Forum 115
Management Issues in Cutaneous Lymphomas

Management of Transformed Mycosis Fungoides

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Large cell transformation (LCT) defined as tumor cells with nuclei > 4x normal size.

Epidermotrophic T Cells
Pautrier’s abscesses
Nodes, Blood

CD25+ 80% response to Ontak vs 20% neg

CD30+ has better OS
Response to Brentuximab vedotin
Antibody conjugate

Talpur et al. JID 126 (3) March 2006, 575-583
Mycosis fungoides & Sezary Syndrome
Transformation can occur at any T-stage - 73% at advanced stage

- Patch
- Plaque
- Woringer-Kolopp Disease
- Pagetoid reticulosis
- Erythrodermic
- Tumor
Mycosis Fungoides (MF or T-MF)
Secondary Cutaneous ALCL
PTCL-NOS, HTLV-1 ATL
Hodgkin Lymphoma (HL)

Primary cutaneous Anaplastic T-cell Lymphoma
Lymphomatoid Papulosis

CD30+ Cutaneous T cell lymphomas

Lymphomatoid Papulosis (LyP)
Primary Cutaneous ALCL (c-ALCL)
Mycosis Fungoides, MF or T-MF
Secondary Cutaneous ALCL

CD30+ Lymphoproliferative Disorders
Large cell transformation (LCT)

- Large cell transformation (LCT) is defined as tumor cells having nuclei > 4 x normal size by histology.

- More aggressive course and shorter overall survival (OS) than untransformed MF

- Median OS was 4.79 years in 186 patients with T-MF among a cohort of 1900 (9.8%)

- Overall survival (OS) similar to published results of non-LCT in T3 (tumor) MF patients (6.24 yrs) but significantly worse than all MF patients (26.26 years) (p=.001).

Talpur et al. Retrospective analysis of prognostic factors
Clinical Lymphoma, Myeloma & Leukemia 16 (1) 49-56, 2016
CASE 1 - 60 yo WF 15 yrs history Patch/Plaque - Stage II B MF LCT
Enterococcus+ skin ulcers treated with IV antibiotics
Combined Modality therapy = Accutane/intron A, CMED, TBSEB, accutane/NM gave 7yrs in partial response. 56% CR late CD30+ eye/CNS
Retrospective analysis of prognostic factors in 187 cases of transformed Mycosis Fungoides. 9.8% of cohort 1900 transformed. Risk factors and response to therapies.

_Talpur et al._
Clinical lymphoma & Myeloma
Vol 16, 49-56, Jan 2016
Median Overall Survival of Transformed MF Cohort

• Risk factors for progression by univariate analysis:
  – age > 60, LDH, CD30 < 10% & LCT at diagnosis

• Overall Survival for all LCT 4.8 yrs
  – Age > 60 = 4.1 yr vs Age < 60 = 10 yrs
  – 73% LCT at Diagnosis: OS 3.6 yrs vs 8.8 yrs if after
  – High LDH – decreased OS (p=.03, HR 1.5)
  – CD30 > 10% skin biopsy had 40% increased survival

• Treatment groups: SCT (n=12), Chemo & Radiation (n=31),
  chemo only (n=84) and biological response modifiers or
  targeted therapies BET (n=37)
Survival by Treatment Group in 186 T-MF

Product-Limit Survival Estimates

- **Radiation**
- **ASCT**
- **Chemo**
- **Chemo/XRT**

**Trt**
- Chemo
- Chemo+Radiation
- Other
- Radiation
- SCT

**Time (year)**

**Survival Probability**

**Talpur et al. Clinical Lymphoma & Myeloma Vol 16, 49-56, Jan 2016**

Chemo vs ASCT

***p = 0.0137***
<table>
<thead>
<tr>
<th>Agent (Class)</th>
<th>Indication</th>
<th>Study</th>
<th>N</th>
<th>ORR</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romidepsin (HDAC inhibitor)</td>
<td>Patients with CTCL who have received systemic therapy</td>
<td>Pivotal</td>
<td>96</td>
<td>34%</td>
<td>15 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supportive</td>
<td>71</td>
<td>35%</td>
<td>11 mo</td>
</tr>
<tr>
<td>Denileukin diftitox (Fusion protein)</td>
<td>Tumors that express CD25</td>
<td>Pivotal</td>
<td>71</td>
<td>30%</td>
<td>4 mo</td>
</tr>
<tr>
<td>Bexarotene (Retinoid x-receptor activator)</td>
<td>Cutaneous manifestations</td>
<td>Pivotal</td>
<td>62</td>
<td>32%</td>
<td>5+ mo</td>
</tr>
<tr>
<td>Vorinostat (HDAC inhibitor)</td>
<td>Cutaneous manifestations</td>
<td>Pivotal</td>
<td>74</td>
<td>30%</td>
<td>6+ mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supportive</td>
<td>33</td>
<td>24%</td>
<td>4 mo</td>
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</tbody>
</table>
CASE 9: 85 yr old man with transformed CTCL – oral vorinostat at 4 weeks
CASE 8 - Partial response to vorinostat

Stage IVB transformed MF tumors - 6 prior therapies
TBSEB, CVP, denileukin diftitox, and bexarotene

Baseline                        Week 8                        Week 24
Romidepsin – pan histone deacetylase inhibitor
Cycle 3 dose 2 – Partial response – allo SCT
**Mechanism of Action**

*Ex vivo* studies suggest that ONTAK interacts with the high-affinity IL-2 receptor on the cell surface. Within 11 minutes of receptor binding, ONTAK is internalized via receptor-mediated endocytosis. In the acidic vesicle, the enzymatic domain is cleaved from the translocation domain. The enzymatic domain is released into the cytosol, leading to:

- Protein synthesis inhibition
- Apoptosis within 40-72 hours

Objective Response Rate (ORR) by Treatment Arm\textsuperscript{1,*}

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Percentage</th>
<th>N</th>
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<tbody>
<tr>
<td>18 mcg/kg/d</td>
<td>46%</td>
<td>55</td>
</tr>
<tr>
<td>9 mcg/kg/d</td>
<td>37%</td>
<td>45</td>
</tr>
<tr>
<td>Placebo</td>
<td>15%</td>
<td>44</td>
</tr>
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</table>

\textsuperscript{*}Adjusted for disease stage and changes in randomization ratios.

