Clinical Updates and Issues: T-Cell Lymphomas
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Memorial Sloan Kettering Cancer Center

Learning Objectives

• Summarize the current and evolving therapeutic options for the treatment of T-cell lymphomas.
• Construct a treatment plan for the management of newly-diagnosed and relapsed PTCL.
• Discuss the role of stem-cell transplantation in treatment of T-cell lymphomas.
Lymphoma 101

- Of all cancers, lymphomas represent 4.9% cases in US
  - 81,000 new cases in US in 2015
    - Most common hematologic malignancy
- Neoplasms arising from cells of the lymphoid lineage
- Based on pathologic and clinical features
  - REAL classification
  - NHL v. HL
  - Aggressive v. indolent
- Risk factors not fully understood
- There are >70 types of lymphoma
  - Majority are NHL


Peripheral T-Cell Lymphomas

- Represent ~10-15% of all cases of NHL
- Broadly classified as systemic or cutaneous
  - Heterogenous group of lymphomas
  - Treatment plan depends on extent of involvement
- Typically aggressive
- Making the diagnosis can be challenging
- 5 yr OS ranges, depending on risk factors
  - 6-74%


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T-Cell neoplasms

“Systemic T-cell Lymphoma”
- Peripheral T-cell lymphoma NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic Large Cell-ALK-1 negative
- Anaplastic Large Cell-ALK-1 positive
- Enteropathy-type intestinal lymphoma
- Extranodal NK/T-cell lymphoma-nasal
- Adult T-cell leukemia/lymphoma (HTLV-1)
- Hepatosplenic T-cell lymphoma (may be derived from an immature T-cell)

“CTCL”
- Mycosis Fungoides
- Sezary syndrome
- Subcutaneous panniculitis-like
- Primary cutaneous ALCCL
- Lymphomatoid papulosis
- Primary cutaneous small/medium CD4+
- T-cell lymphoma
- Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma

Cancers of Immature T-cells
- ALL (Precursor T cell)
- Lymphoblastic lymphoma/leukemia

Distribution of subtypes among 1,314 cases

- Peripheral T-cell Lymphoma: 25.9%
- Angioimmunoblastic: 12.2%
- Natural killer/T-cell lymphoma: 6.6%
- Adult T-cell leukemia/lymphoma: 9.6%
- Anaplastic large cell lymphoma, ALK+: 5.5%
- Anaplastic large cell lymphoma, ALK-: 4.7%
- Enteropathy-type T-cell: 1.7%
- Primary cutaneous ALCCL: 1.4%
- Hepatosplenic T-cell: 0.9%
- Subcutaneous panniculitis-like: 0.9%
- Unclassifiable PTCL: 2.5%
- Other disorders: 10.4%
Making that diagnosis...

- **Biopsy** is the golden ticket
  - More than a FNA
  - Discuss clinical context with pathologist
  - Expert review is essential
  - Agreement is not universal
- **Morphology**
  - Small, medium, or large cells
  - Cytoplasm/nucleoli
- **Phenotype**
  - CD2, CD3, CD4, CD5, CD7, CD8 as pan T markers
  - EBV
  - ALK-1
  - Proliferation index
- **Genotype**
  - Looking for T-cell receptor (TCR) chain rearrangement
- **Objective quantification**
  - mSWAT
  - PET/CT
  - Bone marrow biopsy
  - HTLV-1 serology
- **International Prognostic Index (for NHL)**
  - Age
  - LDH
  - Performance status
  - Ann Arbor Stage
  - # extranodal sites
- **Prognostic Index for PTCL-U (PIT)**
  - Age
  - LDH
  - Performance status
  - BM involvement


Pathology example
Cutaneous T-Cell Lymphomas (CTCL)

- Mycosis fungoides (MF) and Sezary syndrome (SS) are most common subtypes
- Accumulation of atypical memory T cells in epidermis and dermis
- Median OS 24 years\(^1\)
  - 140 advanced MF/SS patients with median OS 2.47 years\(^2\)
  - Presence of patches, plaques, and/or LN correlate with prognosis

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CTCL: skin lesions

Mycosis Fungoides

MF/SS Therapy: Skin-directed

**Limited**
- Steroids
- Topical chemotherapy (mechlorethamine)
- Local radiation
- Topical retinoids (bexarotene)
- Phototherapy (UVB/PUVA)
- Topical immune response modifiers (imiquimod, resiquimod)

