What’s New in Cutaneous Lymphoma

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Stanford University School of Medicine
Disclosure of Conflicts of Interest

Youn H. Kim, M.D.

*What’s New in Cutaneous Lymphoma*

Co-investigator in clinical trials sponsored by BioCryst, Coley/Pfizer, Aton/Merck, Curagen, Gloucester, Genmab, Seagen; Honorarium/grants from Scimed, Merck, Ligand, Ovation
What’s New in Cutaneous Lymphoma

• Classification
• Diagnosis
• Staging
• Therapy
Multidisciplinary Cutaneous Lymphoma Clinic/Program

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Richard Hoppe, Co-Director, Radiation Oncology
Ranjana Advani, Sunil Reddy, Medical Oncology
Sabine Kohler, Uma Sundrum, David Cassarino, Dermatopathology
Sunil Reddy, Anjali Varma, Cutaneous Lymphoma Fellows
Natalie Viakhireva, Physician Assistant
Katherine Sutherland, Research Assistant
Carol Bruce, Nurse Coordinator
Dermatology Residents

Web Site: cutaneouslymphoma.stanford.edu
# Cutaneous T- and NK/T-cell Lymphomas

## New WHO-EORTC Classification

<table>
<thead>
<tr>
<th>Category</th>
<th>Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis fungoides and variants/subtypes</td>
<td></td>
</tr>
<tr>
<td>Sézary syndrome</td>
<td></td>
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<td>• PTCL, other</td>
<td></td>
</tr>
</tbody>
</table>

Mycosis Fungoides

Clinical & Histologic Variants/Subtypes – Unique Prognosis?

• Hypopigmented/vitiligenous MF
  – Children, African American, Indian; CD8+

• Pagetoid reticulosis (Woringer-Kolopp type only)

• Follicular MF (+/- mucinosis)
  – Head and neck

• Granulomatous MF
  – Granulomatous slack skin

• Bullous MF

• PPE-like MF

• Interstitial MF

• Icthyiosiform MF

• Palmar plantar MF

• Hyperkeratotic/verrucous MF

• Invisible MF

• Papular MF
Staging Evaluation, Mycosis Fungoides

- Thorough skin examination
- Comprehensive general physical examination
- Complete blood count with Sézary cell analysis
- Screening chemistries, LDH, urinalysis
- Chest x-ray
- If significant lymphadenopathy or T3, T4
  - CT CAP w/ contrast or PET/CT
  - LN biopsy if LN >1.5 cm (or sig PET+)
- Suspected sites of visceral involvement should be confirmed with appropriate imaging studies and/or histologic evaluation when possible
Staging accuracy in mycosis fungoides and Sèzary syndrome using integrated PET and CT
Tsai et al, Arch Dermatol 142:577, 2006

- Integrated PET/CT more sensitive for detection of LN involvement than CT alone
  - Can detect LN involvement earlier leading to sooner intervention and better outcome
- Intensity of PET activity (SUV) correlated with histologic severity
## Proposed Revisions to TNMB Classification and staging for MF/SS, ISCL Consensus Document

<table>
<thead>
<tr>
<th>T (Skin)</th>
<th>N (Nodes)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1</strong> Limited patch/plaque</td>
<td><strong>N0</strong> No clinically abnormal LNs</td>
</tr>
<tr>
<td>(&lt; 10% of total skin surface)</td>
<td></td>
</tr>
<tr>
<td><strong>T2</strong> Generalized patch/plaque</td>
<td><strong>N1</strong> Clinically abnormal LNs;</td>
</tr>
<tr>
<td>(≥ 10% of total skin surface)</td>
<td>histopath Dutch Gr 1 or NCI LN0-2</td>
</tr>
<tr>
<td></td>
<td>(clone +/-)</td>
</tr>
<tr>
<td><strong>T3</strong> Tumors</td>
<td><strong>N2</strong> Clinically abnormal LNs;</td>
</tr>
<tr>
<td></td>
<td>histopath Dutch Gr 2 or NCI LN 3</td>
</tr>
<tr>
<td></td>
<td>(clone +/-)</td>
</tr>
<tr>
<td><strong>T4</strong> Generalized erythroderma</td>
<td><strong>N3</strong> Clinically abnormal LNs;</td>
</tr>
<tr>
<td></td>
<td>histopath Dutch Gr 3-4 or NCI LN4</td>
</tr>
<tr>
<td></td>
<td>(clone +/-)</td>
</tr>
<tr>
<td></td>
<td><strong>Nx</strong> Clinically abnormal LNs, no</td>
</tr>
<tr>
<td></td>
<td>histo info</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M (Viscera)</th>
<th>B (Blood)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M0</strong> No visceral involvement</td>
<td><strong>B0</strong> No significant blood</td>
</tr>
<tr>
<td></td>
<td>involvement</td>
</tr>
<tr>
<td><strong>M1</strong> Visceral involvement</td>
<td><strong>B1</strong> Low blood tumor burden</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>B2</strong> High blood tumor burden</td>
</tr>
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Proposed Revisions to TNMB Classification and staging for MF/SS, ISCL Consensus Document

