Cutaneous Lymphomas

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City of Hope

How the Experts Treat Hematologic Malignancies
March 10 – 12, 2016
Conflict of Interest Statement

Christiane Querfeld, MD, PhD

- Advisory Board
  - Actelion, Celgene, MiRagen, Therakos

- Consultant
  - Mindera

- Investigator
  - Celgene, Kyowa, Actelion, MiRagen, Soligenix
<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency (%)</th>
<th>5-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indolent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>44</td>
<td>88</td>
</tr>
<tr>
<td>• Folliculotropc MF</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>• Pagetoid reticulosis</td>
<td>&lt;1</td>
<td>100</td>
</tr>
<tr>
<td>• Granulomatous slack skin</td>
<td>&lt;1</td>
<td>100</td>
</tr>
<tr>
<td><strong>CD30⁺ lymphoproliferative disease</strong></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td><strong>Subcutaneous panniculitis-like T-cell lymphoma</strong></td>
<td>1</td>
<td>82</td>
</tr>
<tr>
<td><strong>CD4⁺ small/medium-sized pleomorphic T-cell lymphoma</strong></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>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive Sézary syndrome</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>Primary cutaneous NK/T-cell lymphoma, nasal type</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma</td>
<td>&lt;1</td>
<td>18</td>
</tr>
<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+), Th$_2$- and Th$_{17}$-cell phenotype
  - Th$_2$-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 folliculotropic MF and classic MF

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

A case-control study of clinicopathologic features, prognosis, and therapeutic responses in patients with granulomatous mycosis fungoides

Janet Y. Li, BS, Melissa P. Pulitzer, MD, Patricia L. Myskowski, MD, Stephen W. Dusza, DrPH, Steven Horwitz, MD, Alison Moskowitz, MD, and Christiane Querfeld, MD, PhD

New York, New York
Early and advanced stage granulomatous MF vs classic MF

- 6.3% of MF patients diagnosed with GMF
- More frequent disease progression and poorer response to skin-directed therapies are seen in GMF patients compared to classic MF

Li JY et al. JAAD 2013
48y ♀, MF IB (T2N0M0B0)

31y ♀, MF IA (T1N0M0B0)
Clinical Presentations of Mycosis fungoides
Sézary Syndrome

- Systemic and aggressive variant
- Exfoliative erythroderma
- Ectropion, alopecia, palmoplantar keratoderma
- Severe pruritus
- Circulating, atypical, malignant T-lymphocytes (Sézary cells)
Mycosis Fungoides / Sézary Syndrome
Molecular Biology and Genetics

- Expression of various skin homing ligands/receptors CLA, LFA1, CCR-4, CCR-7, CCR-10, and CXCR4
- Chromosomal aberrations (loss on 1p, 9p, 10q, 17p, and 19, gains on 4q, 17q, and 18)
- Diminished expression/activation of tumor suppressor genes TGF-β receptor II, FAS, p15, and p16
- Enhanced expression/activation of JUNB, Bcl-2, Bcl-2-related genes, STAT3, STAT5 and NF-κB
- Aberrant expression of PLS3, EphA4 and TWIST1
- Microsatellite instability, promoter hypermethylation

Central memory T-cell: **CCR7/L-selectin+  CD27+, CCR4+ , CLA+**

Skin resident effector memory T-cell: **CCR7/L-selectin- CD27 -, CCR4+ , CLA+**
Mycosis fungoides/Sézary syndrome

**Epidemiology**

- Most common cutaneous T-cell lymphoma
- Incidence: 6.4 cases per million people
- Prevalence: 26,000 to 30,000 cases
- 50 years
- M : F = 2:1
- AA>C>Asian
- HLA association: AW31, AW32, B8, BW35, and DR5

*Criscione & Weinstock. Arch Dermatol 2007*
### 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>

*Querfeld C & Rosen ST in Abeloff’s Clinical Oncology, 2013*
Disease-specific survival according to (A) clinical stage and (B) T classification

Risk of Progression
- T-stage
- Folliculotropic MF
- Large cell transformation
- Elevated LDH
- Peripheral blood clone (B0b)
- Tumor distribution

