Cutaneous T-cell Lymphoma: Therapy Update

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Disclosure of Conflicts of Interest

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Advisory Board of Merck, Ovation; Investigator in clinical trials sponsored by BioCryst, Coley/Pfizer, Aton/Merck, Celgene, Curagen, Gloucester, Genmab/Medarex, Seagen
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Web Site: cutaneouslylymphoma.stanford.edu
# Cutaneous T- and NK/T-cell Lymphomas

## New WHO-EORTC Classification

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

*Blood 2005;105:3768-85*
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

*Modified from Dr. Steve Horwitz*
Treatment Alternatives in MF/SS (CTCL)

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

• **Systemic therapy**
  – Biologicals:
    • photopheresis*, interferon, retinoid (bexarotene*), fusion protein/toxin (denileukin diftitox*)
  – HDAC inhibitors: SAHA (vorinostat*)
  – Cytotoxic chemotherapy:
    • MTX, lipo doxorub, gemcitabine, etoposide, pentostatin, combination regimens

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

• **Investigative therapy**
  – Monoclonal antibodies (e.g., CD4, CD30, CD52)
  – HDAC inhibitors (e.g., depsipeptide, PXD101)
  – PNP inhibitors (e.g., forodesine)
  – TLRA (e.g., CpG 7909) -- Vaccine strategies
  – Improved chemo agents -- Allo-HSC transplantation

* FDA approved for CTCL
Treatment Selection Factors in MF/SS

- Clinical stage
- Other prognostic factors
  - follicular, LC transformation, etc.
- Response rate/speed/duration
- Side effect profile
  - pt age, co-morbidities
- Accessibility of treatment options
- Cost-benefit ratio
- Other social and medical issues
MF and SS, Disease-Specific Survival by Clinical Stage,
Stanford Update (n=525), Arch Dermatol 139:857-866, 2003
Treatment Approach in Mycosis Fungoides & Sézary Syndrome

**IA**
- Limited dz, T1
- Top steroids, retinoid (bex) gel
- NM

**IB/IIA**
- Generalized, T2
- UVB
- PUVA ± bex or IFN or vorinostat

**IIB**
- Tumors, T3
- TSEBT ± NM, bex, IFN, ECP, vorinostat

**III**
- Erythroderm, T4
- ECP ± bex, IFN, vorinostat
- Single-agent Chemo
  - (Mtx, lipo dox, gem, pento, chlor, etop, TMZ)
- Combination Chemo
  - Alemtuzumab

**IV**
- Extracut. dz
- Investigative/Newer Therapies
  - (TLRAs, MoAbs, cytokines, HDAls, PNPIs, iMids, vaccines, allo-HSCT)

- Bex, IFN, denileuk dift, vorinostat
  - (single or combination)
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 HDAI and/or ECP
  - TSEBT + IFN and/or systemic retinoid and/or HDAI and/or ECP

- **Combinations of systemic therapies (+/- secondary topical)**
  - IFN + systemic retinoid
  - Systemic retinoid + HDAI
  - ECP + IFN and/or systemic retinoid and/or HDAI
  - Bexarotene + denileukin diftitox
  - Systemic chemotherapy + biologic therapy
Promising Investigative Therapies
A New Era

Monoclonal antibodies
HDAC Inhibitors
TLR Agonists
(CpGs, TLR7A)
PNP Inhibitors
(forodesine)
Recombinant cytokines
New IMiDs
(lenalidomide)
Vaccine therapies
Allogeneic HSCT

Immune-stimulatory, anti-proliferative, pro-apoptotic, gene-modulatory effects
Targeted Monoclonal Antibody Therapy

*Fully Human Anti-CD4 mAb (HuMax-CD4) in MF/SS*

- Cytotoxic and anti-proliferative effect in treated patients mediated by ADCC
  - Depletes and inhibits activation of CD4+ T-cells

- **Clinical efficacy of zanolimumab (HuMax-CD4), two phase II studies in refractory CTCL. Y Kim et al, In Press, Blood**
  - Phase II multi-center trial in refractory MF/SS with 17 weekly IV dosing of 280 mg, 560 mg, or 980 mg (n= 47; MF 38, SS 9)
  - Dose-dependent responses
    - OR 56% in high-dose groups, median response duration of 81 wks
    - OR 15% in low-dose (280 mg)
  - Well-tolerated with no-dose related toxicity
    - Most freq. AEs were low-grade infections, dermatitis

