Staging and Treatment of Cutaneous Lymphomas: Utility of NCCN Practice Guidelines

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Disclosure statement

Youn Kim, MD

• Steering Committee
  – Eisai, Millennium

• Consultant or Advisory board
  – Kyowa, Celgene, Emergent, Medicis

• Investigator
  – Allos, Kyowa, Merck, Millennium, Seattle Genetics, SHAPE, Ceptaris/Yaupon, Eisai, Genentech
Non-Hodgkin’s Lymphomas

Version 1.2013

NCCN.org

NHL => MFSS
US Treatment Guidelines in MF/SS & CBCL

www.nccn.org => NHL => MFSS or CBCL

- First available standard of care treatment guideline in cutaneous lymphoma in US
- Real time updates
- Lack of evidence-based help in CL → important role of consensus guidelines
- Help with insurance auth and reimbursement; given lots of off-label use
# Cutaneous T- and NK/T-cell Lymphomas

<table>
<thead>
<tr>
<th>New WHO-EORTC Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis fungoides and variants/subtypes</td>
</tr>
<tr>
<td>Sézary syndrome</td>
</tr>
<tr>
<td>PC CD30+ lymphoproliferative disorders</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
</tr>
<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
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<tr>
<td>Cutaneous $\gamma/\delta$ T-cell lymphoma</td>
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<tr>
<td>Adult T-cell leukemia/lymphoma</td>
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<tr>
<td>PC peripheral T-cell lymphoma, unspecified</td>
</tr>
<tr>
<td>• Aggressive epidermotropic CD8+ T-cell lymphoma</td>
</tr>
<tr>
<td>• CD4+ sm/med-sized pleomorphic T-cell lymphoma</td>
</tr>
<tr>
<td>• PTCL, other</td>
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</tbody>
</table>

Blood 2005;105:3768-85
WHO monogram, 4th Ed, 2008
Mycosis Fungoides
Treatment of varying skin manifestations

- **Patch** T1-2
- **Plaque** T1-2
- **Tumor** T3
- **Erythroderma** T4
Management of extracutaneous disease
Sézary syndrome—generalized erythroderma, keratoderma, severe itching; freq staph aureus infection
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
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
  - US vs. other countries
  - Insurance barriers
Survival decreased with advancing T class and overall clinical stage

DSS utilizing revised staging system

Patch better than plaque disease, \( P = .007/.002 \)

Agar et al. J Clin Oncol 2010;28:4730
B0 with positive clone (same as skin), B0b, a/w worse outcome

Impact of clonality data

Sig OS/DSS differences by increasing B-classification; p < .001

B0a, n= 658
B0b, n= 86

Pairwise comparisons
OS/DSS:
B0a vs. B0b, p <.001
B1a vs. B1b, not sig
B1 vs. B2, p=.040

Lack of sufficient, relevant data or adequate consensus to change current NCCN practice guideline

Current/revised TNMB/staging for MF/SS needs further validation and modification
-Patch vs. plaque, importance of LN/B-clone

B1 vs. B2, p=.040

Agar et al. J Clin Oncol 2010;28:4730
NCCN Guidelines Version 1.2013
Mycosis Fungoides/Sezary Syndrome

**DIAGNOSIS**
**ESSENTIAL:**
- Biopsy of suspicious skin sites
- Dermatopathology review of slides

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- IHC of skin biopsy (CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD25, CD56, TIA1, granzyme B, β1F)
- Molecular analysis for TCR gene rearrangements (assessment of clonality) of skin biopsy
- Assessment of peripheral blood for Sezary cells (in cases where skin is not diagnostic, especially T4) including Sezary cell prep, flow cytometry, and PCR for TCR gene rearrangement
- Bone marrow biopsy (not required for staging but used to document visceral disease in those suspected to have marrow involvement including B2 blood involvement and in patients with unexplained hematologic abnormality)
- Biopsy of suspicious lymph nodes for identical clones (recommend assessment of clonality for all but particularly NCI LN 2-3) or suspected extracutaneous sites
- Rebiopsy if suspicious of large cell transformation
- Neck CT