\textsuperscript{†}Logistic regression model adjusting for disease stage and changes in randomization ratios over the course of the study; comparisons relative to placebo.
Brentuximab Vedotin Mechanism of Action

Brentuximab vedotin antibody-drug conjugate (ADC)

Monomethyl auristatin E (MMAE), microtubule-disrupting agent
Protease-cleavable linker
Anti-CD30 monoclonal antibody

Brentuximab vedotin binds to CD30

Brentuximab vedotin-CD30 complex is internalized and traffics to lysosome

MMAE is released

MMAE disrupts microtubule network

G2/M cell cycle arrest

Apoptosis

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CD30+ found in Lymphomatoid papulosis, MF, Anaplastic Large T cell lymphoma
59 y/o BF w 50% CD30+ MF tumor response to 7 infusions of BV
Phase II Overall Clinical Response to BV is 54% BV superior to MTX or Bexarotene in phase 3 Dose 1.8 mg/kg every 3 weeks IV

<table>
<thead>
<tr>
<th>Stage</th>
<th>Response Rate</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB (n=6)</td>
<td>17%</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>IIA (n=3)</td>
<td>33%</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>IIB (n=10)</td>
<td>80%</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>IIIA (n=1)</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>IVA (n=4)</td>
<td>75%</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>IVB (n=4)</td>
<td>50%</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total = 28</td>
<td>54%</td>
<td>2</td>
<td>13</td>
<td>12</td>
<td>1</td>
</tr>
</tbody>
</table>
Summary of BV Therapy

- **Brentuximab vedotin** is highly active in CD30+ Lymphoproliferative disorders and MF
- ORR of 73% (35/48) for all patients
- ORR 100% in LyP & ALCL
- ORR 54% in MF irrespective of CD30 level
- Patch/plaques slower than tumors to respond with
- confounding flares and spongiotic drug rash (27%)
- Median Duration Response - Lyp 26 wks, MF 32 wks
- Median Time to Response - Lyp 3 wks, Mf 12 wks
- Side effects: Neuropathy (58%), fatigue (41%)
Therapy for Advanced CTCL
Reported Therapy Outcomes

- Electron beam to skin (90+% RR)
- Combination chemotherapy (90% RR)
- Doxorubicin (80% RR)
- Gemcitabine (70% RR)
- Bortezomib (67% RR)
- Praletrexate (57% RR)
- Histone deacetylase inhibitors (30-40% RR)
PET CT - Response of folliculotropic T- MF IVA

Liposomal Doxorubicin 20mg/m2 q 2 wk x 16 weeks
Bexarotene 300 mg/m2 x 32 wk maintenance
Overall response 41% (14/34)

Case 2  -71 y/o WM IVA with infected tumor ulcers
20 Gy of local beam XRT

Post - Radiation
70 yr old WM failed all available agents except radiation!!

Pralatrexate course 2 with CR of lesions nasal and face tumors lasting 2 years

Pre-Pralatrexate

C1D3

C2 D1
Pralatrexate Selectively Targets Folate Metabolism

150 mg bexarotene - 60% OR, PFS 12.8 mos, 4 CR, 28 mos

Rationally designed potent DHFR inhibitor with efficient cell entry and retention

- Efficient permeant for RFC-1 (transport)
- Effective substrate for FPGS (polyglutamation)
- PDX primarily targets DHFR (pM affinity)
  - Alimta, 5-FU and Tomudex target TS

Duvic et al Clin Cancer Res July 2017
Praletrexate Trials

- **PROPEL PTCL** - 30 mg/m² 6/7 weeks
  12 T-MF RR 25% review, 58% PI
  
  *Foss et al. Clin. Lymph, Myeloma Aug 2012*

- **Phase 2 Dose Ranging MF trial**
  45% ORR - dose 15 mg/m² IV 3 of 4 wks
  17% gr 3 mucositis, 3% gr 4 leukopenia.

- **Horwitz Blood 2012: 119; 4115-4122**

- **Phase II Trial of Praletrexate & bexarotene**

  - 15 mg/m² 3 of 4 weeks. RR 60% 4 CRs

• TBSEB with non-ablative allogenic stem cell transplant can induce complete durable remissions even in T-MF
  – ORR was 58% (28/48) for all patients
  – 79% in Sézary Syndrome
  – 56% for MF with LCT

• Relapse rate
  – 21% in SS, 25% in LCT, 56% in SS/LCT

• 44% died (21/48) or relapsed MF, sepsis/infection, or second malignancy

Topical Imiquimod

- Local stable tumors
- Induces interferon
- Dendritic cells
- Inflammation
- Trials with resiquimod and injectable toll agonists.
Immunotherapy targeting T-cell activation check-point molecules

Nivolumab – anti - PD1  Pembrolizimab – anti PD1L
Conclusions

- Large cell transformation is a histologic diagnosis and can occur at all stages of MF. 9.8% of 1900 MF patients.
- Inferior survival in late stage, at first diagnosis, older age
- CD30+ may occur with LCT - improved OS, new CD30 antibody with high response rate > 50%
- Single chemotherapy: high response rates but relapse
- Biological response modifiers, targeted therapies, SCT, and radiation may improve OS.