How to use the NCCN guidelines to help your patients and optimize clinical practice

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Disclosure statement

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• **Steering Committee**
  – Eisai, Kyowa, Millennium/Takeda

• **Consultant or Advisory Board**
  – Actelion, Seattle Genetics, Forty Seven, Medivir, Takeda

• **Investigator**
  – Kyowa, Merck, Millennium/Takeda, Seattle Genetics, Eisai, Tetralogic, Innate, Neumedicine, Soligenix, mirage, Infinity, Forty Seven, Portola
T-cell Lymphomas

Version 2.2017 — February 21, 2017

NHLs
T-Cell Lymphomas => MFSS, PCTLD, sPTCL, ATLL, NK/TCL
PC BCL => indolent CBCL (MZL/FCL)
B-Cell Lymphomas (systemic) => includes DLBCL, leg-type
NCCN Categories of Evidence and Consensus

• **Category 1**: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

• **Category 2A**: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

• **Category 2B**: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

• **Category 3**: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

NCCN encourages participation in clinical trials for all cancer patients

NCCN Global utilization is increasing

• ~ 50% registered users are non-US
• Adapted for regional use and/or translated (10+ languages) versions
## Cutaneous T- and NK/T-cell Lymphomas

### New WHO-EORTC Classification

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mycosis fungoides and variants/subtypes</strong></td>
<td></td>
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<tr>
<td><strong>Sézary syndrome</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cutaneous CD30+ T-cell lymphoproliferative disorders</strong></td>
<td></td>
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<tr>
<td><strong>Subcutaneous panniculitis-like T-cell lymphoma</strong></td>
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<tr>
<td><strong>Extranodal NK/T-cell lymphoma, nasal type</strong></td>
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<tr>
<td><strong>Cutaneous γ/δ T-cell lymphoma</strong></td>
<td></td>
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<tr>
<td><strong>Adult T-cell leukemia/lymphoma</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Provisional entities:</strong></td>
<td></td>
</tr>
<tr>
<td>• CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>• CD4+ small/medium T-cell lymphoproliferative disorder*</td>
<td></td>
</tr>
<tr>
<td>• Cutaneous acral CD8+ T-cell lymphoma*</td>
<td></td>
</tr>
<tr>
<td><strong>Cutaneous PTCL, NOS</strong></td>
<td></td>
</tr>
</tbody>
</table>

*changes from 2008 WHO classification

Several entities have NCCN guidelines
Sezary flow cytometry needed when suspect SS: Supportive document for MF/SS-specific flow parameter set-up (CD26) or coverage by insurance
Due to the rarity of the condition and the need for an individualized approach, referral to a multidisciplinary academic specialty center is preferred.
Prognosis of early vs advanced stage MF and SS: Appropriate risk-stratification for treatment selection

Stage IA vs. control population: Life-expectancy is not altered in limited patch/plaque disease

Early (IA-IIA) vs Advanced (IIB-IV)

Large-cell transformation (LCT) with worse clinical outcome;
F-MF two prognostic subsets (Hodak et al, 2016)
F-MF not sig independent factor in advanced MF/SS (CLIC Scarisbrick et al, 2015)
Stage-based management with additional risk factors integrated

**Overall goal of treatment (other than allo-HSCT)**
- Not curative intent: good PRs that are durable, well-tolerated, and improve QoL
- Lasting CRs are great but hard to attain and often at risk of undesired AEs

**Appreciate unique approaches in MF/SS**
- Optimize use of **skin-directed and biologic agents**
- **Single agent chemotx** (mileage) over combination chemotx (CHOP, short-lived)
- Often observe **mixed responses**
- Can **re-cycle** treatments
- Optimize utility of **maintenance therapy to sustain response**
- **Supportive therapy** is essential (barrier defect)
  - Chronic control of skin infections (staph, HSV)
  - Use anti-itch regimens, emollients/sealants
<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>Extracutan disease</td>
</tr>
<tr>
<td>Topical steroid, retinoid (bex), NM phototherapy, local RT, imiquimod</td>
<td>Photopheresis + IFN, bexarotene</td>
<td>Phototherapy + bexarotene or IFN</td>
<td>Alemtuzumab</td>
<td>Combination chemo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TSEBT + photopheresis, IFN</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Bexarotene, methotrexate, IFN</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>vorinostat, romidepsin</td>
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<tr>
<td></td>
<td></td>
<td>New targeted or cytotoxic systemic therapy**</td>
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<td></td>
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<td></td>
<td>Allo-HSCT</td>
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</tbody>
</table>