**Ongoing Pivotal Multicenter Trial of HuMax-CD4 in MF**
Production of human antibodies

Gene transfer

Immunization with target protein

Breeding transgenic mice

Four distinct genetic modifications functionally replace the mouse immunoglobulin loci with human immunoglobulin transgenes

1\textsuperscript{st} and 2\textsuperscript{nd} antibody responses and affinity maturation occur naturally in HuMAb\textsuperscript{®} mice
Mechanism of Action of HuMax-CD4 (Zanolimumumab)

- Inhibition of:
  - Proliferation
  - Signal transduction
  - Cytokine production
  - Surface marker expression
- Receptor blockade

ADCC

CDC

Apoptosis

CD4 down-modulation

Cytokines; surface markers

CD4+ T cell

FcγR

C1q

Classical pathway
TLR Agonist, CPG oligodeoxynucleotide (ODN)

• CpG is a synthetic form of DNA-like molecule, optimized for stimulation of human immune functions
• Ongoing trials in solid tumors, melanoma, lymphomas

Three Classes of CpG ODNs with differential Immune activity

<table>
<thead>
<tr>
<th>ODN type</th>
<th>Cytokine Production</th>
<th>B-Cell Activation</th>
<th>pDC Activation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFN-γ</td>
<td>IFN-α</td>
<td></td>
</tr>
<tr>
<td>CpG-A</td>
<td>+</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>CpG-B</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>CpG-C</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>
CpG Motif Stimulates Innate/Adaptive Immunity

- Bacteria have frequent CpG motifs
  \[ ACGTTGAGTTCGTACGCATAACGA \]
- Vertebrates have rare and methylated CpG motifs
  \[ AGCTTTAGTC^{mCGGATGGGTAAGA} \]
- Synthetic CpG mimics bacterial DNA
- CpG binds to Toll-like Receptor 9 (TLR9)
  - Directly activates dendritic cells (DC) and B cells
  - Indirectly activates other immune cells
CpG Bridges Innate Immunity and Adaptive Immunity

**Innate Immunity**
- Increased sensitivity to antigen
- B cell
- DC
- Increased MHC
- TLR9
- CpG

**Adaptive Immunity**
- Increased Ab secretion
- T cell
- CTL
- Antigen-specific T Cells
- Other cytokines / chemokines: IP-10, MIP-1a/b, MCP-1, IL-8
- IFN-α
- TNF-α
- IL-12 (IL15?)
- IFN-γ, IP-10, TRAIL

TLR9

CpG Bridges Innate Immunity and Adaptive Immunity
CpG as monotherapy immune stimulant in CTCL

CTCL Responses to a TLR9 Agonist

CPG 7909: a Phase I/II Study

Y. Kim\(^1\), M. Girardi\(^2\), M. Duvic\(^3\), T. Kuzel\(^4\), A. Rook\(^5\), B. Link\(^6\), L. Pinter-Brown\(^7\), C. Comerci\(^8\), S. McAuley\(^8\), T. Schmalbach\(^8\)

\(^1\)Stanford University, \(^2\)Yale University, \(^3\)MD Anderson Cancer Center, \(^4\)Northwestern University, \(^5\)University of Pennsylvania, \(^6\)University of Iowa Hospitals and Clinics, \(^7\)UCLA, \(^8\)Coley Pharmaceutical Group

*Presented at ASH 2004 Meeting, paper in preparation*
Potential role of CpG immunotherapy in CTCL

• Single-agent immunostimulator

• 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

• Adjuvant for vaccine therapy

• In situ vaccination therapy
  – Low-dose RT + intratumoral CPG

  *Ongoing clinical trial at Stanford*
Epigenetic events are cellular processes that affect cell memory and alter gene activity without modifying the genetic code.

Modification of histones by various enzymes is one example of an epigenetic process.

<table>
<thead>
<tr>
<th>Amino Acid residue</th>
<th>Type of Modification</th>
<th>Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arginine</td>
<td>Methylation</td>
<td></td>
</tr>
<tr>
<td>Histidine</td>
<td>Phosphorylation</td>
<td></td>
</tr>
<tr>
<td>Lysine</td>
<td><strong>Acetylation</strong></td>
<td>HAT and HDAC</td>
</tr>
<tr>
<td></td>
<td>Methylation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ubiquitination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sumoylation</td>
<td></td>
</tr>
<tr>
<td>Serine/Threonine</td>
<td>Phosphorylation</td>
<td></td>
</tr>
</tbody>
</table>

HAT = histone acetyltransferase; HDAC = histone deacetylase
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
  Butyrate, Phenylbutyrate, Valproate, AN-9
- Hydroxamic Acids
  SAHA, LAQ-824, LBH589, PXD101
- Cyclic Tetrapeptides
  FK-228 (Depsipeptide)
- Benzamides
  CI-994, MS-275

