**
4. **CYE = Cytarabine/ Eto + IT MHA**

ThaiPOG protocol 2013
Anaplastic Large Cell Lymphoma

- Express T-cell antigens or can possess a null cell phenotype
- CD30 (Ki-1) positivity is the immunophenotypic hallmark.
- > 90% of pediatric ALCL contain ALK protein gene rearrangements → overexpression of ALK
- Lacking ALK expression are associated with a worse prognosis except subgroup of cutaneous CD30+ ALCL, which characteristically lack ALK expression → carry a favorable prognosis
- Most often presents in peripheral, intrathoracic, or intra-abdominal LNs
- Bone involvement is common (sometimes be the primary site of disease)
## Anaplastic Large Cell Lymphoma

### Risk stratification

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Stage I disease completely resected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard Risk</strong></td>
<td>No skin involvement</td>
</tr>
<tr>
<td></td>
<td>No mediastinal involvement</td>
</tr>
<tr>
<td></td>
<td>No liver, spleen or lung involvement</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td>Includes patients with any of the following features:</td>
</tr>
<tr>
<td></td>
<td>Presence of biopsy proven skin lesions (except skin lesions overlying an involved node or isolated skin disease*)</td>
</tr>
<tr>
<td></td>
<td>Presence of mediastinal involvement</td>
</tr>
<tr>
<td></td>
<td>Presence of liver (liver enlargement $\geq 5$ cm and / or nodular liver), spleen (spleen enlargement and / or nodular spleen) or lung involvement (biopsy is not necessary for obvious lesions)</td>
</tr>
</tbody>
</table>

*Isolated skin lesions is not considered a high risk factor.*
<table>
<thead>
<tr>
<th>Risk group</th>
<th>Pre-Phase</th>
<th>Intensive phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>COP</td>
<td>A1 → B1 → A2</td>
</tr>
<tr>
<td>Standard risk</td>
<td>COP</td>
<td>A1 → B1 → A2 → B2 → A3 → B3</td>
</tr>
<tr>
<td>High risk</td>
<td>COP</td>
<td>AM1 → BM1 → AM2 → BM2 → AM3 → BM3</td>
</tr>
</tbody>
</table>

- COP = CTX/ VCR/ Pred
- A = Dexa/ MTX1/ Ifos/ Cytarabine/ Eto + IT MHA
- B = Dexa/ MTX1/ CTX/ ADR + IT MHA
- AM = Dexa/ MTX3/ Ifos/ Cytarabine/ Eto
- BM = Dexa/ MTX3/ CTX/ ADR

ThaiPOG protocol 2013
Precursor (Lymphoblastic) Lymphomas

- Share biologic features with ALL with different presentations
- Precursor T-LBL (85-90%) is more common than precursor B-LBL (10-15%)
  - T-cell LBL: 70% present with a mediastinal mass +/- BM involvement
  - B-cell LBL: commonly present as localized disease of bone, LNs, and skin
- The standard of care for
  - Localized stage I, II Modified CHOP regimen + MT total duration 9 months
  - Advanced stage III, IV High risk ALL regimen total duration 38 months
Hodgkin Lymphoma

- Origin from Reed-Sternberg cells
- Bimodal distribution Older child & adolescent and adult age > 50 yrs.
- M:F = 2:1-3:1

Histological Classification of Hodgkin Lymphoma (HL) According to the WHO Classification

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>LCA (CD45)</th>
<th>PAX5</th>
<th>CD30 (Ki-1)</th>
<th>CD20</th>
<th>CD3</th>
<th>ALK</th>
<th>Growth Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>cHL, HRS cell</td>
<td>-</td>
<td>+ dim</td>
<td>+</td>
<td>–/+</td>
<td>–</td>
<td>–</td>
<td>Nodular, diffuse</td>
</tr>
<tr>
<td>nLPHL, L&amp;H cell</td>
<td>+</td>
<td>+ dim</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Nodular +/- diffuse</td>
</tr>
</tbody>
</table>
Hodgkin disease

