Cutaneous Lymphoma

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WHO-EORTC classification of cutaneous lymphoma - T cells

- Cutaneous T-cell and NK-cell lymphomas
  - Mycosis fungoides
  - MF variants and subtypes
    - Follicotropism MF
    - Pagetoid reticulosis
    - Granulomatous slack skin
- Sézary syndrome
- Adult T cell leukemia/lymphoma
- Primary cutaneous CD30+ lymphoproliferative disorder
  - Primary cutaneous anaplastic large cell lymphoma
  - Lymphomatoid papulosis
- Subcutaneous panniculitis-like T cell lymphoma
- Extranodal NK-T cell lymphoma, nasal type
- Primary cutaneous peripheral T cell lymphoma unspecified
NCCN Suggested Treatment Regimens for MF and Sézary Syndrome

**Skin-Directed Therapies**
- Corticosteroids
- Topical chemo
- Local radiation (local/limited involvement only)
- Retinoids
- Phototherapy
- Imiquimod (local/limited involvement only)
- Total skin electron beam therapy (generalized involvement only)

**System Therapy (Cat A)**
- Retinoids
- IFN
- HDAC inhibitors (vorinostat, romidepsin)*
- Extracorporeal photopheresis
- Methotrexate (100 mg qw)

**System Therapy (Cat B)**
- Liposomal doxorubicin (1st line)*
- Gemcitabine (1st line)*
- Chlorambucil
- Pentostatin
- Etoposide
- Cyclophosphamide
- Temozolomide
- Methotrexate (> 100 mg qw)
- Bortezomib
- Low-dose pralatrexate*

**Combination Therapy**
- Phototherapy + systemic retinoids
- Phototherapy + IFN
- Phototherapy + photopheresis
- Total skin electron beam + photopheresis

**Combination Systemic Therapy**
- Retinoid + IFN
- Photopheresis + retinoid
- Photopheresis + IFN
- Photopheresis + retinoid + IFN

*Preferred options for LCT MF and stage IV non-Sézary/visceral disease (aggressive growth characteristics).

Therapy for Early-Stage CTCL

- Topical chemotherapy
  - Mechlorethamine (Nitrogen Mustard)
    - Used since 1950’s
    - Commercial formulation (Valchlor®)*
      - 0.02% gel
      - Applied 1-4 times daily
    - Response:
      - Response rate: 69% (by SWAT score)
      - Median time to response -> 26 weeks
        † Complete response -> 19%
      - Duration of response -> 90% at 10+ months
    - Adverse reactions
      - Skin irritation (25%)
      - Dispigmentation (6%)
      - Skin cancer

* FDA labeled indication for CTCL.
Lessin et al. JAMA Dermatol 2013 149:25-32
Therapy for Early-Stage CTCL

- **Retinoids**
  - **Bexarotene gel** *(Targretin®)*
    - Topical gel
    - Partial response - 42%
    - Complete response - 21%
  - **Isotretinoin** *(Accutane®)*
    - Oral
    - Response rate - 40-45%

- **Topical steroids**
  - Medium to high potency
  - Overall response rate
    - T1 disease
      - CR 63%
      - PR 31%
    - T2 disease
      - CR 25%
      - PR 57%

* FDA labeled indication for CTCL
# Non-FDA indication (clinical)

Phototherapy in Early-Stage CTCL

- Psoralen with UVA irradiation (PUVA)
  - Response rates
    - Stage IA: 79% to 88%
    - Stage IB: 52% to 59%
    - Patch disease: 90%
    - Plaque disease: 76%
    - Overall response rates of 50%
  - FFP ~2.5 years
  - Generally well tolerated
  - Adverse reactions:
    - Psoralen can cause nausea, need to protect eyes from light
    - Associated with secondary skin cancers

References:
PUVA + Interferon-α

- Study of 96 patients with stage I and II MF
- Response
  - PUVA - 72%
  - PUVA + INF - 80%
- Less UVA exposure in PUVA + INF treatment

Stadler et al, 2006 JCO 24(suppl):7541
Phototherapy in Early-Stage CTCL

- **UVB irradiation**
  - Remissions - 71% (25 of 35) of patients after a median treatment of 5 months
  - Median duration - 22 months
  - No patients with plaque-stage disease had remission
  - No nausea/? Less secondary skin cancer

