Welcome and Introductions

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Disclosures

• Consulting
  – Millennium, Celgene

T-cell Lymphomas

• T-cell lymphomas account for ~15% of all NHLs in the US; the majority of NHLs in the US are B-cell lymphomas
• Like their B-cell counterparts, T-cell lymphomas are heterogeneous in their clinical presentation, pathologic features, biologic behavior and prognosis
• Interpretation of pathologic material may be difficult; to ensure appropriate management, an accurate diagnosis is necessary
• Classification (subtypes) is changing as more knowledge acquired
• There is no "standard" therapy
• The treatments that work well for B-cell lymphomas do not always work as well in the treatment of T-cell lymphomas, underscoring the need for novel therapies for this patient population

Classification of PTCL

- Peripheral T-cell lymphoma (PTCL) = Mature T-cell lymphoma

Classification of PTCL (cont.)

Mature T-NK neoplasm

Extranodal

Nodal

Leukemic

Extranodal NK/T cell, nodal type
Enteropathy associated (EATL)
Hepatosplenic (1.5)
Subcutaneous Panniculitis-like TCL

PTCL, NOS
ALCL (ALK +/-)
Angioimmunoblastic (ALT)

Adult T-cell leukaemia/lymphoma (ATLL)
Aggressive NK-cell leukemia
T-prolymphocytic leukemia (T-PDLL)
Large granular lymphocytic leukemia (LGL-Leukemia)
**Classification of PTCL (cont.)**

**Cutaneous**

- Mycosis fungoides/Sézary syndrome (MF/SS)
- CD30+ lymphoproliferative disorders
- CD4+ small/medium pleomorphic T-cell lymphoma
- Cutaneous PTCL, NOS
- Cutaneous aggressive CD8+ T-cell lymphoma
- Cutaneous NK/T cell lymphoma, nasal type

**Common Peripheral T-cell Lymphoma Subtypes (excluding CTCLs)**

- Peripheral T-cell lymphoma – not otherwise specified (PTCL-NOS) is the most common subtype
- Anaplastic large cell lymphoma (ALCL) ALK+/- and angioimmunoblastic lymphoma are also common subtypes

![Common Peripheral T-cell Lymphoma Subtypes](chart.png)

PTCL Epidemiology

- The relative incidence of PTCL subtypes varies by geography\textsuperscript{1,2}
  - Incidence is higher in Asian and Caribbean populations\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percentage\textsuperscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>North America</td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>34.4</td>
</tr>
<tr>
<td>Angioimmunoblastic</td>
<td>16.0</td>
</tr>
<tr>
<td>ALCL, ALK+</td>
<td>16.0</td>
</tr>
<tr>
<td>ALCL, ALK-</td>
<td>7.8</td>
</tr>
<tr>
<td>NK/TCL</td>
<td>5.1</td>
</tr>
<tr>
<td>ATLL (HTLV-1+)</td>
<td>2.0</td>
</tr>
<tr>
<td>Enteropathy-type</td>
<td>5.8</td>
</tr>
<tr>
<td>Hepatosplenic</td>
<td>3.0</td>
</tr>
<tr>
<td>Primary cutaneous ALCL</td>
<td>5.4</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like</td>
<td>1.3</td>
</tr>
<tr>
<td>Unclassifiable T-cell</td>
<td>2.3</td>
</tr>
</tbody>
</table>


Diagnostic Workup of a Patient

- Access to an accurate and sufficient patient history is necessary to aid in an accurate diagnosis
- This information guides which diagnostic tests should be run and how to interpret the results of those tests
- In select cases, cytogenetic studies may be useful
- Molecular studies (T-cell gene rearrangement) by themselves do not make a diagnosis!
Diagnosis of PTCL

- Approximately 10% of PTCL cases are incorrectly diagnosed. 
- Diagnosis of PTCL routinely involves immunophenotypic analysis in conjunction with cellular morphology, analysis of lymph node architecture, and molecular genetic assays. 
  - Excisional biopsy is usually required.