<table>
<thead>
<tr>
<th>Clinical Stages</th>
<th>TNM Classification*</th>
</tr>
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<tbody>
<tr>
<td>IA</td>
<td>T1</td>
</tr>
<tr>
<td>IB</td>
<td>T2</td>
</tr>
<tr>
<td>IIA</td>
<td>T1 - 2</td>
</tr>
<tr>
<td>IIB</td>
<td>T3</td>
</tr>
<tr>
<td>IIIA</td>
<td>T4</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4</td>
</tr>
<tr>
<td>IVA</td>
<td>T1 - 4</td>
</tr>
<tr>
<td>IVB</td>
<td>T1 - 4</td>
</tr>
</tbody>
</table>
Adult T-cell Leukemia/Lymphoma

- T-cell neoplasm etiologically a/w HTLV-1
- Neoplastic T-cells are CD3+, CD4+, CD8-, CD25
- Endemic in Japan, the Caribbean, S Americas, Central Africa
- ATLL develop in 1-5% of seropositive individuals after long years of viral persistence
- Most present as acute dz w/ leukemia, LN+, organomegaly, ↑Ca++, 50% w/ skin lesions, most commonly nodules or tumors, generalized papules or plaques
  - Chronic and smoldering variants frequently present w/ skin lesions that resemble MF (lack circulating neoplastic T-cells), transformation into acute dz may occur; demonstration of clonally integrated HTLV-1 genes differentiates from MF
- Therapy is tailored for acuity/severity of disease
## New WHO-EORTC Classification

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</tr>
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Aggressive Epidermotropic CD8+ T-cell Lymphoma

- Proliferation of epidermotropic CD8+ cytotoxic T-cells and an aggressive clinical behavior
- Localized or generalized eruptive papules, nodules, and tumors showing central ulceration and necrosis
- Generalized hyperkeratotic patches and plaques
- Extracutaneous sites are lung, testis, CNS, oral mucosa; LNs often spared
- Combined modality regimens, systemic single or multi agent chemotherapies
Cutaneous $\gamma/\delta$ T-cell Lymphoma

- Clonal proliferation of mature, activated $\gamma/\delta$ T-cells with a cytotoxic phenotype
  - CD2+, CD3+, betaF1-, CD5-, CD56+, cytotoxic proteins
  - Generally CD4-, CD8-, EBV-
  - Epidermotropic, dermal, and/or subcutanous histologic patterns

- Generalized plaques and/or ulceronecrotic nodules or tumors
  - Extremities often involved
  - Mucosal and other extranodal sites frequently involved
  - Involvement of LNs, spleen or BM is uncommon
  - Hemophagocytic syndrome (HPS) may occur

- Tendency for aggressive clinical course (esp. w/ HPS and/or subcutaneous histology)

- Primary treatment is systemic chemotherapy +/- high-dose therapy with SC rescue
Cutaneous T-cell Lymphoma
*Mycosis Fungoides & Sézary Syndrome*

