THE IMMUNOPATHOGENESIS AND TREATMENT OF SEZARY SYNDROME

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High Clinical Response Rates Using Multimodality Immune Therapy Among 100 Sezary Syndrome Patients

- CR: 30%
- PR: 45%
- NR/PD: 25%

B Raphael et al., Arch Dermatol, 2011
Sezary Cell
Characteristics of the Malignant T-Cell

- Typically CD4+ (if CD8+ consider retrovirus)
- CCR4 Hi (Skin Trafficking)
- CCR7+ (Skin Egress) (negative in Mycosis fungoides)
- CLA+ (Skin Trafficking)
- CD26/CD7 Negative
- Produces soluble factors
- PD-1 Hi (negative in MF)
Skin Trafficking T-Cells

TS Kupper. Inflammatory Skin Diseases, T Cells, & Immunosurveillance. NEJM 2000 341:1817-28
Effects of Soluble Factors

EJ Kim et al., JCI, 2005
Low Numbers of DCs Correlates with Decreased Levels of IL-12 and IFNα in Sezary Syndrome Patients.
Increased circulating PD-1+CD4+ T-cells in Sezary patients compared to mycosis fungoides patients or healthy volunteers

S. Samimi, et al., Arch Dermatol, 2010
## Immunological Phenotype In Sezary Syndrome

<table>
<thead>
<tr>
<th>Increased</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+/CLA+/CCR4+ T cells</td>
<td>CD8 T cells</td>
</tr>
<tr>
<td>TH2 cytokines; IL-4, IL-5, IL-10</td>
<td>Loss of normal T-cell repertoire</td>
</tr>
<tr>
<td>Tregs</td>
<td>NK cells</td>
</tr>
<tr>
<td>Programmed Death 1 (PD-1)</td>
<td>TH1 cytokines; IFN-γ</td>
</tr>
<tr>
<td></td>
<td>Dendritic cells,</td>
</tr>
<tr>
<td></td>
<td>IL-12, IFN-α</td>
</tr>
<tr>
<td></td>
<td>CD40 ligand expression</td>
</tr>
</tbody>
</table>
Treatment of Sezary Syndrome

- Photopheresis
- Interferons (and other Cytokines[GMCSF])
- Bexarotene/13 cis or all-trans Retinoic Acid
- Toll Receptor Agonists
- PUVA
- Total Skin Electron Beam
- HDAC Inhibitors
- Campath (Alemtuzumab)
- Anti-CD4 or anti-CCR4 antibodies
- Chemotherapy
- Bone Marrow Transplant
Cutaneous T-Cell Lymphoma is Highly Responsive to Immune Modulation
The Ideal Immune Modifier

• Induces robust antitumor immune response

• Directly induces high levels of apoptosis of tumor cells

• Induces sustained immunologic memory
High Clinical Response Rates Using Multimodality Immune Therapy Among 100 Sezary Syndrome Patients

B Raphael et al., Arch Dermatol, 2011
Administration of Large Numbers of Apoptotic Cells Inhibits Dendritic Cell Function and Th1 Cytokine Production
Products of the Innate Immune Response Are Active for CTCL

- Interferon alpha (plasmacytoid DCs)
- Interleukin-12 (myeloid DCs)
- Interferon gamma (natural killer cells)
Combined Immune Modifiers for Advanced CTCL Produce High Response Rates

- Interferons (alpha, gamma or both)
- Bexarotene (or an RAR specific retinoid)
- GM-CSF
- Photopheresis
Interferon alpha Antitumor Effects

- Activates anti-tumor cytolytic cells (NK & CTLs)
- Inhibits growth of malignant T-cells
- Inhibits production of Th2 cytokines
- Dose dependent response rates of 50-80%
- Response rates may be greater when used in combination (PUVA, Retinoids, Photopheresis, Interferon gamma)
Adverse Effects of IFN α Are Dose Related

• Bone marrow suppression (rapidly reversible)
• Flu like symptoms (transient)
• Fatigue
• Neurological effects
• Cognitive effects
• Autoimmunity
Low Dose Interferon $\alpha$

**Treatment Protocol**

• Initial Dose 1.5-2.5 million Units SQ 3 x per week
• Increase to: 5-7.5 million Units SQ 4-5 x per week
• Typical Dose: 1.5-5 million Units SQ every other day
Bexarotene
Advantages of Bexarotene

- Effective for all stages of CTCL
- Effective for de novo large cell transformation
- Well tolerated
Bexarotene Causes Apoptosis of CD4+ Cells in Sensitive High Tumor Burden CTCL Patients
Bexarotene Effects

• Induces apoptosis of malignant T-cells
• Certain patients are consistently sensitive while others are resistant
• Inhibits IL-4 production by malignant T-cells
• Downregulates CCR4 and inhibits trafficking of malignant T-cells to CCR4 ligands (TARC)
• Recommend using with interferon, PUVA and/or photopheresis
Recommendations for Bexarotene Use

- Initial dosing at 150-200 (up to 300) mg/m²
- Use a statin, fish oil and/or fenofibrate prophylactically
- Requires levothyroxine replacement due to suppression of TSH
- **Consider combined regimes (interferon, PUVA, photopheresis)**
- Resistance can occur due to loss of RXR receptors
Interferon gamma
Interferon Gamma

- Potent Alternative Therapy to Interferon α
- Better Tolerated Than Interferon α
- Preliminary Results Suggest at Least a Comparable Response Rate
- Activates Antigen Presenting Cells
- Activates CD8+ T-cells and NK Cells
- May Inhibit Effects of TGF-β
Interferon Gamma Use

