Disclosures

- Scientific Committee, NovImmune NI-0501 (IFN-γ antibody) Clinical Trials.
- Consultant, Roche.
- There are no drugs approved for use in LCH.

Histiocytoses

- Histiocyte = “Tissue Cell”
  - “Classification” is dynamic with changing understanding of biology.
  - Classification based on presumed cell of origin.
- Histiocytosis = Abnormal proliferation or function of a “histiocyte”

Classification of Histiocytoses

- Disorders of Varied Biological Behavior
- Dendritic Cell Proliferation
  - Langerhans Cell Histiocytosis
  - Xanthogranulomas
- Macrophage Proliferation
  - Rosai-Dorfman Disease
    - Sinus histiocytosis with massive lymphadenopathy
  - Hemophagocytic Lymphohistiocytosis
- “Histiocytic” Malignancies
  - Malignant Histiocytosis
  - Histiocytic Sarcoma
  - AML (M7)

Neoplasms Derived from Histiocytes

<table>
<thead>
<tr>
<th>2001 WHO</th>
<th>2008 WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histiocytic sarcoma</td>
<td>Histiocytic sarcoma</td>
</tr>
<tr>
<td>LCH</td>
<td>Tumors derived from LC (LCH and LC sarcoma)</td>
</tr>
<tr>
<td>LC sarcoma</td>
<td></td>
</tr>
<tr>
<td>IDC sarcoma/tumor</td>
<td>IDC sarcoma</td>
</tr>
<tr>
<td>Follicular DC sarcoma/tumor</td>
<td>Follicular DC sarcoma</td>
</tr>
<tr>
<td>DC sarcoma, NOS</td>
<td>NOS + Indeterminate DC</td>
</tr>
<tr>
<td>Fibroblastic reticular</td>
<td></td>
</tr>
<tr>
<td>Disseminated JXG</td>
<td></td>
</tr>
</tbody>
</table>


M Lim, J Hematopath 2009
“...LCH treatment “strategy” is based more on a roulette wheel than on scientifically based logic. Certainly part of the confusion and lack of consensus is derived from persisting ambivalence as to whether LCH is primarily a neoplastic disorder, an immunodysregulatory disorder, or a disorder with characteristics of both.”
What is LCH?

Hand-Christian-Schuller
Eosinophilic granuloma
Letterer-Siwe
Hashimoto-Pritzker
Pulmonary LCH

Histiocytosis X

Lichtenstein 1953
Histiocytosis X

Langerhans Cell Histiocytosis

What is LCH?

Photo courtesy of Dr. John Hicks

LCH – Histiocyte Society; Gadner, Blood 2008

Survival: High vs Low Risk

High Risk

Low Risk

Frequent “Reactivations”

Minkov et al., J. Pediatr., 2008
LCH: 2010-2015

LCH CD207+ Transcriptome Suggests Immature Myeloid Phenotype

Cell-Specific Gene Expression Experiments

Myeloid Dendritic Cell Precursors in LCH

Shifting Focus: The Myeloid Dendritic Cell in LCH

BRAFV600E: A New Piece of the LCH Puzzle

- 57% of LCH lesions with BRAFV600E
- pMEK and pERK in all cases
- No significant clinical correlation with genotype
**BRAFV600E in Texas:**
Clinical Correlations

- 63% of patients with BRAFV600E
- No significant correlation:
  - high risk vs low risk
  - age (<2, 2-8, >8 years)
  - gender
  - single vs multifocal
  - overall survival

Berres et al., JEM 2014

---

**BRAFV600E: Clinical Correlations**

Kaplan-Meier failure estimates for recurrence

Hazard Ratio: V600E Increased Risk of Recurrence 2.05 (95% CI: 0.99-4.25)