**Diagnosis**

- **Routine histology**
  - >1 punch biopsies, off topical therapy
- **Immunophenotyping**
  - immunohistochemistry, flow cytometry
- **Molecular methods**
  - TCR gene rearrangement (clonality)
    - Multiple sample comparative PCR
  - Gene expression pattern
    - qRT-PCR microarray *(STAT4, GATA3, PLS3, CD1D, TRAIL)*
- **Clinical correlation***
## Algorithm for the Diagnosis of Early MF*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Major (2 Points)</th>
<th>Minor (1 Point)</th>
</tr>
</thead>
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<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent and/or progressive patches and plaques plus</td>
<td>Any 2</td>
<td>Any 1</td>
</tr>
<tr>
<td>1. Non-sun exposed location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Size/shape variation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Poikiloderma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HISTOPATHOLOGICAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial lymphoid infiltrate plus</td>
<td>Both</td>
<td>Either</td>
</tr>
<tr>
<td>1. Epidermotropism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Atypia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MOLECULAR/ BIOLOGICAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonal TCR gene rearrangement</td>
<td></td>
<td>Present</td>
</tr>
<tr>
<td><strong>IMMUNOPATHOLOGICAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. CD2,3,5 &lt;50%</td>
<td></td>
<td>Any 1</td>
</tr>
<tr>
<td>2. CD7 &lt; 10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Epidermal/dermal discordance</td>
<td></td>
<td></td>
</tr>
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## Cutaneous B-cell Lymphomas

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<tr>
<th>New WHO-EORTC Classification</th>
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<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>
Blastic NK-cell Lymphoma
(CD4+/CD56+ hematodermic neoplasm)

• Derived from a plasmacytoid dendritic cell precursor
  – “early plasmacytoid dendritic cell leukemia/lymphoma”

• Commonly presents in the skin w/ solitary or multiple nodules or tumors w/ or w/o concurrent extracutaneous disease
  – 50% w/ LN or BM involvement at presentation; others rapidly develop extracutaneous disease (LN, BM, PB, CNS)

• Non-epidermotropic, monotonous infiltrates of med-sized cells, absent or indistinct nucleoli resembling lymphoblasts or myeloblasts, lacks necrosis or angioinvasion
  – CD4+, CD56+, CD8-, CD2/7+/-, CD45 RA+ absent surface/cyttopl CD3 or cytotoxic proteins, MPO- (r/o leukemia cutis) CD123/TCL1+ (support plasmacytoid dendritic cell origin), EBV-; TCR germline

• Aggressive disease w/ poor prognosis
  – Management similar to NK/T-cell lymphoma or acute leukemias
Goals of Therapies for CTCL

**IDEAL**
- Cure
- Extend Life
- Alleviate symptoms
- Durable response
- High response rate

**REAL**
- Alleviate symptoms
- Variable response
- Variable response duration
- Extend Life
- Cure
Treatment Alternatives in CTCL

• **Topical (skin-directed) therapy**
  – Topical steroid, nitrogen mustard, topical retinoid (Targretin*), BCNU, phototherapy (UVB/PUVA), EBT, topical imiquimod

• **Systemic therapy**
  – Biologicals
    • photopheresis*, interferon, retinoid (Targretin*), fusion protein/toxin (Ontak*)
  – Cytotoxic chemotherapy
    • MTX, Doxil, gemcitabine, etoposide, pentostatin, combination regimens

• **Combined modality therapy**
  – Topical + topical, topical + systemic, systemic + systemic

• **Investigative therapy**
  – Monoclonal antibodies (e.g., CD3, CD4, CD30, CD52)
  – HDAC inhibitors (e.g., depsipeptide, SAHA)
  – PNP inhibitors
  – Cytokines (e.g., rhIL12)
  – Immunostimulatory oligonucleotides (e.g., CpG 7909)
  – Allo-HSC transplantation
Treatment Approach in Mycosis Fungoides & Sézary Syndrome

IA
Limited dz, T1
Top steroids, Targ gel
NM

IB/IIA
Generalized, T2
PUVA ± Targ or IFN
TSEBT ± NM, Targ or IFN (or ECP)

IIB
Tumors, T3
Targ ± IFN, Ontak

III
Erythroderm, T4
ECP ± Targ, IFN
Single-agent Chemo (Mtx, Doxil, Gem, Pento)

IV
Extracut. dz
Combination Chemo
Campath

Investigative/Newer Therapies
(TLRA, MoAb, cytokine, HDAl, PNPI, IMiD, vaccine, allo-HSCT)
TOPICAL NITROGEN MUSTARD