- Initiate at 50 micrograms (0.25 cc or one half vial) three times weekly
- Increase to 100 micrograms three to five times weekly
- May use simultaneously with interferon alpha
- Recommend multimodality approach with interferon alpha, bexarotene and photopheresis
Augmentation of NK Cell Function with Disappearance of the Malignant Clone During Immune Modifier Therapy
Correction of Immune Abnormalities in Sezary Syndrome During Remission

Sezary Syndrome

- $\uparrow$ CD4+/CCR4+/CD26- T-cells
- $\uparrow$ CD8+ T-cells
- $\uparrow$ CD56+ NK cells
- $\downarrow$ Dendritic cells
- $\downarrow$ Cell-Mediated cytotoxicity
- $\downarrow$ IL-12, IFN\(\alpha\), IFN\(\gamma\)
- $\uparrow$ IL-4, IL-5, IL-10
- $\uparrow$ IgE
- $\uparrow$ Eosinophils

Remission (Malignant clone negative by PCR in blood and skin)

- Normal CD4+/CCR4+/CD26- T-cells
- Normal CD8+ T-cells
- Normal NK cells
- Normal Dendritic cells
- Increased or normal cell mediated cytotoxicity
- Normal IL-12, IFN\(\alpha\), IFN\(\gamma\)
- Normal IL-4, IL-5, IL-10
- Normal IgE
- Normal Eosinophils

Immunotherapy

EJ Kim, et al., JCI, 2005
# TSEB Can Clear Circulating Malignant T-Cells

<table>
<thead>
<tr>
<th>Patient</th>
<th>pre-TSEB</th>
<th>post-TSEB</th>
<th>post-TSEB</th>
<th>post-TSEB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD4+CD7 - (%)</td>
<td>CD4+CD2 6- (%)</td>
<td>CD4:CD8 ratio</td>
<td>CD4+CD7 - (%)</td>
</tr>
<tr>
<td>1</td>
<td>33</td>
<td>58</td>
<td>6.2</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>96</td>
<td>&gt;1000</td>
<td>7</td>
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<tr>
<td>3</td>
<td>10</td>
<td>64</td>
<td>30</td>
<td>5</td>
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<tr>
<td>4</td>
<td>55</td>
<td>87</td>
<td>106</td>
<td>20</td>
</tr>
</tbody>
</table>

C Introcaso et al., JAAD, 2008
Psoralen plus ultraviolet A light may be associated with clearing of peripheral blood disease in advanced cutaneous T-cell lymphoma

Brian A. Raphael, BA, Kelly A. Morrissey, MD, Ellen J. Kim, MD, Carmela C. Vittorio, MD, Alain H. Rook, MD

Journal of the American Academy of Dermatology Volume 65, Issue 1, Pages 212-214, July 2011
Imidazoquinolines Are Powerful TLR Agonists

Nature Reviews | Drug Discovery
Toll Like Receptor Agonists Are Therapeutically Active for Cutaneous T-Cell Lymphoma

TLR 8 (Resiquimod)

TLR 9 (CpG)

TLR 7 (Imiquimod)

mDC

CD80

CD86

pDC

CD86

CD80

IL-12, 15, 18

(IFNγ) NK, CTL

Antigen Processing

IFNα

NK, CTL,

Antigen Processing
Resiquimod (007)

- Combined TLR 7 & 8 agonist
- Bioavailability 10 times > imiquimod
- Potency up to 100 times > imiquimod
- 1g application induces a systemic IFN alpha response
Clinical Response to Resiquimod

Pre-Resiquimod

Week 12 Resiquimod
Proinflammatory Effects of Resiquimod
Histology Pre-Resiquimod

Intrafollicular Inflammation

Pauci-Cytotoxic T-cells
Resiquimod Week 8

Dense Inflammatory Infiltrate

Numerous Cytotoxic T-Cells
Toll Receptor Agonists Are Potent Inducers Of Anti-Tumor Immunity
HDAC Inhibitors

Vorinostat

Romidepsin
Examples of Clinical Response

Stage III, CR, failed 2 prior chemotherapy regimens

• Baseline:
  • No lymphadenopathy
  • Normal circulating Sézary cells (<5%)
  • Moderate to severe erythroderma
Bench to Bedside

Direct Inhibition of NK Cell Cytotoxicity by Vorinostat

% K562 Cell Lysis

Med 1 uM Vorinostat

S Stephen, Am J Hematol 2012
Targeted Therapy for CTCL

- Anti-CD52 antibodies (Alemtuzumab) (T, B, NK and DCs)
- IL-2 receptors (Denileukin Diftitox) (T and B)
- Anti-CD4 (all helper T-cells)
- Anti-CCR4 (malignant T-cells, regulatory T-cells, skin-trafficking T-cells)
- AKT inhibitors (targeting increased Phospho-AKT)
Alemtuzumab (Campath)

- 3 mg days 1 and 3
- 10 mg days 5 and 7
- Continue 10 mg every other day until Sezary count \(< 1000/\text{mm}^3\)
- Monitor Sezary count Q2 weeks for one month then Q month
- If Sezary count exceeds 2000/ \text{mm}^3 resume treatment
KW-0761: Anti-CCR4 Monoclonal Antibody with Enhanced ADCC (Potelligent®)

- Defucosylated Fc region
- Leads to an increase in ADCC activity compared to conventional antibodies

Allogeneic Marrow Transplant

Patients without large tumors or bulky lymphadenopathy are excellent candidates for allogeneic transplantation.

Risk of graft versus host disease remains high
Eliminating the Sezary Cell

- Immune Modulatory Therapy
- Induce Immunologic Memory (Interferons)
- Utilize Multimodality Approach
- Target the Skin and Blood
- Targeted Therapy is Coming to Your Neighborhood
- Treat Infection