Berres et al., JEM 2014

---

**Circulating Cells with BRAF-V600E in High Risk LCH**

Berres et al., JEM 2014

---

**BRAF Bar-Code:**

BRAFV600E in CD11c and CD14 cells

Berres et al., JEM 2014

---

**BRAF Bar-Code:**

BRAF-V600E in CD34+ cells

**50% of “normal” bone marrows had BRAF-V600E+ CD34/precursors**

Berres et al., JEM 2014
Expressing V600E in langerin+ DCs

BRAF in langerin+ DCs

BRAF in CD11c+ (pre)DCs

BRAF in CD11c+ (pre)DCs (Berres et al., JEM 2014)

Misguided Myeloid DC Model of LCH

Very Low Mutation Frequency in LCH Patients

Somatic mutation rate (Per MB x 10^-N)

Chakraborty, Blood 2014
Recurrent \textit{MAP2K1} Mutations in LCH

Genomic Landscape of LCH (2017)

More \textit{BRAF} Mutations in LCH

Genomic Landscape of Histiocytoses

Standard of Care: How Are We Doing?

Toward Rationale Cure(s)
Front-Line Randomized Trial

LCH-IV (Histiocyte Society)

*Open Now…*

**Phase III: Pred/Vbl (6MP) 1 vs 2 years**

---

**Can We Improve Chemotherapy?**

Goals: Eliminate myeloid neoplastic clone vs control “recurrence”?

<table>
<thead>
<tr>
<th>Strategy</th>
<th>PFS</th>
<th>Survival</th>
<th>Toxicity</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-CdA</td>
<td>9% (9 month)</td>
<td>RO+: 96%</td>
<td>RO: 48%</td>
<td>Minimal 2009</td>
</tr>
<tr>
<td>2-CdA/Ara-C</td>
<td>79% (3 year)</td>
<td>RO+: 75%, (10/14)</td>
<td>Unfractional Bernard 2005</td>
<td></td>
</tr>
<tr>
<td>Ara-C (100-125 mg/m²)</td>
<td>60% (1 year)</td>
<td>RO+: 100%, (8/8)</td>
<td>RO: 100%</td>
<td>Minimal Simko 2015</td>
</tr>
<tr>
<td>Clofarabine (25mg/m²/day x 5 day)</td>
<td>67% (1 year)</td>
<td>RO+: 75%, (2/3)</td>
<td>RO: 100%</td>
<td>Minimal Simko 2014b</td>
</tr>
</tbody>
</table>

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**Example of Response to HU**

Prior Treatment:
- Ara-C
- Clofarabine
- 6MP/PMTX

Left 9th rib
Right 7th rib
Right iliac crest
Splenomegaly
Needle biopsy = LCH

---

**Hydroxyurea for LCH?**

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**Salvage – BRAFV600E Inhibition**

Vemurafenib in Adult ECD (Haroche JCO 2015)

**Objective:** Retrospective review of outcomes of patients with BRAF-V600E+ ECD

**Primary Response:** PET at 6 months
- -6/6 partial metabolic responders
- Response durable with median 10.5 month follow-up

**Toxicities:**
- -6/6 with severe skin effects (Grade 2-3)
- -1/6 with squamous cell carcinoma
Salvage – BRAFV600E Inhibition

**MSK Basket Trial**

Hyman et al, NEJM 2015

Salvage – BRAFV600E Inhibition

**Toxicity – “C/W other trials”**

Vemurafenib in Multiple Nonmelanoma Cancers with V600E Mutations

Vemurafenib (BRAF- V600E Inhibitor)

**NAD** at 10 months
No toxicity reported

Hyman et al, NEJM 2015

Hyman et al, NEJM 2015

Vemurafenib (BRAF- V600E Inhibitor)

**Vem in Pediatrics**

Heretier JAMA Oncology 2015

Heretier JAMA Oncology 2015

Heretier JAMA Oncology 2015

**LCHIV Trial**

LR Salvage: Pred/VCR/Ara-C with 6MP/MTX + indomethacin vs Pred/VCR/Ara-C with 6MP/MTX

