Chimeric Antigen Receptor (CAR) T-Cell Therapy

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Loma Linda University – Class of 2020
Objectives

- Define CAR T-cell therapy and discuss the physiology
- Understand the CAR T-cell treatment phases
- Identify and discuss major toxicities associated with the therapy
- Discuss the two FDA approved treatments and summarize key clinical studies
- Present the Institute for Clinical and Economic Review (ICER) evaluation
- Discuss CAR T-cell role in therapy and future considerations
CAR T-Cell Technology

- Chimeric Antigen Receptor T-cell therapy is a type of adoptive immunotherapy that uses tumor-specific antigen recognition.

- CAR: engineered receptor that specifically binds to certain proteins on cancer cells.

- It uses a patient’s own modified white blood cells (T-cells) to target and eliminate cancerous cells.

- Most advanced in B-cell cancers with known antigen targets such as CD19 (such as DLBCL, B cell ALL).
Role of CAR T-cell therapy

- **DLBCL** patients who:
  - Failed first line chemotherapy
  - Failed second or greater lines of chemotherapy
  - Relapsed within 12 months of an autologous stem cell transplant
  - Previous therapies must have included an anti-CD20 antibody and an anthracycline

- **ALL** patients that is
  - Refractory
  - Second or later relapse
Development of CAR T-cells

- **1989**: First proposal of CAR T-CELL
- **1998**: Pre-clinical trial with 2nd generation CAR
- **2000-03**: First effective CAR T-cells developed, 2nd generation CARs built to target CD19
- **2010**: First patient successfully treated with anti-CD19 CAR T-cells
- **2017**: First CAR-T therapy approved by FDA
CAR T-cell Design
CARs are fusion proteins designed to do two things:

1. Target cancer cells by engineering a recognition domain (commonly a antibody fragment [scFV]) on the T cell surface

2. Activate the CAR T cell by signaling through the CAR’s intracellular signaling domain resulting in:
   - Proliferation & activation of the T cell
   - CAR T cell-mediated killing of tumor cells

CAR: chimeric antigen receptor; scFV: single chain variable fragment
CAR T-Cell Mechanism of Action
CD19 and B Cell Malignancies

- CAR T-cells recognize and bind to a target antigen CD19
- CD19 is on the surface of B-cells and B-cell malignancies
  - Ideal target for T-cell mediated killing due to its specificity
  - It is present almost throughout the entire B cell maturation process
  - This minimizes off-target toxicity and enhances anti-tumor efficacy
- Various types of lymphomas and acute lymphoblastic leukemia (ALL) can express CD19
- Clinical trials targeting CD19 have shown remarkable success in B cell malignancies
Treatment Phases

2 Pre-apheresis treatment/ modification of treatment

1 Eligibility determined

3 Leukapheresis
Product shipped under stringent temperature controlled conditions to manufacturing facility

4 Preconditioning chemotherapy

5 CAR T cells infused into patient

A T cells isolated and activated

B CAR gene introduced into T cells

C CAR T cells expanded

D Beads removed

E CAR T cells washed, concentrated, quality tested

Leukemia & Lymphoma Society
Treatment Phases Cont.

1. Screening: patients are evaluated for safety and efficacy of the treatment
   - Must have tumors that are CD19 positive
   - Have an adequate number of T-cells
   - No active uncontrolled infection
   - Have adequate performance status and organ function

2. Leukapheresis: T-cells are harvested from the patient by leukapheresis
   - Corticosteroids should be avoided within a certain time prior to the procedure
   - Salvage/rescue chemotherapy within a certain time prior to the procedure

The collected cells may be frozen and shipped to manufacturing facilities for processing

3. T-cells are activated: isolated T-cells are placed in culture and are exposed to antibody-coated beads to activate them

4. The CAR gene is introduced into activated T cells in vitro: use of several viral vectors, which results in permanent genome modification

5. The CAR T-cells are expanded in vitro: following expansion, the cells are washed, concentrated, and samples are removed for quality testing

The CAR T-cells may be frozen for shipment to the infusion sites
6. Patient undergoes “preconditioning” chemotherapy
   - patient receives lymphocyte-depleting chemotherapy days prior to the CAR T-cells infusion
     - Fludarabine, cyclophosphamide or alternatives
   - It allows the engraftment and expansion of CAR T-cells
   - CAR T-cell infusion 2-14 days after completion of lymphodepleting chemotherapy
   - Regimens vary by protocol and individual patient

