An Overview of Chimeric Antigen Receptor T-cells: “CAR-T-ing Away Cancer”

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Conflict of Interest Disclosure

I have no actual or potential conflicts of interest to disclose regarding this presentation.
Objectives

1. Discuss the structure and mechanism of action of chimeric antigen receptor (CAR) T-cells.

2. Describe the pathophysiology and management of cytokine release syndrome (CRS) and CAR-T related encephalopathy syndrome (CRES)

3. Summarize key clinical trials assessing the use of CAR-T cell therapy in acute lymphoblastic leukemia (ALL) and B-cell lymphomas
Audience Response Question #1

What does CAR-T cell stand for?

1. Carrier T cell
2. Chemotherapy/antibody receptor T cell
3. Chimeric antigen receptor T cell
4. Chimeric antibody receptor T cell
Audience Response Question #1

What does CAR-T cell stand for?

1. Carrier T cell
2. Chemotherapy/antibody receptor T cell
3. **Chimeric antigen receptor T cell**
4. Chimeric antibody receptor T cell
CAR-T cells

**Chimeric**: combination of different genes

**Antigen**: substance which initiates an immune response

**Receptor**: molecule which binds a particular substance resulting in a specific effect

**T cell**: type of white blood cell or lymphocyte; component of the adaptive immune system
What is a CAR-T cell?
Hematopoiesis

- Multipotent hematopoietic stem cell (hemocytoblast)
  - Common myeloid progenitor
    - Erythrocyte
    - Mast cell
    - Myeloblast
    - Megakaryocyte
      - Thrombocytes
  - Common lymphoid progenitor
    - Natural killer cell (large granular lymphocyte)
    - Small lymphocyte
      - T lymphocyte
    - B lymphocyte
    - Plasma cell
    - Monocyte
      - Macrophage

Antigen Recognition and Processing

**Bacteria**

- Phagocytosis of bacterial cells by antigen presenting cells (APC).
- Antigen processing into peptide fragments for presentation via the major histocompatibility complex (MHC).

**Viruses**

- Virus invades healthy cell and begins replicating.
- Degradation of viral proteins by the proteasome for presentation via the MHC.

Endogenous T-cell Activation

- APC
- MHC: - Class I: cytotoxic T-cell - Class II: helper T-cell
- Co-Receptor (e.g. CD4, CD8)
- Variable Region
- Constant Region
- T-cell Receptor

CAR-T cell Activation

APC or Cell

Tumor Cell Antigen
- Class I: cytotoxic T-cell
- Class II: helper T-cell

Co-Receptor
(e.g. CD4, CD8)

scFv

Linker

Variable Region

Constant Region

Hinge

Transmembrane Domain

Signaling Domain

CAR-T cell Receptor

scFv = single chain fragment variable

Engineering of CAR-T cells

- Cytotoxicity
- Proliferation & Persistence
- Cytokine Production

TRUCK = T cell redirected for universal cytokine-mediated killing

CAR-T cell Manufacturing and Administration
CAR-T cell Manufacturing Process

- **T-cell Collection**
  - Apheresis
  - T-cell selection

- **CAR Transduction**
  - Lentiviral/retroviral DNA vectors
  - Gene transfer
  - CAR expression

- **CAR-T Expansion**
  - APCs, activation reagents, antibody-coated microbeads
  - Cryopreservation

- **CAR-T Infusion**
  - Administration of lymphodepleting chemotherapy
  - Infusion of CAR-T product

**Autologous versus Allogeneic?**
Autologous versus Allogeneic CAR-T cells

<table>
<thead>
<tr>
<th></th>
<th>Autologous</th>
<th>Allogeneic</th>
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<tbody>
<tr>
<td>Ability to collect</td>
<td>Persistence of CAR-T cells</td>
<td></td>
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<tr>
<td>Quality &amp; functionality</td>
<td>Risk of graft-versus-host disease</td>
<td></td>
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<tr>
<td>Production time</td>
<td></td>
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<tr>
<td>Delays in treatment</td>
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Lymphodepleting Chemotherapy

Cyclophosphamide 500 mg/m² IV once daily

Day -5
Day -4
Day -3

Rest

Day -2
Day -1

Day -5
Day -4
Day -3

Fludarabine 30 mg/m² IV once daily

Day 0

CAR-T cell Infusion

YESCARTA (axicabtagene ciloleucel suspension) [package insert].
Commercially Available CAR-T Products
For which disease states are CAR-T cells currently FDA approved?