**brentuximab, pralatrexate, liposomal doxorubicin, gemcitabine, other**
<table>
<thead>
<tr>
<th><strong>SKIN-DIRECTED THERAPIES</strong></th>
<th><strong>SYSTEMIC THERAPIES</strong></th>
<th><strong>SYSTEMIC THERAPIES (continued)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>For limited/localized skin involvement (Skin-Limited/Local)</td>
<td>Category A (SYST-CAT A)</td>
<td>Category C (SYST-CAT C)</td>
</tr>
<tr>
<td>• Topical corticosteroids</td>
<td>• Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid], acitretin)</td>
<td>(alphabetical order)</td>
</tr>
<tr>
<td>• Topical chemotherapy (methloretamine [nitrogen mustard])</td>
<td>• Interferons (IFN-alpha, IFN-gamma)</td>
<td>• Bortezomib (category 3)</td>
</tr>
<tr>
<td>• Local radiation (8–36 Gy)</td>
<td>• HDAC-inhibitors (vorinostat, romidepsin)</td>
<td>• Brentuximab vedotin</td>
</tr>
<tr>
<td>• Topical retinoids (bexarotene, tazarotene)</td>
<td>• Extracorporeal photopheresis</td>
<td>• Gemcitabine</td>
</tr>
<tr>
<td>• Phototherapy (UVB, NB-UVB for patch/thin plaques; PUVA for thicker plaques)</td>
<td>• Methotrexate (≤100 mg q week)</td>
<td>• Liposomal doxorubicin</td>
</tr>
<tr>
<td>• Topical imiquimod</td>
<td><strong>For generalized skin involvement (Skin-Generalized)</strong></td>
<td>• Low- or standard-dose pralatrexate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Romidepsin</td>
</tr>
<tr>
<td>For generalized skin involvement (Skin-Generalized)</td>
<td>Category B (SYST-CAT B)</td>
<td>See regimens listed on TCEL-B 2 of 5 (PTCL-NOS)</td>
</tr>
<tr>
<td>• Topical corticosteroids</td>
<td>• First-line therapies (alphabetical order)</td>
<td></td>
</tr>
<tr>
<td>• Topical chemotherapy (methloretamine [nitrogen mustard])</td>
<td>‣ Brentuximab vedotin</td>
<td>• Bortezomib (category 3)</td>
</tr>
<tr>
<td>• Phototherapy (UVB, NB-UVB, for patch/thin plaques; PUVA for thicker plaques)</td>
<td>‣ Gemcitabine</td>
<td><strong>COMBINATION THERAPIES</strong></td>
</tr>
<tr>
<td>• Total skin electron beam therapy (TSEBT) (12–36 Gy)</td>
<td>‣ Liposomal doxorubicin</td>
<td>Skin-directed + Systemic</td>
</tr>
<tr>
<td>(12–36 Gy)</td>
<td>‣ Low-dose pralatrexate</td>
<td>• Phototherapy + retinoid</td>
</tr>
<tr>
<td></td>
<td>• Second-line therapies</td>
<td>• Phototherapy + IFN</td>
</tr>
<tr>
<td></td>
<td>‣ Chlorambucil</td>
<td>• Phototherapy + photopheresis</td>
</tr>
<tr>
<td></td>
<td>‣ Pentostatin</td>
<td>• Total skin electron beam + photopheresis</td>
</tr>
<tr>
<td></td>
<td>‣ Etoposide</td>
<td><strong>Systemic + Systemic</strong></td>
</tr>
<tr>
<td></td>
<td>‣ Cyclophosphamide</td>
<td>• Retinoid + IFN</td>
</tr>
<tr>
<td></td>
<td>‣ Temozolomide</td>
<td>• Photopheresis + retinoid</td>
</tr>
<tr>
<td></td>
<td>‣ Methotrexate (&gt;100 mg q week)</td>
<td>• Photopheresis + IFN</td>
</tr>
<tr>
<td></td>
<td>‣ Pembrolizumab (category 2B)</td>
<td>• Photopheresis + retinoid + IFN</td>
</tr>
<tr>
<td></td>
<td>‣ Bortezomib (category 3)</td>
<td></td>
</tr>
</tbody>
</table>

**Milder tx, indolent**

**LCT+ aggressive**

**Fail Cat A, more severe**

**Need more combo studies**
Skin-directed therapies, *NCCN guidelines v1.2017*

- Topical steroids (primary and supportive care roles)
- Topical chemotherapy
  - Topical mechlorethamine (Valchlor gel* or compounded)
  - *Topical BCNU (pending vote to reinsert in NCCN)*
- Topical retinoids (bexarotene*)
- Topical imiquimod
- Phototherapy
  - UVB (narrow band, broad band)
  - PUVA (psoralen + UVA)
- **Radiation, *less is more***
  - Localized therapy (4-12 Gy)
  - Low-dose (12 Gy) total skin electron beam therapy
  - Combine with immune modulation
- *Excimer, photodynamic therapy (not in NCCN)*

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*FDA-approved in MF*
Stage IB (T2a, >30% BSA), mix of hypopigmented and typical patches, no benefit with topical steroids

What therapeutic options?

