A NOVEL THERAPEUTIC REGIMEN FOR
FOLLICULOTROPIC MYCOSIS
FUNGOIDES

ALAIN H ROOK,
PROFESSOR OF DERMATOLOGY
DIRECTOR, CUTANEOUS LYMPHOMA PROGRAM
PERELMAN SCHOOL OF MEDICINE
UNIVERSITY OF PENNSYLVANIA
Potential Conflicts

• Galderma: Clinical trial; license
CLINICAL APPEARANCES OF FOLLICULAR MYCOSIS FUNGOIDES

Actuarial disease-related survival of 49 patients with follicular mycosis fungoides (FMF), 122 with generalized plaque-stage mycosis fungoides (MF) (T2 N0 M0), and 36 with tumor-stage MF (T3 N0 M0)

The Immune Response Plays a Critical Role in Control of Cutaneous T-Cell Lymphoma in Early Stage Disease, AND, in Late Stage Disease.
Localized Folliculotropic MF

• Excellent prognosis is typical

• Imiquimod

• Potent topical steroids

• Carmustine (BCNU) ointment 0.03-04%

• Electron beam
Imidazoquinolines Are Powerful TLR Agonists

Imiquimod (R-837)  Resiquimod (R-848)
Toll Like Receptor Agonists Are Therapeutically Active for Cutaneous T-Cell Lymphoma

mDC

TLR 8 (Resiquimod)

IL-12, 15, 18

(IFNγ) NK, CTL Antigen Processing

pDC

TLR 9 (CpG)

TLR 7 (Imiquimod) (Resiquimod)

IFNα

NK, CTL, Antigen Processing
Site A before treatment measured 4.0 x 2.4 cm

Site A after 2 months of therapy

CARMUSTINE (BCNU)

0.03%-0.04% ointment
Response of FMF to Carmustine (BCNU) Ointment
Carmustine Induced Telangiectases
Extensive Folliculotropic MF

- Prognosis worse than epidermotropic variants
- Combination of systemic and skin directed therapy
  - Carmustine topically
  - Electron beam
  - Interferon gamma (long term use is critical)
  - Isotretinoin
- Potent topical/Intralesional steroids
Effects of Interferon Gamma

- Potent Alternative Therapy to Interferon $\alpha$
- Better Tolerated Than Interferon $\alpha$
- Activates APCs
- Potently Activates CD8+ T-cells and NK Cells
- Inhibits Growth of Malignant T-cells
Interferon gamma
Perifollicular CD8 T-Cells

CD4 Cells

CD8 Cells
ISOTRETINOIN
EFFECTS OF ISOTRETINOIN

• Apoptosis of sebocytes and atrophy of sebaceous unit

• Apoptosis of malignant T-cells

• Malignant T-cell recruitment to skin inhibited

• Possible synergy with interferon gamma
Skin Trafficking T-Cells

TS Kupper. Inflammatory Skin Diseases, T Cells, & Immunosurveillance. NEJM 2000 341:1817-28
Effects of Bexarotene on CCR4 expression

CCR4 Expression at 72Hrs

<table>
<thead>
<tr>
<th></th>
<th>No Treatment</th>
<th>Bexarotene (10uM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%CCR4 Positive Lymphocytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NI Ctrl</td>
<td>8.2%7.2%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Patient 1</td>
<td>27.8%</td>
<td>45.1%</td>
</tr>
<tr>
<td>Patient 2</td>
<td>30.5%</td>
<td>58.3%</td>
</tr>
<tr>
<td>Patient 3</td>
<td>27.9%</td>
<td></td>
</tr>
</tbody>
</table>

S. Richardson, et al., Am J Hematol
Effects of Bexarotene on Chemotaxis

Chemotaxis at 72Hrs in response to TARC (6.25ng/ml)

S. Richardson, et al., Am J Hematol
Toll Like Receptor Agonists Are Therapeutically Active for Cutaneous T-Cell Lymphoma

mDC
- TLR 8 (Resiquimod)
- TLR 9 (CpG)
- TLR 7 (Imiquimod)
- CD80
- CD86
- IL-12, 15, 18
- (IFNγ) NK, CTL
- Antigen Processing

pDC
- TLR 9 (CpG)
- TLR 7 (Imiquimod)
- CD86
- CD80
- IFNα
- NK, CTL
- Antigen Processing
Resiquimod Induces Regression of Both Treated and Untreated CTCL Skin Lesions
Folliculotropic MF Response to Resiquimod Gel
Patient 11

Clearance of Malignant Clone and Restoration of Clonal Diversity

Pre-treatment

Clone: 19% T cells

8 weeks

Clone: 0% T cells
Percent Change in Malignant Clone During Therapy
Prior to Multimodality Therapy
During Multimodality Therapy
Therapy for Folliculotrophic Mycosis Fungoides

- Imiquimod cream for limited disease
- 0.03-0.04% topical carmustine (BCNU) ointment for limited or extensive application
- Isotretinoin in low dose (10-20 mg daily)
- Interferon gamma for extensive disease (Combination therapy for aggressive disease is recommended)
- Electron beam radiation