Cutaneous T-cell Lymphomas: Skin Directed Therapies

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Cutaneous Lymphoma Foundation
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Conflict of Interests

• Seattle genetics
• Acetrics
• Celgene
• Tetralogic
# Mycosis Fungoides and Sézary Syndrome Clinical Staging System

<table>
<thead>
<tr>
<th>Stages</th>
<th>TNM Classification*</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1 N0 M0</td>
<td>96-100%</td>
</tr>
<tr>
<td>IB</td>
<td>T2 N0 M0</td>
<td>73-86%</td>
</tr>
<tr>
<td>IIA</td>
<td>T1-2 N1 M0</td>
<td>49-73%</td>
</tr>
<tr>
<td>IIB</td>
<td>T3 N0-1 M0</td>
<td>40-65%</td>
</tr>
<tr>
<td>IIIA</td>
<td>T4 N0 M0</td>
<td>40-57%</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4 N1 M0</td>
<td>40-57%</td>
</tr>
<tr>
<td>IVA</td>
<td>T1-4 N2-3 M0</td>
<td>15-40%</td>
</tr>
<tr>
<td>IVB</td>
<td>T1-4 N0-3 M1</td>
<td>0-15%</td>
</tr>
</tbody>
</table>

*The “B” classification did not alter clinical stage, but the system is undergoing modifications to reflect the adverse survival of B2 (similar to IVA).

Mycosis Fungoides: Limited Patch/Plaque (T1) - IA

- Single or multiple patches
- <10% involvement
- Poikilodermatous patches with fine wrinkling
- Affect bathing trunk areas

Generalized Patch/Plaque (T2) - IB

- Multiple patches and plaques
- >10% involvement

Erythrodermic (T4) - III

Sezary

- Erythroderma with exfoliative scale
- Severe pruritus
- Lymphadenopathy
- Circulating Sézary cells

CTCL distribution based on stage

Kim et al. Arch Derm 1999
Agar et al. JCO 2010

Disease Stage
Summary of MF/SS Treatment Options

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia &lt;10%</td>
<td>Topical steroids</td>
</tr>
<tr>
<td>Ib &gt;10%</td>
<td>Bexarotene/retinoid gel/Investigational</td>
</tr>
<tr>
<td>IIb tumors</td>
<td>NB-UVB</td>
</tr>
<tr>
<td>III Generalized</td>
<td>Nitrogen mustard</td>
</tr>
<tr>
<td>IV +nodes</td>
<td>PUVA</td>
</tr>
</tbody>
</table>

**Skin directed**
- Topical steroids
- Bexarotene/retinoid gel/Investigational
- NB-UVB
- Nitrogen mustard
- PUVA
- Localized superficial XRT / TSEB

**Systemic**
- Photopheresis
- IFN
- Bexarotene/retinoid capsule
- Denileukin diftitox
- HDAC Inhibitor-vorinostat, romedepsin
- Brentuximab vedotin/Praletrexate
- Chemo-gemzar, doxil

**Investigational agents**

JA Zic 2003 Wintrobe's Clinical Hematology Ch 94 (Modified)
Goal of therapy

- Reduce clinical extent of disease
- Alleviate symptoms
- Prevent progression
- Induce clinical remission
Skin directed therapy

• Appropriate at all stages of CTCL
• Therapies target the skin and alleviate symptoms
• Multiple modalities
  – Topical therapies
  – UV radiation – UVA, UVB, Excimer, photodynamic treatment
  – Radiation – localized superficial radiation, total skin electron beam (TSEB)
Topical therapy

• Appropriate at all stages of CTCL

• Classes of therapy
  – Topical steroid
  – Topical retinoids
  – Immune modulators
    • Toll agonist - imiquimod
  – Topical chemotherapy
    • Nitrogen mustard
  – Novel compounds in development
Topical therapy

• High potency steroids
  – Clobetasol/fluocinonide
  – Early efficacy reported by Farber (1966) *
  – Use locally with occlusion
  – Ointment is most effective
  – Side effects: atrophy