- **Electron beam irradiation**
  - Can control depth of penetration of electrons
    - Most of the radiation delivered to top 5 mm
  - Effective in thick generalized plaques or tumors
  - Response rate of 55-95% in IA/IIA disease
  - Total body E-beam
    - T2: CR 76% with 15 yr FFR of ~15%
    - T3: CR 44% with 10 yr FFR ~15%
  - Increased DFS but not OS

Systemic/Phototherapy for CTCL - Photophoresis (ECP)

- Removal and exposure of white blood cells to UVA light in the presence of psoralen and re-infusing back into patient
- ~10% of white cells treated
- Given on 2 consecutive days monthly
Extracorporeal Photopheresis (ECP)

- ECP more effective for erythroderma than for plaques and tumor disease (CTCL-1)
  - More effective when circulating Sezary cells
- Median time to response was 2-4 months
- Median duration of response varied
  - CTCL-1 > 14 months

Therakos - data on file
Extracorporeal Photopheresis (ECP)

- Retrospective review of the largest series of ECP treatment
  - 16 studies
  - 411 total patients
  - Responses
    - Overall response - 60%
    - Partial response - 36%
    - Complete response - 18%
- Combined with immunostimulatory agents (INF-α)
  - ORR - 75% (35/47 pts)
  - Median survival - 66 months

Management of Late-Stage (IIB–IVB)/Refractory CTCL

- **Chemotherapy**
  - Gemcitabine (*Gemzar*)#
  - Liposome-encapsulated doxorubicin (*Doxil*)*
  - Cladribine (*Leustatin*)*
  - Methotrexate
  - Pralatrexate
  - Pentostatin
  - Cyclophosphamide
  - Temozolomide
  - Etoposide

- **Retinoids**
  - Bexarotene
  - Isotretinoin

- **Histone deacetylase (HDAC) inhibitor**
  - Vorinostat
  - Romidepsin

- **Interferon**
  - Interferon – alpha
  - Interferon - gamma

- **Others**
  - Bortezomib
  - Brentuximab vedotin
  - Alemtuzumab (CamPath)
Gemcitabine treatment of CTCL

- **Treatment**
  - Gemcitabine 1200 mg/m² IV on days 1, 8, 15.
  - Repeated every 28 days (x 3 cycles)

- **Response**
  - Overall response -> 70.5%
    - Complete response -> 11.5%
    - Partial response -> 59%
  - Median response duration -> 15 months (range 6 to 22 months)

- **Toxicity**
  - Anemia, low white cell count, low platelet count
  - Hair loss (mild)
  - Increased liver enzymes

Responses in Patients With CTCL Treated With Oral Bexarotene

Response based on the physician’s global assessment
Summary of Phase 2/3 Experience With Oral Bexarotene

- Responses are dose dependent
- Time to maximum response is several months
- Treatment complicated by hypertriglyceridermia and hypothyroidism
  - Hypertriglyceridermia treated with fibrate or statin (NOT gemfibrozil)
  - Often started on Synthroid
- Hypertriglyceridermia and hypothyroidism resolved with bexarotene stopped

Multiple Proteins Are Regulated by Acetylation/Deacetylation

**Proteins Regulated by Acetylation**

- Histones
- α-Tubulin
- p53
- HIF-1α
- HSP-90

**Transcriptional Activation**
- p21, p27
- Death receptor pathway activation
- Differentiation factors

**Effects**
- G1 and G2/M arrest
- Apoptosis
- Differentiation
- Motility/invasion
- Survival/cell death
- Angiogenesis
- Bcr-Abl; HER-2
- HIF-1α; bFGF
- EGFR; c-Kit
- ER; AR

**Cytoskeleton**

**Re-expression**

**Loss of chaperone function**
Romidepsin – histone deacetylase inhibitor

• Treatment
  » Romidepsin 14 mg/m2 over 4 h IV weekly for 3 weeks
  » Repeat every 4 week
• Median time to response -> 2 months
• Median duration of response -> 11-15 months
Pivotal Open-Label Phase II Study of Romidepsin in Refractory CTCL