Risk stratification

<table>
<thead>
<tr>
<th>Low risk (LR)</th>
<th>Intermediate Risk (IR)</th>
<th>High Risk (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I-A with no bulk</td>
<td>Stage I-E, I-B and I-A with bulk</td>
<td>Stage III-B</td>
</tr>
<tr>
<td>Stage II-A with no bulk</td>
<td>Stage II-E, II-B and II-A with bulk</td>
<td>Stage IV-B</td>
</tr>
<tr>
<td></td>
<td>Stage III-A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage IV-A</td>
<td></td>
</tr>
</tbody>
</table>

Treatment schema

- **Low risk**
  - ABVE x 2 cycle
  - CT/PET/Gal
    - CR (RER)
  - ABVE x 2 cycle
  - CT/PET/Gal
    - CR
    - IFRT
    - Follow up

- **Intermediate risk**
  - ABVE-PC x 2 cycle
  - CT/PET/Gal
    - PR/SD (SER)
    - ABVE x 2 cycle
    - CT/PET/Gal
    - CR
    - PR/SD/PR*:
      - disease reassessment
    - PD
    - Salvage protocol
    - PR
    - IFRT
    - Follow up

- **High risk**
  - CT/PET/Gal
  - PR/SD (SER)
  - MIEG x 2 cycle
  - ABVE-PC x 2 cycle
  - CT/PET/Gal
  - CR (RER)
  - ABVE-PC x 2 cycle
  - SD/PR/CRT
  - Follow up
  - CR

*PR/SD: disease reassessment
*PD patient: salvage therapy

ThaiPOG protocol 2013
### Hodgkin disease

#### Risk stratification

<table>
<thead>
<tr>
<th>Low risk (LR)</th>
<th>Intermediate Risk (IR)</th>
<th>High Risk (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I-A with no bulk</td>
<td>Stage I-E, I-B and I-A with bulk</td>
<td>Stage III-B</td>
</tr>
<tr>
<td>Stage II-A with no bulk</td>
<td>Stage II-E, II-B and II-A with bulk</td>
<td>Stage IV-B</td>
</tr>
<tr>
<td></td>
<td>Stage III-A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage IV-A</td>
<td></td>
</tr>
</tbody>
</table>

#### Treatment schema for ThaiPOG-HOD-1803

- **Hodgkin disease**
  - **I-II**
    - **ABVD x 4**
      - **CR**
        - IFRT
      - **PR**
        - **ABVD x 2 + IFRT**
  - **III-IV**
    - **ABVD x 4**
      - **CR**
        - **ABVD x 2 + IFRT**
      - **PR**
        - **ABVD x 4 + IFRT**

ThaiPOG protocol 2013
5-yr OS of lymphoma patients by type

5-yr OS for lymphoma: 59.5% (95%CI: 53.0% - 65.4%)

