CUTANEOUS T-CELL LYMPHOMA: SYSTEMIC THERAPY

Anne W. Beaven, MD
Associate Professor
Director, Lymphoma Program
University of North Carolina
<table>
<thead>
<tr>
<th>CTCL</th>
<th>Extranodal</th>
<th>Nodal</th>
<th>Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis fungoides</td>
<td>Extranodal NK/T cell lymphoma, nasal type</td>
<td>Peripheral T-cell lymphoma, NOS</td>
<td>Adult T-cell leukemia/lymphoma</td>
</tr>
<tr>
<td>Sezary Syndrome</td>
<td>Enteropathy-associated T-cell lymphoma</td>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td>T-cell prolymphocytic leukemia</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like TCL</td>
<td>Hepatosplenic T-cell lymphoma</td>
<td>Follicular T-cell lymphoma*</td>
<td>T-cell large granular lymphocytic leukemia</td>
</tr>
<tr>
<td>CD30+ T-cell LPDs (LyP, pcALCL)</td>
<td>Monomorphic epitheliotropic intestinal TCL*</td>
<td>Nodal T-cell lymphoma with TFH phenotype*</td>
<td>Aggressive NK-cell leukemia</td>
</tr>
<tr>
<td>PC γδ T-cell lymphoma</td>
<td>Indolent T-cell LPD of the GI tract*</td>
<td>Anaplastic large-cell lymphoma, ALK-pos</td>
<td>Chronic LPD of NK cells</td>
</tr>
<tr>
<td>PC CD8+ epidermotropic cytotoxic TCL</td>
<td>Breast implant-associated ALCL*</td>
<td>Anaplastic large-cell lymphoma, ALK-neg*</td>
<td></td>
</tr>
<tr>
<td>PC acral CD8+ TCL*</td>
<td>Systemic EBV+ TCL of childhood*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC CD4+ small/medium T-cell LPD*</td>
<td>Hydroa Vacciniforme-like LPD*</td>
<td></td>
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</tr>
</tbody>
</table>
CTCL PRIMARY TREATMENT MAP

IA limited patch, plaque
IB, IIA generalized patch, plaque
IIB tumors
III erythroderma
IVA, IVB nodal/visceral involvement

Topical corticosteroids
Bexarotene gel
Nitrogen mustard
UVB
PUVA
PUVA + IFN/other
Oral bexarotene
Electron beam
Vorinostat and romidepsin
Denileukin diftitox
Chemotherapy
Experimental therapy CLINICAL TRIALS

Mycosis Fungoides and Sezary Syndrome are **chronic illnesses**

- Long term treatment required
  - Combination of approaches w/ topical and systemic and radiation therapy
  - Treatments sometimes re-used over the years
  - Chemotherapy only used in advanced stage disease – usually monotherapy
  - Multidisciplinary approach: Dermatology, oncology, radiation oncology, pathologists, wound care

- Complete remission unlikely
  - Minor or partial response not considered failure
  - Aim for durability and low toxicity

- Supportive care – consider antibiotics for prophylaxis of skin infections
“The aim of treatment in relapsed/refractory CTCL is to safely induce prolonged remission without compromising a patient’s immunity or adversely affecting their quality of life.”

WHEN DO WE USE SYSTEMIC THERAPIES IN MF?

- Early stage MF (I/IIA), refractory to skin-directed therapies
- Significant folliculotropic disease, large cell transformation
- Advanced stage MF/SS, IIB-IV – systemic therapy used upfront

Systemic therapy +/- skin directed therapy

Used with permission from Alison Moskowitz, MD
WHAT ARE THE SYSTEMIC THERAPIES?
CLASSIC CHEMOTHERAPY DRUGS

• **Gemcitabine**
  
  • Schedule: IV weekly for 3 of every 4 weeks
  
  • Response (based on skin response):
    • Overall response rate of 68%
    • Complete response 12%
  
  • Most frequent side effects:
  
    • A decrease in blood counts, especially platelets
    • Abnormal liver results on blood tests
    • Fatigue

• **Liposomal doxorubicin**
  
  • Schedule: IV every other week for up to 6 months
  
  • Response (based on skin response):
    • Overall response rate of 41-84%
    • Complete response rate of 6-42%
  