• VEHICLE
  • Aqueous
  • Aquaphor
  • Propylene glycol
    (FDA OPD grant study)

• SURFACE
  • Total skin
  • Regional
  • Lesional

• CONCENTRATION
  • Increase effectively
  • Clear efficiently

• TIMING
  • Primary
  • Adjuvant
  • Combination

• MAINTENANCE
  • Short over long

Multicenter trial for FDA approval, available at Stanford Ovation reimbursement line 1-866-209-7604
Combination Therapy

*Benefit of potential synergy and less of each toxicities*

When single agents fail or w/ aggressive dz

- **Combinations of skin-directed therapies**
  - NM + topical steroid or retinoid
  - Phototherapy + topical steroids or retinoid
- **Skin-directed + systemic therapy options**
  - PUVA + IFN and/or systemic retinoid and/or ECP
  - TSEBT + IFN and/or systemic retinoid and/or ECP
- **Combinations of systemic therapies (+/- secondary topical)**
  - IFN + systemic retinoid
  - ECP + IFN and/or systemic retinoid
  - Targretin + Ontak
  - Systemic chemotherapy + biologic therapy
Promising Investigative Therapies

- Monoclonal antibodies
- HDAC Inhibitors
- PNP Inhibitors
- Recombinant cytokines
- TLR Agonists (CpG ODNs)
- New IMiDs (lenalidomide)
- Vaccine therapies
- Allogeneic HSCT

Diagram:
- CTCL
- LC
- IL7
- CLA+
- TIL
- DD
- E-selectin
Phase II Multi-Dose Study of SGN-30 (anti-CD30 mAb) in PC ALCL, LyP, and LC Transformed MF

- Chimeric form of a novel murine mAb w/ specificity for CD30, unique from other anti-CD30 Ab
  - SGN-30 binding is detected specifically on activated T-cells and not observed in other normal human tissues
- Earlier studies of SGN-30 in HD and non-cutaneous ALCL show great tolerability to IV therapy
- Ongoing multi-center phase II trial in CD30+ LPD (pc ALCL/LyP) and CD30+ LCT-MF, available at Stanford
  - 12 mg/kg q2-3 wks x 6 doses, total 1-3 courses
**Targeted Monoclonal Antibody Therapy**

_Fully Human Anti-CD4 MoAb (HuMax-CD4) in MF/SS_

- Cytotoxic and anti-proliferative effect in treated patients mediated by ADCC
  - Depletes CD4+ T-cells
- Phase II multi-center trial with once weekly IV dosing of 280 mg, 560 mg, or 980 mg (Genmab)
  - Dose-dependent responses, 9-75%

*Ongoing Pivotal Multicenter Trial of HuMax-CD4 in MF, available at Stanford*
TLR Agonist, CPG oligodeoxynucleotide (ODN)

- CPG 7909 is a synthetic form of DNA-like molecule, optimized for stimulation of human immune functions
- Ongoing trials in solid tumors, melanoma, lymphomas
- Rationale for CPG 7909 investigation in CTCL
  - Directly activate B-cells, pDCs → potent stimulator of innate and tumor antigen-specific adaptive immunity
    - Induces secretion of cytokines/chemokines → ↑Th1-like environment
    - ↑IL12 production, IFN-α → NK-cell activation
    - Augment IL12 response by increased production of IP-10, essential for IL12 mediated tumor-specific CD8+ T-cell responses
Toll-like receptors (TLRs) are PAMP-specific:
- TLR2 – Proteoglycans (bacteria)
- TLR3 – dsRNA (RNA viruses)
- TLR4 – Endotoxin/LPS (gram negative bacteria)
- TLR5 – Flagellin (bacteria)
- TLR6 – Proteoglycans (bacteria)
- TLR7 – ssRNA (viruses; bacteria)
- TLR8 – ssRNA (viruses; bacteria)
- TLR9 – ssCpG DNA (bacteria)

Synthetic unmethylated CpG ODN, mimics bacterial DNA => TLR9
- directly activates DCs and B cells
- indirectly activates other immune cells
Phase I/II study in MF/SS with CPG 7909