**WORKUP**
**ESSENTIAL:**
- Complete physical examination
- Examination of entire skin: assessment of %BSA (palm plus digits, ≥1% BSA) and type of skin lesion (patch/plaque, tumor, erythroderma)
- Palpation of peripheral lymph node regions
- Palpation for organomegaly/masses
- Laboratory studies:
  - CBC with Sezary screen (manual slide review, "Sezary cell prep")
  - Sezary flow cytometric study (optional for T1); CD3, CD4, CD7, CD8, CD26 to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype, including loss of CD7 or CD26

**USEFUL IN SELECTED CASES:**

**STAGE**
(MFSS-2 and MFSS-3)

- **Stage IA** → See Primary Treatment (MFSS-4)
- **Stage IB-IIA** → See Primary Treatment (MFSS-5)
- **Stage IIB** → See Primary Treatment (MFSS-6)
- **Stage III** → See Primary Treatment (MFSS-7)
- **Stage IV** → See Primary Treatment (MFSS-8)

Blood 2007;110:1713
www.nccn.org => NHL => MFSS
Staging Evaluation, Mycosis Fungoides/Sézary Syndrome

• Complete PE
  – Thorough skin exam (extent & type)
  – LN, organomeg/masses
• Laboratory studies
  – CBC with Sézary cell analysis
    • Sézary cell count (morphologic exam)
    • Flow cytometry: CD3, CD4, CD7, CD8, CD26 to assess for ↑CD4+, CD4/CD8 or abnormal phenotype (CD4+/CD7-%, CD4+/CD26-%, other)
  – Comp metabolic, LDH
• Imaging studies
  – Chest x-ray
  – Contrast-enhanced CT or whole body PET/CT: >T2, LCT, FMF, ↑LN/labs
• Biopsy of suspicious LNs (>1.5 cm or sig. PET+) or suspected visceral involvement
• BM biopsy considered in B2 (not required)

Updated in NCCN Practice Guidelines, www.nccn.org
Stage-based management
Current Clinical Management of CTCL, 2013

www.nccn.org => NHL => MF/SS

<table>
<thead>
<tr>
<th>IA</th>
<th>IB/IIA</th>
<th>IIB</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited patch/plaque</td>
<td>Generalized patch/plaque</td>
<td>Tumors</td>
<td>Erythroderma</td>
<td>Extracut. Disease</td>
</tr>
</tbody>
</table>

- **IA**
  - Topical steroid, retinoid (bex), NM phototherapy, local RT, imiquimod

- **IB/IIA**
  - Combination chemo (single or combination)
  - Bexarotene, denileukin diftitox, IFN vorinostat, romidepsin (single or combination)

- **IIB**
  - Phototherapy + bexarotene or IFN
  - TSEBT + ECP*, IFN

- **III**
  - ECP* + IFN, bexarotene
  - Single-agent chemotherapy**

- **IV**
  - Alemtuzumab
  - Combination chemo
  - Allo-HSCT

Clinical Trials

*ECP = photopheresis

** Methotrexate, liposomal doxorubicin, gemcitabine, pentostatin, chlorambucil, etoposide, pralatrexate
Skin-directed therapies

- Topical steroids
- Topical chemotherapy (mechloretamine, carmustine)
- Topical retinoids (bexarotene)
- Topical imiquimod
- Phototherapy
  - UVB (narrow band, broad band)
  - PUVA (psoralen + UVA)
- Radiation
  - Local (12-36 Gy)
  - Total skin electron beam therapy (12-36 Gy)
- **Excimer, photodynamic therapy (not in NCCN)**

Actuarial survival of stage IA vs. control population: Life-expectancy is not altered in patients with limited patch/plaque disease

Kim et al, Arch Dermatol 1996;132:1309-13
Reliable skin responses with skin-directed options as primary therapy in stages I-IIA (skin-limited, patch/plaque disease)

