Living with Cutaneous T-cell Lymphoma

Disclaimer

Some of the photographs in this presentation may contain partial nudity of a medical nature.
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Cutaneous T-cell Lymphoma
Mycosis Fungoides/Sézary Syndrome

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Jean-Louis-Marc Alibert (1768–1837) was a pioneer of French dermatology. Originally planning to enter the priesthood, Alibert did not begin studying medicine until he was 26 years old. In 1801 he was appointed médecin adjoint to the Hôpital Saint-Louis where he administered to patients with skin disorders, syphilis and leprosy. Following the Restoration of the French monarchy, Alibert became a personal physician to Louis XVIII. Alibert was a prodigious writer, his best known work being the beautifully illustrated Descriptions des maladies de la peau. In 1806, he was the first to describe a patient with mycosis fungoides. The disease was formerly referred to as “Alibert-Bazin syndrome”, named in conjunction with dermatologist Pierre-Antoine-Ernest Bazin.

### Cutaneous T-cell and NK-cell lymphomas

<table>
<thead>
<tr>
<th>Mycosis fungoides</th>
<th>MF variants and subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folliculotropic MF</td>
<td>Pagetoid reticulosis</td>
</tr>
<tr>
<td>Granulomatous slack skin</td>
<td>Sézary syndrome</td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma</td>
<td>Primary cutaneous CD30⁺ lymphoproliferative disorders</td>
</tr>
<tr>
<td>Primary cutaneous anaplastic large cell lymphoma</td>
<td>Lymphomatoid papulosis</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma*</td>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
</tr>
<tr>
<td>Primary cutaneous peripheral T-cell lymphoma, unspecified</td>
<td>Primary cutaneous aggressive epidermotropic CD8⁺ T-cell lymphoma (provisional)</td>
</tr>
<tr>
<td>Cutaneous γ/δ T-cell lymphoma (provisional)</td>
<td>Primary cutaneous CD4⁺ small/medium-sized pleomorphic T-cell lymphoma (provisional)</td>
</tr>
</tbody>
</table>

Mycosis Fungoides and Sézary Syndrome

Skin Manifestations of CTCL

T1 T2 T3 T4
Recommended Staging of MF/SS

- **Skin staging**
  - Determination of stage T1-T4
  - Histological nuances: folliculotropism, large cell transformation

- **Blood analysis**
  - CBC, LFTs, LDH
  - T-cell gene rearrangements
  - Flow cytometry
  - CD4/CD8 ratio and/or Sézary cell prep

- **Radiology**
  - Early stage does not always need scanning
  - PET or CT scan for more advanced patients

- **Node biopsy**
  - Any ≥1.5 cm or fixed/firm may be biopsied

2007 ISCL/EORTC Staging for Mycosis Fungoides and Sézary Syndrome: Skin

<table>
<thead>
<tr>
<th>T stages</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Patches, papules and plaques covering &lt; 10% of the skin surface</td>
</tr>
<tr>
<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Patches, papules or plaques covering ≥ 10% of the skin surface</td>
</tr>
<tr>
<td>T&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Tumors (≥ 1)</td>
</tr>
<tr>
<td>T&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Confluence of erythematous lesions covering ≥ 80% BSA</td>
</tr>
</tbody>
</table>

1% BSA: patient’s palm plus all 5 fingers

Diagnosis of Early Mycosis Fungoides (4 Points Required)

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>Major (2 points)</th>
<th>Minor (1 point)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent and/or progressive patches/thin plaques plus</td>
<td>Any 2</td>
<td>Any 1</td>
</tr>
<tr>
<td>1) Non-sun exposed location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) Size/shape variation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) Poikiloderma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HISTOPATHOLOGICAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial lymphoid infiltrate plus*</td>
<td>Both</td>
<td>Either</td>
</tr>
<tr>
<td>1) Epidermotropism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) Atypia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Implies no spongiosis</td>
<td></td>
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</tr>
</tbody>
</table>


Survival by Clinical Stage in MF and SS Before Modern Era

Total N = 525

MF/SS Patients Require Many Treatments Over Duration of the Disease

Risk of Progression:
- Stage IA (T1N0): < 10%
- Stage IB: (T2N0): ~25%
- Stage IIA (T1N1-2 or T2N1-2): ~40%


MF/SS: General Treatment Guidelines

- For patch/plaque skin lesions with no extracutaneous involvement, use skin-directed therapies first (if possible), then immunomodulatory agents
- For more extensive disease, combination of treatments, skin directed with immunomodulators (retinoids, IFN, HDAC) is generally more effective than single agent therapy and should be considered early in treatment algorithm
- Avoid chemotherapy in patients with early stage disease (stage I-IIA) and utilize with caution in those with later stage disease. Use single agent chemotherapy if possible
Patch-Stage Disease