**Generalized**
- Steroids
- Topical chemotherapy (mechlorethamine)
- Phototherapy (UVB/PUVA)
- Total skin electron beam therapy (TSEBT)
- Topical tacrolimus

MF/SS: Systemic Therapy

**Biologic response modifiers**
- interferon (IFN-α2a)
- Oral retinoids (isotretinoin, bexarotene)

**HDAC inhibitors**
- Vorinostat
- romidepsin

**Extracorporeal photopheresis (ECP)**
- Methotrexate
- Steroids

**Targeted therapy**
- brentuximab vedotin
- denileukin diftitox

**Chemotherapy**
- gemcitabine
- liposomal doxorubicin
- pralatrexate
- chlorambucil
- pentostatin
- Bortezomib

**Allo transplant?**
### MF/SS: newer agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>N</th>
<th>ORR</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
<td>Anti-CD52 MoAb</td>
<td>various</td>
<td>86-100%</td>
<td>several</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>HDAC inhibitor</td>
<td>139</td>
<td>17.3%</td>
<td>Duvic et al, 2012</td>
</tr>
<tr>
<td>Belinostat</td>
<td>HDAC inhibitor</td>
<td>29 CTCL (24 MF/SS)</td>
<td>13.8%</td>
<td>Foss et al, 2014</td>
</tr>
<tr>
<td>Forodesine</td>
<td>PNP inhibitor</td>
<td>101</td>
<td>11%</td>
<td>Dummer et al, 2014</td>
</tr>
<tr>
<td>Mogamulizumab</td>
<td>Anti-CCR4 MoAb</td>
<td>38</td>
<td>36.8% (SS 47.1%, MF 28.6%)</td>
<td>Duvic, et al 2015</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>immunomodulatory</td>
<td>32</td>
<td>28%</td>
<td>Querfeld, et al 2014</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>Alkylating agent</td>
<td>3</td>
<td>67%</td>
<td>Zaja, et al 2013</td>
</tr>
</tbody>
</table>

### CTCL treatment map

![CTCL treatment map](image)

## Agents in the pipeline

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>NCT identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-3475 (Pembrolizumab)</td>
<td>PD-1 inhibitor</td>
<td>02243579</td>
</tr>
<tr>
<td>SGX301 (Synthetic Hypericin)</td>
<td>topical photosensitizing agent</td>
<td>02448381</td>
</tr>
<tr>
<td>NM-IL-12 (rHuIL-12) + TSEBT</td>
<td>immunotherapy</td>
<td>02542124</td>
</tr>
<tr>
<td>MRG-106</td>
<td>miR-155 inhibitor</td>
<td>02580552</td>
</tr>
<tr>
<td>Intratumoral IL12 Plasmid</td>
<td>Intratumoral immunotherapy</td>
<td>01579318</td>
</tr>
</tbody>
</table>

## Systemic T-Cell Lymphomas
Systemic T-Cell lymphomas

- Peripheral T-Cell lymphoma, not otherwise specified (PTCL, NOS) is the most common subtype
  - Median age of onset is 57 yrs
- Other common subtypes:
  - Angioimmunoblastic T-Cell lymphoma (AITL)
  - Natural killer/T-cell, nasal type (NK/T)
  - Anaplastic large cell lymphoma (ALCL)
    - CD30+ T-cell neoplasm
    - ALK pos v. ALK neg


Swedish Registry: Population- based PTCL cohort

OS nodal PTCL

OS extra-nodal PTCL

PFS nodal PTCL

PFS extra-nodal PTCL

Frontline treatment

- Most histologies:
  - Clinical trial
  - Chemotherapy (CHOP-like)
    - 4-6 cycles
    - +/- involved site radiotherapy (ISRT)
  - If complete response
    - Clinical trial
    - Consolidative high dose therapy + autoSCT (if eligible)
    - There are trials using maintenance therapy after autoSCT
- ALCL, ALK+
  - Chemotherapy (CHOP-like)
  - If early stage, add ISRT