<table>
<thead>
<tr>
<th>Skin Therapy</th>
<th>CR</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical steroids</td>
<td>45-65%</td>
<td>75-95%</td>
</tr>
<tr>
<td>Bexarotene gel</td>
<td>20-35%</td>
<td>50-75%</td>
</tr>
<tr>
<td>Topical NM</td>
<td>25-70%</td>
<td>50-90%</td>
</tr>
<tr>
<td>nbUVB</td>
<td>45-75%</td>
<td>75-100%</td>
</tr>
<tr>
<td>PUVA</td>
<td>50-80%</td>
<td>85-100%</td>
</tr>
<tr>
<td>TSEBT (≥30 Gy)</td>
<td>80-90%</td>
<td>100%</td>
</tr>
</tbody>
</table>

- Systemic agents (e.g., bexarotene, IFN, methotrexate, vorinostat, romidepsin) 30-45% RR in skin with low CR rates

Clinical response to topical nitrogen mustard gel
Localized RT in Woringer Kolopp disease
Systemic therapies for MF/SS-CTCL

• “Milder” therapies => “Category A in NCCN”
  – First-line systemic tx in refractory early dz, IA-IIA
  – Bexarotene, IFNs, HDAC-inhibitors (vorinostat, romidepsin), photopheresis, denileukin diftitox, low-dose methotrexate

• Single-agent cytotoxic therapies
  => “Category B in NCCN”
  – Refractory to Category A agents
  – First-line: liposomal doxorubicin, gemcitabine
  – Second-line: other single agent cytotoxic

• Frontline systemic therapies for aggressive growth pattern (large cell transformation, stage IV non-Sezary)
  => “Category C in NCCN”
  – Liposomal doxorubicin, gemcitabine, denileukin diftitox, romidepsin, pralatrexate, regimens for PTCL (stage IV)
# Efficacy of Systemic Agents in CTCL

<table>
<thead>
<tr>
<th>Agent (Class)</th>
<th>Indication</th>
<th>Year</th>
<th>Study</th>
<th>N</th>
<th>ORR</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romidepsin (HDAC inhibitor)</td>
<td>CTCL with prior systemic therapy</td>
<td>2009</td>
<td>Pivotal</td>
<td>96</td>
<td>34%</td>
<td>15 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Supportive</td>
<td>71</td>
<td>35%</td>
<td>11 mo</td>
</tr>
<tr>
<td>Denileukin diftitox (Fusion protein)</td>
<td>Tumors that express CD25</td>
<td>1999, 2008</td>
<td>Pivotal</td>
<td>71</td>
<td>30%</td>
<td>4 mo</td>
</tr>
<tr>
<td>Bexarotene (RXR activator)</td>
<td>Cutaneous manifestations</td>
<td>1999</td>
<td>Pivotal</td>
<td>62</td>
<td>32%</td>
<td>5+ mo</td>
</tr>
<tr>
<td>Vorinostat (HDAC inhibitor)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30%</td>
<td>6+ mo</td>
</tr>
</tbody>
</table>

*Need better therapies More options*
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 + denileukin diftitox
  – 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?
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.
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
NCCN Guidelines Version 1.2013
Mycosis Fungoides/Sezary Syndrome

STAGE
(MFSS-2 and
MFSS-3)

PRIMARY TREATMENT

RESPONSE TO THERAPY

See Supportive Care for MF/SS (MFSS-B)

Stage IB-IIA

Generalized skin treatment
• See Suggested Treatment Regimens "Skin-Directed Therapies (Skin-Generalized)" (MFSS-A)
± adjuvant local skin treatment
(see stage IA on MFSS-4)

If blood B1 involvement, consider primary treatment for Stage III B1 MFSS-7 (category 2B)

If histologic evidence of folliculotropictic or large-cell transformed MF

Consider primary treatment for Stage IIB (See MFSS-6)

CR/PR° or inadequate response

Relapse with or persistent T1-T2 disease:
• T1 (see stage IA on MFSS-4)
• T2 (see generalized skin treatment) (MFSS-A)

See Suggested Treatment Regimens
• Clinical trial
• Systemic Therapies (SYST-CAT A) (MFSS-A)
• Combination Therapies ± skin-directed therapy

CR/PR° or inadequate response

Refractory disease° or progression to > stage IB-IIA

Refractory disease° or progression

Clinical trial
• TSEBT (if not previously administered)
• Systemic chemotherapy agents used in ≥ stage IIB disease