1. Acute lymphoblastic leukemia (relapsed or refractory)
2. Large B-cell lymphoma (relapsed or refractory)
3. Acute myeloid leukemia (relapsed or refractory)
4. Both A and B
5. All of the above
Audience Response Question #2

For which disease states are CAR-T cells currently FDA approved?

1. Acute lymphoblastic leukemia (relapsed or refractory)
2. Large B-cell lymphoma (relapsed or refractory)
3. Acute myeloid leukemia (relapsed or refractory)
4. Both A and B
5. All of the above
Currently Available CAR-T cell Products

**YESCARTA (axicabtagene ciloleucel)**

- **FDA Approval**: treatment of adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy
- Autologous CAR-T cell product targeting CD19

**KYMRIAH (tisagenlecleucel)**

- **FDA Approval**: treatment of patients up to 25 years of age with relapsed or refractory B-cell precursor acute lymphoblastic leukemia
- Autologous CAR-T cell product targeting CD19
What’s in a name?

axicabtagene ciloleucel

- First Word: corresponds to gene component
- Second Word: corresponds to vector and cell component
What’s in a name?

Prefix is random
What’s in a name?

**axicabta**
- identifies the gene component
  - ‘cabta’ = cell expressed antibody and T cell activation

**gene ciloleu cel**
- identifies the cell type
  - ‘leu’ = lymphocytes/monocytes/APC (white cells)

What’s in a name?

Designate the product as a genetically modified cell-based therapy.

axicabtagene ciloleucrel
# ZUMA-1 Trial

<table>
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<tr>
<th>Design</th>
<th>Multicenter, phase II clinical trial</th>
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<tbody>
<tr>
<td>Population</td>
<td>n = 111</td>
</tr>
<tr>
<td></td>
<td>Adult patients with relapsed or refractory B cell lymphomas*</td>
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<tr>
<td>Intervention</td>
<td>Axicabtagene ciloleucel</td>
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<tr>
<td>Efficacy</td>
<td>ORR = 82%; CR = 52%; median duration of response = 8.1 months</td>
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<td>At 15 months:</td>
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<td>- Median PFS = 44%</td>
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<tr>
<td></td>
<td>- Median OS = 52%</td>
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<tr>
<td>Safety</td>
<td>CRS occurred in 93% of patients, 13% of grade 3 or higher</td>
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<tr>
<td></td>
<td>Neurotoxicity occurred in 64% of patients, 28% of grade 3 or higher</td>
</tr>
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*diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma

ORR = overall response rate; PFS = progression-free survival; OS = overall survival; CRS = cytokine release syndrome
## ELIANA Trial

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<tr>
<th><strong>Design</strong></th>
<th>Multicenter, phase II clinical trial</th>
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</thead>
</table>
| **Population** | - n = 92  
- Pediatric and young adults (≤25 years) with CD19+ relapsed or refractory B-cell ALL |
| **Intervention** | Tisagenlecleucel |
| **Efficacy** | - ORR = 81%; CR = 45%; CRi = 21%; Median duration of response not reached  
- At 12 months:  
  - Median EFS = 50%  
  - Median OS = 76% |
| **Safety** | - CRS occurred in 77% of patients, 46% of grade 3 or higher  
- Neurotoxicity occurred in 40% of patients, 10% of grade 3 |

CRi = complete response with incomplete hematologic recovery; EFS = event free survival
Black Box Warnings

**Cytokine Release Syndrome**
- Fever, hypoxia, hypotension, coagulopathy, acute kidney injury, transaminitis, hyperbilirubinemia

**Neurologic Toxicities**
- Headache, encephalopathy, delirium, anxiety, tremor

**REMS Program**
- Patient wallet card
- Minimum of two doses of tocilizumab available for each patient

REMS Program

YESCARTA (axicabtagene ciloleucel suspension) [package insert].
KYMRIAH (tisagenlecleucel) [package insert].
Cytokine Release Syndrome (CRS)
Pathophysiology of CRS

Tocilizumab

IL-6R = interleukin-6 receptor; IL-6 = interleukin-6

Tocilizumab

IL-6R = interleukin-6 receptor; IL-6 = interleukin-6

Siltuximab

IL-6R = interleukin-6 receptor; IL-6 = interleukin-6
Conclusion

- CAR-T cells are a novel therapeutic approach to cancer therapy

- Over 200 clinical trials actively recruiting participants

- Proper management of CAR-T cell toxicities is critical
  - CRS / Neurotoxicity
  - “On-target, off-tumor” toxicities
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References


