Welcome & Introductions

Treatment and Clinical Trials for PTCL

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Most Common Subtypes of NHL

- Mantle cell (6%)
- Follicular (25%)
- Small lymphocytic (7%)
- MALT-type marginal-zone B cell (7.5%)
- Nodal-type marginal-zone B cell (<2%)
- Lymphoplasmacytic (<2%)
- Diffuse large B cell (DLBCL) (30%)
- Burkitt (2.5%)
- T and NK cell (12%)
- Other subtypes (9%)

Percentages are of all NHLs.
MALT=mucosa-associated lymphoid tissue; NK=natural killer.

T-cell Lymphomas

- T-cell lymphomas account for ~15% of all NHLs
- Less common than B-cell lymphomas
- Can be indolent or clinically aggressive
- Similarly heterogeneous in their clinical presentation, features, and prognosis
- Challenges in treatment:
  - Increasing number of subtypes, making it very difficult to understand and to keep track of these entities
  - Each entity is encountered infrequently


Classification of Peripheral T-cell Lymphoma (PTCL)

- PTCL is a heterogeneous group of aggressive mature T-/NK-cell lymphomas
  - PTCL does not refer to anatomic sites, but rather to the involvement of more mature (post-thymic) T cells vs pre-thymic or immature T cells

Adapted from Swerdlow SH, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 2008.
PTCL Incidence

- PTCL represents 10-15% of new NHL cases per year\(^1\)
- By some estimates, the incidence of PTCL is growing significantly\(^2,3\)
- The growth in PTCL incidence may be driven by an aging population\(^4\)

Staging of PTCL
Ann Arbor Classification System

PTCL most commonly presents with advanced, systemic symptoms (stage III-IV).\[1\]

| Ann Arbor Classification for Hodgkin’s and non-Hodgkin’s Lymphoma\[2\] |
|-------------------------------|------------------------------------------------------------------------------------------------|
| **Principal stages**          |                                                                                             |
| Stage I                      | Cancer is located in a single region, (eg, 1 lymph node and the surrounding area)            |
| Stage II                     | Cancer is located in 2 separate regions but confined to 1 side of the diaphragm               |
| Stage III                    | Cancer has spread to both sides of the diaphragm, including 1 organ or area near the lymph nodes or the spleen |
| Stage IV                     | Diffuse or disseminated involvement of 1 or more extralymphatic organs, including any involvement of the liver, bone marrow, or nodular involvement of the lungs |
| **Modifiers**                |                                                                                             |
| A                            | Absence of constitutional (B-type) symptoms                                                 |
| B                            | Presence of B-type symptoms                                                                |
| E                            | Extranodal disease                                                                         |


Prognostic Indices for PTCL

• The IPI for NHL is commonly utilized in PTCL\[1\]

<table>
<thead>
<tr>
<th>International Prognostic Index (IPI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>• Age (&lt;60 years vs &gt;60 years)</td>
</tr>
<tr>
<td>• Serum LDH (≤1 x ULN vs &gt;1 x ULN)</td>
</tr>
<tr>
<td>• Performance status (0 or 1 vs 2–4)</td>
</tr>
<tr>
<td>• Stage I or II (localized) vs III or IV (advanced)</td>
</tr>
<tr>
<td>• Extranodal involvement (≤1 site vs &gt;1 site)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age-adjusted index (age ≤60 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Stage (I or II vs III or IV)</td>
</tr>
<tr>
<td>• Serum LDH (≤1 x ULN vs &gt;1 x ULN)</td>
</tr>
<tr>
<td>• Performance status (0 or 1 vs 2–4)</td>
</tr>
</tbody>
</table>

The IPI is calculated based on the sum of the number of risk factors present at diagnosis.

- 0-1 Low
- 2 Low/intermediate
- 3 High/intermediate
- 4-5 High

The Prognostic Index for PTCL (PIT) is also in use\[2\]

<table>
<thead>
<tr>
<th>Prognostic Risk Factors for PTCL (PIT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age (&gt;60 years)</td>
</tr>
<tr>
<td>• Performance Status (score ≥2)</td>
</tr>
<tr>
<td>• Elevated LDH</td>
</tr>
<tr>
<td>• Bone marrow involvement</td>
</tr>
</tbody>
</table>

The PIT is based on number of risk factors present at diagnosis.