• See Suggested Treatment Regimens "Systemic Therapies (SYST-CAT B)" (MFSS-A)
Approach to the management of F-MF based on extent/severity of folliculotrophic lesions

**Limited or mild sx**
- Top/IL steroids
- Imiquimod
- Bexarotene gel
- Topical NM
- Local RT
- Phototherapy
- “milder” systemic therapy (bexarotene, mtx)
- Clinical trial

**Generalized or severe sx**
- Skin-directed + systemic agent
  - Phototherapy + bex or IFN
- Systemic agent +/- skin-directed tx
  - Bex, IFN, MTX, vori, romi
- If LCT+, Cat-B/C NCCN
- TSEBT
- Clinical trial

Clinical trial
Combination strategies in refractory folliculotrophic patch/plaque or tumor disease

<table>
<thead>
<tr>
<th>Skin + systemic Therapy</th>
<th>Systemic + systemic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUVA + IFN</td>
<td>Bexarotene + IFN</td>
</tr>
<tr>
<td>PUVA or nbUVB + bexarotene</td>
<td>Bex + denileukin diftitox</td>
</tr>
<tr>
<td>PUVA or nbUVB + photopheresis</td>
<td>Methotrexate + IFN</td>
</tr>
<tr>
<td>PUVA + [Photopheresis + bexarotene +/- IFN]</td>
<td>Methotrexate + bexarotene</td>
</tr>
<tr>
<td>TSEBT + photopheresis</td>
<td>Vorinostat + IFN</td>
</tr>
<tr>
<td>Low-dose TSEBT + HDAC inhibitors</td>
<td>Vorinostat + bexarotene</td>
</tr>
</tbody>
</table>

Hoping for improved synergistic efficacy and/or less toxicity by allowing lower doses of each.
7 yr h/o very slowly enlarging patch/plaque, localized to left forearm, failed top steroids

- Limited or mild sx
- Topical NM
- Local RT
- Bexarotene gel
- Imiquimod
- "milder" systemic therapy (bexarotene, MTX)
- (Excimer, PDT- not in NCCN list)
Localized refractory disease: Predominantly face, refractory to oral bex, MTX, IFN
Durable local control w/ local electron beam therapy (tailored-made “face technique”)
Generalized folliculotrophic disease

- Generalized or severe sx
- Skin-directed + systemic agent
  - Phototherapy + bex or IFN
- Systemic agent +/- skin-directed tx
  - Bex, IFN, MTX
- TSEBT
- Clinical trial
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 folliculotrophic 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 nbUWB. 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, folliculotropic MF

Screening
mSWAT 133
Pruritus 8/10

Wk 16
mSWAT 0 (CR)
Pruritus 0/10
Clinical response with low-dose (12 Gy) TSEBT
69 yo M, stage IIB, folliculotrophic MF
Management of skin “tumor” disease (IIB)

• 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 (Cat-A) +/- skin-directed tx
• Generalized extent tumor disease
  – Indolent (no LCT)
    • TSEBT
    • Category A systemic +/- skin-directed tx
  – Aggressive (+ LCT)
    • TSEBT + Cat-A systemic
    • Category B or C systemic options +/- skin-directed tx
• Refractory disease => clinical trials, combo

Consider
Allo
HSCT
NCCN Guidelines Version 1.2013
Mycosis Fungoides/Sezary Syndrome

STAGE
(MFSS-2 and MFSS-3)

- Limited extent tumor disease ± patch/plaque disease

Stage IIB and/or histologic evidence of folliculotropic or large-cell transformation (LCT)

- Generalized extent tumor, transformed, and/or folliculotropic disease

See Supportive Care for MFSS (MFSS-B)

PRIMARY TREATMENT

- Local RT for limited extent tumor, transformed, and/or folliculotropic disease
  - Systemic Therapies (SYST-CAT A) (MFSS-A) ± skin-directed therapies ± RT

RESPONSE TO THERAPY

- CR/PR or inadequate response

  - Refractory disease or progression

  - Relapse with or persistent T1-T3 limited:
    - T1-2 (see stage IA on MFSS-4 or stage IB-IIA on MFSS-5)
    - T3 limited extent