- Lesions may be hypopigmented, hyperpigmented or erythematous
- Biopsy: performed off topical steroids
- Differential diagnosis includes tinea corporis, eczema, drug reaction
- Skin involvement measured based on % of BSA
- T1 = < 10% BSA
- T2 = ≥ 10% BSA

Plaque Stage Disease

- Skin directed therapy alone could be considered if no folliculotropism or LCT. Total body electron beam therapy reserved for extensive plaque disease
- Systemic immunomodulators
  - Interferon alfa and gamma
  - Oral retinoids (bexarotene, 13-cis retinoic acid, acitretin, all-trans RA)
  - Methotrexate (low dose)
  - HDAC inhibitors
- Combination SDT and systemic therapy or two systemic agents
- ECP +/- other systemic or skin-directed therapies if ≥B1 blood involvement
Skin Directed and Systemic Agents for Early Stage CTCL

**Topicals**
- Steroids
- Mustargen (Valchlor)
- Radiation- electron beam
- Retinoids
- Imiquimod
- Phototherapy (UVA, UVB)

**Combinations**
- Retinoids IFN
- UVA/UVB + retinoids IFN
- ECP + Retinoids
- ECP + Retinoids + IFN
Tumor-stage Disease

- Tumor stage (T3): ≥ 1 nodular lesion > 1 cm
- Biopsy: representative non-ulcerated tumor
  - If large cells, record %
- Perform both T and B clonality studies
- Differential diagnosis includes all types of primary cutaneous lymphoma, pseudolymphoma (B cell) or lymphocytoma cutis (T cell), secondary cutaneous lymphoma, leukemic lesions, and for single lesions, metastatic cancer

Tumor-stage Disease Treatment

- Local XRT (orthovoltage or EB) plus systemic biologic therapies
- Total skin electron beam radiation:
  - If persistent lesions: skin-directed or systemic therapy with single or combination biologic agents
  - If remission achieved: single or combination biologic agents for maintenance therapy
- Single or combination chemotherapy
- Consider BMT or experimental therapy if failed above
Erythrodermic Disease

- Erythroderma (T4) defined as at least 80% BSA with erythematous confluence of lesions
- May be infiltrated or flat
- Hair loss in areas of involvement
- Diagnosis often difficult by skin biopsy alone—must be off topical steroids, it may require multiple biopsies, and requires immunophenotyping and TCR GR analysis—blood and nodal evaluation key
- Differential diagnosis includes atopic dermatitis, hyper IgE, psoriasis, drug reaction

Erythrodermic Disease

- Total body skin-directed therapy may be considered for those with B0 disease
  - Topical nitrogen mustard
  - PUVA or UVB
  - Total skin electron beam
  - Single or combination immunomodulators (interferon, retinoids, photopheresis) ± skin-directed therapy
- Single agent therapy
  - Methotrexate
  - HDAC inhibitors
  - Brentuximab vedotin
Systemic Chemotherapy Agents for CTCL

- Brentuximab vedotin
- Gemcitabine
- Liposomal doxorubicin
- Pralatrexate
- Romidepsin
- Vorinostat
- Chlorambucil
- Pentostatin
- Cytoxan
- Temozolomide
- Methotrexate >100 mg
- Bortezomib

Interferon Alfa in the Treatment of MF

Usual dose
- 3-6 MU IFN α2a/b SQ TIW to QD or low dose pegylated interferon alfa

Efficacy
- ORR: 50% to 80%; CR 20% to 41% including 25% stage I-IIA
- Maximum response usually by 6 months
- Long-lasting remissions, long-term maintenance well tolerated

Expected side effects
- Common (dose related): anorexia, fatigue, depression
- Uncommon (dose related): leukopenia and elevated LFTs
- Adjuvant treatment with phototherapy ± retinoid
- Post TSEB therapy or adjuvant to local XRT with tumor-stage disease

**Bexarotene in the Treatment of MF**

- Retinoid X receptor-selective retinoid
- Monotherapy
  - Dose (target): 300 mg/m²
  - Efficacy
    - IA-IIA: 53% ORR, 7% CR, better with higher dose
    - IIb-IVB: 46% ORR, 5% CR, better with higher dose
- Safety
  - Hyperlipidemia and secondary hypothyroidism - TSH markedly decreased
  - Leukopenia 28%, headache 47%, asthenia 36% at target dose


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**HDAC Inhibitors in MF/SS**