• Midpotency steroid – triamcinolone for large areas of the skin

Topical therapy

• Topical retinoids
  – **Bexarotene** - 0.1% - 1% gel. 67 pts, overall response rate of 63%. FDA approved*.
  – **Tazarotene** - 19 pts, 16 completed at least 4 weeks of topical treatment. 11 of 19 patients (58%) achieved at least a moderate (>50%) global improvement in BSA, and 35% of 99 index lesions cleared completely. (Apisarnthanarax N, et al. J Am Acad Dermatol. 2004 Apr;50(4):600-7)

  – Erythema and irritation is common

Topical therapy - imiquimod

- Stimulates immune response
- Activates interferon-alpha
- Approved for warts and actinic keratosis
- Stage IA to IIB – treatment with 5% cream – 50% response* Deeths et al
- Martinez-Gonzalez et al – 4/4 responded#
- Dummer reported complete clearance of PUVA resistant plaque


Topical Chemotherapy

- Topical mechlorethamine
- Long history of use
- Solution – dilute 10 mg in 60 cc water and apply immediately all over the skin
- Compounded ointment – 0.01 % petrolatum
- Mechlorethamine 0.02% gel – (Lessin et al JAMA Derm 2013) compared gel to ointment. Response 58.5% vs 47.7%. N=260.
• Topical histone deactylase inhibitor-SHAPE topical gel
• Four of 15 patients receiving SHAPE attained an objective response as measured by a greater than 50% improvement in their Composite Assessment of Index Lesion Severity, or CAILS, after 28 days of dosing. No placebo patients responded.
Phototherapy - Ultraviolet light

Phototherapy - PUVA

• Combined with oxsoralen pill to sensitize skin
• Effective in inducing clinical remission
• Side effects of nausea and need photoprotection after treatment
• Availability limited to few offices

Phototherapy – Narrow band UVB

• UV action spectrum for psoriasis is 296-300 nm*.

• Minimized erythema but retained therapeutic spectrum of UVB

• TL-01 bulbs = peak output at 311 nm present in NB-UVB devices

• Effective in early-stage MF

94% complete clearing in those with patch MF

http://www.solarcsystems.com/us_narrowband_uvb.html
Phototherapy comparison


Phototherapy - 308 Excimer laser

- Excimer treatment of patch/plaques
- Focused UV in narrow band range
- Effective in localize treatment of patch/plaques
- Well tolerated
- Numerous reports of success

Photodynamic therapy for MF

- Topical methylaminolevulinate (MAL) to sensitize lesion, followed by exposure to visible light.

Radiation therapy – Orthovoltage X-ray

- Orthovoltage – lower energy photons to treat tumors on the skin or close to the skin. May penetrate superficial tissue, e.g., muscle, blood vessel and can not be used widespread sites
  - Grenz rays—beam potentials from 10 to 20 kVp.
  - Contact therapy—beam potentials of up to 50 kVp.
  - Superficial therapy—beam potentials of 50 to 150 kVp.
  - Orthovoltage or deep therapy—beam potentials from 150 to 500 kVp.

- Target lesions directly for treatment
Radiation - Electron beam

- Electron beam radiation - electrically charged particles, electrons, generated in linear accelerator directed towards the skin.
- Total skin electron beam – directed to the entire skin surface, standard dose of 3600 cGy in small fractions over 10 weeks.
- Response is high
<table>
<thead>
<tr>
<th>Stage</th>
<th>CR Rate</th>
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<tr>
<td>IA</td>
<td>84-96%</td>
</tr>
<tr>
<td>IB</td>
<td>56-81%</td>
</tr>
<tr>
<td>IIA</td>
<td>63-74%</td>
</tr>
<tr>
<td>IIB</td>
<td>24-53%</td>
</tr>
<tr>
<td>IIIA</td>
<td>26-50%</td>
</tr>
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</table>

From Jones et al., Hem/Onc Clinics NA 1995; 9:1109-1116
Radiation side effects

- Erythema and xerosis
- Alopecia
- Anhydrosis
- Teleangiectasia
- Secondary malignancies – rare and seen in patients who have also received PUVA
Summary

• Numerous options for skin directed treatment of CTCL
• Responses can be achieved with many therapies. Topical treatments show gradual response for many therapies.
• Phototherapy is an effective modality for the treatment of CTCL.
• Radiation treatment highly effective but has limit of frequency of use
• Combination therapies can be used to enhance response