- TSEBT
  - See Suggested Treatment Regimens
    - Systemic Therapies (SYST-CAT A) (MFSS-A)
    - Systemic Therapies (SYST-CAT B) (MFSS-A)
    - Systemic Therapies (SYST-CAT C) (MFSS-A)
    - Combination Therapies ± skin-directed therapy

- CR/PR or inadequate response

  - Refractory disease or progression

  - Relapse with or persistent T1-T3:
    - T1-2 (see stage IA on MFSS-4 or stage IB-IIA on MFSS-5)
    - T3

  - Multi-agent chemotherapy
    - Consider allogeneic transplant
    - Clinical trial

Notes:
- It is preferred that treatment occur at centers with expertise in the management of the disease.
- Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis.
- Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published (Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2596-2607).
- Patients achieving a response and/or a clinical benefit should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.
- Refractory or intolerant to multiple previous therapies.
- Rebiopsy if suspect large cell transformation.
- If histologic evidence of LCT often, but not always corresponds to a more aggressive growth rate. If there is no evidence of more aggressive growth, choosing systemic therapies from SYST-CAT A or SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.
MF w/ large cell transformation with worse prognosis

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

Cat-B or C NCCN options, trials

- Romidepsin
- Liposomal doxorubicin
- Pralatrexate
- Gemcitabine
- Clinical trial (e.g., brentuximab vedotin)
- +/- local RT
Management of erythrodermic (T4) disease

• Approach based on peripheral blood Sezary burden
  – B0, B1, vs. B2 (Sezary syndrome)
• Erythrodermic (T4) MF, stage III
  – B0 => generalized skin-directed options or Cat-A
  – B1 => “milder” systemic options (NCCN Cat-A)
• Refractory disease
  – Combination therapies
    • Skin tx + Cat-A, Cat-A + Cat-A
  – Alemtuzumab
• Essential to optimize supportive care
  – Emollients, topical steroids +
  – Vigilant infection control (staph, HSV/VZV)
  – Anti-itch support (gabapentin)
Evidence for treatment stratification by blood tumor burden in SS

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

- Refractory disease
  - Alemtuzumab
  - Clinical trials

Allo HSCT
Preserve immune response whenever possible
Low threshold to cover skin pathogens
Supportive/combination care (topicals, anti-itch)
NCCN Guidelines Version 1.2013
Mycosis Fungoides/Sezary Syndrome

STAGE
(MFSS-2 and MFSS-3)

• Sezary syndrome

Stage IV

• Non Sezary or Visceral disease (solid organ)

PRIMARY TREATMENT

• See Suggested Treatment Regimens
  • Systemic Therapies (SYST-CAT A) (MFSS-A)
  • Combination Therapies

RESPONSE TO THERAPY

CR/PR\(^{a}\) or inadequate response

• Relapse or persistent disease
  • Consider allogeneic transplant,\(^{y}\)
    as appropriate

Refractory disease\(^{p}\) or progression

• See Suggested Treatment Regimens - Systemic Therapies (SYST-CAT B) (MFSS-A)
  • Alemtuzumab\(^{cc}\)
  • Clinical trial

Category B (SYST-CAT B)

• First-line therapies
  • Liposomal doxorubicin
  • Gemcitabine

• Second-line therapies
  • Chlorambucil
  • Pentostatin
  • Etoposide
  • Cyclophosphamide
  • Temozolomide
  • Methotrexate (>100 mg q week)
  • Bortezomib
  • Low-dose pralatrexate
Phase II Multi-Institutional Trial of the Histone Deacetylase Inhibitor Romidepsin As Monotherapy for Patients With Cutaneous T-Cell Lymphoma


J Clin Oncol. 2009;27:5410-5417

Final Results From a Multicenter, International, Pivotal Study of Romidepsin in Refractory Cutaneous T-Cell Lymphoma

