The Early Chimeric Antigen Receptor (CAR) T-cell Experience From An Academic Perspective

**CARs: LEARNING TO DRIVE**

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CASE:

- Diagnosed with follicular lymphoma in 2006 at age 61
- Active observation until 2010
- Treatment history
  - Rituximab (R) monotherapy in 1/2010 (PD after 6 months)
  - R-bendamustine in 3/2012 (CR)
  - R-CHOP in 3/2013 (PR)
  - Ibrutinib (clinical trial) 10/2013 (PR)
  - R-lenalidomide 3/2014 (PD)
  - Progression 3/2015 – hospice evaluation
  - Enrolled on UPCC13413 in 2015 with anti-CD19 CAR T-cells
  - Remains in CR
Targeting CD19+ B-cells with CAR-Modified T-cells

- Gene transfer (lentiviral vector) to stably express CAR on T cells confers novel antigen specificity
- CAR modified T cells can now recognize and kill CD19+ cells

CAR, chimeric antigen receptor; TCR, T-cell receptor.
Slide: Courtesy of Dr. David Porter
Timeline of Cellular Therapy at Penn

Preclinical work in laboratory of Dr. Carl June and early cellular therapy trials:

• Immunology of bone marrow transplant
• Adoptive T-cell therapy for HIV
• Adoptive T-cell therapy in oncology patients
  CD3/CD28 co-stimulated T-cells
Timeline of Cellular Therapy at Penn

CAR T-cell trials:

• 2006  First draft of clinical trial written
• 2009  IRB approval of protocol
• 2010  First 3 CLL patients treated
• 2011  No patients treated (lack of funding)
• 2011  First publication
First Publication

The New England Journal of Medicine

Brief Report

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

Timeline of Cellular Therapy at Penn

- 2012  Penn-Novartis Alliance formed
- 2012  Institutional trials for B-ALL at CHOP/HUP and CLL at HUP
- 2013  Institutional trial for B-cell lymphomas
Timeline of Non-Institutional Cellular Studies

- **2014**  
  Receives FDA breakthrough therapy designation

- **2015**  
  Multisite Novartis/CTL019 trials
  » Eliana study for B-ALL
  » Juliet study for DLBCL (27 centers, 10 countries)
  Other CART19 trials (Kite, Juno)

- **2017**  
  FDA approval
tisagenlecleucel (Novartis) for r/r B-ALL (age: up to 25)
axicabtagene ciloleucel (Kite) for r/r DLBCL
LEARNING FROM INSTITUTIONAL TRIALS

1. Toxicities/Management

2. Collaboration: Academic and Industry

3. Other Challenges
TOXICITIES

• Recognition of unique side effects of cellular therapy
  – Cytokine release syndrome
  – Neurotoxicity
  – Hypogammaglobulinemia

• Development of management strategies
## DEVELOPMENT OF PENN CRS GRADING SYSTEM

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Supportive care only</td>
</tr>
<tr>
<td>2</td>
<td>IV therapies +/- hospitalization</td>
</tr>
<tr>
<td>3</td>
<td>Hypotension requiring IV fluids or low dose vasoactive or hypoxemia requiring supplemental oxygen</td>
</tr>
<tr>
<td>4</td>
<td>Hypotension requiring high-dose vasoactives or hypoxemia requiring mechanical ventilation</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>
• **CRS:**
  - **ALL (100%)**
  - **Lymphoma (57%)**
    • Less severe
    • Not associated with response in DLBCL

• **Neurotoxicity**

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**Table 2. Adverse Events of Special Interest That May Have Been Related to CTL019 Therapy.**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>Total Events</th>
<th>Grade 3 or Higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome</td>
<td>0</td>
<td>11</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>16 (57%)</td>
<td>5 (18%)</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>11 (39%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3 (27%)</td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (18%)</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (18%)</td>
<td></td>
</tr>
<tr>
<td>Cognitive disturbance</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Involuntary movements</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Memory impairment</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

* A list of all adverse events is provided in the Supplementary Appendix.

HYPOGAMMAGLOBULINEMIA

- Differences depending on disease
  - In ALL
    - B-cell aplasia in all responding patients
    - IgG replacement given
  - In Lymphoma
    - Most patients do not need routine IgG replacement
    - Ig recovery noticed despite CTL019 persistence

MANAGEMENT OF TOXICITIES

  – IL-6 receptor blocking antibody previously used in rheumatology

• Supportive care/steroids for neurotoxicity

• Immunoglobulin replacements for B-cell aplasia
COLLABORATION: ACADEMICS-INDUSTRY

- High quality control
- Documentation
- Monitoring
- Safety focus
OTHER CHALLENGES DURING DEVELOPMENT

- Patient volume after first reports of long term remissions
- Patients outside of US interested in trials
- Rapid growth of non-CTL019 trials (BCMA-CAR, solid oncology targets) and limited T-cell apheresis/production pace
- Patient selection
- Educating personnel within the Penn system
  - Research team
  - Non-oncology teams (ER, intensive care, neurology, house-staff)
FUTURE CHALLENGES

• Designing new clinical trials to improve efficacy

• Better understanding the toxicity profile of CAR T-cell therapies and developing effective management strategy

• Commercial product
  – Building structure and staffing within our division
  – Insurance reimbursement
  – Patient volume and selection
CARs: LEARNING TO DRIVE

• Case reports
  – Many unknowns, unexpected toxicities

• Smaller institutional trials for B-ALL, CLL, and lymphomas
  – Systemic monitoring of toxicities
  – Developed effective strategies to treat adverse events

• Larger multi-institutional trials
  – Efficacy/adverse events were similar to Penn trials

• Commercial CAR products