HIV-virus Inspires Effective Anti-Leukemia Therapy
Disclosures

- None
Educational Objectives

- Provide an overview of CAR therapy
- Review the current state of the art for CAR therapy in ALL
- Discuss limitations to CAR therapy
Severe immune system to destroy leukemic cells

An Immune System Trained to Kill Cancer

By DENISE GRADY  SEPT. 12, 2011

How HIV Became a Cancer Cure

The immunologist behind the revolutionary new treatment set to win approval from the FDA.
What is a CAR?

- **Chimeric Antigen Receptor**
  - Customized receptor
    - Extracellular antigen-binding domain
    - Intracellular signaling domain of T cells
  - Retains the functionality of a T-cells with the antigen recognition properties of antibody
Process of Making CAR T-Cells

1) T Cell Collection

2) T Cell Transfection
   - 1. Binding
   - 2. Fusion

3) T Cell Adoptive Transfer
   - 3. Integration
   - +/- Lymphodepleting conditioning
   - 4. Transcription and protein expression
   - 5. CAR cell membrane insertion

4) Patient Monitoring
   a) Disease response
      - CT scans
      - Bone marrow biopsies
      - Peripheral blood flow cytometry
   b) CAR-T Cell persistence
      - Immunohistochemistry of bone marrow biopsy
      - RT-PCR and flow cytometry of blood and bone marrow aspirate
Role for HIV?

• Retroviruses, in particular lentivirus, are particularly skilled at entering T-cells

• Used to introduce genetic material into a T-cell which is then incorporated into the host cell genome

• Modified virus used to introduce anti-leukemia targeted antigen recognition properties
Childhood ALL

• Most commonly diagnosed childhood cancer

• 2900 cases/year

• Relapsed refractory disease remains a therapeutic challenge

• Outcomes in the AYA population remain poor

Improved Survival by Study Era

Data courtesy of GH Reaman, H Sather, Children’s Oncology Group
CD19 CAR

• CD19 is a B-cell marker

• First used to target CLL (chronic lymphocytic leukemia)

• Associated with cytokine release syndrome

• First child treated in 2012

• Several centers had simultaneous clinical trials
Cytokine Release Syndrome

**Neurologic:**
- Headaches
- Changes in level of consciousness
- Delirium
- Aphasia
- Apraxia
- Ataxia
- Hallucinations
- Tremor
- Dizziness
- Myoclonus
- Facial palsy
- Seizures

**Constitutional:**
- FEVER
- Rigors
- Malaise
- Fatigue
- Anorexia
- Anorexia

**Cardiovascular:**
- Tachycardia
- Widened pulse pressure
- Hypotension
- Arrhythmias
- Decreased left ventricular ejection fraction
- Troponinin
- QT prolongation

**Pulmonary:**
- Tachypnea
- Hypoxia

**Renal:**
- Acute kidney injury
- Hypotension
- Hypokalemia
- Hypophosphatemia
- Tumor lysis syndrome

**Gastrointestinal:**
- Nausea
- Vomiting
- Diarrhea

**Musculoskeletal:**
- Myalgias
- Elevated creatine kinase
- Weakness

**Hepatic:**
- Transaminitis
- Hyperbilirubinemia

**Hematologic:**
- Anemia
- Thrombocytopenia
- Neutropenia
- Febrile neutropenia
- Lymphopenia
- B-cell aplasia
- Prolonged prothrombin time
- Prolonged activated partial thromboplastin time
- Elevated D-Dimer
- Hypofibrinogenemia
- Disseminated intravascular coagulation
- Hemophagocytic lymphohistiocytosis

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**GRADING ASSESSMENT**

<table>
<thead>
<tr>
<th>Grade 1 CRS</th>
<th>Grade 2 CRS</th>
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<tbody>
<tr>
<td>Fever, constitutional symptoms</td>
<td>Hypotension: responds to fluids or one low dose pressor</td>
</tr>
</tbody>
</table>

**TREATMENT**

- Assess for infection
  - If neutropenic, treat for F&N
  - Monitor fluid balance
  - Antipyretics, analgesics as needed

**Grade 2 CRS**

- Hypotension: responds to fluids or one low dose pressor
- Hypoxia: responds to <40% O2
- Grade 2 organ toxicity

<table>
<thead>
<tr>
<th>Extensive co-morbidities or older age?</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
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</tbody>
</table>

**Grade 3 CRS**

- Hypotension: requires multiple pressors or high dose pressors
- Hypoxia: requires ≥40% O2
- Grade 3 organ toxicity, Grade 4 transaminities

**Grade 4 CRS**

- Mechanical ventilation
- Grade 4 organ toxicity, excluding transaminities

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*Lee/Mackall Blood 2014*  
*Brudno/Kochenderfer Blood 2017*
CD19 CAR Clinical Updates

90% CR rate (not ITT)
All with CRS

67% CR rate (ITT)
All responders with CRS

Novartis sponsored global CD19 CAR registration trial (“ELIANA”)
82% (41 of 50) patients achieved CR
65% CR on ITT

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, Yangzhao Liu, Cindy Bellevol, Steven A Rosenberg, Terry J Fry, Rimma Orentas, Marianna Sabatino, Niral N Shah, Seth M Steinberg, David L Carter, Nick Tscharna, Congfang Cao, Le Wei, Zhang, Ling Zhang, Steven A Rosenberg, Alan S Wayne, Crystal L Mackall

Lee et al. Lancet 2015

JEJM 2014
FDA Approval!!

FDA News Release

FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

August 30, 2017

FDA News Release

FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma

October 18, 2017
Will CD19 CAR be “THE” Answer?

NO ONE FIGHTS ALONE.

CAR-T in April 2012
Anti-CD22 CAR Construct

- Second generation CAR
- Utilizes m971 anti-CD22 scFv
- 4-1BB/CD3-zeta signaling

Haso et al, Blood 2013
Phase I Study of Anti-CD22 CAR T-Cells: Dose-Dependent Response

*Progressive disease by peripheral blasts
#MRD Negative CR

Fry, Shah et al, Nat Medicine 2017
Relapse Remains a Problem

Fry, Shah et al, Nat Medicine 2017
Future Directions

- Simultaneous multi-antigen targeting
- Expanding to other disease subtypes and presentations
  - AML
  - Central nervous system disease
  - Lymphoma
- Solid Tumors and Brain Tumors
- Exploring Toxicity
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