- **Vorinostat***
  - Orally bioavailable
  - 30% PR across all stages at 400 mg per day
  - Adverse effects: diarrhea most disabling and dose related. Anemia, thrombocytopenia, increased creatinine less common

**Vorinostat—Visible Improvements in Skin Lesions**

**Baseline: Stage IIB MF**

- **Baseline**
- **Week 5**
- **Week 45**

Patient remained on vorinostat for >4 years having received 4 prior therapies

*Sample responses during treatment with vorinostat*


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**Romidepsin**

- IV preparation only
- 34% response rate
- Dose is 14 mg/m2 over 4 hr infusion days 1,8, and 15 q 28 days
- Adverse effects
  - EKG shows QT prolongation
  - Nausea, fatigue, vomiting and anorexia, low blood counts

Romidepsin—HDAC Inhibitor

*Piekarz et al., JCO 2009; Whittaker et al, JCO 2010.*
Pralatrexate

- Approved for relapsed/refractory PTCL and MF with LCT
- Open label Phase I clinical research study in CTCL*
  - 54 patients who failed at least one prior systemic therapy
  - Treated with maximum (and optimal) dose of 15 mg/m² weekly for 3 weeks of a 4 week cycle
  - Objective response rate of 41% (including 35% PR, 6% CR)
  - Most frequent AEs: fatigue, mucositis, nausea, epistaxis, edema and vomiting. Grade 3-4 AEs: mucositis (17%), thrombocytopenia (3%)


Brentuximab vedotin

- Targets CD30 receptor on T cells
- CD30 expression in most MF patients
- Major side effects are neurotoxicity (paresthesias)
- Drug is given IV once every 3 weeks
**ALCANZA Study: Brentuximab Vedotin**

### Treatment Arm

- **All Randomized:** N=131
  - N=66 (50 MF, 16 pcALCL)

- **Safety Population:** N=128
  - N=66 (50 MF, 16 pcALCL)
  - N=64 (48 MF, 16 pcALCL)

### Comparator Arm

- **Physician’s choice**
  - N=65 (50 MF, 15 pcALCL)
  - N=62 (49 MF, 13 pcALCL)

3 patients on brentuximab vedotin are still on treatment at the time of analysis

*CD30 assay changed during the study, patients were CD30+ under original assay


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**ALCANZA STUDY: ORR4 and Response Rates by Disease Type**

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Brentuximab Vedotin</th>
<th>Bexarotene or Methotrexate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N = 64</td>
<td>ORR4 (%)</td>
<td>ORR (%)</td>
</tr>
<tr>
<td>ITT population</td>
<td>64 (100)</td>
<td>56</td>
</tr>
<tr>
<td>MF</td>
<td>48 (75)</td>
<td>50</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA-IIA</td>
<td>15 (31)</td>
<td>40</td>
</tr>
<tr>
<td>II</td>
<td>19 (40)</td>
<td>63</td>
</tr>
<tr>
<td>IIIA-IIIB</td>
<td>4 (8)</td>
<td>50</td>
</tr>
<tr>
<td>IVA</td>
<td>2 (4)</td>
<td>100</td>
</tr>
<tr>
<td>IVB</td>
<td>7 (13)</td>
<td>29</td>
</tr>
<tr>
<td>pcALCL</td>
<td>16 (25)</td>
<td>75</td>
</tr>
<tr>
<td>Disease involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin-only</td>
<td>9 (56)</td>
<td>89</td>
</tr>
<tr>
<td>Extracutaneous disease</td>
<td>7 (44)</td>
<td>57</td>
</tr>
</tbody>
</table>

NA, not applicable.
**Mogamulizumab: Anti-CCR4 Monoclonal Antibody**

Approved in Japan for HTLV-1 associated T cell leukemia/lymphoma

<table>
<thead>
<tr>
<th>Lymphoma Subtype</th>
<th>N</th>
<th>ORR(%)</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCL</td>
<td>29</td>
<td>34</td>
<td>[18 - 54]</td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>16</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>AITL</td>
<td>12</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>ALCL ALK(-)</td>
<td>1</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>CTCL</td>
<td>8</td>
<td>38</td>
<td>[9 - 76]</td>
</tr>
</tbody>
</table>


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**MAVORIC: Open-label, randomized study of anti-CCR4 monoclonal antibody, mogamulizumab (KW-0761) vs vorinostat in patients with previously treated CTCL**