7. CAR T-cells infusion
   - Generally reach peak level between 1-2 weeks after infusion
   - The degree of expansion and persistence of CAR T-cells is one indicator of efficacy

On average, the production of CAR T-cells takes approximately 10-14 days. The time from cell collection to infusion varies but typically ranges from 1-4 weeks
Recommended Timing to Stop Therapies Before Leukapheresis

- **Allogeneic cell therapy**: Stop 12 weeks
- **T cell lytic agents (e.g., ATG, alemtuzumab)**: Stop 8 weeks
- **Cisplatin**: Stop 8 weeks
- **Donor lymphocyte infusions completed**: Stop 4 weeks
- **Pegylated drugs (e.g., asparaginase)**: Stop 4 weeks
- **Low-dose daily or weekly maintenance chemotherapy (e.g., VCR, MTX, 6MP)**: Stop 2 weeks
- **GVHD therapies (e.g., calcineurin inhibitors)**: Stop 2 weeks
- **Immunomodulatory drugs (e.g., rituximab)**: Stop 2 weeks
- **Long-acting growth factors**: Stop 2 weeks
- **Intrathecal MTX**: Stop 7 days
- **Short-acting growth factors**: Stop 5 days
- **Therapeutic doses of steroids**: Stop 3 days
- **Short-acting cytotoxic/antiproliferative drugs (e.g., HU, TKIs)**: Stop 3 days
Patient Eligibility Considerations

- Adequate blood cell count for leukapheresis
- Relative disease stability
  - CART manufacturing generally 2 – 4 weeks
  - Disease not progressing rapidly through manufacturing period
- Patient ability to tolerate CAR T toxicities
  - Major organ functionality
    - heart, lung, kidney, liver
  - Neurologic considerations
    - Seizure risk, CVA, CNS disease
## FDA Approved Therapies

<table>
<thead>
<tr>
<th>Brand</th>
<th>KYMRIAH®</th>
<th>YESCARTA®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>Tisagenlecleucel</td>
<td>Axicabtagene ciloleucel</td>
</tr>
<tr>
<td>FDA approval</td>
<td>August 30, 2017</td>
<td>October 18, 2017</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Novartis</td>
<td>Kite Pharma (Gilead)</td>
</tr>
<tr>
<td>Signaling domain</td>
<td>4-1BB</td>
<td>CD28</td>
</tr>
<tr>
<td>REMS</td>
<td>Required</td>
<td></td>
</tr>
<tr>
<td>Contraindications</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>FDA Indications</td>
<td>ALL (≤25 years of age)</td>
<td>DLBCL</td>
</tr>
<tr>
<td></td>
<td>DLBCL (adults)</td>
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</tr>
</tbody>
</table>

**ALL**: acute lymphoblastic leukemia  
**DLBCL**: diffuse large B-cell lymphoma  
**NHL**: non-Hodgkin’s lymphoma
REMS Requirements

- Healthcare facilities that dispense and administer YESCARTA or KYMRIAH must be enrolled and comply with the REMS requirements.

- Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA or KYMRIAH infusion, if needed for treatment of CRS.

- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA or KYMRIAH are trained about the management of CRS and neurologic toxicities.
Indications

- Relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy in adults, including diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma and DLBCL arising from follicular lymphoma
- Refractory or in second or later relapse B-cell acute lymphoblastic leukemia (ALL) in patient ≤25 years of age

It is NOT indicated for treatment of primary central nervous system lymphoma

Dosage

- Based on the number of CAR-positive viable T cells and patient weight
  - ≤25 yo ALL → 50kg or less: 0.2 to 5.0 x 10^6 CAR-positive viable T-cells per kg body weight
    - above 50 kg: 0.1 to 2.5 x 10^8 CAR-positive viable T-cells
  - Adult DLBCL → 0.6 to 6.0 x 10^8 CAR-positive viable T-cells
  - Infusion bag volume ranges 10-50mL
- IV use only: infuse at 10 to 20mL per minute
KYMRIAH Initial Approval Criteria (Centene)

**Acute Lymphoblastic Leukemia*** (must meet all): *Only for initial treatment dose; subsequent doses will not be covered.*