Sean J. Whittaker, Marie-France Demierre, Ellen J. Kim, Alain H. Rook, Adam Lerner, Madeleine Duvic, Julia Scarisbrick, Sunil Reddy, Tadeusz Robak, Jürgen C. Becker, Alexey Samtsov, William McCulloch, and Youn H. Kim

J Clin Oncol, 2010;28:4485-4491
Sezary syndrome response to romidepsin
Patient 37-018 (failed 3 chemo regimens)
Sezary syndrome response to romidepsin
Patient 37-018

Screening

Cycle 6, Day 1
Romidepsin Activity in Blood

_Pivotal Study, Patients with Significant Blood Sezary Burden_*

_Pivotal study_
- B2 (> 1000 /µl and/or > 20%, n = 13), ORR 31%

* > 1,000 Sézary cells/µl
<table>
<thead>
<tr>
<th>IA</th>
<th>IB/IIA</th>
<th>IIB</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Limited</strong> patch/plaque</td>
<td><strong>Generalized</strong> patch/plaque</td>
<td><strong>Tumors</strong></td>
<td><strong>Erythroderma</strong></td>
<td><strong>Extracut. Disease</strong></td>
</tr>
</tbody>
</table>

- **IA**:
  - Topical steroid, retinoid (bex), NM phototherapy, local RT, imiquimod

- **IB/IIA**:
  - Phototherapy + bexarotene or IFN
  - TSEBT + ECP*, IFN
  - Bexarotene, *denileukin diftitox*, IFN, vorinostat, romidepsin (single or combination)

- **IIIB**:
  - Single-agent chemotherapy**

- **IIIC**:
  - ECP* + IFN, bexarotene

- **IV**:
  - Alemtuzumab
  - Combination chemo
  - Allo-HSCT

---

*ECP = photopheresis
** Methotrexate, liposomal doxorubicin, gemcitabine, pentostatin, chlorambucil, etoposide, **pralatrexate**
Hematopoietic stem 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

Stem cell | Progenitor cells | Precursor cells | Mature cells

- BFU-E derived colony (erythroid)
- CFU-GM derived colony (myeloid)
- CFU-Meg derived colony (megakaryocyte)

Lymphocytes

Donor Immune System to destroy lymphoma cells

Sezary 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
**Primary Cutaneous B-cell Lymphomas**

<table>
<thead>
<tr>
<th>New WHO-EORTC Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marginal zone B-cell lymphoma</td>
</tr>
<tr>
<td>Follicle center lymphoma</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma, leg-type</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma, other</td>
</tr>
</tbody>
</table>

Most primary cutaneous CBCL are “good” except DLBCL, leg-type/other

Blood 2005;105:3768-85
WHO monogram, 4th Ed, 2008
DSS, n = 280 Dutch patients

Differential gene expression patterns, PCFCL vs. DLBCL leg-type
Hoefnagel et al, Blood 105;3674, 2005
### PCBCL, Stanford Experience, $n = 222$

<table>
<thead>
<tr>
<th></th>
<th>Follicle Center Lymphoma (n=115)</th>
<th>Marginal Zone Lymphoma (n=96)</th>
<th>Diffuse Large Cell Lymphoma-leg type (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age median</strong></td>
<td>52 (17-88)</td>
<td>49 (14-80)</td>
<td>71 (41-90)</td>
</tr>
<tr>
<td><strong>% Male/Female</strong></td>
<td>72/28</td>
<td>61/39</td>
<td>63/37</td>
</tr>
<tr>
<td><strong>OS, 5-year</strong></td>
<td>95%</td>
<td>100%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>RFS, 5-year</strong></td>
<td>44%</td>
<td>38%</td>
<td>17%</td>
</tr>
<tr>
<td><strong>Sites for localized disease</strong></td>
<td>H/N 54%</td>
<td>H/N 31%</td>
<td>Leg 100%</td>
</tr>
<tr>
<td></td>
<td>Arm 11%</td>
<td>Arms 37%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Torso 27%</td>
<td>Torso 23%</td>
<td></td>
</tr>
</tbody>
</table>

*In indolent CBCL (MZL/FCL), when relapse occurs, majority are limited to skin and respond well to salvage therapy*
PC Marginal-Zone B-cell Lymphoma

