Treatments for Advanced Stage Disease

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Staging of MF/CTCL involves the evaluation of skin, lymph nodes, viscera, and blood

<table>
<thead>
<tr>
<th>Essential Workup</th>
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<tbody>
<tr>
<td><strong>Physical Exam</strong></td>
</tr>
<tr>
<td>Examination of entire skin</td>
</tr>
<tr>
<td>mSWAT</td>
</tr>
<tr>
<td>Palpation of peripheral lymph node regions</td>
</tr>
<tr>
<td>Palpation for organomegaly/masses</td>
</tr>
<tr>
<td>Rule out other - ANA</td>
</tr>
</tbody>
</table>

**CBC:** complete blood count; **CT:** computed tomography; **TCR:** t-cell receptor; **PET:** positron emission tomography; **LDH:** lactate dehydrogenase
%TSBA = (Total Body Surface Area)

- The body is divided into 12 regions with pre-assigned %TSBA based on methodology used to assess burns.
- The extent of skin disease is assessed for each region and quantified by using the patient’s palm as the ‘ruler’ to measure the %TBSA involvement with each region.
  - Patient’s palm with 4 fingers, excluding the thumb and measured from wrist to fingertips, is 1% of TBSA.
  - Patient’s palm without fingers is 0.05% of TBSA.
<table>
<thead>
<tr>
<th>TNMB stages</th>
<th>Staging parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin (T)</strong></td>
<td></td>
</tr>
</tbody>
</table>
| **T₁** | Patches and/or plaques covering <10% BSA;  
Further stratified into T₁₁ (patch only) versus T₁₂ (plaque ± patch) |
| **T₂** | Patches and/or plaques covering ≥10% BSA;  
Further stratified into T₂₁ (patch only) versus T₂₂ (plaque ± patch) |
| **T₃** | One or more tumors (≥1 cm diameter) |
| **T₄** | Coalescing erythema covering ≥80% of skin surface |
| **LN (N)** |                     |
| **N₀** | No clinically abnormal lymph nodes |
| **N₁** | Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN0-2  
Further stratified into N₁₁ (TCR non clonal) versus N₁₂ (TCR clonal) |
| **N₂** | Clinically abnormal lymph nodes; histopathology Dutch grade 2 or NCI LN3  
Further stratified into N₂₁ (TCR non clonal) versus N₂₂ (TCR clonal) |
| **N₃** | Clinically abnormal lymph nodes; histopathology Dutch grades 3-4 or NCI LN4;  
clone positive or negative |
| **Nₓ** | Clinically abnormal lymph nodes; no histologic confirmation |
| **Visceral (M)** |                     |
| **M₀** | No visceral organ involvement |
| **M₁** | Visceral involvement, pathologically confirmed + organ involved specified) |
| **Blood (B)** |                     |
| **B₀** | No significant blood involvement: <5% Sézary cells. For clinical trials, B₀ may also be defined as  
<250/mL Sézary cells CD4+CD26- or CD4+CD7- cells or CD4+CD26- and CD4+CD7- cells <15% |
| **B₀ₐ** | Clone negative |
| **B₀ₜ** | Clone positive |
| **B₁** | Low tumor burden. Does not fit B₀ or B₂ criteria |
| **B₁ₐ** | Clone negative |
| **B₁ₜ** | Clone positive |
| **B₂** | High blood tumor burden: Positive clone plus one of the following:  
>1000/mL Sézary cells;  
CD4/CD8 ≥10  
CD4+CD7- cells ≥40 percent  
CD4+CD26- cells ≥30 percent  
For clinical trials, B₂ may also be defined as >1000/mL CD4+CD26- or CD4+CD7- cells. |

**For skin**, plaque is any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikiloderma should be noted. Features such as folliculotropism (FT) or large-cell transformation (LCT; >25% large cells), CD30+, and ulceration are important to document. Tumor indicates at least one 1 cm solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, largest size lesion, region of body involved, and histologic features such as FT or LCT, CD30+.  
**For node**, abnormal lymph node (LN) indicates any LN ≥1.5 cm.  
**For viscera**, spleen and liver may be diagnosed by imaging criteria alone.  
# COMPOSITE ISCL/EORTC STAGING

## 2007 ISCL/EORTC Revision to the Staging System of MF and SS

<table>
<thead>
<tr>
<th>Stage</th>
<th>T (Skin)</th>
<th>N (Lymph Node)</th>
<th>M (Viscera)</th>
<th>B (Blood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>IB</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>IIA</td>
<td>1,2</td>
<td>1,2</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>IIB</td>
<td>3</td>
<td>0-2</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>0-2</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>IIIA</td>
<td>4</td>
<td>0-2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIIB</td>
<td>4</td>
<td>0-2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>IVA₁</td>
<td>1-4</td>
<td>0-2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>IVA₂</td>
<td>1-4</td>
<td>3</td>
<td>0</td>
<td>0-2</td>
</tr>
<tr>
<td>IVB</td>
<td>1-4</td>
<td>0-3</td>
<td>1</td>
<td>0-2</td>
</tr>
</tbody>
</table>

