T CELL LYMPHOMA
CUTANEOUS AND PERIPHERAL

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How the Experts Treat Hematologic Malignancies
Las Vegas, NV
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DISCLOSURES

Christiane Querfeld, MD, PhD:
Advisory Board: Actelion, Celgene, MiRagen, Therakos; Consultant: Mindera; Investigator: Celgene, Kyowa, Actelion, MiRagen, Soligenix

Jasmine Zain, MD:
Speakers bureau with Spectrum, Seattle Genetics and Celgene. Advisory Board: Celgene and Spectrum

Erin Kopp, ACNP-BC
No Disclosures
<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency (%)</th>
<th>5-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indolent</td>
<td></td>
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<tr>
<td>Mycosis fungoides</td>
<td>44</td>
<td>88</td>
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<tr>
<td>- Folliculotrophic MF</td>
<td>4</td>
<td>80</td>
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<tr>
<td>- Pagetoid reticulosis</td>
<td>&lt;1</td>
<td>100</td>
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<tr>
<td>- Granulomatous slack skin</td>
<td>&lt;1</td>
<td>100</td>
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<tr>
<td>CD30+ lymphoproliferative disease</td>
<td></td>
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<tr>
<td>- Anaplastic large cell lymphoma</td>
<td>8</td>
<td>95</td>
</tr>
<tr>
<td>- Lymphomatoid papulosis</td>
<td>12</td>
<td>100</td>
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<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>1</td>
<td>82</td>
</tr>
<tr>
<td>CD4+ small/medium-sized pleomorphic T-cell lymphoma</td>
<td>2</td>
<td>75</td>
</tr>
</tbody>
</table>

*WHO-EORTC (1905 patients), Blood 2005*
<table>
<thead>
<tr>
<th>WHO-EORTC Classification</th>
<th>Frequency (%)</th>
<th>5-Year Survival (%)</th>
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<tbody>
<tr>
<td>Aggressive</td>
<td></td>
<td></td>
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<tr>
<td>Sézary syndrome</td>
<td>3</td>
<td>24</td>
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<tr>
<td>Primary cutaneous NK/T-cell lymphoma, nasal type</td>
<td>&lt;1</td>
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<tr>
<td>Primary cutaneous aggressive epidermotropic CD8⁺ T-cell lymphoma</td>
<td>&lt;1</td>
<td>18</td>
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<tr>
<td>Primary cutaneous γ/δT-cell lymphoma</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>Primary cutaneous peripheral T-cell lymphoma, unspecified</td>
<td>2</td>
<td>16</td>
</tr>
</tbody>
</table>

*WHO-EORTC (1905 patients). Blood 2005*
MYCOSIS FUNGOIDES

- Prototype of CTCL
- Low-grade lymphoma
- Post-thymic T-cell malignancy (CD4+/CD45RO+)
- Malignancy of 3 different T-cell populations:
  - Features of T-regulatory (CD25+FoxP3+), Th2- and Th17-cell phenotype
  - **Th2-driven** immunosuppressive properties
    - Secretion of IL-4, IL-5, IL-6, IL-10
    - Peripheral eosinophilia, elevated IgE
    - Decreased antigen-specific T-cell response
    - Impaired cell mediated cytotoxicity
- Patch, plaque, tumors and erythroderma

*Berger C et al. 2005; Dummer R et al. 1996; Krejsgaard T et al. 2010*
Histopathology

CD4

CD8
Overall Survival
Early and late stage folliculotrophic MF and classic MF

- Aggressive disease course
- Worse outcome between 10 - 15 y after initial onset disease

SÉZARY SYNDROME

- Systemic and aggressive variant
- Exfoliative erythroderma
- Ectropion, alopecia, palmoplantar keratoderma
- Severe pruritus
- Circulating, atypical, malignant T-lymphocytes (Sézary cells)
## Skin manifestations of CTCL at diagnosis

