Clinical Trials 101

Eric Jacobsen, MD
Assistant Professor of Medicine
Harvard Medical School
Types of treatments

- **Chemotherapy**: typically kills cells by damaging DNA, preventing DNA synthesis, blocking cell division, or disrupting metabolism
- **Immunotherapy**: directly or indirectly uses immune system to kill cells (antibodies, vaccines, CAR-T cells)
- **Targeted therapies**: blocks a specific cell signaling pathway (vemurafenib, cobimetinib)
- **Gene therapy**: replace a damaged gene (CRISPR)
Benefits of clinical trials

- Access to new medications
- Some studies show better outcomes in patients treated on clinical trials
- Improve scientific knowledge
- Altruism

Only about 5% of adult cancer patients participate in clinical trials
Patient concerns about clinical trials

• “I don’t want to be a guinea pig”
• I don’t want a placebo
• Travel
• Cost
• More visits, more scans
• Less scheduling flexibility
• Loss of autonomy
• Unknowns: effectiveness, side effects
Pre-clinical testing – reducing uncertainty
Xenografts
Phases of Clinical Trials

• **Phase I**: primary purpose is to assess safety, find optimal dose
• **Phase II**: larger trial to assess efficacy, expanded assessment of safety
• **Phase III**: typically compares new treatment to established standard (often randomized)
• **Phase IV**: post-marketing surveillance
• Registries
Process for initiating a trial

• Submit a letter of intent (LOI) or grant application
• Reviewed by funding source
• Concept review
• Write full protocol and consent form
• Scientific Review Committee, Institutional Review Board
• Activation
• Enrollment and data collection
• Publication
Metrics of success

• Historically in cancer studies we have focused on response rates, length of remission

• Increasing emphasis on symptom improvement, quality of life, resource utilization
FDA Approval Process

• Historical average: 12 years, $350-800 million
• 3.5 years of preclinical testing (999/1000 end here)
• Phase I testing: 1 year
• Phase II: 2 years
• Phase III: 3 years
• Application (100,000 pages): 2.5 years

Source: Drugs.com
## Other ways to gain access to medications

### NCCN Guidelines Version 5.2018

#### Diffuse Large B-Cell Lymphoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>First-Line Therapy**</th>
<th>Interim Restaging After 2-4 Cycles†</th>
<th>Clinical Trial of RCHOP, (category 1)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonbulky (≤7.5 cm)</td>
<td>RCHOP(\textsuperscript{o} \times 3) cycles followed by RTP(\textsuperscript{p}) (category 1)</td>
<td>See BCEL-6</td>
<td>RCHOP(\textsuperscript{o} \times 6) cycles ± RTP(\textsuperscript{p})</td>
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<td>RCHOP(\textsuperscript{o} \times 6) cycles ± RTP(\textsuperscript{p})</td>
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<td>RCHOP(\textsuperscript{o} \times 4-6) cycles ± RTP(\textsuperscript{p})</td>
<td></td>
<td>RCHOP(\textsuperscript{o} \times 6) cycles ± RTP(\textsuperscript{p})</td>
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</tbody>
</table>

**Note:** All recommendations are category 2A unless otherwise indicated.

- **RT** planned: See Pre RT Evaluation (BCEL-4)
- RT not planned: See End-of-Treatment Restaging (BCEL-5)

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*See BCEL-C for regimens used in patients with poor left ventricular function and patients >80 years of age with comorbidities.

†See Principles of Radiation Therapy (NHODG-D)

‡If not used, interim staging after 3-4 cycles of RCHOP is appropriate to confirm response in clinical trials. RCHOP is preferable due to reduced toxicity, but other comparable anthracycline-based regimens are also acceptable (see BCEL-C).

§In selected cases, RT to initially bulky sites of disease may be beneficial (category 2B).

¶PET/CT scan at interim restaging can lead to increased false positives and should be carefully considered in selected cases. If PET/CT scan performed and positive, rebiopsy before changing course of treatment.
Challenges of clinical trials in rare diseases

- Lack of preclinical models
- Difficulty generating interest from drug manufacturers
- Limited funding
- Limited number of centers with expertise
- Small patient population (more ideas than patients)
- FDA approvals can be challenging
Examples of ECD Studies

Phase II:

Long-term Outcome After Vemurafenib / BRAF Inhibitors
Interruption in Erdheim-chester Disease

Dabrafenib and Trametinib in People With BRAF V600E Mutation Positive Lesions in Erdheim Chester Disease

Registry

Recruiting Registry for Patients With Erdheim-Chester Disease

Quality of life

A Study of Memory, Thinking, and Brain Imaging in Adults With Histiocytosis
Conclusions

• Clinical trials are critical to improving treatments
• Participation in clinical trials can be intimidating but there are resources to help you
• We can learn from studies even when they don’t involve new treatments
• There are barriers to conducting clinical trials in rare diseases but these can be overcome

• Learn more:
  – Clinicaltrials.gov
  – ECD Global Alliance