### Characteristics and Results of Main Studies in Childhood (18 years of age) B-Cell Lymphoma

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Study Groups</th>
<th>Randomization</th>
<th>Criteria for Stratification and Risk Groups</th>
<th>No. of Patients (%)</th>
<th>No. of 3- or 5-Year EFS (%)</th>
<th>No. of Courses</th>
<th>CNS Prophylaxis MTX (g/m²) and Infusion Duration</th>
<th>TD Cyclophosphamide (g/m²)</th>
<th>TD Ifosfamide (g/m²)</th>
<th>TD Doxorubicin (mg/m²)</th>
<th>TD Etoposide (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMB89</td>
<td>SFOP</td>
<td>No</td>
<td>Stage, resection, CNS, response at day 7</td>
<td>581</td>
<td>91%</td>
<td>2</td>
<td>No</td>
<td>3</td>
<td>120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A: stage I and II resected</td>
<td>52 (9%)</td>
<td>98%</td>
<td>5</td>
<td>5 HDMTX = 3 g/m² (3 hours), 10 DIT</td>
<td>5.3</td>
<td>180</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B: not A not C</td>
<td>386 (69%)</td>
<td>92%</td>
<td>8</td>
<td>5 HDMTX = 8 g/m² (4 hours), 2</td>
<td>6.8</td>
<td>240</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: CNS involvement and/or BM &gt; 70%</td>
<td>123 (22%)</td>
<td>84%</td>
<td>8</td>
<td>HDAre-C (CYVE), 10 TIT</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(no CNS involvement, 90%; CNS involvement, 79%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAB/LMB95</td>
<td>SFOP</td>
<td>Yes</td>
<td>Idem LMB89</td>
<td>1,111</td>
<td>88%</td>
<td>2</td>
<td>No</td>
<td>3</td>
<td>120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A: idem LMB89</td>
<td>132 (12%)</td>
<td>99%</td>
<td>4</td>
<td>Idem LMB89</td>
<td>3.3*</td>
<td>120*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B: not A not C</td>
<td>744 (67%)</td>
<td>89%</td>
<td>8</td>
<td>Idem LMB89</td>
<td>6.8*</td>
<td>240*</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: CNS involvement, BM &gt; 25%</td>
<td>235 (21%)</td>
<td>79%</td>
<td>8</td>
<td>Idem LMB89</td>
<td>6.8*</td>
<td>240*</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>UKCCSG</td>
<td>Yes</td>
<td>Resection, site, LDH (500 IU/L), BM, CNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R1: complete resection</td>
<td>71 (17%)</td>
<td>100%</td>
<td>2</td>
<td>MTX 0.5 g/m² (24 hours), 3 TIT</td>
<td>2</td>
<td>4</td>
<td>50</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R2: extra-abdominal only or abdominal and LDH &lt; 500 IU/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BFM</td>
<td>No</td>
<td>Resection, site, LDH (500 IU/L), BM, CNS</td>
<td>413</td>
<td>88%</td>
<td>2</td>
<td>MTX 0.5 g/m² (24 hours), 3 TIT</td>
<td>2</td>
<td>4</td>
<td>50</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Random: HDMTX 4 h v 24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes R1: stage I and II resected</td>
<td>48 (10%)</td>
<td>94%</td>
<td>4</td>
<td>HDMTX 5 g/m² (24 hours), 1 TIT</td>
<td>2.4</td>
<td>8</td>
<td>100</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes R2: stage I and II resected, stage III and LDH &lt; 500 IU/L</td>
<td>233 (46%)</td>
<td>94%</td>
<td>4</td>
<td>HDMTX 5 g/m² (24 hours), 1 TIT</td>
<td>2.4</td>
<td>8</td>
<td>100</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes R3: stage III and LDH &lt; 1,000 IU/L, stage IV/blast, and LDH &lt; 1,000 IU/L</td>
<td>82 (16%)</td>
<td>85%</td>
<td>5</td>
<td>HDMTX 5 g/m² (24 hours), 1 TIT</td>
<td>2.4</td>
<td>8</td>
<td>100</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes R4: LDH &gt; 1,000 IU/L, CNS involvement</td>
<td>142 (28%)</td>
<td>81%</td>
<td>6</td>
<td>HDMTX 5 g/m² (24 hours), 1 TIT</td>
<td>2.4</td>
<td>8</td>
<td>100</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-NHL03</td>
<td>JPLSG</td>
<td>No</td>
<td>Stage, resection, BM, CNS</td>
<td>321</td>
<td>87%</td>
<td>6</td>
<td>2 DIT</td>
<td>1.5</td>
<td>120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G1: stage I and II resected</td>
<td>17</td>
<td>84%</td>
<td>6</td>
<td>2 DIT, 2 DIT, 2 HDMTX 3 g/m² (24 hours)</td>
<td>1.5</td>
<td>120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G2:stage I and II nonresected</td>
<td>103</td>
<td>99%</td>
<td>6</td>
<td>2 DIT, 2 DIT, 2 HDMTX 3 g/m² (24 hours)</td>
<td>1.5</td>
<td>120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G3: stage III and IV, no CNS involvement</td>
<td>111</td>
<td>84%</td>
<td>6</td>
<td>2 DIT, 2 DIT, 2 HDMTX 3 g/m² (24 hours)</td>
<td>3</td>
<td>240</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G4: stage IV, CNS involvement, and B-AL</td>
<td>90</td>
<td>78%</td>
<td>6</td>
<td>2 DIT, 2 DIT, 2 HDMTX 3 g/m² (24 hours)</td>
<td>5.5</td>
<td>240</td>
<td>0.9</td>
<td>0</td>
</tr>
</tbody>
</table>