**B0** Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes or <250/mcL Sezary cells or <15% CD4+CD26- or CD4+CD7-

**B1** Low blood tumor burden: >5% of peripheral blood lymphocytes are Sezary cells but not meet criteria for B2

**B2** High blood tumor burden: ≥1000/mcL Sezary cells or CD4/CD8 ≥10 or ≥40% CD4+CD7- or ≥CD4+CD26- cells
Prognosis in MF best predicted by TNMB staging

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Median Survival (years)</th>
</tr>
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<tbody>
<tr>
<td>IA</td>
<td>35.5</td>
</tr>
<tr>
<td>IB</td>
<td>21.5</td>
</tr>
<tr>
<td>IIA</td>
<td>15.9</td>
</tr>
<tr>
<td>IIB</td>
<td>4.7</td>
</tr>
<tr>
<td>IIIA</td>
<td>4.7</td>
</tr>
<tr>
<td>IIIB</td>
<td>3.4</td>
</tr>
<tr>
<td>IVA1</td>
<td>3.9</td>
</tr>
<tr>
<td>IVA2</td>
<td>2.1</td>
</tr>
<tr>
<td>IVB</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Agar et al. JCO, 2010
Advanced Stage CTCL (Stage ≥ IIB) predicts a poor prognosis

IA: Limited patch <10%
IB-IIA: Patch/plaques >10%

AS-CTCL (Stage ≥ IIB)
- Tumor Stage (>1cm)
- Nodal, visceral, or blood involvement
Significant variability in AS-CTCL

- Teleological factors responsible for this variability are not well known.
- Prognostic markers include folliculotropism\(^1\), large cell transformation (LCT)\(^2\) & number of tumors\(^3\)
- Easily quantifiable markers (e.g. LDH\(^2\), elevated cell free EBV-DNA\(^4\)) of advanced systemic disease are needed
- Independent px factors in large retrospective study:
  - Stage IV, Age >60yo, LCT, increased LDH
  - w/5 yr survival 68% (0-1 factor), 44% (2 factors), 28% (3-4 factors)

Overview of CTCL Treatments

**Skin Directed**

- Topical corticosteroids
- Topical chemotherapy
  - Nitrogen mustard (*Mustargen*)
  - Carmustine (*BCNU*)
  - Mechlorethamine (*Valchlor*)
- Topical retinoids
  - Bexarotene gel (*Targretin* gel)
- Phototherapy
  - Narrow-band UVB (NBUVB)
  - Psoralen with UVA (PUVA)
- Radiation therapy
  - Total-skin electron beam therapy (TSEBT)
  - Site-directed radiation

**Systemic**

- Vorinostat (*ZOLINZA™*)
- Bexarotene capsules (*Targretin*)
- Romidepsin
- Pralatrexate
- Denileukin diftitox (*Ontak*)
- Alemtuzumab (*Campath*)
- Interferon
- Extracorporeal photopheresis
- Chemotherapy—single agent
  - Chlorambucil (*Leukeran*)
  - Cladribine (*Leustatin*)
  - Fludarabine (*Fludara*)
  - Methotrexate (*Trexall, Rheumatrex*)
  - Gemcitabine (*Gemzar*)
  - Pegylated doxorubicin (*Doxil*)
  - Pentostatin (*Nipent*)
- Combination chemotherapies
  - CHOP, EPOCH, Gem/Dox
Clinical Management of CTCL

**IA LIMITED DISEASE**
- Skin-Directed Therapy

**IB/IIA GENERALIZED**
- Photopheresis
- Single-Agent Chemotherapy
- Systemic (Single or Combination)
- Phototherapy ± Systemic
- Total Skin Electron Beam Therapy

**IIB TUMORS**
- Photopheresis
- Single-Agent Chemotherapy
- Systemic (Single or Combination)

**III ERYTHRODERMA**
- Photopheresis
- Single-Agent Chemotherapy
- Systemic (Single or Combination)
- Phototherapy ± Systemic
- Total Skin Electron Beam Therapy

**IV EXTRACUTANEOUS DISEASE**
- Photopheresis
- Single-Agent Chemotherapy
- Systemic (Single or Combination)
- Phototherapy ± Systemic
- Total Skin Electron Beam Therapy
- Allogeneic SCT
- Clinical Trial

