Cutaneous Lymphomas

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City of Hope

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How the Experts Treat Hematologic Malignancies Symposium
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Disclosures

- **Advisory Board**
  - MiRagen, Actelion, Celgene, Therakos

- **Consultant**
  - Mindera

- **Investigator**
  - Celgene, MiRagen, Trillium Therapeutics, Actelion, Kyowa, Soligenix
<table>
<thead>
<tr>
<th>Cutaneous T cell lymphomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td>• Folliculotropism type</td>
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<tr>
<td>• Pagetoid reticulosis</td>
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<tr>
<td>• Granulomatous slack skin</td>
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<tr>
<td>Sézary syndrome</td>
</tr>
<tr>
<td>Primary cutaneous CD30+ lymphoproliferative disorders</td>
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<tr>
<td>• Lymphomatoid papulosis (type A-E)</td>
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<tr>
<td>• Primary cutaneous anaplastic large cell lymphoma</td>
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<tr>
<td>Subcutaneous panniculitis-like T cell lymphoma</td>
</tr>
<tr>
<td>Primary cutaneous γδ T cell lymphoma</td>
</tr>
<tr>
<td>Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T cell lymphoma</td>
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<tr>
<td>Primary cutaneous acral CD8+ T cell lymphoma</td>
</tr>
<tr>
<td>CD4+ small/medium-sized pleomorphic T-cell lymphoproliferative disorder</td>
</tr>
<tr>
<td>Primary cutaneous peripheral T cell lymphoma, NOS</td>
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</tbody>
</table>

Swerdlow SH et al. Blood 2016 127:2375-2390
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*
Folliculotropic MF
Sézary Syndrome

- Systemic and aggressive variant
- Exfoliative erythroderma
- Ectropion, alopecia, palmoplantar keratoderma
- Severe pruritus
- Circulating, atypical, malignant T-lymphocytes (Sézary cells)
CTCL Staging

**All patients**
- Physical exam
  - Skin burden, nodes
- Skin biopsy
  - Immunophenotyping
  - TCR analysis
- CBC, CMP, LDH

**Selected patients**
- Sézary cell counts by flow cytometry
  - CD4+/CD7-; CD4+/CD26-
  - CD4:CD8 ratio
- TCR analysis in PBMCs
- HTLV-1 titer
- PET/CT scans
- Lymph node biopsy
- Bone marrow biopsy
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
Stage-based Treatment Algorithm for Mycosis Fungoides and Sézary Syndrome

<table>
<thead>
<tr>
<th>Stage</th>
<th>IA</th>
<th>IB/IIIA</th>
<th>IIB</th>
<th>IIIA/B</th>
<th>IVA₁/₂</th>
<th>IVB</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Patches/Plaques $(T₁/₂N₀M₀B₀/₁)$</td>
<td>Tumors $(T₃N₀₋₂M₀B₀/₁)$</td>
<td>Erythroderma $(T₄N₀₋₂M₀B₀/₁)$</td>
<td>Erythroderma or Nodal $(T₁₋₄N₀₋₂M₀B₀₋₁)$</td>
<td>Visceral $(T₁₋₄N₀₋₂M₁B₀₋₂)$</td>
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</table>

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

- **Phototherapy +/- IFN-α and/or +/- bexarotene**
- **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**
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
Disabling Pruritus and Pain

<table>
<thead>
<tr>
<th>Days</th>
<th>Treatment</th>
<th>06/27/16</th>
<th>06/28/16</th>
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<tbody>
<tr>
<td>Tuesday</td>
<td>Monotolite</td>
<td>6/17/16</td>
<td>6/18/16</td>
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<td>Monday</td>
<td>Treatment</td>
<td>6/17/16</td>
<td>6/18/16</td>
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<tr>
<td>Thursday</td>
<td>Treatment</td>
<td>6/13/16</td>
<td>6/14/16</td>
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<tr>
<td>Saturday</td>
<td>Treatment</td>
<td>6/15/16</td>
<td>6/16/16</td>
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<tr>
<td>Sunday</td>
<td>Treatment</td>
<td>6/16/16</td>
<td>6/17/16</td>
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<table>
<thead>
<tr>
<th>Itching</th>
<th>Pain (Skin)</th>
<th>Rash, Color of Skin</th>
<th>Other Symptoms: Night Sleep, Night Waking</th>
</tr>
</thead>
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<thead>
<tr>
<th>Benadryl</th>
<th>Allegra</th>
<th>Topiramate</th>
<th>Lamotrigine</th>
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bad day
CD 30 + Lymphoproliferative Disorders
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
Cutaneous Anaplastic Large Cell Lymphoma

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

**LyP:**
- Observation
- **PUVA**
- Low dose weekly oral methotrexate
- NB-UVB and low dose oral Targretin (150 mg daily)
- topical steroid, topical bexarotene
- I.V. Brentuximab

**ALCL:**
- Radiation (solitary/localized)
- Weekly oral methotrexate
- Pegylated doxorubicin
- I.V. Brentuximab
25% - 30% of all cutaneous lymphomas are B-cell derived:

