Recent Advances in Cutaneous Lymphomas
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Disclosures

I have no industry relationships or other potential conflicts of interest to disclose
I will discuss off-label use of medications in this presentation
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OFF LABEL!

Topics

• Folliculotropic mycosis fungoides: not always a bad actor
• Primary cutaneous CD4+ small-medium T-cell lymphoproliferative disorder: no longer a lymphoma
• Imiquimod for mycosis fungoides
• Brentuximab vedotin: not just for CD30+ disease
• Histone deacetylase inhibitors
• Mogamulizumab: FDA-approved for refractory / relapsed MF and Sézary disease
Folliculotropic mycosis fungoides: not always a bad actor
Folliculotropic MF (FMF)
aka follicular MF
Patches and plaques with alopecia and/or follicular accentuation
May be associated with alopecia mucinosa
Histopathology

Similar to classical MF, but with additional features:
- Folliculotropic infiltrate of small, medium and large cerebriform T-cells
- Large cells may be CD30+
- Follicular mucinosis variable (may be absent)

Prognosis of FMF has long been thought to be worse than non-follicular MF.
Recently, a non-aggressive subset of folliculotropic MF has been confirmed.


- 203 patients with folliculotropic MF
- 64% head and neck predominant
- 80% alopecia of involved skin; 50% eyebrow involvement with alopecia
- 92% skin-limited disease (stage I-III); 8% visceral / nodal disease (stage IV)

<table>
<thead>
<tr>
<th>Most severe type of skin lesions at diagnosis</th>
<th>67 (31)</th>
<th>50 (29)</th>
<th>55 (27)</th>
<th>0 (3)</th>
<th>17 (8)</th>
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<tbody>
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<td>Patches and/or follicular papules</td>
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<td>Plaques</td>
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<td>Tumors and nodules</td>
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<td>Erythroderma</td>
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<td>Nodal/visceral involvement</td>
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FMF survival

- Patches and/or follicular papules (Stage IA-B): 5-yr OS 92% / DSS 95%
- Tumors and/or nodules (Stage IIB): 5-yr OS 50% / DSS 59%
- "Early plaque-stage" (small atypical lymphocytes, sparse infiltrate, mucin): similar to Stage IA-B
- "Advanced plaque-stage" (medium and large lymphocytes, dense infiltrate, less mucin): similar to Stage IIB
Primary cutaneous small/medium CD4+ T-cell lymphoproliferative disorder
T-Cell Lymphomas
2005 WHO-EORTC Classification

Mycosis fungoides
  Pagetoid reticulosis
  Folliculotrophic, syringotropic, granulomatous variants
  Granulomatous slack skin
Sézary syndrome
CD30+ T-cell lymphoproliferative disorders
  Lymphomatoid papulosis
  Anaplastic large cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Peripheral T-cell lymphoma, unspecified
  Aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma
  Gamma/delta positive T-cell lymphoma
  Small/medium CD4+ T-cell lymphoma*
Extranodal NK/T cell lymphoma
  Hydroa vacciniforme-like lymphoma
  Adult T-cell leukemia/lymphoma
  Angioimmunoblastic T-cell lymphoma

* Proposed reclassification in 2014 as "lymphoproliferative disorder", not lymphoma
Primary cutaneous small/medium CD4+ T-cell lymphoproliferative disorder

- Small (<3cm) dermal nodules or small plaques
- Minimal epidermal change
- Often solitary lesion
- Head and neck, upper trunk, upper arm

Pathology:
- Small and medium CD4+ lymphocytes (<30% large)
- CD4+ 8- 30- 56-
- Variable epidermotropism
- Polymorphous infiltrate with CD8+ T-cells, B-cells, eosinophils
Primary cutaneous small/medium CD4+ T-cell lymphoproliferative disorder

Pathology:
• Small and medium CD4+ lymphocytes (<30% large)
• CD4+ 8-30-56-
• Variable epidermotropism
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Primary cutaneous small/medium CD4+ T-cell lymphoproliferative disorder

• Usually indolent
• Responds to IL steroids, excision, or local radiation
• Beware aggressive subset: multiple, large (>5cm), rapidly-growing tumors and sometimes fatal course
Imiquimod for mycosis fungoides

OFF LABEL!
Imiquimod for mycosis fungoides

- 23 publications on imiquimod for MF 2003 - 2019
- No RCTs
- A few small open-label series
- Caveat scriptor!

Imiquimod for mycosis fungoides

- Presumed mechanism is via IFN production
- May offer an alternative to radiation for patients with frequent new plaques, nodules or tumors
- RCTs needed
Brentuximab vedotin: not just for CD30+ disease
Brentuximab vedotin: not just for CD30+ disease

- 2011 FDA approved for relapsed Hodgkin lymphoma and anaplastic large cell lymphoma (ALCL)
- 2017 FDA approved for primary cutaneous ALCL and CD30-expressing MF (for pts who have received prior systemic therapy)

Drug has 3 components:
- Brentuximab: chimeric monoclonal antibody that binds CD30 on cell surface
- Cathepsin-cleavable peptide linker
- Monomethyl auristatin E (MMAE), an antimitotic agent
Brentuximab vedotin: not just for CD30+ disease

- Interestingly, it is proving useful for some cases of CD30-negative MF (off label!)
- Mechanism unclear; may involve uptake of MMAE moiety by lymphoma cells without binding of brentuximab to CD30 on cell surface
- MMAE may diffuse out of scattered CD30+ cells into neighboring CD30-neg cells
Brentuximab vedotin: not just for CD30+ disease

(off label!)