1. Age ≤ 25 years
2. Documentation of CD19 tumor expression
3. Recent (within the last 30 days) documentation of one of the following (a or b):
   a. Absolute lymphocyte count (ALC) ≥ 500/µL
   b. CD3 (T-cells) cell count of ≥ 150/µL if ALC < 500/µL
4. Request meets one of the following (a, b, or c):
   a. Refractory disease or member has had ≥ 2 relapses
   b. Philadelphia chromosome positive: Failure of 2 lines of chemotherapy that include 2 tyrosine kinase inhibitors
   c. Relapse following hematopoietic stem cell transplantation (HSCT) and must be ≥ 6 months from HSCT at the time of Kymriah infusion
5. No active or primary central nervous system (CNS) disease
6. Dose does not exceed (a or b):
   a. Weight ≤ 50 kg: $5.0 \times 10^6$ chimeric antigen receptor (CAR)-positive viable T cells per kg
   b. Weight > 50 kg: $2.5 \times 10^8$ CAR-positive viable T cells

**Approval duration:** 3 months *(1 dose only, with 4 doses of tocilizumab (Actemra) at up to 800 mg per dose)*
KYMRIAH Initial Approval Criteria (Centene)

Large B-Cell Lymphoma (must meet all):

1. Age ≥ 18 years
2. Recent (within the last 30 days) ALC ≥ 300/μL
3. Disease is refractory or member has relapsed after ≥ 2 lines of systemic therapy that includes Rituxan® and one anthracycline-containing regimen (e.g., doxorubicin)
4. No active or primary CNS disease
5. Dose does not exceed 6.0 x 10^8 CAR-positive viable T cells

Approval duration: 3 months *(1 dose only, with 4 doses of tocilizumab (Actemra) at up to 800 mg per dose)*
Indications
- Relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy in adults, including diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
- It is NOT indicated for treatment of primary central nervous system lymphoma.

Dosage
- Based on the number of CAR-positive viable T cells and patient weight:
  - Each single infusion bag of YESCARTA contains a suspension of CAR-positive T cells in approximately 68 mL. The target dose is $2 \times 10^6$ CAR-positive viable T cells per kg body weight, with a maximum of $2 \times 10^8$ CAR-positive viable T cells.
- IV use only: the entire bag has to be infused within 30 minutes.
Large B-Cell Lymphoma* (must meet all):
*Only for initial treatment dose; subsequent doses will not be covered.
1. Diagnosis of LBCL
2. Prescribed by or in consultation with an oncologist or hematologist
3. Age ≥ 18 years
4. Recent (within the last 30 days) absolute lymphocyte count (ALC) ≥ 100/μL
5. Disease is refractory or member has relapsed after ≥ 2 lines of systemic therapy that includes Rituxan® and one anthracycline-containing regimen (e.g., doxorubicin)
6. No active or primary central nervous system (CNS) disease
7. Dose does not exceed 2 x 10^8 chimeric antigen receptor (CAR)-positive viable T cells

Approval duration: 3 months (1 dose only, with 4 doses of tocilizumab (Actemra) at up to 800 mg per dose)
Monitoring

- Patient should be monitored daily for 7 days at a certified healthcare facility following infusion
- Patient should stay within proximity of the treatment center for at least 4 weeks after infusion to monitor
- Warning and precautions
  - Hypersensitivity reactions
  - Serious infections
  - Prolonged cytopenias: Monitor blood count
  - Hypogammaglobulinemia
  - Secondary malignancies
- Routine long-term monitoring is recommended
# Toxicities

<table>
<thead>
<tr>
<th>Cytokine release syndrome (CRS)</th>
<th>Signs and Symptoms</th>
<th>Timing</th>
<th>Management</th>
</tr>
</thead>
</table>
|                                 | Fever, myalgia, hypotension, hypoxia, potential organ failure | Usually within the first 1-3 weeks postinfusion | • Tocilizumab  
• Corticosteroids  
• Severe CRS may require vasopressors, ventilatory support and supportive care in the ICU |
| Neurotoxicity                    | Confusion, delirium, hallucinations, encephalopathy, aphasia, facial paresis, mutism, myoclonus, tremors, somnolence, seizures | May not be concurrent with CRS | • Corticosteroids  
• Supportive care, which may include anti-epileptic medication |
| Macrophage activation syndrome (MAS) | High levels of ferritin, CRP, d-dimer; hypofibrinogenemia associated with bleeding, transaminitis and elevated triglycerides | Concurrently or shortly after CRS | • Tocilizumab |
| B-cell aplasia                   | Hypogammaglobulinemia | Within first few weeks postinfusion, may last indefinitely | • Immunoglobulin replacement therapy  
• Prophylactic antibiotics in some cases |
# CRS and Neurotoxicity