  • Notable side effects:
    • Rash
    • Cardiac (heart) toxicity

# HISTONE DEACYLASE INHIBITORS

**FDA APPROVED FOR CTCL**

<table>
<thead>
<tr>
<th></th>
<th>ORR, %</th>
<th>CR Rate, %</th>
<th>Median TTFR, mo</th>
<th>Median DOR, mo</th>
<th>Median TTP, mo</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vorinostat Study 1 (N=74)⁸</td>
<td>30</td>
<td>1</td>
<td>2</td>
<td>5.6</td>
<td>5</td>
<td>Thromboembolism, thrombocytopenia, anemia, nausea, vomiting, diarrhea (may require electrolyte replacement), fatigue</td>
</tr>
<tr>
<td>Vorinostat Study 2 (N=33)¹³</td>
<td>24</td>
<td>0</td>
<td>3</td>
<td>3.5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Romidepsin Study 1 (N=96)¹⁰,¹¹</td>
<td>34</td>
<td>6</td>
<td>2</td>
<td>15</td>
<td>Not reported</td>
<td>Neutropenia, thrombocytopenia, anemia, nausea, fatigue, T-wave changes, QT prolongation requiring electrolyte monitoring</td>
</tr>
<tr>
<td>Romidepsin Study 2 (N=71)¹²</td>
<td>35</td>
<td>6</td>
<td>2</td>
<td>13.7</td>
<td>15.1</td>
<td></td>
</tr>
</tbody>
</table>

**ORR:** Overall response rate  
**CR:** Complete response rate  
**TTFR:** Time to First Response  
**DOR:** Duration of response
PRALATREXATE
ANTINEOPLASTIC FOLATE THAT PREVENTS DNA SYNTHESIS AND CAUSES CELL DEATH

• Patients (n=54):
  • Median of 4 prior systemic therapies
  • ≥ stage Ib
• Schedule: IV weekly for three of every 4 weeks
• Response:
  • Overall response rate: 41% (mostly partial responses)
  • Median time to best response 57 days
• Most frequent side effects:
  • Sores in mouth 56% (severe 17%)
    • All patients will get vitamin B12 and folic acid supplements to decrease risk
  • Fatigue 41%
  • Mild nausea 39%

IMMUNOTHERAPY FOR CTCL

Picture from https://myepqlog.wordpress.com/2017/01/20/what-is-immunotherapy/ accessed on 10/3/18
ALEMTUZUMAB

• Monoclonal Antibody against CD52
  • CD52 is expressed on B and T cells
• Schedule:
  • Monday, Wednesday and Friday for up to 3 months
  • IV or as a shot
• Outcomes:
  • Overall response rates of 38-100% - most reports are around 80%
  • Complete response rates 21-100%
  • Duration of response: 6-12 months – some long term responders
• Mostly used in sezary syndrome
• Adverse Events: infections so patients maintained on anti-infectious medications

Brentuximab vedotin (SGN-35) ADC

- Monomethyl auristatin E (MMAE), potent antimicrotubule agent
- Protease-cleavable linker
- Anti-CD30 MoAb

1. ADC binds to CD30
2. ADC-CD30 complex traffics to lysosome
3. MMAE is released
4. MMAE disrupts microtubule network
5. G2/M cell cycle arrest
6. Apoptosis

Used with permission from Frederick Lansigan, MD
ALCANZA Phase III study

Eligibility
- CD30+ cutaneous lymphoma
- MF made up 75% of patients
- 131 patients were enrolled

Primary endpoint
- ORR4 = rate of objective response lasting ≥4 months
- Global response of all compartments using consensus criteria (mSWAT for skin evaluation, radiographic assessment, and circulating Sézary cell assessment as appropriate)

Brentuximab vedotin: 1.8 mg/kg IV, every 3 weeks

VS

Methotrexate: 5–50 mg
Or
Bexarotene: 300 mg/m²

Used with permission from Alison Moskowitz, MD
## ALCANZA PHASE III STUDY RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Brentuximab Vedotin</th>
<th>MTX or Bexarotene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>67%</td>
<td>20%</td>
</tr>
<tr>
<td>Response lasting ≥4 months all patients</td>
<td>56%</td>
<td>12%</td>
</tr>
<tr>
<td>Complete Response Rate</td>
<td>16%</td>
<td>2%</td>
</tr>
<tr>
<td>Median Duration of Response</td>
<td>15 months</td>
<td>18 months</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>67%</td>
<td>6%</td>
</tr>
</tbody>
</table>

MOGAMULIZUMAB:
MONOCLONAL ANTIBODY TARGETING THE CHEMOKINE RECEPTOR CCR4
CCR4 IS EXPRESSED ON MYCOSIS FUNGOIDES CELLS AND T REGULATORY CELLS

Mogamulizumab allows your immune system to better attack the cancer cells
Phase III Mavoric study

<table>
<thead>
<tr>
<th>Mogamulizumab 1mg/kg IV, q14 days</th>
<th>VS</th>
<th>Vorinostat 400mg po daily</th>
</tr>
</thead>
</table>

- 372 patients with CTCL randomized
  - Stage Ib-IVb
  - Median age 64 years
  - Median of 3 prior therapies

- Excluded
  - Large cell transformation
  - Patients with active autoimmune disease