Common immunohistochemistry stains for the diagnosis of PTCL:

- CD3 (pan T-cell marker)
- CD20 (pan/mature B-cell marker)
- CD4 (helper T-cell marker)
- CD8 (cytotoxic T-cell marker)
- CD10 (precursor T- and B-cell marker)
- CXCL13 (germinal center T-cell marker)
- CD2 (pan T/NK cell marker)
- CD5 (activated T-cell marker)
- CD30 (activated T- and B-cell marker)

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 ALCI</td>
<td>CHOP-21</td>
<td>Not needed if in remission</td>
</tr>
<tr>
<td></td>
<td>CHOEP-21</td>
<td></td>
</tr>
</tbody>
</table>
| All other subtypes: stage I-IV | **Clinical trial preferred**  
  Multiagent chemotherapy* (6 cycles) | Clinical trial or  
  Consider consolidation with high-dose therapy with stem cell rescue or Observe |

*Suggested regimens:
- CHOP-14 or 21 (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)
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


Suggested Treatment Regimens for Second-line Therapy of PTCL
(in alphabetical order)¹

<table>
<thead>
<tr>
<th>Candidates for Transplant</th>
<th>Non-candidates for Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial preferred</td>
<td></td>
</tr>
<tr>
<td>Brentuximab vedotin (systemic ALCL only) or systemic CD30+ PTCL</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 or CD30+ PTCL)</td>
</tr>
<tr>
<td>GDP (gemcitabine, dexamethasone, cisplatin)</td>
<td>Cyclophosphamide (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 (in AITL has limited activity)</td>
</tr>
<tr>
<td>Pralatrexate (category 2B)</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>Romidepsin</td>
</tr>
</tbody>
</table>

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⁽¹⁾ (NCI)</td>
<td>14 mg/m² weekly x 3 every 28 days</td>
<td>47</td>
<td>38</td>
<td>18</td>
<td>8.9</td>
</tr>
<tr>
<td>Romidepsin⁽²⁾ (pivotal)</td>
<td>14 mg/m² weekly x 3 every 28 days</td>
<td>131</td>
<td>25</td>
<td>14</td>
<td>17.0</td>
</tr>
<tr>
<td>Pralatrexate⁽³⁾ (pivotal)</td>
<td>30 mg/m² 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⁽⁴⁾ (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>

**Update on PTCL**

**Pralatrexate**

Compared to MTX
- PDX more efficiently enters tumor cells (RFC-1) and is more readily polyglutamylated (FPGS)

**HDAC Inhibitors in MF/SS**

**Vorinostat**
- Orally bioavailable
- FDA approved only for CTCL
- AEs
  - Diarrhea (most disabling and dose related)
  - Fatigue
  - Anorexia >20%
  - Anemia, thrombocytopenia, increased creatinine less common

**Romidepsin**
- IV preparation
- FDA approved for CTCL and PTCL
- AEs
  - Prolonged QT with concomitant use of other drugs that inhibit CYP3A4
  - Nausea
  - Fatigue
  - Vomiting
  - Anorexia
  - Lymphopenia
  - Granulocytopenia

Histone Deacetylation Results in Transcriptional Repression

Open chromatin results in transcriptional activation

Closed chromatin results in transcriptional repression

Brentuximab Vedotin (SGN-35) Antibody-Drug Conjugate

- 3 components:
  - Chimeric antibody SGN-30
  - Synthetic analog (MMAE) of the antitubulin agent dolastatin 10
  - Stable drug linker
- Proposed mechanism of action
  - Binds to CD30
  - Internalized into the tumor cell
  - MMAE is released
  - Tumor cell undergoes G2/M phase cell cycle arrest and apoptosis
- Preclinical activity observed both in vitro and in vivo
- Administered IV

ADC=antibody-drug conjugate; MMAE=monomethylauristatin E.
## Ongoing Phase III Trials

### PTCL

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Population</th>
<th>Primary Endpoints</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab + CHOP14 + G-CSF vs CHOP14 + G-CSF</td>
<td>Newly diagnosed PTCL</td>
<td>EFS</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Alisertib vs pralatrexate or gemcitabine or romidepsin</td>
<td>Relapsed/Refractory PTCL</td>
<td>ORR, PFS</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Brentuximab vedotin + CHP vs CHOP</td>
<td>CD30+ PTCL</td>
<td>PFS</td>
<td>Recruiting</td>
</tr>
<tr>
<td>CHOP → pralatrexate</td>
<td>Newly diagnosed PTCL</td>
<td>PFS, OS</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Romidepsin + CHOP vs CHOP</td>
<td>Newly diagnosed PTCL</td>
<td>PFS</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Heliostat+ CHOP vs CHOP</td>
<td>Newly diagnosed PTCL</td>
<td>PFS</td>
<td>To open soon</td>
</tr>
</tbody>
</table>

1. ClinicalTrials.gov NCT00646854.
2. ClinicalTrials.gov NCT01482962.
3. ClinicalTrials.gov NCT01777152.
5. ClinicalTrials.gov NCT01796002.