<table>
<thead>
<tr>
<th>Stage at diagnosis</th>
<th>Patients at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1: Patches/plaques covering &lt;10% of body surface</td>
<td>42%</td>
</tr>
<tr>
<td>T2: Patches/plaques covering ≥10% of body surface</td>
<td>30%</td>
</tr>
<tr>
<td>T3: Tumor(s)</td>
<td>15%</td>
</tr>
<tr>
<td>T4: Erythroderma</td>
<td>12%</td>
</tr>
</tbody>
</table>
CTCL STAGING

All patients
- Physical exam (mSWAT)
- Skin biopsy
  - H&E, IHC, TCR
- CBC, CMP, LDH

Selected patients
- Sézary cell counts by flow cytometry
  - CD4+/CD7-; CD4+/CD26-
- TCR analysis in PBMCs
- PET/PCT scan and/or PET scan
- Lymph node biopsy
- Bone marrow biopsy
<table>
<thead>
<tr>
<th>Chemotherapy Regimen</th>
<th>N</th>
<th>Median TTNT (months)</th>
<th>TTNT 95% CI (months)</th>
<th>1-y free from further treatment (%)</th>
<th>2-y free from further treatment (%)</th>
<th>Median line of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All chemotherapy</strong></td>
<td>144</td>
<td>3.9</td>
<td>3.2-5.1</td>
<td>10.7</td>
<td>5.4</td>
<td>4</td>
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<tr>
<td>Hyper CVAD</td>
<td>13</td>
<td>5.0</td>
<td>2.6-5.5</td>
<td>7.7</td>
<td>—</td>
<td>2</td>
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<tr>
<td>CHOP-like regimens</td>
<td>28</td>
<td>5.7</td>
<td>2.3-7.7</td>
<td>14.3</td>
<td>14.3</td>
<td>2.5</td>
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<tr>
<td>Non-CHOP “salvage” regimens</td>
<td>13</td>
<td>2.5</td>
<td>1.7-3.7</td>
<td>7.7</td>
<td>—</td>
<td>6</td>
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<tr>
<td>Gemcitabine-based therapy</td>
<td>30</td>
<td>4.0</td>
<td>3.0-5.7</td>
<td>11.1</td>
<td>—</td>
<td>5</td>
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<tr>
<td>Fludarabine-based therapy</td>
<td>8</td>
<td>2.3</td>
<td>0.3-7.4</td>
<td>12.5</td>
<td>—</td>
<td>5.5</td>
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<tr>
<td>Chlorambucil</td>
<td>14</td>
<td>4.8</td>
<td>2.1-9.0</td>
<td>21.4</td>
<td>21.4</td>
<td>2</td>
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<td>Cyclophosphamide-based therapy</td>
<td>20</td>
<td>3.8</td>
<td>2.7-5.9</td>
<td>10.5</td>
<td>—</td>
<td>4</td>
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<tr>
<td>Mitozantrone-based therapy</td>
<td>3</td>
<td>5.8</td>
<td>2.5-N/A</td>
<td>0</td>
<td>0</td>
<td>3</td>
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<tr>
<td>Single-agent anthracycline</td>
<td>6</td>
<td>1.8</td>
<td>0.7-N/A</td>
<td>—</td>
<td>—</td>
<td>5</td>
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<tr>
<td>Bendamustine</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
<td>4</td>
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<tr>
<td>Etoposide</td>
<td>3</td>
<td>3.2</td>
<td>1.6-N/A</td>
<td>0</td>
<td>0</td>
<td>6</td>
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<tr>
<td>Other purine analogs</td>
<td>6</td>
<td>3.9</td>
<td>2.0-N/A</td>
<td>0</td>
<td>0</td>
<td>7</td>
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## BIOLOGIC THERAPY RESULTS IN CTCL:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median TTNT (mo)</th>
<th>TTNT 95% CI (mo)</th>
<th>1-y free from further treatment (%)</th>
<th>2-y free from further treatment (%)</th>
<th>Median line of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treatments</td>
<td>5.4</td>
<td>5.1-6.1</td>
<td>29.2</td>
<td>21.4</td>
<td>3</td>
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<tr>
<td>Chemotherapy</td>
<td>3.9</td>
<td>3.2-5.1</td>
<td>10.7</td>
<td>5.4</td>
<td>4</td>
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<tr>
<td>α-interferon</td>
<td>8.7</td>
<td>6.0-18.0</td>
<td>41.7</td>
<td>29.1</td>
<td>2</td>
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<tr>
<td>HDACi</td>
<td>4.5</td>
<td>4.0-6.1</td>
<td>20.0</td>
<td>14.5</td>
<td>3</td>
</tr>
<tr>
<td>Bexarotene</td>
<td>7.3</td>
<td>2.6-110.8</td>
<td>47.4</td>
<td>36.8</td>
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<tr>
<td>Alemtuzumab</td>
<td>4.1</td>
<td>2.7-6.5</td>
<td>27.8</td>
<td>27.8</td>
<td>3.5</td>
</tr>
<tr>
<td>Denileukin diftitox</td>
<td>5.1</td>
<td>2.7-6.5</td>
<td>22.7</td>
<td>22.7</td>
<td>4</td>
</tr>
<tr>
<td>AuSCT</td>
<td>7.8</td>
<td>4.7-24.4</td>
<td>41.5</td>
<td>28.4</td>
<td>3</td>
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<tr>
<td>AlloSCT</td>
<td>34.6</td>
<td>11.5-N/A</td>
<td>80.0</td>
<td>53.3</td>
<td>6</td>
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<td>ECP</td>
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<td>5.9-12.8</td>
<td>39.1</td>
<td>25.7</td>
<td>2</td>
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<tr>
<td>TSEB</td>
<td>7.8</td>
<td>4.4-14.7</td>
<td>39.0</td>
<td>26.5</td>
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<tr>
<td>Low-dose methotrexate</td>
<td>5.0</td>
<td>3.6-6.5</td>
<td>25.1</td>
<td>21.2</td>
<td>2</td>
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</table>