- **Refractory CTCL**
- **Responder**
- **Nonresponder**

- **mSWAT**
  - **Responder**
  - **Nonresponder**
  - (n = 53)

- **Erythroderma**
  - **Responder**
  - **Nonresponder**
  - (n = 34)

- **Nodal Response**
  - **Responder**
  - **Nonresponder**
  - (n = 37)

- **Pruritus**
  - **Responder**
  - **Nonresponder**
  - (n = 85)

ZOLINZA™ (vorinostat)
Study 1: Clinical Results

- Histone deacetylase (HDAC) inhibitor
- Response rate
  - Overall response rate -> 29.7%
  - Stage IIB and higher CTCL -> 29.5
- Median times to response was ~ 55 days (range 28 to 171 days)
- Median duration of response not reached but estimated at ~6 months
Pralatrexate Mechanism of Action

Rationally designed antifolate to improve cellular uptake and retention

Reduced flux due to decreased THF levels
Pralatrexate

- **Treatment schedule**
  - 15 mg/m² weekly for 3 of 4 weeks

- **Response rate**
  - Overall -> 41%
  - Partial response -> 35%

- **Side effects**
  - Mouth sores -> 54%
  - Fatigue -> 43%
  - Skin toxicity -> 28%
  - Edema -> 26%
  - Anemia -> 22%
  - Fevers -> 22%

Brentuximab Vedotin Mechanism of Action

Brentuximab vedotin antibody-drug conjugate (ADC)

- Monomethyl auristatin E (MMAE), microtubule-disrupting agent
- Protease-cleavable linker
- Anti-CD30 monoclonal antibody

1. Brentuximab vedotin binds to CD30
2. Brentuximab vedotin-CD30 complex is internalized and traffics to lysosome
3. MMAE is released
4. MMAE disrupts microtubule network
5. G2/M cell cycle arrest
6. Apoptosis
**ALCANZA: ORR4, PFS, CR, and Change in Symptom Burden**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Brentuximab Vedotin (n = 64)</th>
<th>Methotrexate or Bexarotene (n = 64)</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR4, n (%)</td>
<td>36 (56.3)</td>
<td>8 (12.5)</td>
<td>43.8 (29.1 to 58.4)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>10 (15.6)</td>
<td>1 (1.6)</td>
<td>14.1 (-4.0 to 31.5)</td>
<td>.0046*</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>16.7</td>
<td>3.5</td>
<td>--</td>
<td>&lt; .0001*†</td>
</tr>
<tr>
<td>Mean max. reduction in Skindex-29 symptom domain, points</td>
<td>-27.96</td>
<td>-8.62</td>
<td>-18.9 (-26.6 to -11.2)</td>
<td>&lt; .0001*</td>
</tr>
</tbody>
</table>

*Adjusted P value from weighted Holm’s procedure.
†HR: 0.270 (95% CI: 0.169-0.430).

- PFS significantly improved for subgroups defined by pt characteristics (baseline ECOG PS of 0, sex, age < 65 yrs, geographical region), disease characteristics (MF and pcALCL, skin involvement, baseline skin tumor score), and treatment (bexarotene and methotrexate)

Combination Chemotherapy for Advanced MF/SS

- Combination chemotherapy
  - Small studies
  - Various regiments
  - +/- electron beam irradiation or nitrogen mustard

- Retrospective analysis
  - 24 studies involving 331 patients
  - Response rate
    - Complete responses - 38%
    - Partial responses - 43%
  - Duration - 5 to 41 months

- Unclear if improved survival

Bunn et al. 1994; Ann Int. Med. 121:592-602
WHO-EORTC classification of cutaneous lymphoma - B cells

- **Cutaneous B-cell lymphoma**
  - Primary cutaneous marginal zone B-cell lymphoma
  - Primary cutaneous follicle center lymphoma
  - Primary cutaneous diffuse large B-cell lymphoma, leg type
  - Primary cutaneous diffuse large B-cell lymphoma, other
    - Intravascular large B cell lymphoma

- **Precursor hematologic neoplasm**
  - CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma)
Primary cutaneous B cell lymphoma - survival

Cumulative Survival

Duration of follow-up (mo)