• CPG 7909 has significant anti-tumor activity in CTCL as single agent immunotherapy (weekly SC injections)
  – Clinical anti-tumor responses begin within a few weeks and reach best response of PR (6/28) or CR (3/28) by 4-20 weeks

• CPG 7909 is well-tolerated
  – Mostly grade 1-2 injection site reactions or flu-like symptoms

Clinical trial in CTCL closed, will be available thru approval in lung cancer
Potential role of CPG 7909 in CTCL therapy

• Single-agent immunostimulator
• Adjuvant for vaccine therapy
• Effective agent in combination regimens with synergistic or response enhancing results
  – Chemotherapy or radiation (shown in mouse models)
  – PUVA
  – ECP, retinoids, monoclonal antibodies, HDAI, cytokine
• In situ vaccination therapy
  – Low-dose RT + intratumoral CPG
  *Ongoing clinical trial at Stanford*
In situ Vaccination with CpG
Intratumoral CpG + local RT in CTCL

Radiotherapy Days 1 & 2 (2 Gy x 2)

CpG injection, Days 1 & 2, then weekly x 8

Assess clinical response

Days 1, 2
RT 2 Gy x 2

Expect reduction of radiated tumor

Assess clinical response of non-radiated MF lesions

Pre-, during, and post-treatment blood and tissue studies
# Acetylation Defects in Cancer

**An Epigenetic Abnormality**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Acetylation Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>HAT fusions</td>
</tr>
<tr>
<td></td>
<td>MOZ/CBP</td>
</tr>
<tr>
<td></td>
<td>MOZ/p300</td>
</tr>
<tr>
<td></td>
<td>MOZ/TIF-2</td>
</tr>
<tr>
<td></td>
<td>MLL/CBP</td>
</tr>
<tr>
<td></td>
<td>MLL/p300</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>HDAC mediated</td>
</tr>
<tr>
<td></td>
<td>PML/RARalpha</td>
</tr>
<tr>
<td></td>
<td>PLZF/RARalpha</td>
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<tr>
<td></td>
<td>AML1 fusion</td>
</tr>
<tr>
<td>Epithelial cancers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p300 mutations in colorectal, gastric, breast, pancreatic carcinomas/cancer cell lines</td>
</tr>
<tr>
<td>Gastric Cancer</td>
<td>Elevated expression of HDAC1</td>
</tr>
<tr>
<td>Prostate Cancer</td>
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<td>Esophageal Cancer</td>
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</table>
Histone Acetylation/Deacetylation Regulates Transcription

Balanced HDAC and HAT activity = Normal cell cycle

Ac=acetyl group; HAT=histone acetyltransferase; HDAC=histone deacetylase; Lys=lysine.

Adapted from Richon VM. Mechanism of Action of HDAC Inhibitor SAHA. Paper presented at 9th International Conference on Malignant Lymphoma; June 7, 2005; Lugano, Switzerland.
Mechanism of Growth Inhibition Mediated by HDAC Inhibition (Histone Hyperacetylation)

Deacetylated Histones

↓

Transcriptional Repression of Pre-Programmed Set of Genes

↓

Cell Growth

↓

Tumor Growth

Hyperacetylated Histones

↓

Transcriptional Activation of Pre-Programmed Set of Genes

↓

Cell Growth Arrest, Differentiation and/or Apoptosis

↓

Inhibition of Tumor Growth
Histone Deacetylase Inhibitors in Clinical Development

• Short Chain Fatty Acids
  \textit{Butyrate, Phenylbutyrate, Valproate, AN-9}

• Hydroxamic Acids
  \textit{SAHA, LAQ-824, PXD101}

• Cyclic Tetrapeptides
  \textit{FK-228 (Depsipeptide)}

• Benzamides
  \textit{CI-994, MS-275}

\textit{Phase IIb Multicenter Trial of Oral Suberoylanilide Hydroxamic Acid (SAHA: Vorinostat under review by FDA) in MF/SS}

\begin{itemize}
  \item 30\% response rate; diarrhea, fatigue, nausea
\end{itemize}