Phototherapy (nbUVB)
Topical mechlorethamine +/- TS
Collaboration with dermatologist for supportive care is essential.

**Pruritus**
- Assessment
  - Pruritus should be assessed at each visit using consistent measurements
  - Generalized pruritus and localized pruritus should be distinguished
  - Correlation between sites of disease and localization of pruritus should be noted
  - Other potential causes for pruritus should be ruled out

- Treatment
  - Moisturizers and emollients
  - Topical steroid (appropriate strength for body region) ± occlusion
  - Optimize skin-directed and systemic therapy
  - Topical preparations - camphor/menthol formulations, pramoxine formulations
  - Systemic agents
    - First-line
      - Antihistamines\(^1\)
        - Doxepin\(^1\)
        - Gabapentin\(^2,3\)
    - Second-line
      - Aprepitant\(^4,5\)
      - Mirtazapine\(^6\)
      - Selective serotonin reuptake inhibitors\(^7\)
    - Third-line
      - Naltrexone

**Infections**
- Active or Suspected Infections
  - Cutaneous viral infections
    - High risk for skin dissemination of localized viral infections (HSV/VZV)
  - Erythroderma:
    - Skin swab and nares cultures for Staphylococcus aureus (S. aureus) infection or colonization
    - Intranasal mupirocin
    - Oral dicloxacillin or cephalaxin
    - Sulfamethoxazole/trimethoprim, doxycycline if suspect MRSA
    - Vancomycin if no improvement or bacteremia
    - Bleach baths or soaks (if limited area)
  - Ulcerated and necrotic tumors:
    - Gram-negative rods (GNR) common in necrotic tumors may lead to bacteremia and sepsis
    - If high suspicion for infection, obtain blood cultures, start antibiotics even if fever absent
    - Role of wound cultures not clear due to colonization
    - Empirical therapy for both GNR and gram-positive coecal infections is necessary initially

- Prophylaxis
  - Optimize skin barrier protection
  - Mupirocin for S. aureus colonization
  - Diluted bleach baths or soaks (if limited area)
    - Either 2 teaspoons of bleach in 1 gallon of water OR 1 quarter of a cup (NOT 1 cup) of bleach in a bathtub of water
  - Avoid central lines (especially in erythrodermic patients)
  - For patients receiving alemtuzumab, [see LYMP-A](#).
When do we use systemic therapies MF?

- Early stage MF, I/IIA (T1/T2) - Refractory to skin directed therapies
- Significant folliculotrophic disease, large cell transformation, or other adverse factors a/w worse clinical outcome
- Advanced stage MF/SS, IIB-IV – used upfront

Systemic Therapy
+/- skin directed tx
Systemic agents in CTCL
Few FDA-approved

**SYSTEMIC THERAPIES**

**Category A (SYST-CAT A)**
- Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid], acitretin)
- Interferons (IFN-alpha, IFN-gamma)
- HDAC-inhibitors (vorinostat, romidepsin)^e
- Extracorporeal photopheresis^f
- Methotrexate (≤100 mg q week)

**Category B (SYST-CAT B)**
- First-line therapies (alphabetical order)
  - Brentuximab vedotin
  - Gemcitabine
  - Liposomal doxorubicin
  - Low-dose pralatrexate
- Second-line therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphamide
  - Temozolomide
  - Methotrexate (>100 mg q week)
  - Bortezomib (category 3)

**SYSTEMIC THERAPIES (alphabetical order)**

**Category C (SYST-CAT C)**
- Bortezomib (category 3)
- Brentuximab vedotin
- Gemcitabine
- Liposomal doxorubicin
- Low- or standard-dose pralatrexate
- Romidepsin
- See regimens listed on TCEL-B 2 of 5 (PTCL-NOS)^h

**COMBINATION THERAPIES**

**Skin-directed + Systemic**
- Phototherapy + retinoid
- Phototherapy + IFN
- Phototherapy + photopheresis^f
- Total skin electron beam + photopheresis^f

**Systemic + Systemic**
- Retinoid + IFN
- Photopheresis^f + retinoid
- Photopheresis^f + IFN
- Photopheresis^f + retinoid + IFN

**Added 2016**

Hoping for synergy, less of each, address different compartments: need more studies
Systemic agents in MF/SS

Real-time updates!