Notes:
- TD: Treatment Duration
- MTX: Methotrexate
- HDMTX: High-Dose Methotrexate
- HDAre-C: High-Dose Ara-C
- CYVE: Cyclophosphamide, Ifosfamide, Etoposide, and Vincristine
## Results of the Main Series of Pediatric ALCL

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Study Group and Period of Study</th>
<th>Treatment Strategy</th>
<th>Treatment Duration (months)</th>
<th>No. of Patients</th>
<th>3- to 5-Year EFS (%)</th>
<th>3- to 5-Year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HM89-9172</td>
<td>SFOP, 1989-1997</td>
<td>B-cell regimen (COPADM + maintenance)</td>
<td>7-8</td>
<td>82</td>
<td>66</td>
<td>83</td>
</tr>
<tr>
<td>NHL-BFM9074</td>
<td>BFM, 1990-1995</td>
<td>B-cell regimen (BFM-B)</td>
<td>2-5</td>
<td>89</td>
<td>76</td>
<td>—</td>
</tr>
<tr>
<td>NHL 9000 and 960275</td>
<td>UKCCSG, 1990-1998</td>
<td>B-cell regimen (LMB)</td>
<td>4-5</td>
<td>72</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>LNH9276</td>
<td>AEIOP, 1993-1997</td>
<td>T-cell regimen</td>
<td>24</td>
<td>34</td>
<td>65</td>
<td>85</td>
</tr>
<tr>
<td>POG931578</td>
<td>POG, 1994-2000</td>
<td>APO + randomization of HDMTX and HD Ara-C</td>
<td>12</td>
<td>86</td>
<td>72</td>
<td>88</td>
</tr>
<tr>
<td>CCG94173</td>
<td>CCG, 1996-2001</td>
<td>Compressed T-cell regimen</td>
<td>11</td>
<td>86</td>
<td>68</td>
<td>80</td>
</tr>
<tr>
<td>ALCL9973,80</td>
<td>EICNH, 1999-2006</td>
<td>B-cell regimen (BFM-B) + randomization of vinblastine</td>
<td>4-12</td>
<td>352</td>
<td>73</td>
<td>92</td>
</tr>
<tr>
<td>ANHL013179</td>
<td>COG, 2004-2008</td>
<td>APO + randomization of vinblastine</td>
<td>12</td>
<td>125</td>
<td>74</td>
<td>84</td>
</tr>
</tbody>
</table>
Case presentation

• A nine-old boy presented with weight loss and abdominal mass.
  • CT chest and whole abdomen: large mass at bowel with chronic intussusception, mesenteric lymphadenopathy with hepatosplenomegaly.
  • BM examination: L3 type large blasts with vacuoles ~70-80%
    • CD20+, CD10+, BCL6+/-, MUM1-, EBER-, Tdt-, CD34-, Ki67+ >99%
  • Bone scan: active bone lesion at left parietal bone
  • Diagnosis: Burkitt leukemia
**High Risk: Induction (COPADM8 course 1)**

COPADM8 course 1 should start on day 6 of COP pre-phase therapy, as long as clinical condition permits. Please note that COPADM8 course 1 and 2 are different.