Phase IIb Multicenter Trial of Oral Suberoylanilide Hydroxamic Acid (Vorinostat: SAHA approved by FDA) in CTCL

Phase II Multicenter Trial of Depsipeptide in CTCL

Phase II Multicenter Trial of PXD101 in CTCL
Phase IIb Multicenter Clinical Trial of Vorinostat in Advanced Cutaneous T-cell Lymphoma (CTCL)

Elise Olsen,1 Youn Kim,2 Timothy Kuzel,3 Theresa Pacheco,4 Francine Foss,5 Sareeta Parker,6 Gene Wang,7 Stanley Frankel,7 Joy Lis,7 Madeleine Duvic8

1Duke University, Durham, NC, 2Stanford University, Stanford, CA, 3Northwestern University, Chicago, IL, 4UCHSC at Fitzsimons, Aurora, CO, 5Yale Medical Oncology, New Haven, CT, 6Emory University, Atlanta, GA, 7Merck & Co., Inc., Blue Bell, PA, 8MD Anderson, Houston, TX
## Baseline Characteristics: Staging (N = 74)

<table>
<thead>
<tr>
<th>Stage/tumor burden</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB (T2N0M0)</td>
<td>11</td>
<td>(14.9)</td>
</tr>
<tr>
<td>IIA (T2N1M0)</td>
<td>2</td>
<td>(2.7)</td>
</tr>
<tr>
<td>IIB (T3N0-1M0)</td>
<td>19</td>
<td>(25.7)</td>
</tr>
<tr>
<td>III (T4N0-1M0)</td>
<td>20</td>
<td>(27.0)</td>
</tr>
<tr>
<td>IVA (T1-4N3M0)</td>
<td>17</td>
<td>(23.0)</td>
</tr>
<tr>
<td>IVB (T1-4N0-3M1)</td>
<td>5</td>
<td>(6.8)</td>
</tr>
</tbody>
</table>
Maximum mSWAT Score Change (Patients $\geq$ Stage IIB)

- Patients with more than 100% increase in mSWAT

% of Change

Progression

Improvement
Vorinostat (SAHA)

- Inhibits HDAC1, HDAC2, HDAC3 (Class I), HDAC6 (Class II)
- Overall 30% response in previously treated patients, n=74
  - Significant pruritus relief in erythrodermic/Sezary patients
- Acceptable (mostly Gr 1-2) and reversible (dose-related) AEs
  - Fatigue (52%, 3%), diarrhea (52%, 0%), nausea (41%, 3%), dysgeusia (28%, 0%), thrombocytopenia (26%, 6%), anorexia (24%, 2%), muscle spasms (20%, 2%), anemia (14%, 2%): (% Gr 1-2, % Gr 3-4), no Gr 5
  - 11% pts required dose-reduction, 9% discontinued
- Drug-related SAEs, n=86
  - Most common SAEs: PE (4.7%, 4/86), anemia (2.3%, 2/86)
  - 1 death reported of unclear cause
- FDA-approval in 10/2006 for “the treatment of cutaneous manifestations of CTCL who have tried and failed other therapies”
Vorinostat (Zolinza™)

• Recommend starting at 400mg qd (100 mg capsules)
  – Dose reduction with significant AEs
    • 300 mg qd => 300 mg 5x per wk

• Encourage po fluid (2 L/day)

• Laboratory monitoring
  – CBC/plts, chemistries (lytes, glu, Cr) q 2wks in first 2 mo, then q mo

• Baseline ECG and f/u as needed

• Warnings and precautions
  – Be aware of thromboembolic, hematologic AE symptoms
  – Correct hypokalemia or hypomag prior to dosing
  – Drug interaction with Coumadin and other HDACI (valproic acid)
  – Caution with drugs that prolong QTc interval
  – Caution in patients with thrombocytopenia, cardiac arrhythmias
Treatment Approach in Mycosis Fungoides & Sézary Syndrome

**IA**
- Limited dz, T1
- Top steroids, retinoid (bex*) gel
- NM

**IB/IIA**
- Generalized, T2
- UVB
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**Investigative/Newer Therapies**
- (TLRAs, MoAbs, cytokines, HDAIs, PNPIs, iMids, vaccines, allo-HSCT)

* Bex, IFN, denileuk dift*, vorinostat (single or combination)

Combination Chemo
- Alemtuzumab
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

Improve QOL, closer toward a cure…