What are the key prognostic markers that can help guide clinical management of CTCL?
The 30-year survival of patients with stage IA MF is similar to the expected survival of a race-, age-, and sex-matched control population. The median survival was not been reached at 32½ years.
Topical corticosteroids

Topical chemotherapy
  - Nitrogen mustard
  - Carmustine (BCNU)

Topical retinoids/rexinoids
  - Bexarotene 1% gel
  - Tazarotene 0.1% gel

Phototherapy
  - Narrow band UVB (NB-UVB)
  - Psoralen with UVA (PUVA)
  - UVA-1

Radiation
  - Total skin electron beam radiation (TSEBT)
  - Site-directed radiation

ORR ~ 60-100%
MYCOSIS FUNGOIDES / SÉZARY SYNDROME
SYSTEMIC THERAPIES

- Steroids (short term relief)
- Biologic Therapies
  - IFN-α, IFN-γ, pegylated IFN-α
  - Bexarotene (Targretin)
  - HDACi (vorinostat [Zolinza], romidepsin [Istodax])
  - Romidepsin-lenalidomide (investigational)

- Targeted Therapies
  - Alemtuzumab (Campath)
  - Anti-CCR4 (investigational)
  - Anti-PD1 (investigational)
  - Brentuximab-vedotin (anti-CD30; investigational)

- Extracoporeal photochemotherapy (+/- IFN; investigational)

- Chemotherapy
  - Methotrexate, pralatrexate (Folotyn)
  - Nucleoside analogs, gemcitabine, forodesine
  - Pegylated doxorubicin
  - Combination Chemotherapy (e.g.CHOP)

- Allogeneic stem cell transplantation
• Targeted Therapies
  – Alemtuzumab (Campath)
  – Anti-CCR4 (investigational)
  – Anti-PD1 (investigational)
  – Brentuximab-vedotin (anti-CD30; investigational)
• Extracoporeal photochemotherapy (+/- IFN; +/- bex)
• Chemotherapy
  – Methotrexate, pralatrexate (Folotyn)
  – Nucleoside analogs, gemcitabine, forodesine
  – Pegylated doxorubicin
  – Combination Chemotherapy (e.g.CHOP, ESHAP)
• Allogeneic stem cell transplantation
Stage-based Treatment Algorithm for Mycosis Fungoides and Sézary Syndrome