Pembrolizumab added based on ASH 12/2016, abstract #181
Tumor cell surface molecules (e.g., CD4, CD25, CD30, CD52, CCR4, CD158k/KIR3DL2)

Tumor proliferation, metabolism, survival, progression mechanisms:
- Signal transduction/transcription activation pathways (e.g., TNFR2, proteasome, AKT/PI3K/mTOR, JAK/STAT, ITK)
- Apoptotic pathways (e.g., Bcl/Bax, TNFR, Fas, miRNAs)
- Epigenetics (e.g., histone, non-histone proteins)
- Metabolic/survival pathways (e.g., RFC-1, PARP)

CTCL

CD8+ TILs

Microenvironment, immune mechanisms (e.g., PD-1, PD-L1, CTLA-4, SIRPα/CD47, IDO, MDSC, Tregs)

Newer therapies in clinical development in CTCL

- Brentuximab vedotin
- Mogamulizumab
- Anti-CD25 fusion toxin
- Anti-CD3 fusion toxin
- Anti-CD37 ADC
- Anti-KIR3DL2 mab

- Proteosome inhibitors
- PI3k inhibitors
- mTOR inhibitors
- Jak inhibitors
- Syk-Jak dual inhibitor
- ITK inhibitor
- Anti-apoptotic agents
- Anti-miR-155
- New HDAC inhibitors
- Demethylating agents
- New anti-folates (pralatrexate)

- Anti-PD-1/PD-L1 mAbs
- Anti-CTLA-4 mAbs
- Anti-CD47 mAb/SIRPα Fc decoy, anti-SIRPα mAb
- IDO inhibitor
- Lenalidomide
- Treg depleting agents

Multiple combination therapies under investigation
NCCN Guidelines Version 2.2017
Mycosis Fungoides/Sezary Syndrome

STAGE
(MFSS-2 and MFSS-3)

Limited tumor lesions

Primary Treatment:\nSkin-directed therapies ± local RT^z
or Systemic Therapies (SYST-CAT A) (MFSS-A) ± local RT^z

Response to Therapy:\nCR/PR^s or inadequate response
- Relapse with or persistent T1-T3 limited:
  - T1-2 (see stage IA on MFSS-5 or stage IB-IIA on MFSS-6)
  - T3 limited extent
- Refractory disease to multiple previous therapies or progression

Stage IIb^w

Generalized tumor lesions^x,y

Primary Treatment:\n- TSEBT^aa
  - See Suggested Treatment Regimens^x,y ± skin-directed therapy
    - Systemic Therapies (SYST-CAT A) (MFSS-A)
    - Systemic Therapies (SYST-CAT B) (MFSS-A)
    - Systemic Therapies (SYST-CAT C) (MFSS-A)
    - Combination Therapies

Response to Therapy:\nCR/PR^s or inadequate response
- Relapse with or persistent T1-T3:
  - T1-2 (see stage IA on MFSS-5 or stage IB-IIA on MFSS-6)
  - T3
- Refractory disease to multiple previous therapies or progression
  - Multi-agent chemotherapy^bb
  - Consider allogeneic transplant^cc
  - Clinical trial

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

Pit is preferred that treatment occur at centers with expertise in the management of the disease.
MF w/ large cell transformation with aggressive clinical behavior

Cat-C NCCN options, trials

NCCN CAT-C options for LCT+
- Brentuximab vedotin
- Pralatrexate
- Romidepsin
- Liposomal doxorubicin
- [Gemcitabine]
- [TSEBT (12-36 Gy) + bex, IFN]
- Clinical trials
- TCEL-B, sPTCL options (EC+ dz)
  +/- local RT
- Preserve immune response whenever possible
- Low threshold to cover skin pathogens
- Supportive/comboination care (topicals, anti-itch)
Management of non-Sezary, stage IV disease

- Management based LN dz burden (+/- LCT), visceral disease
  - Cat B or C options
    - Single agents: brentuximab, pralatrexate, romidepsin, liposomal doxorubicin, gemcitabine; etoposide, cyclophosphamide, bortezomib
    - Multi-agent chemotherapy/PTCL-NOS for high-burden LN dz or visceral dz, especially if followed by allo HSCT
  - Clinical trials
  - RT for local control
  - Consider allo HSCT

Category B or C
- Brentuximab vedotin
- Pralatrexate (15-30 mg/m2)
- HDAC-i (romidepsin)
- Liposomal doxorubicin
- Gemcitabine
- Other single agents
- Clinical trial
- Options for PTCL-NOS
Take home: utilize NCCN guidelines to optimize clinical practice

- NCCN practice guidelines are **the** standard-of-care guideline developed by leading academic cancer centers or institutions, that medicare and other insurances follow in the US

- Globally utilized, modified with regional available/allowed practice

- Offers true real-time updates based on evidence and consensus
  - Updates in diagnostic/prognostic elements, approved/off-label therapies

- Additional general care guidance and resources
  - Age-related general recommendations and guidelines/resources for patients
  - Supportive care guidelines (pain, emesis, fatigue, palliative care, survivorship)
  - Biomarker compendia

- Appropriate use of these NCCN practice guidelines will aid in delivering optimal care for our patients and securing their insurance coverage