CHOP: The regimen of choice

<table>
<thead>
<tr>
<th>Citation</th>
<th>Regimen</th>
<th>Population</th>
<th>N</th>
<th>ORR</th>
<th>CR</th>
<th>PFS/EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savage, et al.</td>
<td>CHOP (retrospective)</td>
<td>PTCL-NOS</td>
<td>117</td>
<td>84%</td>
<td>64%</td>
<td>29% (5 yr)</td>
</tr>
<tr>
<td>Reimer, et al.</td>
<td>CHOP→ASCT</td>
<td>PTCL/AITL/ALCL</td>
<td>83</td>
<td>79%</td>
<td>39%</td>
<td>36% (3 yr), with ASCT</td>
</tr>
<tr>
<td>Simon, et al.</td>
<td>CHOP v. VIP-rABVD</td>
<td>PTCL/AITL/ALCL</td>
<td>43</td>
<td>62%</td>
<td>39%</td>
<td>42% (2yr)</td>
</tr>
</tbody>
</table>

CHOP-based therapy for Peripheral T/NK Lymphomas

**Always**
- Anaplastic Large Cell-ALK-1 positive

**Sometimes**
- Peripheral T-cell lymphoma NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic Large Cell-ALK-1 negative
- Enteropathy-type intestinal lymphoma
- Subcutaneous panniculitis-like T-cell

**Never**
- Mycosis Fungoides
- Sezary syndrome
- Primary cutaneous CD30+ disorders
  - Primary cutaneous Anaplastic large cell lymphoma
  - Lymphomatoid papulosis
- T-cell large granular lymphocytic
- Extranodal NK/T-cell lymphoma-nasal
- Hepatosplenic T-cell lymphoma
- NK/T-cell leukemia/lymphoma
- Adult T-cell leukemia/lymphoma
- T-cell prolymphocytic leukemia

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**Improving upon CHOP**

Swedish Lymphoma Registry

<table>
<thead>
<tr>
<th></th>
<th>CHOP (n=145)</th>
<th>CHOEP (n=107)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>70%</td>
<td>81%</td>
<td>0.052</td>
</tr>
<tr>
<td>5 yr OS</td>
<td>30%</td>
<td>47%</td>
<td>ns</td>
</tr>
<tr>
<td>5 yr PFS</td>
<td>23%</td>
<td>40%</td>
<td>ns*</td>
</tr>
</tbody>
</table>

In patients 60 or younger, addition of etoposide was associated with improved PFS (HR 0.49, p=0.008)

Fredrik Ellin et al. *Blood* 2014;124:1570-1577
German High -Grade NHL Study Group (DSHNHL) Trials

NHL-B1 trial

ALCL, ALK positive

NHL-B1 & Hi-CHOEP trials

Other subtypes


Additional attempts to improve CHOP

<table>
<thead>
<tr>
<th>Citation</th>
<th>Regimen</th>
<th>N</th>
<th>%ORR / CR</th>
<th>PFS / EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallamini A, et al</td>
<td>Alemtuzumab + CHOP</td>
<td>24</td>
<td>75 / 71</td>
<td>48% (2 yr)</td>
</tr>
<tr>
<td>Kim SJ, et al</td>
<td>Bortezomib + CHOP</td>
<td>46</td>
<td>76 / 65</td>
<td>35% (PTCL 31%)</td>
</tr>
<tr>
<td>Simon A, et al</td>
<td>VIP-rABVD</td>
<td>43</td>
<td>58 / 44</td>
<td>45% (2 yr) ND than CHOP</td>
</tr>
<tr>
<td>Dupuis J. et al</td>
<td>Ro-CHOP</td>
<td>18</td>
<td>78 / 66</td>
<td>57% (12 mo)</td>
</tr>
<tr>
<td>Mahadevan D, et al</td>
<td>PEGS</td>
<td>20</td>
<td>39 / 24</td>
<td>14% (2 yr) In untreated</td>
</tr>
<tr>
<td>Advani, RH, et al</td>
<td>CEOP + PDX</td>
<td>33</td>
<td>70/52</td>
<td>48% (1 yr), 39% (2 yr)</td>
</tr>
</tbody>
</table>

Brentuximab vedotin plus CHOP/CHP for CD30+ PTCL – Phase I

Treatment schema

<table>
<thead>
<tr>
<th>Treatment schema</th>
<th>Patients</th>
<th>ORR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sequential treatment:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BV x2 -&gt; CHOPx6 -&gt; BV x8</td>
<td>13 ALCL</td>
<td>85%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Combination treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BV plus CHP x6 -&gt; BV x 10</td>
<td>19 ALCL</td>
<td>100%</td>
<td>88%</td>
</tr>
</tbody>
</table>