<table>
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<tr>
<th>IA</th>
<th>IB/IIA</th>
<th>IIB</th>
<th>IIIA/B</th>
<th>IVA₁/₂</th>
<th>IVB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patches/Plaques</td>
<td>Tumors (T₃N₀-3M₀B₀/₁)</td>
<td>Erythroderma (T₄N₀-3M₀B₀/₁)</td>
<td>Erythroderma or Nodal (T₁₄N₀-2M₀B₀-₁)</td>
<td>Visceral (T₁₄N₀-2M₁B₀-₂)</td>
<td></td>
</tr>
</tbody>
</table>

- **Topical steroids (intermittent)**
- **Phototherapy (NB-UVB, PUVA)**
- **Bexarotene gel**
- **Tazarotene gel/cream**
- **Investigational agents (skin-directed)**

**ECP +/- IFN-α and/or +/- bexarotene, romidepsin, alemtuzumab**

**Spot radiation, TSEBT**

**Methotrexate, bexarotene, IFN-α**

**HDACi (romidepsin, vorinostat)**

**Investigational trials (e.g. brentuximab vedotin, anti-CCR-4)**

**Single or multi-agent chemotherapy (gemcitabine, pegylated doxorubicin, CHOP/CHOP-like regimens)**

**Allogeneic transplant**
MF/SS LARGE CELL TRANSFORMATION

Large cell morphology
CD30- > CD30+
Increased LDH, β2-microglobulin
Systemic symptoms
Poor prognosis
Transformation rate?
S/P multiple regimens  
Romidepsin, 
Gemcitabine, Doxil,
Prognostic factors in transformed mycosis fungoides: a retrospective analysis of 100 cases

Marchina F. Benner,1 Patty M. Jansen,2 Maarten H. Vermeer,1 and Rein Willemze1

Departments of 1Dermatology and 2Pathology, Leiden University Medical Center, Leiden, The Netherlands

Blood 119: 1643-9, 2012

No association between percentages of blast cells (25% > 75%).
LYMPHOMATOID PAPULOSIS

- Recurrent papulonodular lesions
  - Frequent ulceration
  - Spontaneous involution
- Indolent course
  - 10-20% associated with malignancy
- Fascin and CD134 predict progression
- TRAF1 expression distinguishes from ALCL
- Observation vs palliative treatment
  - PUVA, low dose methotrexate, topical steroid, topical bexarotene
  - Brentuximab
LyP: Histology

- Type A: Reed-Sternberg-like cells
- Type B: MF-like
- Type C: Large lymphoid cells
- Type D: CD8+
- Type E: Angiocentrism
- Type F: Folliculotropism
CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA

- Solitary or localized (ulcerating) nodules or tumors
- CD4⁺ CD30⁺ helper T-cell phenotype
- Overlap with LyP and cutaneous Hodgkin’s disease
- Anaplastic morphology, non-epidermotropic, large lymphocytes
- No t(2;5) translocation; ALK negative

Therapy:
- Radiation (localized)
- Methotrexate
- Pegylated doxorubicin
- Brentuximab
SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA

- Deep subcutaneous nodules and plaques
- α/β TCR
- CD4⁻/⁺, CD8⁺, CD56⁻/⁺ phenotype
- Systemic symptoms
  - Weight loss, fever, fatigue
  - Variable hemophagocytic syndrome
- Pleomorphic T-cells, panniculitis-like infiltrate with inflammation and necrosis
- 5-year survival > 80%
- Bexarotene, radiation, HDACi, pralatrexate, CHOP-like chemo
SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA

At diagnosis

After 3 months of Targretin Tx
(600 mg daily)
SMALL/MEDIUM-SIZED CD4+ PLEOMORPHIC T-CELL LYMPHOMA

- Deep infiltrated papules, plaques or nodules
- Dense diffuse/nodular infiltrate with small/medium pleomorphic T-cells
- Excision, I.L. steroids, low-dose radiation
SMALL TO MEDIUM-SIZED PLEOMORPHIC CD4+T CELL LYMPHOMA
Multicenter Case Series of Indolent Small/Medium-sized CD8+ Lymphoid Proliferations with Predilection for the Ear and Face