Agar N S et al. JCO 2010;28:4730-4739
# Clinical Staging - Simplified Version

<table>
<thead>
<tr>
<th></th>
<th>T1: Limited patch/plaque (&lt;10% BSA)</th>
<th>T2: Generalized patch/plaque (≥10% BSA)</th>
<th>T3: Tumor</th>
<th>T4: Erythroderma</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0: Nodes clinically uninvolved</td>
<td>M0</td>
<td>IA</td>
<td>IB</td>
<td>IIIB</td>
</tr>
<tr>
<td>N1: Nodes enlarged, histologically uninvolved</td>
<td>M0</td>
<td>IIA</td>
<td>IIIB</td>
<td>IIIA</td>
</tr>
<tr>
<td>N2-3: Nodes enlarged, histologically involved</td>
<td>M0</td>
<td>IVA</td>
<td>IVB</td>
<td>IIIB</td>
</tr>
<tr>
<td>N0-3: M1: visceral involvement</td>
<td>M1</td>
<td>IVB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **B0**: Absence of significant peripheral blood Sézary cells
- **B1**: Low tumor burden that does not meet the criteria of B2 cells
- **B2**: Significant peripheral blood >1000/μL Sézary cells with positive clone


= Early-stage disease  = Advanced disease
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/CT scans
- Lymph node biopsy
- Bone marrow biopsy
Chemotherapy Results in CTCL:

<table>
<thead>
<tr>
<th>Therapy Type</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>All chemotherapy</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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<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>Mitoxantrone-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>
</tr>
<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>
</tr>
<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>
</tr>
</tbody>
</table>

## 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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
<td>2</td>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>ECP</td>
<td>9.2</td>
<td>5.9-12.8</td>
<td>39.1</td>
<td>25.7</td>
<td>2</td>
</tr>
<tr>
<td>TSEB</td>
<td>7.8</td>
<td>4.4-14.7</td>
<td>39.0</td>
<td>26.5</td>
<td>2</td>
</tr>
<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>
</tr>
</tbody>
</table>

The role of the immune microenvironment in CTCL

**Tumor microenvironment**
- Langerhans cells, dendritic cells, macrophages, NK cells
- Tissue structure (collagen, proteins)

**Chronic Antigen Stimulation**
- Cytotoxic CD8+ T-cells
- Th1 T-cell functions (IFN-γ, IL12)
- Regulatory T-cells (CD25+)

**Suppression**
- Cytotoxicity

**Favoring tumor growth:**
- Cytokines
- Breakdown of tissue proteins

**Escape mechanisms by cancerous cells**
- Change in surface receptors/adhesion molecules
- Cytokines (IL-10; TGF-β)
- PD-1 and CTLA-4 ↑ (immune tolerance)
- Death receptor: FAS ↓; defective apoptosis

**Adaptive immune response**
Prognostic impact of the immune microenvironment

Better prognosis
- High Langerhans cell numbers >90/mm²
- Increased numbers of CD8+ and CD1a+ cells
- Higher numbers of Tregs (FoxP3+)

Worse prognosis/disease progression
- Dense infiltrates of macrophages [CD163+; CD68+]
- Dense infiltrates of mast cells

Meissner et al. 1990; Goteri et al. 2003; Gjerdrum et al. 2007; Sugaya et al. 2012; Rabenhorst et al. 2012
Figure 3.

A: Patch  
B: Plaque  
C: Tumor
Stage: bright yellow: IVA; yellow: IIB; blue: IB; bright blue: IA
Clinical: bright yellow: erythroderma; yellow: tumor; blue: patch/plaque; black: SCC
Mycosis Fungoides/Sézary Syndrome

Clinical signs

Skin pathology
Laboratory tests

Molecular tests

Prognostication

What are the key prognostic markers that can help guide clinical management of CTCL?

Management
Clinical Stage IA (Limited Patch and Plaque) Mycosis Fungoides: A Long-term Outcome Analysis

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.

2% (3 pts.) died of disease.