Notable grade ≥3 adverse events in combination arm:
- Febrile neutropenia 31%
- Peripheral sensory neuropathy 8%
- Cardiac failure 8%

Studies building upon CHOP in PTCL

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT</th>
<th>Study Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECHELON-2</td>
<td>01777152</td>
<td>A Comparison of Brentuximab Vedotin and CHP With Standard-of-care CHOP in the Treatment of Patients With CD30-positive Mature T-cell Lymphomas</td>
</tr>
<tr>
<td>Ro-CHOP</td>
<td>02796002</td>
<td>Phase 3 Multi-center Randomized Study to Compare Efficacy and Safety of Romidepsin CHOP (Ro-CHOP) Versus CHOP in Patients With Previously Untreated Peripheral T-Cell Lymphoma</td>
</tr>
<tr>
<td>A-CHOP-14</td>
<td>00725231</td>
<td>Immunotherapy in Peripheral T Cell Lymphoma - the Role of Alemtuzumab in Addition to Dose Dense CHOP</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>01420679</td>
<td>Study of Pralatrexate Versus Observation Following CHOP-based Chemotherapy in Previously Undiagnosed Peripheral T-cell Lymphoma Patients</td>
</tr>
<tr>
<td>RADCHOP</td>
<td>01198665</td>
<td>RAD001 (everolimus) Combined With CHOP in Newly Diagnosed Peripheral T-cell Lymphomas</td>
</tr>
</tbody>
</table>
Upfront consolidation with autologous transplant

Swedish Lymphoma Registry¹

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Auto-SCT ITT (n=128)</th>
<th>Non-auto-SCT (n=124)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year PFS (%)</td>
<td>41</td>
<td>20</td>
<td>0.002</td>
</tr>
<tr>
<td>5 year OS (%)</td>
<td>48</td>
<td>26</td>
<td>0.004</td>
</tr>
</tbody>
</table>

MSKCC series – PTCL patients with intent for front-line transplant²

<table>
<thead>
<tr>
<th>Patients (n=65)</th>
<th>4 year PFS</th>
<th>4 year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All: 32 PTCL-NOS, 21 AITL, 12 ALK-neg ALCL</td>
<td>38%</td>
<td>52%</td>
</tr>
<tr>
<td>Auto-SCT (n=34)</td>
<td>55%</td>
<td>66%</td>
</tr>
<tr>
<td>Allo-SCT (n=5)</td>
<td>30%</td>
<td>67%</td>
</tr>
<tr>
<td>No transplant</td>
<td>16.5%</td>
<td>27%</td>
</tr>
</tbody>
</table>


Prospective phase II study: Up-front auto-SCT

CHOP x 4-6
N=83
ORR 79%, CR 39%

BEAM or ESHAP
N=65 (78%)

HDT (Cy/TBI) and auto-SCT
n=55 (66%)

3 yr OS 48%
3 yr PFS 36%

Reimer et al. JCO 2009;27:106-113
**CHOEP followed by auto-SCT - Nordic Lymphoma Group Trial 1**

**CHO(E)P-14 x 6**  
* n=160  
* ORR 82%  
* CR 51%

↓

**BEAM or BEAC auto-SCT**  
* n=115 (72%)

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d'Amore et al. JCO 2012;30:3093-3099

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**Relapsed/Refractory PTCL**
Treatment Strategy for Relapsed/Refractory Disease

CIBMTR: PFS excluding pt in CR1 (Most patients ALCL)

Autologous Transplantation in Relapsed PTCL

CIBMTR, Center for International Blood and Marrow Transplant Research
**Allogeneic stem cell transplant**

French Registry N = 77, TRM 34%

MSKCC N = 34, TRM 18%

- Data on allo-SCT is limited
- OS curves reach a plateau at > 50%
- Small numbers raise questions about patient selection and general applicability