Janet Y. Li, BS¹, Joan Guitart, MD², Melissa P. Pulitzer, MD³, Antonio Subtil, MD⁴, Uma Sundram, MD, PhD⁵, Youn Kim, MD⁶, Janyana Deonizio, MD⁵, Patricia L. Myskowski, MD,¹ Alison Moskowitz, MD⁷, Steven Horwitz, MD⁷, Christiane Querfeld, MD, PhD¹
Comparison of CD4+ SMPTCL and CD8+ PTCL to PTCL NOS

Kaplan-Meier survival estimates

Survival proportion

Analysis time (months)

CD4+ SMPTCL
CD8+ PTCL
PTCL NOS
CUTANEOUS AGGRESSIVE EPIDERMOTROPIC CD8$^+$ CYTOTOXIC T-CELL LYMPHOMA

- M > F
- Necrotic and hemorrhagic plaques
- CD2$^-$, CD3$^+$, CD4$^-$, CD8$^+$, CD45RA$^+$, CD56$^+/-$ phenotype
- Cytotoxic protein (TIA-1, granzyme B, perforin) expression
- TCR$^+$
- EBV negative
- Aggressive with rapid systemic dissemination
- Allo SCT
CLINICAL AND HISTOLOGIC FEATURES

- Panniculitis-like, ulceration and necrosis
- Most common: CD3+, CD4-, CD5-, CD8-/+, gamma M3+, CD45RA-, CD7-
- Cytotoxic protein expression (TIA-1, granzyme B)
- Angioinvasion/-destruction
- Karyorrhexis
- Treatment: SMILE, brentuximab, allo transplant
γ/δ T-cell lymphoma
Thank you

City of Hope
- Steven Rosen
- Dennis Weisenburger
- Steven Forman

MSKCC
- Jim Young/Young lab
- A. Halpern

NWU
- Timothy Kuzel
- Joan Guitart

Supported by Ted Schwartz Foundation

cquerfeld@coh.org
PERIPHERAL T-CELL LYMPHOMA, PTCL MATURE

“Usually Aggressive Systemic T-cell Lymphoma (PTCL)”
- 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*
- Hepatosplenic T-cell lymphoma (may be derived from an immature T-cell)

“Aggressive CTCL”
- Cutaneous aggressive epidermotropic CD8+ cytotoxic TCL
- Cutaneous g/d TCL

“Usually Indolent CTCL”
- Mycosis Fungoides
- Sezary syndrome
- Subcutaneous panniculitis-like
- Primary cutaneous ALCL
- Lymphomatoid papulosis
- Primary cutaneous small / medium CD4+ T-cell lymphoma

*skin lesions are common in these entities
CHALLENGES IN UNDERSTANDING T/NK CELL LYMPHOMAS

- PTCL cell of origin is poorly characterized
- T cell differentiation system is complex - innate and adaptive immunity
- Marked functional diversity of effector cells
- Overlap and plasticity of T cells and NK cells subsets
SUBTYPES OF PTCL

…it is not one disease
PTCL-NOS

- Most common subtype of PTCL in western countries
- M>F at a ratio of 1.5
- Median age 61
- Present with high IPI
- No clinical differences in the varied histologies

Variants: T-zone, Lennert's and follicular
ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA

Nodal presentation, median age 64, M>F

Skin rashes, B symptoms, serositis and effusions, arthritis, polyclonal hyper gammaglobulinemia
Immunological dysfunction

T follicular helper ( TFH ) phenotype and are positive for CD3, CD4, CD10 and CD279 ( PD-10) and CXCL13, EBER+

Cytogenetic abnormality - trisomy 3, trisomy 7 and additional X chromosome

IDH2 genes have been described in 20-40% of cases

HDACI are effective, romidpesin 42%, belinostat 66%

Rituximab, lenalidomide, cyclosporin, low dose methotrexate can be effective in some cases
Anaplastic large cell lymphoma