Kim YH et al; Arch Dermatol 1996
Mycosis fungoides / Sézary syndrome

Skin Directed Therapies

- 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%

NCCN Practice Guidelines in Oncology - Mycosis fungoides and Sézary syndrome v.3.2.2012
Mycosis fungoides / Sézary syndrome

**Systemic Therapies**

- **Steroids** (short term relief)
- **Biologic Therapies**
  - IFN-α, IFN-γ, pegylated IFN-α
  - Bexarotene
  - HDACi (vorinostat, romidepsin)
  - Romidepsin-lenalidomide (investigational)
- **Targeted Therapies**
  - Alemtuzumab
  - Anti-CCR4 (investigational)
  - Anti-PD1, anti-PD-L1, anti-CD47 (investigational)
  - Brentuximab-vedotin (anti-CD30; investigational)
- **Extracorporeal photochemotherapy (+/- IFN; +/- bex)**
- **Chemotherapy**
  - Methotrexate, pralatrexate
  - Nucleoside analogs, gemcitabine, forodesine
  - Liposomal doxorubicin
  - Combination Chemotherapy (CHOP, ESHAP)
- **Allogeneic stem cell transplantation**
## Stage-based Treatment Algorithm for Mycosis Fungoides and Sézary Syndrome

<table>
<thead>
<tr>
<th>Stage</th>
<th>IA</th>
<th>IB/IIA</th>
<th>IIB</th>
<th>IIIA/B</th>
<th>IVA_{1/2}</th>
<th>IVB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patches/Plaques $\left(T_{1/2}N_0M_0B_{0/1}\right)$</td>
<td>Tumors $\left(T_{3}N_0M_0B_{0/1}\right)$</td>
<td>Erythroderma $\left(T_{4}N_0M_0B_{0/1}\right)$</td>
<td>Erythroderma or Nodal $\left(T_{1-4}N_0M_0B_{0-1}\right)$</td>
<td>Visceral $\left(T_{1-4}N_0M_1B_{0-2}\right)$</td>
<td></td>
</tr>
</tbody>
</table>

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

### IA

- **Investigational agents (skin-directed)**

### IB/IIA

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

### IIB

- **Methotrexate, bexarotene, IFN-α**
- **HDACi (romidepsin, vorinostat)**

### IIIA/B

- **Investigational trials (e.g. brentuximab vedotin, anti-CCR-4)**
- **Single or multi-agent chemotherapy (gemcitabine, pegylated doxorubicin, CHOP/CHOP-like regimens)**
- **Allogeneic transplant**
# Systemic Agents Approved in CTCL

<table>
<thead>
<tr>
<th>Agent (class)</th>
<th>Dosage</th>
<th>Toxicity</th>
<th>N</th>
<th>Stage</th>
<th>ORR</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denileukin diftitox (fusion protein) (E7777 currently in clinical trial)</td>
<td>18ug/kg/day IV x 5 days – q3weeks</td>
<td>Increased LFTs, Capillary leak syndrome</td>
<td>71</td>
<td>IB-IVA</td>
<td>30%</td>
<td>4 mo</td>
</tr>
<tr>
<td>Bexarotene (retinoic X-receptor agonist)</td>
<td>300mg/m²/daily PO</td>
<td>Hypothyroidism, Hyperlipidemia</td>
<td>62</td>
<td>IIB-IVA</td>
<td>32%</td>
<td>5 mo</td>
</tr>
<tr>
<td>Vorinostat (class I/II HDAC inhibitor)</td>
<td>400mg daily PO</td>
<td>Asthenia, Diarrhea, Cytopenia</td>
<td>74</td>
<td>IB-IVB</td>
<td>30%</td>
<td>6 mo</td>
</tr>
<tr>
<td>Romidepsin (pan HDAC inhibitor)</td>
<td>14mg/m²/ IV 1, 8, 15 q month</td>
<td>Asthenia, Cytopenia</td>
<td>96</td>
<td>IB-IVA</td>
<td>34%</td>
<td>15 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>71</td>
<td></td>
<td>35%</td>
<td>11 mo</td>
</tr>
</tbody>
</table>
Care and Quality of Life

- Monitor for cutaneous infections
  - Bacterial (S. aureus)
  - Viral (HSV, VZV, HHV6)
- Monitor for other skin cancers
- Pruritus, pain
- Nutritional deficiencies
- Psychological needs
MF/SS large cell transformation

Large cell morphology
CD30- > CD30+
Increased LDH, β2-microglobulin
Systemic symptoms
Poor prognosis
Transformation rate ?
SS/IVA2; 1/14/2013