<table>
<thead>
<tr>
<th>Days</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucovorin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple-IT</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G-CSF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Rituximab</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Given dose/day**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>2 mg/m² (max dose 2 mg) IV bolus</td>
<td>1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>80 mg/m²/day (divided into bid doses) orally</td>
<td>1-7</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>8,000 mg/m² IV infusion over 4 hours</td>
<td>1</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>15 mg/m² PO or IV q 6 hours for a total of 12 doses (or as required)</td>
<td>2-4</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>250 mg/m²/dose IV drip in 15 minutes q 12 hr (6 doses). The first dose is given before start of the doxorubicin infusion. Continue hydration until 12 hours after the last dose of cyclophosphamide.</td>
<td>2-4</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>60 mg/m² IV drip in 6 hours, start after the first dose of cyclophosphamide.</td>
<td>2</td>
</tr>
<tr>
<td>IT medications</td>
<td>Methotrexate, cytarabine, and hydrocortisone IT. Administer Day 2 IT at 12 - 24 hours after HDXT starts and before leucovorin rescue begins. (See Intrathecal Treatment for dosing)</td>
<td>2,4,6</td>
</tr>
<tr>
<td>G-CSF</td>
<td>5 mcg/kg/day subcutaneously, G-CSF should be discontinued when the post nadir ANC reaches 2,000/mm³ even if prior to Day 21.</td>
<td>7-21</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m² dose for CD20+ B-lymphoma only. Carriers of hepatitis B should be closely monitored for active HBV infection and for signs of hepatitis.</td>
<td>1</td>
</tr>
</tbody>
</table>
Pediatric Lymphoma

Role of Targeted Therapy??

• Targeting CD20
• Targeting CD30
• Inhibition of the Anaplastic Lymphoma Kinase (ALK)
• Other targeted therapies
  • Programmed Cell Death Protein 1 (PD-1) and PD-1 Ligand (PD-L1) Inhibition
  • Targeting molecular pathway
  • Epigenetic treatment options
  • Targeted T-Cell Therapies
Targeting CD20

- Rituximab, a chimeric anti-CD20 mAb
- The first mAb approved for the treatment of adult B-NHL, and has become standard of care.
- CD20+ in 100% of the pediatric BL and 98% of DLBCL
- In children, rituximab was initially used in post-transplant lymphoproliferative disease (PTLD).

A Study of Rituximab and Ifosfamide, Carboplatin, and Etoposide Chemotherapy in Children with Recurrent/Refractory B-Cell (CD20+) Non-Hodgkin Lymphoma and Mature B-Cell Acute Lymphoblastic Leukemia: A Report From the Children’s Oncology Group

- Phase II pilot COG study, ANHL 0121
- Patients received rituximab and ICE for 3 cycles
  - Rituximab (375 mg/m2) was given on day -2 and 3 of ICE
- 6 with r/r DLBCL, 3 achieved CR (1 SD and 2 PD)
- 14 with r/r BL, 4 achieved CR (5 PR, 1 SD and 5 PD)

CR/PR = 12/20 (60%)
3-yr OS – 37.5%

CCG 5921 DECAL for r/r lymphoma
5-yr EFS 23%, OS 29%

(DECAL) Dexamethasone, etoposide, cisplatin, high-dose cytarabine, and L-asparaginase


Study to examine activity and tolerability of rituximab in newly diagnosed pediatric B-NHL.

- 136 patients were enrolled from 42 centers. (2004-2008), BFM group
- Patients not receive any chemotherapy and/or corticosteroids during the window, except for (1) intrathecal (IT) therapy on days 1 and 3 for CNS- positive only.
- Responders had > 25% decrease of at least one lesion or BM or PB blasts and no disease progress at other sites.