Sinusoidal pattern

CD30

Anaplastic morphology

- CD30+
- T/null
- CD45 +/-
- BSAP-
- EMA +/-
- CD15- (+)
- Cytotoxic markers (+)
- EBV-
<table>
<thead>
<tr>
<th></th>
<th>Alk expression (IHC)</th>
<th>Cytogenetics/molecular markers</th>
<th>Clinical features</th>
<th>Unique therapy</th>
<th>prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALK+ ALCL</strong></td>
<td>+</td>
<td>T(2,5)- classic-expression of NPM/LK Other translocations may partner with alk on ch 2</td>
<td>Median age -35 Extranodal features</td>
<td>Brentuximab vedotin targeting CD30, Alk inhibitors like Crizotinib</td>
<td>Excellent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ALK- ALCL</strong></td>
<td>-</td>
<td>DUSP22, TP63 affect prognosis, mutually exclusive DUSP22 – outcome similar to ALK+ALCL, TP63- worse prognosis</td>
<td>Older age groups</td>
<td>Brentuximab Vedotin targeting CD30</td>
<td>Intermediate between alk+ ALVL and PTCL-nos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary cutaneous ALCL</strong></td>
<td>-</td>
<td>Skin only presentation overlap with LyP</td>
<td>Skin directed therapies Low dose MTX Radiation</td>
<td></td>
<td>Excellent 100% 5 year survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Seroma associated ALCL of breast</strong></td>
<td>-</td>
<td>Associated with breast implants Median time to presentation is 8 years Arise in the seroma associated with the implant Can be aggressive and have invasive features</td>
<td>Remove the seroma and the implant Radiation or chemotherapy based on extent of disease</td>
<td></td>
<td>Excellent if confined to the seroma</td>
</tr>
</tbody>
</table>

HEPATOSPLENIC T CELL LYMPHOMA

- Rare form of PTCL arises from γδ T cells of the liver sinuses and splenic red pulp
- Median age is 35
- More common in males
- Iatrogenic immunosuppression - Infliximab, purine analogues, Crohn’s disease and recipients of solid organ transplantation disease
- Aggressive with a median survival of 16 months
- ICE or IVAC were more likely to lead to remissions as a bridge to stem cell transplant with a median PFS of 13.3 months and OS of 59 months of the 7/14 surviving patients; Voss, M.H., et al.

- Cells are medium in size - marked pattern of sinusoidal infiltration in the liver and spleen as well as bone marrow
- Immunophenotypically the cells are positive for CD56 or CD16 but negative for CD4, CD8 (CD8+ can be seen occasionally)
- TIA-1 is usually positive but other cytotoxic markers of activation like granzyme and perforin are negative
- The most consistent chromosomal abnormality is isochromosome 7q and trisomy
## ENTEROPATHY ASSOCIATE T-CELL LYMPHOMA

<table>
<thead>
<tr>
<th>EATLI</th>
<th>EATLII</th>
<th>INDOLENT</th>
<th>INTESTINAL INVOLVEMENT OF PTCL-NOS, NK/T-cell lymphoma</th>
</tr>
</thead>
</table>
| Associated with celiac disease  
Anit gliadin antibody positive | No association with Celiac disease | No association with Celiac disease | Clinical features will support the differential diagnosis |
| Common in Northern Europe | Common in Asia | | Intestinal involvement is common in other types of PTCL |
| αβ subtype-express mucosal homing receptor CD103 (HML1)  
Invasion of intestinal mucosa  
Villous atrophy of surrounding tissue | Epitheliotropism, surrounding mucosa intact  
γδ origin, CD8 and CD56 positive | Small mature lymphoid cells that are mostly CD8+ with no evidence of STAT3 SH2 domain mutation | Pathologic features consistent with diagnosis |
| EATL type I and II are aggressive and present with abdominal symptoms and multifocal intestinal involvement that can lead to perforation and other complications. Outcomes are poor with 5 year survival of less than 20% | Indolent clinical course | Treat as per primary diagnosis | |
| Upfront transplant in first remission after CHOEP - 5 yr PFS 38% and OS of 48%- D’Amore et al  
IVE/MTX-ASCT - ORR 69%, PFS 52%, OS 60% -Sieniawski et al 2010 | Do not require aggressive therapy | High incidence of GIT bleed and other complications | |
Subcutaneous nodules - affect the extremities are trunk and vary in size from 0.5 to several cm in size

Atypical lymphoid cells that rim individual fat cells. Surrounding infiltrate can have reactive histiocytes and can show vascular invasion, necrosis and karyorrhexis

Immunophenotyping shows the cells to be positive for CD8 and they are of the αβ type.