S/p romidepsin, gemcitabine, liposomal doxorubicin, bexarotene, pralatrexate, PI3K inhibitor

7/1/2013
## Mycosis Fungoides - LCT

<table>
<thead>
<tr>
<th>Study</th>
<th>#</th>
<th>LCT at diagnosis of MF (%)</th>
<th>IA-IIA IV</th>
<th>Stage at LCT (%)</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dmitrovsky et al. 1987</td>
<td>12</td>
<td>0/12 (0)</td>
<td>1/12 (8)</td>
<td>11/12 (92)</td>
<td>2</td>
</tr>
<tr>
<td>Salhani et al. 1988</td>
<td>17</td>
<td>7/17 (41)</td>
<td>6/17 (35)</td>
<td>11/17 (65)</td>
<td>12</td>
</tr>
<tr>
<td>Greer et al. 1990</td>
<td>22</td>
<td>9/22 (41)</td>
<td>9/22 (41)</td>
<td>13/22 (59)</td>
<td>12</td>
</tr>
<tr>
<td>Diamandidou et al. 1998</td>
<td>26</td>
<td>9/26 (35)</td>
<td>7/26 (27)</td>
<td>10/26 (38)</td>
<td>19</td>
</tr>
<tr>
<td>Vergier et al. 2000</td>
<td>45</td>
<td>8/45 (18)</td>
<td>2/45 (4)</td>
<td>24/45 (53)</td>
<td>36</td>
</tr>
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<td>Barberio et al. 2007</td>
<td>17</td>
<td>2/17 (12)</td>
<td>7/17 (41)</td>
<td>7/17 (41)</td>
<td>27</td>
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<td>Arulogun et al. 2008.</td>
<td>22</td>
<td>7/22 (32)</td>
<td>3/22 (14)</td>
<td>11/22 (50)</td>
<td>27</td>
</tr>
<tr>
<td>Agar et al. 2010</td>
<td>70</td>
<td>70/70 (100)</td>
<td>NR</td>
<td>NR</td>
<td>100</td>
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<tr>
<td>Benner et al. 2012</td>
<td>100</td>
<td>42/100 (42)</td>
<td>10 (10)</td>
<td>65 (65)</td>
<td>24</td>
</tr>
</tbody>
</table>
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%)
CTCL subtypes
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
  - Liposomal 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, methotrexate, pralatrexate, HDACi
Subcutaneous panniculitis-like T-cell lymphoma

At diagnosis

After 3 months of bexarotene (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, BS\textsuperscript{1}, Joan Guitart, MD\textsuperscript{2}, Melissa P. Pulitzer, MD\textsuperscript{3}, Antonio Subtil, MD\textsuperscript{4}, Uma Sundram, MD, PhD\textsuperscript{5}, Youn Kim, MD\textsuperscript{6}, Janyana Deonizio, MD\textsuperscript{2}, Patricia L. Myskowski, MD\textsuperscript{1}, Alison Moskowitz, MD\textsuperscript{7}, Steven Horwitz, MD\textsuperscript{7}, Christiane Querfeld, MD, PhD\textsuperscript{1}

Li JY et al Am J Dermatopathol 2013 (in press)
Comparison of CD4+ SMPTCL and CD8+ PTCL to PTCL NOS

Kaplan-Meier survival estimates

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
Cutaneous γ/δ T-cell lymphoma

- Disseminated (ulcerated) plaques, nodules or tumors with frequent involvement of mucosal & extranodal sites
- CD3⁺, CD4⁻, CD5⁻, CD7⁻/+ , CD8⁻/+ , TIA1⁺, granzyme B⁺, CD56⁺ phenotype
- Systemic symptoms frequent
  - Weight loss, fever, fatigue
- Hemophagocytic syndrome associated with panniculitis-like tumors
- Median survival 15 months
- Aggressive chemotherapy (SMILE-like), allogeneic transplantation