Phase II Window Study on Rituximab in Newly Diagnosed Pediatric Mature B-Cell Non-Hodgkin’s Lymphoma and Burkitt Leukemia

- Toxicity Criteria 3/4 toxicities attributable to rituximab
  - Fatigue, 13%; anaphylaxis, 7%; infection, 3%
  - No capillary leakage; and no toxic death.
- 82 evaluable patients, 34 were responders
  (Response rate, 41.4%; 95% CI, 31%-52%)
  - 27 of 67 with BL and 7 of 15 with DLBCL
  - A response was more frequently observed in BM compared with solid tumor lesions (P .007)
Rituximab and FAB/LMB 96 chemotherapy in children with Stage III/IV B-cell non-Hodgkin lymphoma: a Children’s Oncology Group report

- COG ANHL01P1
- Newly diagnosed Intermediate risk- CD20 positive, mature B-cell lymphoma
- 45 patients were included during 2004-2006
  - BL 56%
  - DLBCL 22%
  - Mediastinal primary B-cell lymphoma 9%
- Dose-dense rituximab therapy can be safely added to chemotherapy

Rituximab with chemotherapy in children and adolescents with central nervous system and/or bone marrow-positive Burkitt lymphoma/leukaemia: a Children’s Oncology Group Report

- COG ANHL01P1
- 40 patients with HR-BL
- The incidence of grade III/IV mucositis during induction cycles was 31% and 26% respectively.
- Two toxic death during induction
- The 3-year event-free survival (EFS)/overall survival (OS)
  - 90% (95% CI, 76–96%) in entire cohort
  - 93% (95% CI, 61–99%) in CNS+ disease.
- Rituximab can be safely added to the FAB/LMB 96 chemotherapy to B-NHL

Results of the randomized Intergroup trial Inter-B-NHL Ritux 2010 for children and adolescents with high-risk B-cell non-Hodgkin lymphoma (B-NHL) and mature acute leukemia (B-AL): Evaluation of rituximab (R) efficacy in addition to standard LMB chemotherapy

- Presented in ASCO and SIOP meeting 2016.
- Phase III trial sponsored by Gustave Roussy and COG
- Compared the standard LMB CT to the same CT+R in pts < 18 years with high risk B-NHL (stage III with LDH level > 2N, stage IV) and B-AL.
- Rituximab was given (375 mg/m²) in total of 6 infusions (day 1-2)
- The first interim analysis was done in Aug 2015
  - 27 events (37.5% information) occurring in 310 pts (155/arm) randomized since Dec 2011.
- 85% with Burkitt lymphoma (51% were in group B, 39% in C1 and 10% in C3)

Minard-Colin V, et al. JCO 2016 (abstr);34:10507.
Results of the randomized Intergroup trial Inter-B-NHL Ritux 2010 for children and adolescents with high-risk B-cell non-Hodgkin lymphoma (B-NHL) and mature acute leukemia (B-AL): Evaluation of rituximab (R) efficacy in addition to standard LMB chemotherapy

• Median follow-up of 11.5 months
• Patients on the R arm achieved better EFS than control arm
• 1-year EFS (95%CI) 94.2% (88.5-97.2) vs. 81.5% (73.0-87.8)
• The HR was 0.33 (90%CI: 0.16-0.69), one-sided p-value = 0.006.
• The conditional power analysis demonstrated high likelihood of getting a positive study in later interim/final analyses.
• The randomization was stopped in Nov 2015.

Conclusions: Rituximab in addition to standard LMB therapy improves EFS of children/adolescents with high risk B-NHL

Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma

Phase 2, prospective study of infusional dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R) and filgrastim without radiotherapy in 51 adult with PMBL

- Median of 5 years of follow-up, the EFS was 93%, and the OS was 97%.
- Therapy with DA-EPOCH-R obviated the need for radiotherapy in patients with PMBL

The biologic characteristics of the PMBL in children are similar to adults.

Current regimens for pediatric B-NHL had limited efficacy in the treatment of PMBL.