- Group 1 0 risk factor (62% 5-yr OS)
- Group 2 1 risk factor (53% 5-yr OS)
- Group 3 2 risk factors (33% 5-yr OS)
- Group 4 3-4 risk factors (18% 5-yr OS)

The International PTCL and NK/TCL Study: OS in PTCL

- Majority of patients (>85%) received an anthracycline-containing regimen

### PTCL Subtypes

<table>
<thead>
<tr>
<th>PTCL Subtypes</th>
<th>ALK+ ALCL</th>
<th>ALK– ALCL</th>
<th>PTCL-NOS</th>
<th>AITL</th>
<th>NK/TCL</th>
<th>ATLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr OS rate</td>
<td>70%</td>
<td>49%</td>
<td>32%</td>
<td>32%</td>
<td>32%</td>
<td>14%</td>
</tr>
</tbody>
</table>


### NCCN Guidelines for Initial Treatment of PTCL

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Induction Therapy</th>
<th>Consolidation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK-positive ALCL</td>
<td>CHOP -21&lt;br&gt;CHOEP-21</td>
<td>Not needed if in remission</td>
</tr>
<tr>
<td>All other subtypes: stage I-II (low/low intermediate risk)</td>
<td>• Clinical trial preferred&lt;br&gt;• Multiagent chemotherapy* (4-6 cycles) with adjuvant locoregional RT</td>
<td>Consider consolidation with high-dose therapy and stem cell rescue for all patients except low-risk (aaIPI)</td>
</tr>
<tr>
<td>All other subtypes: stage I-II (high/high-intermediate risk), stage III-IV</td>
<td>• Clinical trial preferred&lt;br&gt;• Multiagent chemotherapy (6-8 cycles) ± RT</td>
<td></td>
</tr>
</tbody>
</table>

*Suggested regimens:
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
- CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine
- CHOP followed by ICE (ifosfamide, carboplatin, etoposide) or IVE (ifosfamide, etoposide, and epirubicin) alternating with intermediate-dose methotrexate [New Castle Regimen]
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)

**Adding Etoposide to CHOP: German Prospective High-Grade NHL Studies**

<table>
<thead>
<tr>
<th>PTCL Subtype</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCL, ALK+</td>
<td>78</td>
</tr>
<tr>
<td>ALCL, ALK-</td>
<td>113</td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>70</td>
</tr>
<tr>
<td>AITL</td>
<td>28</td>
</tr>
<tr>
<td>Other</td>
<td>31</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>320</td>
</tr>
</tbody>
</table>

EFS, aged < 60 yrs

**Benefit**


![Graph showing comparison between EFS with and without etoposide]

**German Prospective Trial of ASCT in First Remission**

- N = 83 untreated patients
- CHOP x 4-6
- If ≥ PR, dexamethasone or ESHAP
- dexamethasone or ESHAP ± TBI, ASCT
- Median follow-up: 33 mos

![Graph showing proportion achieving OS for transplanted and non-transplanted patients]

- Transplanted (n = 55)
- Non-transplanted (n = 28)

**PIT group 1: 0 risk factors**
**PIT group 2: 1 risk factor**
**PIT group 3: 2 risk factors**
**PIT group 4: 3-4 risk factors**

NCCN Treatment Guidelines for Relapsed/Refractory PTCL

- NCCN recommends clinical trials for treatment of relapsed or refractory PTCL
- Patients may be evaluated as candidates for high-dose therapy
- Patients who are not candidates for high-dose therapy may receive experimental treatments

<table>
<thead>
<tr>
<th>Candidates for Transplant</th>
<th>Non-candidates for Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentuximab vedotin (systemic ALCL only)</td>
<td>Clinical trial preferred</td>
</tr>
<tr>
<td>DHAP (dexamethasone, cisplatin, cytarabine)</td>
<td>Alemtuzumab</td>
</tr>
<tr>
<td>ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)</td>
<td>Bortezomib</td>
</tr>
<tr>
<td>Dose-Adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)</td>
<td>Brentuximab vedotin (systemic ALCL only)</td>
</tr>
<tr>
<td>GDP (gemcitabine, dexamethasone, cisplatin)</td>
<td>Cyclosporine (AITL only)</td>
</tr>
<tr>
<td>GemOx (gemcitabine, oxaliplatin)</td>
<td>Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)</td>
</tr>
<tr>
<td>ICE (ifosfamide, carboplatin, etoposide)</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td>MINE (mesna, ifosfamide, mitoxantrone, etoposide)</td>
<td>Pralatrexate</td>
</tr>
<tr>
<td>Pralatrexate (category 2B)</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>Romidepsin</td>
</tr>
</tbody>
</table>