WHO-EORTC 2005
Clinical and Histologic Features

- Panniculitis-like, ulceration and necrosis
- Intermediate-sized T-cells
- Most common: CD3+, CD4-, CD5-, CD8-/+, gamma M3+, CD45RA-, CD7-
- Cytotoxic protein expression (TIA-1, granzyme B)
- Angioinvasion/-destruction
- Karyorrhexis
γ/δ T-cell lymphoma
Legs most commonly involved
  - Deep plaques resembling panniculitis
  - Patches resembling psoriasis

Extensive ulceration assoc w progression

Constitutional symptoms

↑LDH

Autoimmunity

CD3+, CD4-/CD8-, BF1-, γ-M1+, TIA-1+, Gr-B+, CD45RA-, CD7-
Chemotherapy:

- Modified methotrexate, ifosfamide, L-asparaginase, etoposide (SMILE) adopted from regimen with NK/T cell lymphomas
- Brentuximab for cases with CD30 expression
- Evaluated for allogeneic HSCT
<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency (%)</th>
<th>5-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indolent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous marginal zone B-cell</td>
<td>7</td>
<td>99</td>
</tr>
<tr>
<td>lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous follicle center</td>
<td>11</td>
<td>95</td>
</tr>
<tr>
<td>lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous diffuse large B-cell</td>
<td>4</td>
<td>55</td>
</tr>
<tr>
<td>lymphoma, leg type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous diffuse large B-cell</td>
<td>&lt;1</td>
<td>50</td>
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<tr>
<td>lymphoma, other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Anaplastic and plasmablastic subtypes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(HIV-associated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• T-cell/histiocyte-rich large B-cell</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lymphomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Intravascular large B-cell lymphoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*WHO-EORTC (1905 patients), Blood 2005*
<table>
<thead>
<tr>
<th></th>
<th><strong>MZL</strong></th>
<th><strong>FCCL</strong></th>
<th><strong>DLBC, LT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td>❯ Solitary or multiple papules, plaques or nodules preferentially localized on the extremities</td>
<td>❯ Solitary or grouped tumors presenting on the head or on the trunk</td>
<td>❯ Solitary or multiple tumors presenting mainly on the leg(s) and rarely at other sites</td>
</tr>
<tr>
<td></td>
<td>❯ Can be associated with B. burgdorferi</td>
<td>❯ Cutaneous relapses in 20%</td>
<td>❯ Frequent relapses and extracutaneous dissemination</td>
</tr>
<tr>
<td></td>
<td>❯ Frequent cutaneous relapses, rarely extracutaneous dissemination</td>
<td>❯ Extracutaneous dissemination in 5-10%</td>
<td></td>
</tr>
<tr>
<td><strong>Histological features</strong></td>
<td>❯ Patchy or diffuse infiltrates of small B-cells</td>
<td>❯ Follicular or diffuse infiltrates of follicle center cells</td>
<td>❯ Diffuse infiltrates</td>
</tr>
<tr>
<td></td>
<td>❯ Lymphoplasmacytoid &amp; plasma cells</td>
<td>❯ Mix of centrocytes &amp; centroblasts</td>
<td>❯ Predominance of centroblasts and immunoblasts</td>
</tr>
<tr>
<td><strong>Immunophenotype</strong></td>
<td>❯ monotypic cIg, CD5-, CD79a+, Bcl-2+, Bcl-6-, CD10-, MUM-1+ (plasma cells)</td>
<td>❯ monotypic sIg, CD20+, CD79a+, Bcl-2-, Bcl-6+, CD10+/-, MUM-1-, FOXP1+/-</td>
<td>❯ monotypic sIg or cIg, CD20+, CD79a+, Bcl-2+, Bcl-6+/-, CD10-</td>
</tr>
<tr>
<td><strong>5-year survival</strong></td>
<td>98%</td>
<td>95%</td>
<td>50%</td>
</tr>
</tbody>
</table>
Clinical and histologic features:

- Patchy/diffuse heterogeneous infiltrate
  - Small lymphocytes including marginal zone cells (centrocyte-like)
  - Lymphoplasmacytoid cells with intranuclear inclusions, plasma cells
  - Reactive germinal centers
GI problems in 61.2%

Autoimmunity in 20% (16 pts)
  - Hashimoto thyroiditis (8)
  - ANA (3)
  - LE (3)
  - Sjögren (1)
Primary Cutaneous Follicle Center Lymphoma