Kim et al. Lancet Oncology 2018;19:1192-1204
### PHASE III MAVORIC STUDY RESULTS

<table>
<thead>
<tr>
<th></th>
<th><strong>Mogamulizumab</strong></th>
<th><strong>Vorinostat</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global Response Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Skin response</td>
<td>28%</td>
<td>5%</td>
</tr>
<tr>
<td>• Lymph node response</td>
<td>42%</td>
<td>16%</td>
</tr>
<tr>
<td>• Blood response</td>
<td>15%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>67%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Median Duration of Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Skin</td>
<td>20 months</td>
<td>10.7 months</td>
</tr>
<tr>
<td>• Lymph node</td>
<td>15 months</td>
<td>NE</td>
</tr>
<tr>
<td>• Blood</td>
<td>25 months</td>
<td>NE</td>
</tr>
<tr>
<td><strong>Median Time to Response</strong></td>
<td>3.3 months</td>
<td>5.1 months</td>
</tr>
<tr>
<td><strong>NE</strong>=Not evaluable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kim et al. Lancet Oncology 2018;19:1192-1204
MOGAMULIZUMAB SIDE EFFECTS

- Rash:
  - 25% of patients
  - Severe rash in 3.6%
- Infusion reaction while receiving drug:
  - Chills, nausea, fever, fast heart rate, headache, vomiting
  - 1/3 of patients; severe in 8%
  - Usually 1st cycle
- Autoimmune complications to thyroid, lungs, liver etc.
  - Severe in <5%

Kim et al. Lancet Oncology 2018;19:1192-1204
Patients:
- 24 patients with relapsed/refractory CTCL
- 63% had received ≥ 4 prior therapies

Results:
- ORR 38% (CR 4%)
- 6 of 9 responders had a 90% decrease in skin disease
- Sustained response in 8 of 9 responders

Side effects:
- Flare up of the skin disease
- Autoimmune issues (diarrhea, pneumonitis)

CLINICAL TRIAL AT UNC
CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELLS

- Hybrid molecule:
  - Extracellular antigen-recognition site from an antibody
  - Intracellular signaling domain of T-cell receptor

- CAR binds antigen on surface of tumor cells -> T cell activation and killing of tumor cells

Slide courtesy of Natalie Grover, MD
Patient’s T cell (immune fighting cell)

Protein targeting CD30 marker
(CD30 is what brentuximab vedotin targets)

Slide courtesy of Natalie Grover, MD
LCCC 1606: HOW TO OPTIMIZE BENEFIT OF CAR-T CELLS FOR CD30+ LYMPHOMA?

- CD30.CART enhanced with expression of CCR4 (same target as mogamulizumab)

- Hypothesis: Improved targeting of CAR-CD30 modified T cells to tumor site, leading to increased anti-lymphoma activity

Slide courtesy of Natalie Grover, MD
1. Collect blood
Blood is collected from the study participant.

2. Activate T cells
The T cells are isolated from the blood and activated using anti-CD3 and CD28 antibodies.

3. Express CAR
Viral vector
A virus is used to transfer DNA information into the T cells that instructs the T cells to produce a chimeric antigen receptor (CAR) on its surface. The result is a CAR-T cell that is designed to recognize and attack cancer cells.

4. Expand T cells
Researchers use growth factors to spur the CAR-T cells to multiply by the tens of thousands.

5. Testing and freezing
Once there is a sufficient number of CAR-T cells, they are tested for functionality, confirmed to be sterile and frozen until needed.

6. Infusion
The CAR-T cells are thawed and administered to the study participant via an IV infusion. Monitoring for safety and response is performed at specific intervals.

UNC Lineberger Comprehensive Cancer Center
# PROSPECTIVE DATA IN CTCL

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>CR</th>
<th>Median DOR. months</th>
<th>Pruritus Improved</th>
<th>FDA approved for CTCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>64%</td>
<td>9%</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>HDAC-I (romidepsin, vorinostat)</td>
<td>14-34%</td>
<td>0-10%</td>
<td>1.4-15</td>
<td>Y</td>
<td>Yes</td>
</tr>
<tr>
<td>Alemtuzumab*</td>
<td>38-84%</td>
<td>0-47%</td>
<td>2.2-6</td>
<td>Y</td>
<td>No</td>
</tr>
<tr>
<td>Brentuximab vedotin**</td>
<td>67-73%</td>
<td>16-35%</td>
<td>7.4-15</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Liposomal Doxorubicin</td>
<td>41%</td>
<td>6%</td>
<td>6</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>41%</td>
<td>6%</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Mogamulizumab</td>
<td>28%</td>
<td>NR</td>
<td>14</td>
<td>NR</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NR=Not reported;  CR=complete response; ORR=overall response rate; DOR=duration of response
*Most benefit seen in sezary syndrome/erythoderma
** Responses seen even with very low level of CD30 expression
HDAC-I- Histone deacetylase inhibitor

Most commonly: indolent, chronic disease

Focus of treatment:
- Improve symptoms
- Minimize toxicity
- Improve and maintain quality of life

Management is very individualized and involves input from dermatology and oncology and radiation oncology

CTCL - Take home messages
THANK YOU FOR YOUR ATTENTION