Demystifying Medicine 2019
Cellular Immunotherapy of Cancer

CAR-T Cell Therapy in Pediatric Leukemia

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Disclosures

- No disclosures to report

- I will be discussing utilization of novel (non-FDA approved) CAR-T cell approaches in pediatric leukemia
Educational Objectives

• Provide a general overview of CAR-T Cell therapy in pediatric acute lymphoblastic leukemia (ALL)

• Discuss future directions and challenges in immunotherapy for ALL
Childhood Acute Lymphoblastic Leukemia (ALL)

- Most common cancer diagnosed in children.
  - 41 cases/million in children aged < 14
  - 17 cases/million in teens between ages 15-19
  - 25% of all new cancer diagnosis

- 85-90% of patients will be cured.

- “Poster-child” for efficacy and importance of cooperative groups and clinical trial participation.

Data courtesy of GH Reaman, H Sather, Children’s Oncology Group
Current Treatment Plan

- Combinatorial chemotherapy treatment strategy with non-competing mechanisms of action.
- Series of intensified/de-intensified treatment cycles.
- Prolonged maintenance phase (2-3 years)
- Risk-adapted approach
Outcomes for Relapsed/Refractory Disease

Table 4 Comparison of unadjusted CR rates of patients with medullary relapsed/refractory ALL between two sequential TACLC studies

<table>
<thead>
<tr>
<th>Number of salvage attempt</th>
<th>CR rate (SE) [95% confidence interval]</th>
<th>2005–2013 (Sun et al.)</th>
<th>Difference (Sun–Ko) (SE) (testing proportion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second salvage attempt</td>
<td>44.44 % (4.78) [34.88, 54.32]</td>
<td>50.91 % (3.89) [43.02, 58.76]</td>
<td>0.0647 (0.0616) (-0.0561, 0.1855) p = 0.2955</td>
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<tr>
<td>Third salvage attempt</td>
<td>26.78 % (5.92) [15.83, 40.30]</td>
<td>36.99 % (5.65) [25.97, 49.09]</td>
<td>0.1021 (0.0818) (-0.0583, 0.2624) p = 0.2200</td>
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<tr>
<td>Fourth through eighth</td>
<td>12.31 % (4.07) [5.47, 22.82]</td>
<td>30.77 % (6.40) [18.72, 45.10]</td>
<td>0.1846 (0.0759) (0.0358, 0.3333) p = 0.0140</td>
</tr>
</tbody>
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CR complete remission, SE standard error

Sun/Whitlock, Leukemia, 2018
Challenges

- Curative options for relapsed/refractory disease remains a therapeutic challenge

- Outcomes for the adolescent young adult (AYA) population remain particularly poor

- Toxicity from cumulative therapy not insignificant

- Novel therapies are needed
Let's meet our special guest...
Treatment Overview

• Diagnosis: May 2016, standard risk → but with poor response at day 8

• Transitioned to high-risk treatment arm, but with relapse during maintenance (October 2017)

• Started re-induction chemotherapy and randomized to receiving blinatumomab (anti-CD19/CD3 targeted therapy)
  • Transient incomplete response

• Referred to CD19 CAR T cell therapy (April 2018)

• Achieved remission but relapsed July 2018
Blinatumomab

- 50-70% CR rate in adults
- 30-40% CR rate in children
TCRs and CARs

- **TCR**: T-cell receptor
  - Recognize processed antigens and are MHC dependent, and require co-stimulatory signals for T-cell activation

- **CAR-T cell**: chimeric antigen receptor T-cell
  - Recognize cell surface antigens independent of MHC, have co-stimulatory signals integrated
  - Retains the functionality of a T-cell with the antigen recognition properties of antibody

Making a CAR-T Cell

1. Apheresis
2. Stimulation and Transduction
3. Expansion
4. Lymphodepletion
5. Infusion

Image, Courtesy of NIH Medical Arts
CD19 CAR Clinical Updates (NCI-POB)

T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial

Daniel W. Lee, James N. Kochenderfer, Maryalice Stetler-Stevenson, Yongzhi K. Cui, Cindy Delbrook, Steven A. Feldman, Terry J. Fry, Rimas Orentas, Marianna Sabatino, Niral N. Shah, Seth M. Steinberg, Dave Stroncek, Nick Tschernia, Constance Yuan, Hua Zhang, Ling Zhang, Steven A. Rosenberg, Alan S. Wayne, Crystal L. Mackall

Lee et al. Lancet 2015
67% CR rate (ITT)
All responders with CRS
CD19 CAR Clinical Updates (Novartis)