“Immunocytoma”, part of extranodal MZL of MALT (GI tract, salivary gland, lung, H/N, ocular adnexa, skin, thyroid, breast)
Precursor lesions of MALT lymphomas

- Pre-existing chronic inflammatory disorder resulting in accumulation of extranodal lymphoid tissue
- Infectious cause
  - H. pylori (gastric MALT lymphoma)
  - Chlamydia psittaci (ocular adnexal MALT)
  - Campylobacter jejuni (IPSID- small intestine)
  - Borrelia burgdorferi (cutaneous- geographic diversity)
- Autoimmune based inflammation
  - Sjögren’s (salivary gland MALT lymphoma)
  - Hashimoto’s thyroiditis (thyroid gland MALT)
Acrodermatitis chronica atrophicans, B-cell LPDs in Europe is primarily caused by *B afzelii*

*B afzelii* is NOT found in the US

=> CBCL a/w borrelia is most likely a European phenomenon as *B burgdorferi* sensu lato, either *B burgdorferi* or *B afzelii*, has NOT been demonstrated by PCR in affected tissue in the US cases

Checking borrelia serology or treating with oral antibiotics for borrelia is NOT in the NCCN guidelines
PC Follicle Center Lymphoma
45M with 1 yr h/o slowly enlarging tumors on scalp/forehead

25 yrs later
PCFCL
Localized T1, 2
PCFCL
Multifocal/generalized, T3
72 yo M initially noted R ankle swelling, then 5 mo h/o rapidly progressive tumor nodules along the R lower leg
PC Diffuse Large B-cell Lymphoma, Leg-Type

- PCLBCL w/ predominance or confluent sheets of centroblasts and immunoblasts
  - CD20+, CD79a+, monotypic light chain expression
  - Bcl-2+ (strong), Bcl-6+/-, CD10-, IRF4/MUM1+, FOXP1+, IgM+, IgD+/-
  - Lack t(14;18) despite strong Bcl-2; lack IRF4 rearrangement
  - Inactivation of p15, p16 in 11%, 44%; chromosomal imbalances in 85% w/ gains of 18q, 7p, loss of regions of 9p21.3 (CDKN2A/B); translocations of myc, bcl-6, IgH
  - Frequent clonal IgH gene rearrangement by PCR

- Rapidly growing red-violaceous tumor(s), most commonly on leg(s), but can affect non-leg sites (10-15%)
  - Common in elderly
  - Less favorable prognosis w/ increased risk of development of extracutaneous disease => 5-yr OS 35-50%
DLBCL leg-type,
leg or non-leg location
IgM Expression on Paraffin Sections Distinguishes Primary Cutaneous Large B-cell Lymphoma, Leg Type From Primary Cutaneous Follicle Center Lymphoma

Lianne Koen, MD,* Maarten H. Vermeer, MD, PhD,† Rein Willemze, MD, PhD,† and Patty M. Jansen, MD, PhD*


• 100% (40/40) of DLBCL leg type => cytoplasmic IgM+; 18/40 IgD+
• 10% (5/53) of FCL are IgM+ and/or IgD+

IHC for IgM, IgD can be very helpful in distinguishing FCL vs. DLBCL leg type
DIAGNOSIS

ESSENTIAL:
- Review of all slides with at least one paraffin block representative of the tumor should be done by a pathologist with expertise in the diagnosis of primary cutaneous B-cell lymphoma. Rebiopsy if consult material is nondiagnostic.
- Histopathology review of adequate biopsy (punch, incisional, excisional).
- Adequate immunohistochemical review to establish diagnosis.
- IHC panel: CD20, CD79a, CD3, CD5, CD10, BCL2, BCL6, kappa/lambda, IFR4/MUM1.

USEFUL IN CERTAIN CIRCUMSTANCES:
- Additional immunohistochemical studies to establish lymphoma subtype.
- IHC panel: Ki-67, CD43, CD21, CD23.
- Paraffin panel: Cyclin D1.
- Assessment of IgM and IgD expression (to further help in distinguishing DLBCL, leg type from follicle center lymphoma).
- Molecular analysis to detect: antigen receptor gene rearrangements; Ig gene rearrangement by PCR.
- Cytogenetics or FISH: t(14;18).
- If adequate biopsy material available, flow cytometry can be useful in determining B-cell clonality.