**Single-agent activity in Relapsed/Refractory PTCL**

<table>
<thead>
<tr>
<th>Agent</th>
<th>n</th>
<th>ORR</th>
<th>CR</th>
<th>DOR (mo)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romidepsin</td>
<td>130</td>
<td>25%</td>
<td>15%</td>
<td>17</td>
<td>Coiffer, et al. JCO 2012</td>
</tr>
<tr>
<td>Belinostat</td>
<td>129</td>
<td>26%</td>
<td>10%</td>
<td>8.3</td>
<td>O’Connor, et al. JCO 2015</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>111</td>
<td>29%</td>
<td>13%</td>
<td>10.5</td>
<td>O’Connor, et al. JCO 2011</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>60</td>
<td>50%</td>
<td>28%</td>
<td>3.5</td>
<td>Damaj, et al. JCO 2013</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>58</td>
<td>86%</td>
<td>57%</td>
<td>12.6</td>
<td>Pro, et al. JCO 2012</td>
</tr>
<tr>
<td>(ALCL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brentuximab (non-ALCL)</td>
<td>35</td>
<td>41%</td>
<td>23%</td>
<td>7.6</td>
<td>Horwitz, et al. Blood 2014</td>
</tr>
</tbody>
</table>
Recent promising studies in PTCL

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>N</th>
<th>ORR</th>
<th>N in CR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duvelisib</td>
<td>PI3-kinase, γδ</td>
<td>33</td>
<td>47% (PTCL)</td>
<td>2</td>
<td>Horwitz, et al. ASH 2014</td>
</tr>
<tr>
<td>Everolimus</td>
<td>mTOR</td>
<td>16</td>
<td>44%</td>
<td>1</td>
<td>Witzig, et al. Blood 2015</td>
</tr>
<tr>
<td>Alisertib</td>
<td>Aurora kinase</td>
<td>37</td>
<td>30% (PTCL)</td>
<td>2</td>
<td>Barr, et al. JCO 2015</td>
</tr>
<tr>
<td>Romidepsin/Lenalidomide</td>
<td>HDAC/immune-modulatory</td>
<td>21</td>
<td>53% (PTCL/CTCL)</td>
<td>2</td>
<td>Mehta-Shah, et al. ASCO 2015</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Multikinase inhibitor</td>
<td>12</td>
<td>42% (PTCL/CTCL)</td>
<td>4</td>
<td>Gibson, et al. 2014</td>
</tr>
<tr>
<td>Plitidepsin</td>
<td>Cyclic depsipeptide</td>
<td>29</td>
<td>20.7% (PTCL)</td>
<td>2</td>
<td>Ribrag, et al. 2013</td>
</tr>
</tbody>
</table>

The Future....
PTCL: Gene expression signatures - towards more precise classification

- 372 PTCL cases analyzed
- 37% PTCL-NOS re-classified based upon gene-expression signature

PTCL-NOS molecular subgroups

**GATA3**
- 33% of cases
- TH2 Transcription factor
- 5 yr OS = 19%
- Poor clinical outcome
- PI3K and mTOR pathways

**TBX21**
- 49% of cases
- TH1 Transcription factor
- Plasma cell-like gene signature (good outcome)
- 5 yr OS = 38%
- Cytotoxic cell-like gene signature (poor outcome)
- NFκB and STAT3

- 18% unclassifiable
Distinct molecular signatures

ALK(−)ALCL is molecularly distinct from PTCL-NOS and ALK(+)ALCL.

Iqbal et al. Blood 2014;123:2915-2923

ALK negative ALCL: Prognostic impact of DUSP22 and TP63 rearrangements


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SYK as a target in PTCL

- 94% cases PTCL over express SYK
- 38% with ITK-SYK rearrangement
- Inhibition of SYK = inhibition of proliferation + cell death

Pathways and potential targets in PTCL

T-cell lymphoma - Summary

Looking Back
- **Classification** - morphologically based, leaving many cases un-classified
- **Up-front transplant** - still the standard of care, if possible for your patient disease
- **Relapsed/Refractory disease** - choice of treatment mostly empiric

Looking Ahead
- **Genetic-based classification** – better precision will ultimately translate into more specific treatments
- **New targets** - Correlative studies will inform future combination studies through identification of predictors of response and resistance

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- **MSKCC Lymphoma Service**
  - Alison Moskowitz, MD
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  - Craig Moskowitz, MD
  - Ariela Noy, MD
  - Lia Palomba, MD
  - Carol Portlock, MD
  - David Straus, MD
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  - Santosha Vardhana, MD
  - Connie Batlevi, MD, PhD

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- **Nuclear medicine**
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