**Inclusion:**
- Stage I B – IV B, MF or SS (B2)
- At least one prior course of systemic therapy

**Exclusion:**
- Patients with large cell transformation

**Mogamulizumab**
- 1.0 mg/kg i.v.
  - Weekly for first 28-day cycle; days 1 and 15 of subsequent cycles

**Vorinostat**
- 400 mg PO daily

One-way crossover after PD or intolerable toxicity

Patients could remain in the treatment phase up until progression or intolerable toxicity
- Vorinostat was administered in accordance with US prescribing information, targeting maximum tolerated effective dose; crossover allowed with approval
- CCR4 expression was not a requirement for participation
- Patients were enrolled at 61 centers across 11 countries
Allogeneic Stem Cell Transplantation in CTCL

- 133 pts in registry with CTCL
- RI regimens in 64%
- Only 8 were in CR
- 100 day TRM 16%
- PFS and OS 36% and 44% at 2 yrs

CIBMTR Retrospective Study

Lechowicz et al. BMT 2014.
Yale Allogeneic HSCT Guidelines

- **Indications for HSCT**
  - **Mycosis fungoides (MF):**
    - Tumor stage or folliculotropic MF, refractory to multiple therapies
    - MF with large cell transformation or visceral involvement
    - Sezary Syndrome that is chemoresistant to multiple agents

- **Conditioning Treatment**
  - Pentostatin + low dose TBI - activity in refractory T cell lymphoma
  - Total skin electron beam as part of conditioning
  - Haploidentical transplants

CITN-10: Phase 2 Trial of Pembrolizumab in Relapsed or Refractory CTCL

Overall response rate: 38%

Khodadoust, Kim, and CITN investigators.
Inhibitors of Micro RNA: miR-155

- Highly expressed in ALK-ALCL and in MF/SS
- Drives growth of ALCL xenografts
- Directly targets SOCS1 and C/EBPb
  - Supresses IL-8, induces IL-22
  - Induces py-Stat3 activation
  - Phase I trial in MF/SS
    - Intraleision
    - Subcutaneous

The United States Cutaneous Lymphoma Consortium (USCLC.org)

- Nonprofit, physician run organization founded in September 2007
- Mission Statement: To foster a multidisciplinary approach to patient care, education and clinical and basic research in the area of cutaneous lymphomas
- Goals: To establish an organization of physicians with expertise in cutaneous lymphomas to:
  1. Create a national registry of patients with cutaneous lymphomas
  2. Develop and participate in cooperative clinical trials of cutaneous lymphomas and/or other collaborative/cooperative research projects
  3. Develop guidelines of therapy and standardization of clinical trials for cutaneous lymphomas
  4. Develop a national virtual tissue bank for cutaneous lymphomas
- Will have a patient portal for patient registry
Conclusions

- Multiple treatment approaches for patients with CTCL
- Focus on improvement in quality of life
- Stem cell transplant has led to cures
- New agents and mechanisms are being identified
- 53 studies on ClinicalTrials.gov for mycosis fungoides
- Advocacy through Cutaneous Lymphoma Foundation, The Leukemia & Lymphoma Society, and Lymphoma Research Foundation

Q&A Session
The Leukemia & Lymphoma Society Offers:

- **Information Specialists**: Master’s level oncology professionals available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  - TOLL-FREE PHONE: 1-800-955-4572
  - EMAIL: infocenter@LLS.org
- **Free Education Booklets**: [www.LLS.org/booklets](http://www.LLS.org/booklets)
- **Free Telephone/Web Programs**: [www.LLS.org/programs](http://www.LLS.org/programs)
- **Live, weekly Online Chats**: [www.LLS.org/chat](http://www.LLS.org/chat)

The Leukemia & Lymphoma Society Offers:

- **LLS Podcast, The Bloodline with LLS**: Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: [www.LLS.org/thebloodline](http://www.LLS.org/thebloodline)
  - ‘CTCL: Skin Lymphoma, Not Skin Cancer’ episode
- **Education Video**: Free education videos about survivorship, treatment, disease updates and other topics: [www.LLS.org/educationvideos](http://www.LLS.org/educationvideos)
- **Patti Robinson Kaufmann First Connection Program**: Peer-to-peer program that matches newly diagnosed patients and their families: [www.LLS.org/firstconnection](http://www.LLS.org/firstconnection)
- **Free Nutrition Consults**: Telephone and email consultations with a Registered Dietitian: [www.LLS.org/nutrition](http://www.LLS.org/nutrition)
- **What to ask**: Questions to ask your treatment team: [www.LLS.org/whattosay](http://www.LLS.org/whattosay)
- **Support Resources**: LLS Community, discussion boards, blogs, support groups, financial assistance and more: [www.LLS.org/support](http://www.LLS.org/support)
BEATING CANCER IS IN OUR BLOOD.