NOTE: A germinai (or follicle) center phenotype and large cells in a skin lesion is not equivalent to DLBCL but is consistent with primary cutaneous germinal/follicle center lymphoma.

WORKUP

ESSENTIAL:
- History and physical exam, including complete skin exam.
- CBC, differential, comprehensive metabolic panel.
- LDH.
- Hepatitis B testing if rituximab considered.
- Chest/abdominal/pelvic CT.
- Bone marrow biopsy, if PC-DLBCL, Leg type.
- Pregnancy testing in women of child-bearing age (if chemotherapy planned).

USEFUL IN SELECTED CASES:
- PET-CT scan.
- Bone marrow biopsy.
  - Consider if PCFCL.
  - Optional if PCMZL.
- Peripheral blood flow cytometry, if CBC demonstrates lymphocytosis.
- SPEP/quantitative immunoglobulins for PCMZL.

PCMZL: Primary Cutaneous Marginal Zone Lymphoma
PCFCL: Primary Cutaneous Follicle Center Lymphoma
PC-DLBCL, Leg type: Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg type.
Management of PCBCL

**Indolent (MZL/FCL)**

- **Solitary / Regional (T1-2)**
  - RT
  - Excision
  - Observation
  - Topical tx
    - NM, imiq, retinoid
  - IL steroids

- **Generalized (T3)**
  - Observation
  - RT for sx+ lesions
  - Topical tx
    - NM, imiq, retinoid
  - IL steroids
  - Biologics
    - Rituximab
  - Chemotherapy ± R
    - Single or Combination
  - Clinical Trials

**Aggressive (DLBCL leg-type)**

- **Solitary (T1)**
  - RT (caution)
  - R-CHOP ± IFRT
  - Clinical Trials

- **Multiple (T2-3)**
  - R-CHOP ± IFRT
  - Clinical Trials

*Intralesional rituximab, IFN-α in indolent CBCLs more common in Europe*

www.nccn.org => NHL => PCBCL
Blood 2008;112:1600-1609
PCFCL
Localized T1, 2
PCFCL
Multifocal/generalized, T3

Rituximab

Local RT
72 yo M initially noted R ankle swelling, then 5 mo h/o rapidly progressive tumor nodules along the R lower leg

R-CHOP +/- IFRT
PC CBCL - Take Home Summary

- **Indolent** (FCL/MZL) vs. **aggressive** (DLBCL leg-type)
- Need more specific molecular and/or tissue markers to differentiate CBCLs or prognosticate => aid in management
- **Do not over treat the indolent cases**
- **Do not under treat aggressive cases** (age appropriate)
- If precise classification difficult, manage according to clinical behavior
- **Utilize NCCN practice guidelines**
  - NCCN.org => NHL => CBCL
Other than MF/SS CTCL treatment strategy (not in NCCN)

Indolent clinical behavior (pcALCL, CD4+ sm/med pleomorphic T-cell LPD, SPTCL w/o HPs)

Solitary or regional (T1-2) ↔ Multi-focal/generalized (T3)

Observation

Localized therapies
- Radiation
- Topicals (NM, bex, imiquimod)
- Intralesional steroid

Systemic therapies
- Systemic steroids (SPTCL)
- Methotrexate
- Bexarotene
- HDAC inhibitors
- Clinical trials

Aggressive clinical behavior (SPTCL w/ HPS, γ/δ TCL, PTCL NOS)
- Romidepsin
- single-agent chemo (liposomal doxorubicin, gemcitabine, pralatrexate)
- Upfront intensive combination chemotherapy
- HSC transplantation
- Clinical trials

Observation
Stanford Multidisciplinary Cutaneous Lymphoma Group

Ranjana Advani
Med Onc partners

Holbrook Kohrt
Sunil Reddy
Ron Levy

Wen-Kai Weng
Sally Arai
Katherine Wolpin
BMT partners

Michael Krathen
Rich Hoppe
Lynn Million