National Comprehensive Cancer Network. www.nccn.org
General concepts in managing MF/SS-CTCL

- Lack of evidence-based help
- Consensus-based management
- Do no harm (refer to those who like skin or collaborate)
- Appreciate unique features of skin disease
  - Supportive therapy is essential (barrier defect)
    - Chronic control of skin infections (staph, HSV)
    - Use anti-itch regimens, emollients/sealants
  - Things that work in LNs may not work in skin
  - Often observe mixed responses
  - Can re-cycle treatments
  - Optimize utility of maintenance therapy

NCCN guidelines
Key treatment selection factors

- **Clinical stage/TNMB**
  - MF vs. SS

- **Other prognostic factors**
  - **Large cell transformation**
    - limited vs. generalized
  - **Folliculotropic disease**
    - infiltrate deeper/thicker => refractory to topicals

- **Age, co-morbidities, concomitant meds**

- **Availability/access issues**
  - TSEBT, photopheresis
  - U.S. vs. other countries
  - Insurance barriers
Mycosis Fungoides - the greatest masquerader

Clinical & Histologic Variants/Subtypes

Unique Prognosis?

- Hypopigmented/vitiligenous MF
  - Children, African American, Indian; CD8+
- Pagetoid reticulosis (Woringer-Kolopp type only)
- Folliculotropic MF (+/- FM)
  - Head and neck
- Granulomatous MF
  - Granulomatous slack skin
- Bullous MF
- PPE-like MF
- Interstitial MF
- Icthyiosiform MF
- Palmar plantar MF
- Hyperkeratotic/verrucous MF
- Papular MF
- Invisible MF

Worse clinical outcome =>
separated out in NCCN guidelines
F-MF + LCT => even worse

Arch Dermatol 144:738, 2008
Arch Dermatol 146:607, 2010
JCO 28:4730, 2010
Blood 119:1643, 2012
When need to intensify therapy in MF/SS
“Combination strategies” are utilized

• **Skin-directed + Systemic**
  – Phototherapy + retinoid
  – Phototherapy + IFN
  – Phototherapy + photopheresis*
  – TSEBT + photopheresis*

• **Systemic + Systemic**
  – Retinoid + IFN
  – Bexarotene + vorinostat
  – Photopheresis* + retinoid
  – Photopheresis* + IFN
  – Photopheresis* + retinoid + IFN

*Photopheresis comb more appropriate in pts with blood involvement, B1-2

Is combination therapy “better”?

• No comparative data
• Lower doses of each (less toxicity)
• Synergy?
Clinical Cases
50 yo male, generalized disease, progressive with increasing nodular lesions, IIB. Prior therapies: topical steroids, NM, local RT, nbUVB.

=> Failed oral bex, IFN, MTX

- Generalized F-MF +/- LCT
- Skin-directed + systemic agent
- Systemic agent +/- skin-directed tx
- TSEBT
- Clinical trial
- Brentuximab vedotin => PR
Severely symptomatic folliculotropic MF

Standard dose TSEBT
36 Gy

NOT CURATIVE,
Relapse within 2 yrs,
Retreatment limited

Why not use lower dose?
Low-Dose TSEBT Regimen

*Less is better?*

- Low-dose, 12 Gy (3 wks) vs. standard, 36 Gy (10 wks)
- Standard dose not-curative, protracted tx course, sig skin toxicity
- Reliable/efficient reduction in skin disease
- Less side effects
  - No permanent hairloss, less skin toxicity
- Can be given repetitively in pt’s course
- Low-dose can be followed or combined with other therapies to boost response and duration of benefit
69 yo male w/ 5 yr h/o scaly plaques on face/scalp, trunk, extremities, progressive worsening. Partial response to topical steroids, NM, and nbUVB. Recently noted scalp tumor nodules; multiple comorbidities.

Case F-MF, stage IIB
Clinical response with low-dose (12 Gy) TSEBT
69 yo M, stage IIB, folliculotrophic MF
Clinical response with low-dose (12 Gy) TSEBT
69 yo M, stage IIB, folliculotropis MF

Screening
mSWAT 133
Pruritus 8/10

Wk 16
mSWAT 0 (CR)
Pruritus 0/10
Management of skin “tumor” disease (II B)

• Limited vs. generalized extent tumor disease
• Intensify therapy for aggressive growth pattern, e.g., large cell transformation (LCT)
• Limited extent tumor disease
  – Local RT for limited tumor disease +/- skin-directed therapy for patch/plaque disease
  – “Milder” systemic options +/- skin-directed tx
• Generalized extent tumor disease
  – Indolent (no LCT) and <4 tumors
    • Systemic (e.g. targretin) +/- skin-directed tx
  – Aggressive (+ LCT) or ≥4 tumors
    • Systemic options +/- skin-directed tx
• Refractory disease => clinical trials, combo