### CTCL

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Population</th>
<th>Primary Endpoints</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. vedotin vs investigator’s choice (methotrexate or bexarotene)</td>
<td>CD30+ CTCL</td>
<td>ORR lasting ≥4 months</td>
<td>Recruiting</td>
</tr>
<tr>
<td>KW-0761 vs vorinostat</td>
<td>Relapsed/Refractory CTCL</td>
<td>PFS</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

1. ClinicalTrials.gov NCT01579499.
2. ClinicalTrials.gov NCT01728805.
Alisertib: Kinase Inhibitor

- Aurora kinases regulate mitotic signaling
- Inhibition of AAK is associated with mitotic errors, apoptosis, and senescence
- Alisertib is an oral, investigational ATP competitor and AAK inhibitor


Mogamulizumab (KW-0761): Anti-CCR4 Monoclonal Antibody

- Approved in Japan for treatment of ATLL (Adult T-cell leukemia/lymphoma)
Drugs to watch out for

• PI3-kinase inhibitors (GS 1101 and others)
• PD-1 inhibitors
• Dual PI3-kinase/MTOR inhibitors

How might we treat in the future? How are we treating now?

• Increasing attention should be paid to whether a lymphoma is a T-cell vs B-cell lymphoma
• Increasing attention should be paid to subtype of T-cell lymphoma. Examples of specific treatments that work better for specific subtypes are:
  - T/NK nasal lymphoma: SMILE regimen
  - ATLL: Mogamulizumab
  - EATL: Newcastle regimen
  - AITL: Cyclosporine; HDACi over pralatrexate
  - ALCL: B. vedotin
Update on PTCL

Functional Subsets of PTCL

• Report from the lymphoma workshop of the XVIth meeting of the EAHP and SHP…
• “In past years, genomic techniques have been applied to both normal and neoplastic T-cells leading to the recognition of distinctive functional subsets”
  - (1) AITL and T-follicular-helper cell-associated lymphomas
  - (2) CD30+ T-cell lymphomas/lymphoproliferative diseases
  - (3) Extranodal T-cell and NK-cell neoplasms
  - (4) EBV-associated T-cell/NK-cell lymphomas/lymphoproliferative diseases
  - (5) PTCL, NOS, PTLD, and mimics


Communication Among Patients And Healthcare Providers

• Open communication with your treatment team is essential to understanding your diagnosis and in making informed treatment decisions.

• Don’t be afraid to ask your treatment team questions (What exactly is my diagnosis? Is there a standard treatment for my disease? Are you the right doctor for my disease? Are there clinical trials available for my disease?)

• Should I get a second opinion? It’s okay to let your doctor know that you’d like a second opinion; most doctors are used to patients seeking second opinions and even encourage it.

• Feel free to speak with your treatment team regarding time and effort commitment: travel, parking, work, life events, etc.
Update on PTCL

Question & Answer Session

The speaker’s slides are available for download at www.LLS.org/programs

The Leukemia & Lymphoma Society (LLS) offers:

- Live, weekly Online Chats that provide a friendly forum to share experiences and chat with others about anything from the initial phase of diagnosis to treatment and survivorship. Each chat is moderated by an oncology social worker and is password protected.
  ➢ WEBSITE: www.LLS.org/chat

- Co-Pay Assistance Program offers financial assistance to qualified cancer 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
  ➢ TOLL-FREE PHONE: (877) LLS-COPAY

- For more information about blood cancers and other LLS programs, please contact an LLS Information Specialist.
  ➢ TOLL-FREE PHONE: (800) 955-4572
  ➢ EMAIL: infocenter@LLS.org