γδ subtype is a primary cutaneous γδ T cell lymphoma- the median age at presentation is 30 years but can be seen in children as well.

Associated with a hemophagocytic syndrome that confers a poor prognosis and can occur either before, concurrent with or even after the disease has been treated
ATLL

- HTLV-I virus is endemic in Japan, Caribbean, parts of Africa – prevalence is 6-37%
- Vertical transmission, cell to cell contact
- HTLV1 encodes 3 structural gene (pol, gag and tax) and 2 regulatory genes (tax and rex)
- 2.5% will develop ATLL
- Median age is 45 years
- Prognosis is poor for acute ATLL, allogeneic transplant early
- Mogamolizumab approved in Japan for R/R disease
EXTRANODAL NK/T CELL LYMPHOMAS - NASAL TYPE

- EBV associated, common in Asia, central and South America, native American populations
- Median age – 50
- Nasal or midline facial lesion, skin, GIT, upper respiratory tract or other organs.
- Hemophagocytic syndrome - negative prognostic value
- CD2, cytoplasmic CD3, CD7, CD56, TCR –ve, cytotoxic granules+, EBV+
- Notch-1, wnt, AKT, NF kappa B
  Somatic activating mutations of JAK3 gene have been identified in 35% of cases of NK/T cell lymphoma
- Express MDR associated p-glycoprotein – MTX and asparaginase effective
- Radiation sensitive

PTCL PROGNOSIS

CITY OF HOPE ALGORITHIM
FOR TREATING PTCL/EXCLUDING NK/T CELL LYMPHOMA

Clinical trial
CHOEP x6
CHOP x6 if elderly
ICE/IVAC for HSTCL
IVE+MTX for EATL

CR
clinical trial
autologous stem cell transplant
allogeneic transplant for HSTCL, gamma delta TCL, aggressive
Observation
relapse/ progression

PR/SD/POD
clinical trial
ICE- transplant candidate
HDACI- AITL
Brentuximab vedotin- ALCL, CD30 positive
Pralatrexate

CR/PR
Allogeneic stem cell transplant
Observation
Progression

POD
Clinical trial
Second line therapy
CITY OF HOPE ALGORITHM FOR NK/T CELL LYMPHOMA

Extranodal NK/T cell lymphoma

- stage I/II
  - Combined chemo + radiation (sequential)
    - radiation 45-50 Gy + SMILE
    - Radiation alone if frail
  - Consider stem cell transplant

- stage III/IV
  - clinical trial SMILE
  - CR/PR
    - Consider stem cell transplant
  - Relapse
    - Clinical trial Gelox
Cutaneous T cell lymphoma Impact on Patients

- Significant cosmetic changes
- Increased infection risk
- Risk for other skin lesions/disorders
- Itching
- Psychosocial needs
- Medication/treatment side effects
Cosmetic Changes

- Patches, plaques, and lesions
- Flaking, ulcerated skin
- Tumors
- Inability to wear “regular” clothes
- Erythroderma
Erythroderma
Icthyotic Changes
Plaque
Plaques, patches, and tumor
Necrotic lesions pre debridement
Post debridement
Tumor
Infection Risk

- Scratching
- Presence of colonized bacteria on skin
- Mupirocin
- Bleach bath
Concurrent Skin Conditions

- Not all skin lesions are lymphoma
- Skin cancer risks
- Strict skin surveillance required
Itching

- Relentless
- Anxiety, depression, insomnia
- Does not respond to traditional approaches
- May be alleviated as treatment progresses
- Hydroxyzine, tricyclic anti-depressants, Neurontin/lyrica
- Topical-amlactin, calamine, sarna
Psychosocial Needs

- Relationships
- Intimacy
- Financial challenges
- Transportation
- Work
Utilization and Management of Skin Based Therapies