HR Salvage: Response after 2 courses Ara-C/2-CDA

**Coming Soon...**

NACHO-Clo: (Open)
Clofarabine salvage for LR and HR

NCI COG MATCH:
Vemurafenib (BRAF- V600E Inhibitor)
Selumetinib (MEK Inhibitor)

BASKET:
Multiple novel agents
2nd Generation BRAF Inhibitors
ERK Inhibitors
PD-1/PD-L1

**It’s just LCH...**

- Median time to biopsy: >3 mo
- % patients with presumed skin-limited with multisystem: 50%

**Skin**
Skin-limited vs Multisystem

A. Age at diagnosis (months)

B. Number of patients

C. CNS Lesions:

“Clean margins” impair remodeling

CNS

Skull Lesions:

Collin and Allen, HO Clinic, MA 2015

Simko J Peds 2014
Peripheral Blood Progenitors in LCH-ND?

Response to BRAFi in LCH-ND

Model: LCH-ND is LCH

Implications:
1. Treat LCH to eradicate clone.
2. Look for LCH-ND in some systematic fashion (MRI/blood).
3. Treat early

Lung LCH: A Case of Surgical Cure

Cytarabine x 12 months
**Cousins of LCH**

**Juvenile Xanthogranuloma**

**Erdheim-Chester Disease**

**Rosai-Dorfman Disease**

**Evolving Models of Histiocytoses**
Coffee Break Question

- **LCH: (Inflammatory) Myeloid Neoplasia?**

  Table 2. WHO classification of myeloid neoplasms and acute leukemia

<table>
<thead>
<tr>
<th>Myeloproliferative neoplasms (MPN)</th>
<th>Chronic myelogenous leukemia, BCR-ABL 1-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic neutrophilic leukemia</td>
<td></td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td></td>
</tr>
<tr>
<td>Primary myelofibrosis</td>
<td></td>
</tr>
<tr>
<td>Essential thrombocythemia</td>
<td></td>
</tr>
<tr>
<td>Chronic eosinophilic leukemia, not otherwise specified</td>
<td></td>
</tr>
<tr>
<td>Mastocytosis</td>
<td></td>
</tr>
<tr>
<td>Myeloproliferative neoplasms, unclassifiable</td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)</td>
<td></td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia</td>
<td></td>
</tr>
<tr>
<td>Acute myelomonocytic leukemia, BCR-ABL 1-negative</td>
<td></td>
</tr>
<tr>
<td>Juvenile myelomonocytic leukemia</td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic/myeloproliferative neoplasm, unclassifiable</td>
<td></td>
</tr>
</tbody>
</table>

  Vardiman et al., Blood 2009

Bonus Case

12 month male with history of skin rash and poor weight gain, now with fever and abdominal distension

Images courtesy of Dr. Choladda Curry

Bonus Case

Poor response to vinblastine/prednisone, recurrent fever, abdominal distention, sIL2Ra>10k, ferritin>10k

Bonus Case: Bone Marrow

Bone marrow

CD163

CD1a

Fascin

Factor XIIIa

Bonus Case: Molecular Path

- **BRAF-V600E+**
  - 3.1% of blood pbmc
  - 2.5% of bone marrow aspirate pbmc

<table>
<thead>
<tr>
<th>CD3</th>
<th>CD19</th>
<th>CD16</th>
<th>CD68</th>
<th>CD11c</th>
<th>CD11a+CD14</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

Clinical Interpretation: Refractory BRAF-V600E+ mixed histiocytic myeloid neoplastic disorder (LCH + JXG) with reactive macrophage activation
Coffee Break Question #2:

- CD1a, CD207, fascin, Factor XIIIa, CD163 for all “LCH”?  

- BRAF qPCR (and/or sequencing) for all “LCH”? 

Conclusions

Back to Histiocytosis X,Y,Z...

Pathways to LCH (JXG, ECD, RDD)

[Diagram showing pathways to LCH with specific markers and processes]