NHL-BFM study recommended DA-EPOCH-R for children and adolescents with PMBL.

Between 2010 and May 2012, a total of 15 patients diagnosed with PMBCL were treated with DA-EPOCH-R.

Median age: 16 years (11.5 - 17.8), median follow up: 19.2 months (9.6 - 28.8).

The mean (±SD) 2 years event-free and overall survival rates at were both 92±8%.

Observation confirms the efficacy of DA-EPOCH-R in the treatment of PMBL in children and adolescents.

แนวทางกำกับการใช้ยา Rituximab

ชื่อปั่งใช้ non-Hodgkin lymphoma ชนิด diffuse large B-cell (DLBCL)

3. คุณสมบัติของแพทย์ผู้ทำการรักษา

เป็นแพทย์ผู้เชี่ยวชาญที่ได้รับหนังสืออนุมัติหรือรูปแบบการรักษาจากหน่วยงานสุขภาพในสถาบันที่มีการรักษาด้วยยา Rituximab หรือยาที่มีอยู่มากในประเทศ

4. เกณฑ์อนุมัติการใช้ยา

อนุมัติการใช้ยา rituximab ใน non-Hodgkin lymphoma ชนิด DLBCL โดยมีเกณฑ์ระบุข้อต้องต้องดังนี้

4.1 ไม่เป็นผู้ป่วยระยะสุดท้าย (terminally ill)
4.2 ผู้ป่วยต้องมีอายุไม่เกิน 80 ปี
4.3 ผู้ป่วยต้องมีการตรวจด้วย Eastern Co-operation Oncology Group (ECOG) performance status ตั้งแต่ 0 ถึง 2 (หรือ ECOG 0-2) ในกรณีที่ ECOG performance status 3-4 ขึ้น ต้องเป็นผลจากโรค DLBCL เอง (ไม่ได้เกิดจาก co-morbidity อื่น)
4.4 ผู้ป่วยได้รับการตรวจภูมิจุลินทรีย์แบบชีววิทยา และตรวจพบ CD-20 positive โดยวิธี Immunochemistry
4.5 ผู้ป่วย DLBCL ต้องอยู่ในระยะของโรค (staging) ระดับ II-IV โดยยืนยันด้วยการตรวจร่างกายทั่วคลิมิก การตรวจทางท้องปฏิบัติการฟื้นฟูใจช่องอก (chest X-ray หรือ CT scan) ภาพถ่ายต่างท้อง (ultrasound หรือ CT scan) และการตรวจกระดูก (bone marrow aspiration/biopsy)

4.6 อนุมัติให้ใช้ยา rituximab ในผู้ป่วยต้องต้องตั้งใจ

4.6.1 ผู้ป่วยที่ไม่เคยได้รับ first-line therapy และก่อน
4.6.2 ผู้ป่วยที่วางแผนจะให้ R-CHOP เป็น first-line therapy แต่ไม่สามารถพร้อมการอนุมัติ rituximab ได้และมีความจำเป็นต้องให้ CHOP ไปก่อน
Targeting CD30

• CD30, a member of the TNF-receptor family. Role in apoptosis regulation.
• Express almost exclusively on HL and ALCL cells.
• Brentuximab vedotin (Bv)
  – Antibody-drug conjugate (ADC): selectively delivers monomethyl auristatin E (MMAE), an antimicrotubule agent, into CD30-expressing cells
  – FDA has approved for adult patients with HL
    • Failure of AHSCT
    • After failure of at least two prior multi-agent chemotherapy regimens in patients who cannot undergo AHSCT
Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients With Relapsed or Refractory Hodgkin’s Lymphoma

- 102 patients were treated with Bv 1.8 mg/kg by intravenous infusion every 3 weeks (maximum of 16 cycles)
- Five patients aged 12–17 years with HL were enrolled. (total of 102 patients)
- No common severe toxicities or premature discontinuation of the drug
- Recommended phase II dosage was 1.8 mg/kg given every 3 weeks