<table>
<thead>
<tr>
<th>WHO-EORTC Classification Cutaneous B-cell Lymphomas</th>
<th>Frequency (%)</th>
<th>5-Year Survival (%)</th>
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</thead>
<tbody>
<tr>
<td><strong>Indolent</strong></td>
<td></td>
<td></td>
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<tr>
<td>Primary cutaneous marginal zone lymphoma</td>
<td>7</td>
<td>99</td>
</tr>
<tr>
<td>Primary cutaneous follicular lymphoma</td>
<td>11</td>
<td>95</td>
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<tr>
<td><strong>Aggressive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous diffuse large B-cell lymphoma, leg type</td>
<td>4</td>
<td>55</td>
</tr>
<tr>
<td>Primary cutaneous diffuse large B-cell lymphoma, other</td>
<td>&lt;1</td>
<td>50</td>
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*WHO-EORTC (1905 patients), Blood 2005*
Primary Cutaneous Follicle Center Lymphoma

- Most common type of cutaneous B cell lymphoma
- Solitary plaques/tumors on trunk, head or scalp; rarely grouped lesions
- $\text{CD20}^+, \text{Bcl-6}^+, \text{CD10}^+, \text{Bcl-2}^-, \text{MUM-1}^-$ (germinal center origin)
- Follicular, diffuse or mixed 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
- No t(14:18)
- Cutaneous relapses $\sim$50%, extracutaneous dissemination 5-10%
Primary Cutaneous Marginal Zone Lymphoma (Immunocytoma)

- MALT-type lymphoma
- Solitary or multiple red-violaceous papules, plaques, nodules on trunk and arms
- Association with B. afzelii (Europe), but not USA
- Frequent relapses, rarely extracutaneous dissemination
- $\text{CD20}^+$, CD79a$, \text{CD5}^-$, $\text{CD10}^-$, $\text{Bcl-6}^-$, $\text{Bcl-2}^+$, phenotype
- $\text{MUM-1}^+$ (plasma cells)
- Transformation to diffuse large B-cell lymphoma possible
- Relapse rate 40-45%
Marginal Zone Lymphoma

Clinicopathologic Features
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
- CD20\(^+\), CD5\(^-\), CD79a\(^+\),
- **Bcl-2\(^+/-\)**, **Bcl-6\(^+/-\)**, CD10\(^-\), **MUM-1\(^+\)**, **FOXP1\(^+/-\)**
- Frequent cutaneous relapses and extracutaneous dissemination
- No t(14:18)
- Chromosomal gains on chromosome 7p and 18q, loss of 6q
- Sheets of centroblasts and immunoblasts
- 5-year survival (multiple lesions): 50%
Primary Cutaneous DLBCL- Leg Type
Recategorization 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
<table>
<thead>
<tr>
<th>PCBCL subtype</th>
<th>Treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indolent entities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PCFCL and PCMZL</td>
<td>• Observation</td>
<td>• No published data</td>
</tr>
<tr>
<td></td>
<td>• Intraleosonal steroids</td>
<td>• ORR 100%, CRR 44%</td>
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<tr>
<td></td>
<td>• Local radiation</td>
<td>• CRR 100%</td>
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<tr>
<td></td>
<td>• Surgical excision</td>
<td>• CRR100%</td>
</tr>
<tr>
<td></td>
<td>• Intraleosonal interferon-α</td>
<td>• CRR 100%</td>
</tr>
<tr>
<td></td>
<td>• Intraleosonal rituximab</td>
<td>• CRR 71%, PRR 23%</td>
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<tr>
<td>• Solitary and/or localized skin lesions</td>
<td>• Observation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IV rituximab</td>
<td>• No published data</td>
</tr>
<tr>
<td></td>
<td>• Chemoimmunotherapy (R-Bendamustine)</td>
<td>• ORR 87%, CRR 60%</td>
</tr>
<tr>
<td>• Disseminated skin lesions</td>
<td>• Systemic antibiotics (doxycycline, cefotaxime)</td>
<td>• CRR 85%</td>
</tr>
<tr>
<td>• Cases associated with Lyme disease</td>
<td></td>
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<tr>
<td>• Aggressive entities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PCDLBCL-LT</td>
<td>• Chemoimmunotherapy (R-CHOP)</td>
<td>• CRR 92%</td>
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<tr>
<td></td>
<td>• Chemoimmunotherapy + RT (localized disease)</td>
<td>• No published data</td>
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<tr>
<td></td>
<td>• Palliative RT (localized disease)</td>
<td>• No published data</td>
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<tr>
<td></td>
<td>• Autologous stem cell transplant (relapse/ refractory cases)</td>
<td>• Isolated cases with CR</td>
</tr>
<tr>
<td></td>
<td>• Lenalidomide</td>
<td>• ORR 20%</td>
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<tr>
<td></td>
<td>• Clinical trials: Aurora kinase inhibitors, ofatumumab, leniliximab, dacetuzumab, ibrutinib, pembrolizumab.</td>
<td>• No published data</td>
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Thank You

City of Hope
- Steven Rosen
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