Consider Allogeneic transplant
MF w/ large cell transformation with worse prognosis

NOTE: CD30+ pcALCL should be differentiated from MF with large cell transformation (T-MF) with CD30+ tumor cells

- Brentuximab
- Pralatrexate +/- targretin
- Romidepsin
- Gemcitabine
- Clinical trial
- +/- local RT
Management of erythrodermic (T4) disease

• Approach **based on peripheral blood burden**
  – B0, B1, vs. B2 (Sezary syndrome)

• Erythrodermic (T4) MF, stage III
  – B0 => generalized skin-directed options
  – B1 => “milder” systemic options
  – Refractory disease
  – Combination therapies
    • Skin tx + Systemic
      – Photopheresis, Romidepsin

• Essential to optimize supportive care
  – Emollients, topical steroids +/- occlusion
  – Vigilant infection control (staph, HSV/VZV
  – Anti-itch support (gabapentin, doxepin)
Evidence for treatment stratification by blood tumor burden

- Current B2 $\geq$ 1,000 /mm$^3$
- Evidence that $\geq$ 5K or $\geq$ 10K are important prognostic or therapy outcome levels
  - $\geq$ 5K as worse px group
    (Vonderheid et al. leukemia Lymph 2006;47:1841)
  - ↑death rate in $\geq$ 10K
    (Scarisbrick et al. Blood 2001;97:624)
  - Reduced survival in $\geq$ 10K
  - Combination biologics less effective in $\geq$ 10K (Stanford group, WCCL abstract 2010)
- $\geq$ 10K /mm$^3$ may be important prognostic threshold
Management of Sezary Syndrome, B2/stage IV

- Stratification based on blood Sezary burden
- Given risk for staph sepsis, utilize agents that spare further immune dysfunction

- **Low-intermediate Sezary burden**
  - “Milder” systemic therapies: biologics (bexarotene, photopheresis, interferon), methotrexate

- **High Sezary burden (> 5-10K/mm³)**
  - Combination therapies (e.g. ECP+IFN)
  - Romidepsin
  - Alemtuzumab or Brentuximab

- Refractory disease
  - Alemtuzumab or Brentuximab
  - Clinical trials

Allo HSCT
The Future of Lymphoma Treatment

Genomic Analysis
- Exome Sequencing
- RNA Seq

Functional Analysis
In vitro
- Compound screen

Analysis ➞ Choosing the Right Drug(s)

Minimal Residual Disease Testing

![Graph showing Lymphoma cells over time with viability levels.](image)
Road to a CURE
How do we make the nice responses last?
Partnering with immunotherapy

% Survival

Time

Tumor-directed killing

Immune modulatory therapy
Immunotherapy strategies in CTCL

- Tumor-specific monoclonal antibodies
- Immune-modulating agents or antibodies
- Vaccine-based approaches
- Cytokine therapy
- Adoptive T-cell transfer
- Allogeneic HSCT

Lymphoma

TILs
Hematopoietic cell transplantation in mycosis fungoides and Sézary syndrome

Considered for patients with refractory/advanced disease (stages IIB-IV)

**Autologous** → High-dose therapy followed by stem cell rescue
- Benefit of no GVHD
- No durable response in MF/SS, not recommended

**Allogeneic** → Graft vs. lymphoma (GVL) effect
- Risk of GVHD
- Increasing evidence of durable clinical, cytogenetic, molecular remissions in MF/SS

*How to maximize GVL effect while minimizing GVHD risk*

Harnessing the graft-versus-lymphoma effect as the ultimate cellular immune therapy

Donor Cell Transplant

Replacement of Host Blood System

Donor Immune System to destroy lymphoma cells
Mycosis fungoides, stage IVA w/ LCT in skin/LNs: CR

Pre-TSEBT

3 yr (NED, no GVHD)
Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

Pre-TSEBT
CD4+/CD26-: 99%, abs 19,780

2 yr (NED, no GVHD)
CD4+/CD26-: normalized
Sezary syndrome, stage IVA w/ LCT in skin/LNs: CR

Pre-transplant

2 yr (NED, no GVHD)
Management of CTCL

Summary & Take-Home Messages

• MF and SS is very heterogeneous in clinical disease and responses to therapies- important to individualize

• With lack of evidence based help, utilization of consensus guidelines, such as NCCN, is important

• Stage-based management is essential, esp. not to over-treat early stages of MF

• Systemic or combination therapies are for refractory early stage or more advanced stages of MF and SS

• Given no curative therapies, participation in clinical trials should be considered whenever appropriate, and allogeneic HSCT considered in patients with advanced/aggressive/refractory disease
Questions