Suggested Treatment Regimens for Second-line Therapy of PTCL (in alphabetical order)

Relapsed/Refractory PTCL: FDA-Approved Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Regimen</th>
<th>N</th>
<th>ORR, %</th>
<th>CR, %</th>
<th>Response Duration, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romidepsin&lt;sup&gt;[1]&lt;/sup&gt; (NCI)</td>
<td>14 mg/m&lt;sup&gt;2&lt;/sup&gt; weekly x 3 every 28 days</td>
<td>47</td>
<td>38</td>
<td>18</td>
<td>8.9</td>
</tr>
<tr>
<td>Romidepsin&lt;sup&gt;[2]&lt;/sup&gt; (pivotal)</td>
<td>14 mg/m&lt;sup&gt;2&lt;/sup&gt; weekly x 3 every 28 days</td>
<td>131</td>
<td>25</td>
<td>14</td>
<td>17.0</td>
</tr>
<tr>
<td>Pralatrexate&lt;sup&gt;[3]&lt;/sup&gt; (pivotal)</td>
<td>30 mg/m&lt;sup&gt;2&lt;/sup&gt; weekly x 6 of 7 wks</td>
<td>111</td>
<td>29</td>
<td>11</td>
<td>10.1</td>
</tr>
<tr>
<td>Brentuximab vedotin&lt;sup&gt;[4]&lt;/sup&gt; (ALCL)</td>
<td>1.8 mg/kg every 21 days</td>
<td>58</td>
<td>86</td>
<td>57</td>
<td>12.6</td>
</tr>
</tbody>
</table>

**Pralatrexate Mechanism of Action**

Pralatrexate is a selective antifolate designed to accumulate preferentially in cancer cells.

**Entry**
- Pralatrexate selectively enters cells expressing RFC-1, a protein that is overexpressed on cancer cells compared to normal cells.

**Accumulation**
- Once inside cancer cells, pralatrexate is efficiently polyglutamylated, which leads to high intracellular drug retention.

**Inhibition**
- Acting on the folate pathway, pralatrexate interferes with DNA synthesis and triggers cancer cell death.


**PROPEL: A Multi-center Phase 2 Open-label Study of Pralatrexate with Vitamin B₁₂ and Folic Acid Supplementation in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)**

**Out-patient dosing schedule**
- **PDX 30 mg/m²** once weekly IV push × 6 weeks
- **Vitamin B₁₂ 1 mg IM** q 8 - 10 weeks
- **Folic acid 1.0 - 1.25 mg PO QD**

- **Cycle 1**
- **Cycle 2**
- **Cycle 3**
- **Cycle 4**

- **Weeks 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28**

- **Response assessment**

Treat until progression or intolerance.
Depsipeptide in Rel/Ref PTCL: Treatment Schedule

Schedule:
4-hour infusion 14 mg/m² on days 1, 8, & 15 every 28 days

Brentuximab Vedotin Mechanism of Action

Brentuximab vedotin (SGN-35) ADC
- monomethyl auristatin E (MMAE), potent antitubulin agent
- protease-cleavable linker
- anti-CD30 monoclonal antibody

ADC binds to CD30
ADC-CD30 complex traffics to lysosome
MMAE is released
MMAE disrupts microtubule network
G2/M cell cycle arrest
Apoptosis
Targeting T-cell Lymphoma

Surface Antigens/Receptors
- CD2
- CD4
- CD25
- CD30
- Chemokine receptors

Microenvironmental Factors
- Angiogenesis
- Immunomodulation
- Viral Pathogens

Cellular Survival Mechanisms
- Proteasome Inhibition
- HDAC inhibition
- Death Receptors & Ligands
- Cell Cycle Arrest
- Signal Transduction Inhibition