- Most common PCBCL
- Solitary or grouped papules or plaques on head and trunk
- CD20⁺, CD79a⁺, CD5⁻, CD10⁺, bcl-6⁺, bcl-2⁻, MUM-1⁻ phenotype
- Cutaneous relapses ~50% , extracutaneous dissemination 5-10%
- Follicular, follicular/diffuse or diffuse dermal infiltrate
  - Neoplastic follicle center cells
  - > Centrocytes (small to large cleaved cells) in low-grade PFCL
  - > Centroblasts (large round cells with prominent nuclei) in high-grade PFCL
- Inactivation of p15 and p16 gene in 10-30%
- No t(14:18)
- Therapy
  - Radiation
  - Systemic/ intralesional Rituximab
  - Palliative Chemotherapy and/or Rituximab
Cutaneous Follicle Center Lymphoma
- Follicular structures with centrocytes and centroblasts
- Poorly formed mantle zone
- No tingible body macrophages
Primary Cutaneous Follicular Proliferation
When to worry:

- Multiple lesions (different anatomic regions)
- Large and deep nodules
- Large cell morphology
- Bcl-2 expression
- Older patient population
Primary cutaneous diffuse large B-cell lymphoma, leg type

- Elderly females
- Solitary or multiple red-violaceous tumors mostly on lower legs, rarely at other sites
- $\text{CD20}^+$, $\text{CD5}^-$, $\text{CD79a}^+$, $\text{bcl-2}^{+/-}$, $\text{CD10}^-$, $\text{bcl-6}^{+/-}$ $\text{MUM-1}^+$, $\text{FOXP1}^{+/-}$
- Frequent cutaneous relapses and extracutaneous dissemination
- No $\text{t}(14:18)$
- Chromosomal gains on chromosome 7p and 18q, loss of 6q
- Diffuse infiltrates with predominance of confluent sheets of centroblasts and immunoblasts
- 5-year survival (multiple lesions): 50%
- Systemic chemotherapy and/or Rituximab, radiation
Clinical and Histologic Features:
Primary cutaneous diffuse large B-cell lymphoma, leg type
Specific survival of 115 patients with a primary cutaneous diffuse large B-cell lymphoma, leg type
Reclassification of 300 Primary Cutaneous B-Cell Lymphomas According to the New WHO–EORTC Classification for Cutaneous Lymphomas: Comparison With Previous Classifications and Identification of Prognostic Markers

Nancy J. Senff, Juliette J. Hoefnagel, Patty M. Jansen, Maarten H. Vermeer, Joop van Baarlen, Willeke A. Blokx, Marijke R. Canninga-van Dijk, Marie-Louise Geerts, Konnie M. Hebeda, Philip M. Klain, King H. Lam, Chris J. L. M. Meijer, and Rein Willemze

5-y DSS:
- 71 pcMZL 98%
- 171 pcFCL 95%
- 58 DLBCL-LT 50%

Multivariate analysis for pcFCL: FoxP1 expression and localization on leg carries poor prognosis
Cutaneous B-cell lymphomas

ISCL/EORTC staging recommendations

- Complete history and review of systems (e.g. B-symptoms, organ-specific signs) and physical examination.
- Laboratory studies: CBC & diff, CMP, LDH, S-PEP, U-PEP
- Serology and/or PCR for B. afzelii (certain areas associated with MZL)
- Imaging studies (chest, abdomen and pelvis,) and neck in cases of skin lesions in the head and neck area
- Bone marrow biopsy and aspirate are required in LBCL, LT, but optional in indolent CBCL (MZL and FCL)
Additional Tests:

- ANA
- RPR or VDRL
- H. pylori AB
- Hepatitis A, B, C panel
Results of bone marrow examination in 275 patients with histological features that suggest an indolent type of cutaneous B-cell lymphoma

Summary

Whether or not bone marrow biopsies should be performed routinely in patients with skin lesions that show histological features consistent with an indolent B-cell lymphoma [marginal zone lymphoma (MZL) or follicle centre lymphoma (FCL)] has been debated. As no studies have addressed this question for this group of lymphomas, we evaluated the results of bone