• At UVA, we have found it useful for some CD30-neg mycosis fungoides and for MTX-refractory lymphomatoid papulosis, in addition to approved indications (pcALCL, MF with large cell transformation)

• Peripheral polyneuropathy is major limiting toxicity
Histone deacetylase inhibitors

CTCL progression is linked to aberrant gene expression patterns that are not due to mutations, but rather aberrant gene transcription (epigenetic shifts)
Histone deacetylase inhibitors

Histone deacetylases (HDACs) regulate gene transcription in CTCL, and HDAC overactivity is associated with tumor growth and disease progression generally.

VORINOSTAT

- 2006 FDA approved vorinostat for relapsed / refractory mycosis fungoides
- Off-label use for Sézary syndrome
- Oral administration
Histone deacetylase inhibitors

Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma.

Objective: To evaluate the activity and safety of the histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid) in persistent, refractory, or recurrent mycosis fungoides or Sézary syndrome (MFS/S) cutaneous T-cell lymphoma (CTCL) subtypes.

Patients and Methods: Patients with stage IB or IV MFS/S were treated with 400 mg of oral vorinostat daily until disease progression or unacceptable toxicity to this open-label phase II trial (NCT00301150). Patients must have received at least two prior systemic therapies at least one month apart including two or more subtypes of systemic therapies that are not interchangeable. The primary endpoint was the objective response rate (ORR), measured by the modified 7-point visual analog scale and secondary endpoints were time to progression, duration of response, and quality of life as assessed by an investigator-rated assessment tool and secondary endpoints were time to response, time to progression, duration of response, and quality of life. Safety and tolerability were also evaluated.

Results: Forty-four patients were enrolled, including 61% with at least stage II disease. The ORR was 29% overall and 23% in stage III patients. Median TTR was 56 days. Median ORR was 67% with the intent-to-treat group estimated to be 0.05 at 24 weeks (36% at 48 weeks). Median TTR was 4.1 months overall and 3.0 months for stage A or B patients. Overall, 22% of patients had progressive disease. The most common adverse events were fatigue (58%), nausea (14%), and anemia (22%). Most were grade 1 or 2 but those grades 3 or higher included fatigue (1%), pulmonary embolism (1%), thrombocytopenia (2%), and anemia (1%). Eleven patients required dose modification and nine discontinuations due to AE.

Conclusions: Oral vorinostat was effective in treatment-refractory MF/S with an acceptable safety profile.
Histone deacetylase inhibitors

ROMIDEPSIN

• 2009 FDA approved for CTCL
• 2011 FDA approved for peripheral T-cell lymphomas
• I.V. infusion (3x / month for as long as response lasts)
Histone deacetylase inhibitors

**Abstract**

**Purpose** Romidepsin (depsipeptide or FK228) is a member of a new class of histone deacetylase inhibitors. In a phase I trial, a phase II trial of romidepsin in patients with T-cell lymphoma was conducted. **Patients and Methods** The trial cohort included patients with cutaneous T-cell lymphoma (CTCL), or subtypes of mycosis fungoides and Sézary syndrome, who had received no more than two prior systemic regimens. There were no limits on other types of therapy. Subsequently, the protocol was expanded to enroll patients who had received more than two prior systemic regimens. Twenty-seven patients were enrolled onto the first cohort, and a total of 71 patients are included in this analysis. These patients had undergone a median of four prior treatments, and 42 patients (67%) had advanced-stage disease (stage III, N = 15; stage IV, N = 5, or stage IV, N = 3). Toxicities included nausea, vomiting, fatigue, and transient thrombocytopenia and granulocytopenia. Pharmacokinetics were evaluated after the first administration of romidepsin. Complete responses were observed in four patients, and partial responses were observed in 20 patients for an overall response rate of 58% (95% CI: 23% to 48%). The median duration of response was 13.7 months.

**Conclusion** The histone deacetylase inhibitor romidepsin has single-agent clinical activity with significant and durable responses in patients with CTCL.
Mogamulizumab

- 2018 approved by FDA for MF and Sézary syndrome
- Monoclonal antibody to CC chemokine receptor 4 (CCR4), expressed on MF and SS cells
- Approval based on results of the MAVORIC trial, the first RCT that has used progression-free survival as primary outcome
Mogamulizumab

MAVORIC III compared mogamulizumab to vorinostat

Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial

Kim YH et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol 2018 Sep;19(9):1192-1204
UVA Interdisciplinary Cutaneous Lymphoma Clinic

TO REFER YOUR PATIENT:

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- Demographics & Insurance info
- Office Notes
- Pathology Reports

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