Maximum percent reduction in the sum of the product of diameters in individual patients
- Tumor size reductions were observed in 96 (94%) of 102 patients
Brentuximab vedotin with gemcitabine for paediatric and young adult patients with relapsed or refractory Hodgkin’s lymphoma (AHOD1221): a Children’s Oncology Group, multicentre single-arm, phase 1–2 trial

- 46 patients, Age < 30 yrs, (median 17) during 2013-2016
  - Primary refractory HL
  - High-risk relapse
    - relapse < 6 months from the completion
    - advanced disease (stages III or IV) with relapse <1 year from the completion
- Dose of Bv was 1.8 mg/kg + gemcitabine 1000 mg/m² q 21 days x 4
- The most common grade 3–4 AE; neutropenia 36%, rash 36%, transaminitis 21%, and pruritus 10%
- No treatment-related deaths
- Safe combination treatment with a tolerable toxicity for r/r Hodgkin lymphoma

24/42 of patients had a CR within the first four cycles of treatment.

**Targeting CD30**

**Brentuximab Vedotin and Combination Chemotherapy in Treating Children and Young Adults With Stage IIB or Stage IIIB-IVB Hodgkin Lymphoma (AHOD 1331)**
- Randomized phase III COG trial
- Arm I (ABVE-PC)
- ARM II (Bv-AVEPC)
- Omitting Bleomycin

NCT02166463

**Adcetris (Brentuximab Vedotin), Combination Chemotherapy, and Radiation Therapy in Treating Younger Patients With Stage IIB, IIIB and IV Hodgkin Lymphoma**
- Phase II trial NCT01920932 of the St Jude–Stanford–Dana Farber consortium
- Incorporated Bv into the OEPA-COPDAC (Vincristine, etoposide, prednisone, and doxorubicin) (cyclophosphamide, vincristine, prednisone, and dacarbazine)
- Omitting VCR

NCT01920932
Inhibition of the Anaplastic Lymphoma Kinase (ALK)

- ALK, a transmembrane receptor tyrosine kinase; identified in the majority of pediatric ALCL.
- Crizotinib, an ALK/MET/ROS1 inhibitor
  - FDA approved in 2013 for use in ALK-positive, non-small cell lung cancers

Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children’s Oncology Group phase 1 consortium study

- Open-label, phase 1 dose-escalation trial, patients older than 12 months and younger than 22 years.
- Crizotinib was well tolerated
- Objective tumour responses were documented in eight of nine (88%) pediatric ALCL cases

Brentuximab Vedotin or Crizotinib and Combination Chemotherapy in Treating Patients With Newly Diagnosed Stage II-IV Anaplastic Large Cell Lymphoma (COG ANHL12P1)

- Randomized phase II COG trial
- Backbone ALCL99
- Arm BV (brentuximab vedotin, combination chemotherapy)
- Arm CZ (crizotinib, combination chemotherapy)

NCT02166463

Inhibition of the Anaplastic Lymphoma Kinase (ALK)
Conclusion

• Most pediatric lymphoma are initially treated with risk-adapted chemotherapy alone.

• Pediatric Lymphoma: Role of Targeted Therapy
  • Avoidance of broader organ toxicity
  • Replacing conventional cytotoxic drugs and radiotherapy reductions
  • The ultimate judge of a novel therapeutic strategy will be the RCT trial
  • Second/third line treatment of relapsed/refractory disease

• The potential side effects of the new drugs are as yet mostly only known from adult trials.
Acknowledgements

Thai-POG

Prof. Surapon Wiengnon
Prof. Suradaj Hongeng
Asso. Prof. Kleebsabai Sanpakit
All ThaiPOG members

Ped-Hem Onc Chula

Asso. Prof. Panya Seksarn
Asso. Prof. Darint Sosothikul
Suppanan Lauhasurayothin, MD
Kanhatai Chiengthong, MD
Fellows and lab members