New Agents for T-cell Lymphoma

- Nucleoside analogs/pathway inhibitors
  - Gemcitabine
  - Fludarabine
  - Cladribine
  - Forodesine
  - Clofarabine
  - Nelarabine
- HDAC inhibitors
  - Depsipeptide
  - Vorinostat
  - Panabinostat
  - Belinostat
- Antifolate
  - Pralatrexate
- Proteasome inhibitors
  - Bortezomib
  - Carfilzomib
- Immunomodulators
  - Lenalidomide
- Monoclonal antibodies
  - Alemtuzumab
  - Anti-CD30
  - Zanolimumab
  - Siplizumab
- Immunotoxins /immunoconjugates
  - Denileukin diftitox
  - SGN-35
  - Daclizumab
- Syk inhibitors
  - Fostamatinib disodium
- Kinase Inhibitors
  - PDGFRβ inhibitor
  - TKI/Src inhibitors
  - JAK2-Stat inhibitors
Alisertib: Investigational Aurora A Kinase Inhibitor

- Results in mitotic defects
  - Abnormal spindles
  - Unseparated centrosomes
  - Delayed mitotic progression
- Apoptosis or senescence

Anti-CCR4 Antibody: KW-0761

- Defucosylated humanized IgG1 MoAb
- Targets CCR4
  - Shown to be overexpressed on tumor cells
    - 88% of patients with ATLL
    - 38% of patients with PTCL
  - CCR4 expression associated with unfavorable prognosis in both diseases
- Phase II studies under way in relapsed/refractory ATLL and PTCL patients
### Lenalidomide in Relapsed/Refractory Aggressive NHL: Results

<table>
<thead>
<tr>
<th>Histology</th>
<th>n</th>
<th>ORR</th>
<th>PFS (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>108</td>
<td>28%</td>
<td>2.3</td>
</tr>
<tr>
<td>Mantle</td>
<td>57</td>
<td>42%</td>
<td>5.7</td>
</tr>
<tr>
<td>Follicular (grade 3)</td>
<td>19</td>
<td>42%</td>
<td>6.3</td>
</tr>
<tr>
<td>T-cell</td>
<td>33</td>
<td>45%</td>
<td>4.6</td>
</tr>
</tbody>
</table>

ORR in patients with prior SCT = 37% (27/73)
Gr 3-4 neutropenia 41%, thrombocytopenia 19%

Witzig et al. Blood 2009; 114: ASH Abstract #1676

### Gene Expression Profiles (GEP) in PTCL-nos

- PTCL-nos can be separated into 3 subgroups on the basis of gene expression profiles (U1, U2, and U3)
- It has not been established whether these subgroups correlate with clinical outcome
  - Preliminary findings indicate that PTCL-U1 tended to have a worse outcome than PTCL-U2 or -U3

<table>
<thead>
<tr>
<th>Molecular subgroup</th>
<th>Gene expression signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>U1</td>
<td>Included genes involved with poor outcome in other tumors (CCND2)</td>
</tr>
<tr>
<td>U2</td>
<td>Over-expression of genes involved in T-cell activation and apoptosis (NFKB1, BCL-2)</td>
</tr>
<tr>
<td>U3</td>
<td>Over-expression of genes involved in IFN/JAK/STAT pathway</td>
</tr>
</tbody>
</table>

Future for PTCL Therapy

• Standard CHOP – does not work well
• Need to identify novel agents or combinations
• GEP may help us identify specific targets
• Induction therapy, consolidation, and/or maintenance therapy may be needed
• Consider PSCT for selected patients
• Novel therapies added to PSCT also an option
• Clinical trials essential for all PTCL patients
The Leukemia & Lymphoma Society’s (LLS) Co-Pay Assistance Program offers financial assistance to qualified lymphoma patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.

- **WEBSITE:** [www.LLS.org/copay](http://www.LLS.org/copay)
- **TOLL-FREE PHONE:** (877) LLS-COPAY

For more information about peripheral T-cell lymphoma and other LLS programs, please contact an LLS Information Specialist.

- **TOLL-FREE PHONE:** (800) 955-4572
- **EMAIL:** infocenter@LLS.org