- Topical corticosteroids
- Topical chemotherapy
  - Nitrogen mustard
  - Carmustine (BCNU)
- Topical retinoids/rexinoids
  - Bexarotene (Targretin)
  - Tazarotene

- Phototherapy
  - NB-UVB
  - PUVA
- Radiation
  - Electron beam radiation
  - Spot directed radiation
Topical Steroids

- Cream or ointment, once or twice daily
- High response rates
- Convenient
- Less expensive

- Skin irritation, allergy
- Skin thinning, stretch marks
- Systemic absorption
Nitrogen Mustard

Mechlorethamine (Valchlor) 0.016% gel

Topical chemotherapy
Requires care when applying. Utilization of gloves important

Skin irritation
SIGNIFICANT redness, burning

Darkening of skin
Often occurs as lesions are resolving. Patients may think disease is progressing
May take 6 months or longer to clear skin
Retinoid Inhibitor

Vitamin A derivatives:

Applied once daily

- Redness, itching, warmth, swelling, burning, scaling, or other irritation
- Increase sensitivity to light-ensure sunscreen
- Expensive
Phototherapy: PUVA or Narrowband-UVB

- 2-3 x week
- Stops the abnormal proliferation of malignant T-cells in the skin by preventing the cells from duplicating their DNA
- Highly effective, with 70-90% of patients experiencing partial or complete response
- Long-term responses

- Skin burn
- Itch
- Nausea (psoralen)
- Risk of skin cancer with long-term exposure of PUVA
Light Therapy

- Narrowband UVB-photosensitivity
- UVB
- PUVA:
  - Nausea
  - Increased risk for skin cancer (SCC and melanoma)
  - Psoralen 2 hours prior to light therapy
Bexarotene

- Systemic retinoid
- Metabolized by P450 3A4
- Can cause primary hypothyroidism
- Can lead to dyslipidemia
- Monitor TSH, and Free T4, triglyceride every 8 weeks
- Leukopenia and neutropenia
- Take with food-high fat food
Bexarotene

- Diarrhea, fatigue, rash, anemia, abdominal pain, muscle spasm, confusion, chills, eosinophilia, increased coag times, arthralgia, depression/agitation, pharyngitis
- Headache, asthenia, rash most common outside of endocrine and lipid
Peripheral T Cell Lymphoma

- Lenalidomide
- Romidepsin
- Brentuximab Vedotin
- Pralatrexate
- Belinostat
Lenalidomide

- Will cause serious birth defect-registry with pregnancy test involved
- Neutropenia
- Thrombocytopenia
- Blood clots- full strength aspirin; careful with exogenous hormones
- Tumor lysis syndrome
- S/E include diarrhea, constipation, itching, fatigue, rash
- Tumor flare
Romidepsin

- Myelosuppression
- Infection-sepsis, viral reactivation (EBV)
- Prolonged QT-monitor other drugs, Magnesium and potassium level with each dose, EKG
- TLS
- S/E-pancytopenia, fatigue, infection
- Nausea-highly emetogenic
Brentuximab Vedotin

- 1.8mg/kg every 3 weeks up to 16 cycles
- Peripheral neuropathy
- Infusion reaction
- Neutropenia
- TLS
- Progressive Multifocal Leukoencephalopathy
- S/E-fatigue, nausea, URI, diarrhea, pyrexia, rash, cough, vomiting
Pralatrexate

- 30mg/m² once weekly for 6 weeks in a 7 week cycle
- Vitamin B12 1 mg IM every 8-10 weeks
- Folic acid 1mg daily
- Pancytopenia
- Mucositis
- Fetal harm
- Watch renal and hepatic function
- Sepsis, febrile neutropenia, dehydration, dyspnea
Belinostat

- 1000 mg/m2 on day 1-5 in a 21 day cycle
- Pancytopenia
- Liver function test increase
- TLS
- Infection
- Nausea, fatigue, pyrexia, vomiting
Summary

- T Cell lymphoma is a rare disease that requires specialized care to ensure positive outcomes
- Approach must be holistic as this disease is often visible to the patient and to others
- Significant adverse effects possible due to therapeutic regimens
- Nursing assessment, intervention, collaboration, and evaluation are critical