Single-agent dabrafenib for BRAF\(^{V600E}\)-mutated histiocytosis

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Introduction

- ECD and LCH are clonal disorders of the monocyte/macrophage and dendritic cell lineages
- Infiltration of multiple organ systems is common with a wide range of clinical phenotypes
- Both harbor BRAF V600E mutations in ~50% of cases

Vemurafenib / Dabrafenib

- Several retrospective and one prospective clinical trial demonstrated robust and durable response to vemurafenib
- Dabrafenib is another oral BRAF V600E inhibitor
- There is modest evidence of a lower incidence of adverse reactions in melanoma with dabrafenib
- Only single cases of dabrafenib for ECD
- No studies have explored the use of dabrafenib in vemurafenib intolerance

Objective

- Retrospective review of 10 patients with ECD or ECD/LCH treated with single agent dabrafenib as
  1) Initial histiocytosis therapy
  2) Following failure of conventional therapy
  3) Following discontinuation of vemurafenib therapy for toxicity or intolerance
Methods

• Patients were treated at MSKCC, Shaare Zedek Medical Center, and University of Florida.

• All patients met previously published criteria for the diagnosis of ECD and underwent genomic analysis for BRAF V600E mutational status.

• Doses ranged from 50mg BID to 150mg BID.

• Best overall response by FDG PET/CT was used as a primary response assessment and MRI brain when appropriate.

# Results: Partial response with dabrafenib as initial ECD/LCH therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/ Sex</th>
<th>Clinical symptoms</th>
<th>Organs involved (LCH in bold)</th>
<th>Prior therapies</th>
<th>Toxicities (reason for dose reduction in bold)</th>
<th>Final dose</th>
<th>Response</th>
<th>Duration of therapy (ongoing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66F</td>
<td>Ear pain, hearing loss, bone pain</td>
<td>Skullbase, bones</td>
<td>Skullbase radiation</td>
<td>Panniculitis (Grade 1)</td>
<td>50mg BID</td>
<td>PMR</td>
<td>11 months</td>
</tr>
<tr>
<td>2</td>
<td>31M</td>
<td>Dizziness, hearing loss, diabetes insipidus</td>
<td>Skullbase, cerebellum bones, retroperitoneum</td>
<td>Cytarabine</td>
<td>None</td>
<td>150mg BID</td>
<td>PMR</td>
<td>13 months</td>
</tr>
<tr>
<td>3</td>
<td>70M</td>
<td>Skin and oral lesions, dyspnea</td>
<td>Skin, oral mucosa, lungs, bones</td>
<td>Prednisone</td>
<td>Fever (Grade 3), Periorbital swelling (Grade 1)</td>
<td>50mg BID</td>
<td>PMR</td>
<td>5 months</td>
</tr>
<tr>
<td>4</td>
<td>59M</td>
<td>Jaw pain, skin lesions</td>
<td>Skin, bones, dura</td>
<td>None</td>
<td>None</td>
<td>50mg BID</td>
<td>PMR</td>
<td>3 months</td>
</tr>
<tr>
<td>Patient</td>
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<tr>
<td>4</td>
<td>49M</td>
<td>Bone pain</td>
<td>Retroperitoneum, bones, right atrium, peri-aortic tissues</td>
<td>Vinblastine/ prednisone, Vemurafenib, IFN-α</td>
<td>keratoacanthoma (Grade 1)</td>
<td>75mg BID</td>
<td>Maintained</td>
<td>PMR from vemurafenib and interferon</td>
</tr>
<tr>
<td>6</td>
<td>58F</td>
<td>Bone pain, skin lesions, dysarthria, ataxia</td>
<td>Skin, bones, brain, peri-aortic tissues</td>
<td>Vemurafenib</td>
<td>Fever (Grade 1), arthralgia (Grade 1)</td>
<td>100mg BID</td>
<td>Maintained</td>
<td>PMR from vemurafenib</td>
</tr>
<tr>
<td>7</td>
<td>75F</td>
<td>Bone pain, skin lesions, exophthalmos ataxia</td>
<td>Bones, orbits, dura, retroperitoneum skin (xanthelesma), right atrium</td>
<td>Vemurafenib</td>
<td>Fatigue (Grade 2), arthralgia (Grade 2)</td>
<td>50mg BID</td>
<td>Maintained</td>
<td>PMR from vemurafenib</td>
</tr>
<tr>
<td>9</td>
<td>77M</td>
<td>Proptosis, bone pain</td>
<td>Bones, orbit, craniofacial bones</td>
<td>Anakinra, Vemurafenib</td>
<td>Fatigue (Grade 2)</td>
<td>50mg BID</td>
<td>Maintained</td>
<td>PMR from vemurafenib</td>
</tr>
</tbody>
</table>
## Results: Recapturing a response with dabrafenib after stopping vemurafenib

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Clinical symptoms</th>
<th>Organs involved (LCH in bold)</th>
<th>Prior therapies</th>
<th>Toxicities (reason for dose reduction in bold)</th>
<th>Final dose</th>
<th>Response (FDG-PET)</th>
<th>Duration of therapy (ongoing in bold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>55M</td>
<td>Ataxia, spasticity</td>
<td>Brain, bones, retroperitoneum, peri-aortic tissues, brain, spinal cord</td>
<td>Methotrexate, IFN-α, Vemurafenib</td>
<td>Fever (Grade 2), keratosis pilaris (Grade 2), hypophosphatemia (Grade 2)</td>
<td>100mg BID</td>
<td>PMR of relapsed disease after cessation of vemurafenib</td>
<td>43 months</td>
</tr>
<tr>
<td>8</td>
<td>35M</td>
<td>Proptosis, ataxia, bone pain</td>
<td>Brainstem, skullbase, heart, orbits, retroperitoneum, peri-aortic tissue, bones</td>
<td>Vemurafenib</td>
<td>None</td>
<td>150mg BID</td>
<td>CMR of relapsed disease after cessation of vemurafenib</td>
<td>16 months</td>
</tr>
</tbody>
</table>
Pre- and post-vemurafenib

Pre- and post-dabrafenib

Relapsed disease

Cessation of vemurafenib
Conclusions

• Treatment with dabrafenib was effective for BRAF V600E-mutant histiocytosis patients
  • Including CNS
  • Responses seen as initial therapy, maintaining a response to vemurafenib, or by recapturing a response in relapsed disease
  • Dabrafenib was tolerated, including patients who could not tolerate vemurafenib
  • Doses as low as 50mg BID were therapeutic
Moving forward

• Optimal dosing, duration of treatment with BRAF inhibitors unknown
• LOVE study demonstrated frequent relapse after cessation of vemurafenib
• Combination of BRAF / MEK inhibitors?
Acknowledgements

- Eli L. Diamond
- Gary Ulaner
- Raajit Rampal
- Davidy Hyman
- Omar Abdel-Wahab
- Benjamin Durham
- Ahmet Dogan
- Neval Ozkaya
- Julio Hajdenberg
- Chezi Ganzel
- Lisa DeAngelis