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia


81% Complete remission rate (not ITT)
Cytokine Release Syndrome

General
- Fever
- Chills
- Feeling tired
- Feeling itchy
- Pain

Lungs
- Breathing fast
- Decreased levels of oxygen in the blood
- Difficulty breathing

Gastrointestinal
- Poor appetite
- Nausea
- Vomiting
- Diarrhea

Liver
- Elevated liver tests

Kidneys
- Decreased urine output
- Decreased electrolytes (sodium in the blood)

Blood system
- Decreased hemoglobin
- Decreased platelets
- Decreased ability to fight infection
- Increased risk of bleeding

Muscles
- Muscle aches
- Weakness

Neurologic
- Headache
- Depression
- Confusion
- Difficulty finding words
- Seeing and hearing things
double
- Dizziness

Heart
- Fast heartbeat
- Decreased blood pressure
- Decreased heart function
- Leaky blood vessels

Cytokines (pg/mL)

Images, Courtesy of NIH Medical Arts
Lee/Mackall Lancet 2015
CAR Therapies: FDA Approval

- Kymriah™ (tisagenlecleucel, Novartis): For children up to age 25 with ALL (August 2017)

- Tocilizumab: To treat CAR T-cell related CRS (August 2017)

- Yescarta™ (axicabtagene ciloleucel, KITE): For adults with Diffuse Large B Cell Lymphoma (October 2017)

- Complete remission rates: +/- 50-80%
Limitations to Durable Remissions
Oh Where... Oh Where... Has my CD19 gone?

- At least ONE identified mechanism:
  - Loss of the surface epitope, but retention of the target protein (in part)
  - Due to clustering of nonsense and missense mutations in exon 2 of CD19
  - Specific frameshift mutation eliminates full-length CD19 but allows expression of an isoform
    - Mostly cytosolic and hidden from T cells
  - Hallmark of relapsed leukemia post CAR was lack of the full-length isoform

*Sotillo/Thomas-Tikhonenko, Cancer Discovery 2015*
Lineage Switch (ALL $\rightarrow$ AML)

- *MLL*-rearranged B-ALL (11q23) rearrangement
  - “Infant” ALL $\rightarrow$ VERY poor prognosis

- Gardner et al.
  - 7 of 7 with *MLLr*-ALL attained MRD neg CR post –CD19 CAR
  - Relapses seen in 2 with myeloid phenotype

- Similar experience seen in *MLLr*-ALL treated with blinatumomab

- Jacoby et al.
  - CD19 CAR immune pressure induces lineage switch

Gardner/Turtle, Blood 2015
O’Brien, Pediatric Blood Cancer 2016
Jacoby/Fry Nat Commun 2016
Phase I Study of Anti-CD22 CAR

- Novel CAR construct targeting CD22
- Heavily pre-treated population
- CRS was less severe (Grades 1 and 2)
- Limited neurotoxicity
- Unique toxicities:
  - Capillary leak
  - Coagulopathy
  - Hemolytic uremic syndrome

Fry TJ, Nat. Medicine 2018
CD22 Antigen Expression at Relapse

- Decrease in Site Density
- Antigen loss
- Both
- No genomic mutation, modulation of gene expression or altered isoform expression was found in patients with relapse (limited samples)
Treatment Overview

- Treated on CD22 CAR T cells
- Achieved remission
- Proceeded to Bone marrow transplant
Bench to Bedside to Bench

Our Patients Inspire Change
Options for Simultaneous Targeting of CD19 and CD22 (Fry Lab)

- **Bivalent-Bispecific Receptor**
- **Co-administration**
- **Co-expression**
Phase 1 Dose Escalation Study of Anti-CD19/CD22 Chimeric Antigen Receptor (CAR) T Cells in Children and Young Adults with Recurrent or Refractory CD19/CD22-expressing B Cell Malignancies

- Hypothesis: Simultaneous targeting of CD19 and CD22 could diminish the risk of antigen loss escape
- Novel bivalent, bispecific CAR to be tested in the clinic
- Actively enrolling

Activity of Bispecific CAR:
*In vivo* activity against CD19+/22+ B-ALL

Qin et. al. Molecular Therapy Oncolytics
Future Directions

- Novel CAR constructs:
  - AML CAR
  - Bi-specific CAR

- Optimizing second infusions

- Improving CAR persistence

- Increasing tumor sensitivity by enhancing antigen expression

- Bringing CAR constructs earlier into the therapeutic plan

- Exploring response in lymphoma and CNS disease

- Decreasing toxicity

- Improving access to therapy
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