\textit{Phase II Multicenter Trial of Depsipeptide in MF/SS}

\textit{Phase II Multicenter Trial of PXD101 in MF/SS}
Purine Nucleoside Phosphorylase (PNP) Inhibitor Forodesine HCl (BCX-1777) Activity in CTCL

• Profound suppression of T-cell immunity seen in patients with an inherited PNP deficiency

• Children with PNP deficiency have
  - < 5% of the normal PNP activity
  - Selective depletion of T-cells
  - T-cell responses to mitogenic and allogenic stimuli are severely compromised
  - Elevated levels of deoxyguanosine (dGuo) in urine and plasma
  - Elevated levels of dGTP in RBC

• Rationale for targeting PNP in therapeutics of T-cell disorders
Mechanism of T-cell Inhibition by PNP Inhibitor

\[
\begin{align*}
\text{dGuo} & \xrightarrow{\text{PNP}} \text{guanine} + \text{deoxyribose-1-phosphate} \\
& \xrightarrow{\text{Kinase (dCK)}} \\
\text{dGTP} & \xrightarrow{\text{}} \\
& \xrightarrow{\text{}} \\
& \text{Alteration in deoxynucleotide pools} \\
& \xrightarrow{\text{}} \\
& \text{T-cell apoptosis}
\end{align*}
\]
Purine Nucleoside Phosphorylase (PNP) Inhibitor
Forodesine HCl (BCX-1777) Activity in CTCL

- Initial good response data in 13 pts w/ 4 responses (3 CR), given IV forodesine
- Well-tolerated without dose-limiting toxicities in CTCL trial
  - Previously reported AEs: nausea, H/A, fatigue, pain, edema, anemia, infection, diarrhea, dec platelets, insomnia, cough

Ongoing Phase I/II Multicenter Trial of an Oral Forodesine HCl, available at Stanford
IMids, Novel Immunomodulators

Lenalidomide

4-amino-glutamyl analogue of thalidomide

Thalidomide

Lenalidomide

Knight R, Semin Oncol 2005
**IMids**  
*Lenalidomide*

Rationale for use in CTCL

- **T-cell co-stimulation**
  - ↑ IFN-γ, IL2
  - Selective stimulation of CD8 over CD4
  - Stimulate NK activity

- **Angiogenesis inhibition**

- **Cell cycle arrest and promotion of apoptosis**

- **FDA-approved in MM and MDS**

- **Pilot clinical study in MF/SS with observed responses**
  - *Multicenter study launching (NW, Stanford, MD Anderson)*
Other investigative immunotherapies in CTCL

• Gene delivery-based immunotherapy
  – Adenovirus-human IFN-γ cDNA

• Vaccine strategies
  – Transimmunization
  – Dendritic cell based immunization
  – Mimotope vaccines
  – Idiotype vaccines
Hematopoietic Stem Cell or BM Transplantation

Considered for patients with advanced disease (stage IIB-IV)

**Autologous** → High-dose chemo and RT (cytoreduction) followed by stem cell rescue
- Avoid GVHD
- No durable response in MF/SS

**Allogeneic** → Cytoreduction + *graft vs. tumor effect*
- Risk of GVHD
- Increasing evidence of durable clinical, cytogenetic, molecular remissions in MF/SS
  
  *Molina A, J Clin Oncol, 2005*
  *Wu, Stockerl-Goldstein, Lavori, Kim, SID 2006*

*Studies ongoing to maximize GVL effect while minimizing GVHD risk*
Strategies in CTCL Treatment with Newer Options

Skin-directed Therapies
(Topicals, Phototherapy, XRT)

Systemic Biologic Therapies
(IFN, Retinoids, ECP)

Cytotoxic Chemotherapy
(Single-agent, Combination)

MF/SS IA-IIA
Primary
Salvage
Adjuvant
Primary
MF/SS IIB-IV

HDAI
TLRA
MoAb
PNPI
IMiD
HSCT
Therapeutic Advances

Newer Approaches
- Monoclonal antibodies
- HDAC Inhibitors
- PNP Inhibitors
- Recombinant cytokines
- TLR Agonists
- (CpG ODNs)
- New IMiDs
  - (lenalidomide)
- Vaccine therapies
- Allogeneic HSCT

Improved QOL, closer toward a cure…
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THANK YOU for thinking lymphoma today!