<table>
<thead>
<tr>
<th></th>
<th>MZL</th>
<th>FCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>107</td>
<td>250</td>
</tr>
<tr>
<td>No BM biopsy - 5 DSS</td>
<td>23</td>
<td>43</td>
</tr>
<tr>
<td>BM biopsy – 5 DSS</td>
<td>82</td>
<td>193</td>
</tr>
<tr>
<td>Staging negative</td>
<td>76</td>
<td>157</td>
</tr>
<tr>
<td>Staging positive</td>
<td>6</td>
<td>36</td>
</tr>
<tr>
<td>BM involvement</td>
<td>2 (2%)</td>
<td>22 (11%)</td>
</tr>
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</table>
FCL patients with BM involvement had more extensive extracutaneous involvement and worse overall survival.
<table>
<thead>
<tr>
<th>First and second line therapies</th>
<th>Investigational therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>Photodynamic therapy</td>
</tr>
<tr>
<td>Excision</td>
<td>Intrallesional Cisplatin</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Mechloretamine/Clobetasol</td>
</tr>
<tr>
<td>Local Radiation</td>
<td>Adenovirus-mediated IFNγ gene transfer</td>
</tr>
<tr>
<td>Intrallesional IFN alpha 2a</td>
<td>Thalidomide, Lenalidomide</td>
</tr>
<tr>
<td>Intrallesional Rituximab</td>
<td>Topical Imiquimod</td>
</tr>
<tr>
<td>Systemic multi-agent chemotherapy, R-CHOP</td>
<td>Topical hexadecylphosphocholine</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Yttrium-90 ibritumomab tiuxetan radioimmunotherapy</td>
</tr>
<tr>
<td>Radiochemotherapy</td>
<td></td>
</tr>
</tbody>
</table>
Therapy results in PCMZL

<table>
<thead>
<tr>
<th>Cumulative studies on:</th>
<th>Patients (N=)</th>
<th>CR (%)</th>
<th>Relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>132</td>
<td>130/132 (99%)</td>
<td>60/130 (46%)</td>
</tr>
<tr>
<td>Excision</td>
<td>75</td>
<td>74/75 (99%)</td>
<td>32/74 (43%)</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>8</td>
<td>100%</td>
<td>2/8 (25%)</td>
</tr>
<tr>
<td>Rituximab i.l.</td>
<td>9</td>
<td>8/9 (89%)</td>
<td>5/8 (62%)</td>
</tr>
<tr>
<td>Rituximab i.v.</td>
<td>3</td>
<td>2/3 (67%)</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>14</td>
<td>9/14 (64%)</td>
<td>3/9 (33%)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>14</td>
<td>6/14 (43%)</td>
<td>1/5 (20%)*</td>
</tr>
<tr>
<td>Multi-agent chemotherapy</td>
<td>33</td>
<td>28/33 (85%)</td>
<td>16/28 (57%)</td>
</tr>
</tbody>
</table>

* Data on relapse rate were not available in all patients

Willemze et al 2008
## Therapy results in PCFCL

<table>
<thead>
<tr>
<th>Cumulative studies on:</th>
<th>Patients (N=)</th>
<th>CR (%)</th>
<th>Relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>460</td>
<td>457/460 (99%)</td>
<td>216/457 (47%)</td>
</tr>
<tr>
<td>Excision</td>
<td>93</td>
<td>91/93 (98%)</td>
<td>36/91 (40%)</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>7</td>
<td>100%</td>
<td>2/7 (29%)</td>
</tr>
<tr>
<td>Rituximab i.l.</td>
<td>12</td>
<td>10/12 (83%)</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td>Rituximab i.v.</td>
<td>28</td>
<td>21/28 (75%)</td>
<td>3/19 (16%)*</td>
</tr>
<tr>
<td>Multi-agent chemotherapy</td>
<td>104</td>
<td>88/104 (85%)</td>
<td>42/83 (51%)*</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>2</td>
<td>1/2 (50%)</td>
<td>0/1 (0%)</td>
</tr>
<tr>
<td>Chemoradiotherapy</td>
<td>7</td>
<td>100%</td>
<td>1/7 (14%)</td>
</tr>
</tbody>
</table>

* Data on relapse rate were not available in all patients

Willemze et al 2008
Thank you

City of Hope
- Steven Rosen
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