<table>
<thead>
<tr>
<th>Product</th>
<th>Kymriah</th>
<th>Yescarta</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALL (ELIANA)</td>
<td>DLBCL (JULIETA)</td>
</tr>
<tr>
<td>CRS</td>
<td>78%</td>
<td>74%</td>
</tr>
<tr>
<td>CRS grade ≥3</td>
<td>47%</td>
<td>18%</td>
</tr>
<tr>
<td>Median time to onset of CRS</td>
<td>3 days (1-51)</td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>72%</td>
<td>58%</td>
</tr>
<tr>
<td>Median time to onset of neurotoxicity</td>
<td>6 days</td>
<td>14 days</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>50%</td>
<td>21%</td>
</tr>
<tr>
<td>Steroids</td>
<td>26%</td>
<td>13%</td>
</tr>
</tbody>
</table>
The major acute toxicities associated with CAR T-cells therapy
Symptoms and severity varies, features mimic infection
Duration is variable, but it typically resolves within a few days to 2-3 weeks after CAR-T
For CRT T-cell associated CRS, severe CRS (grade 3,4 maybe 2) are considered
Tocilizumab +/- corticosteroids
- patients <30 kg – Tocilizumab 12 mg/kg
- patients ≥30 kg – Tocilizumab 8 mg/kg; max 800 mg
Hydrocortisone 100 mg every eight hours, dexamethasone 10 mg up to four times daily, or methylprednisolone 1 mg/kg/day until there is improvement in CRS
**ICER Analysis**

### Discounted Lifetime Costs

<table>
<thead>
<tr>
<th>Cost Category</th>
<th>B-ALL</th>
<th>Clofarbine</th>
<th>Axicabtagene Cileoleucel</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAR-T Treatment Costs</td>
<td>$405,490</td>
<td>$0</td>
<td>$438,284</td>
<td>$0</td>
</tr>
<tr>
<td>Chemotherapy Treatment Costs</td>
<td>$15,309</td>
<td>$163,686</td>
<td>$0</td>
<td>$40,142</td>
</tr>
<tr>
<td>Palliative Chemotherapy</td>
<td>$2,648</td>
<td>$3,973</td>
<td>$3,748</td>
<td>$6,103</td>
</tr>
<tr>
<td>Treatment Costs</td>
<td>$2,979</td>
<td>$0</td>
<td>$4,585</td>
<td>$0</td>
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<tr>
<td>Pre-Treatment Costs</td>
<td>$47,744</td>
<td>$64,648</td>
<td>$13,345</td>
<td>$62,094</td>
</tr>
<tr>
<td>Adverse Event Costs*</td>
<td>$33,534</td>
<td>$0</td>
<td>$16,029</td>
<td>$7,046</td>
</tr>
<tr>
<td>Administration/</td>
<td>$111,548</td>
<td>$93,032</td>
<td>$44,165</td>
<td>$1,045</td>
</tr>
<tr>
<td>Monitoring Costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Future Healthcare Costs</td>
<td>$45,901</td>
<td>$9,069</td>
<td>$95,223</td>
<td>$36,286</td>
</tr>
<tr>
<td>End of Life Costs</td>
<td>$1,602</td>
<td>$2,848</td>
<td>$1,547</td>
<td>$2,169</td>
</tr>
<tr>
<td><strong>TOTAL COSTS</strong></td>
<td>$666,754</td>
<td>$337,256</td>
<td>$616,927</td>
<td>$154,884</td>
</tr>
</tbody>
</table>

### Discounted Lifetime Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>B-ALL</th>
<th>Clofarbine</th>
<th>Axicabtagene Cileoleucel</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life Years (responding to treatment)</td>
<td>9.84</td>
<td>2.09</td>
<td>6.92</td>
<td>2.91</td>
</tr>
<tr>
<td>Life Years (not responding to treatment)</td>
<td>0.51</td>
<td>0.34</td>
<td>0.43</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>TOTAL LIFE YEARS</strong></td>
<td>10.34</td>
<td>2.43</td>
<td>7.35</td>
<td>3.23</td>
</tr>
<tr>
<td>QALYs (responding to treatment)</td>
<td>8.95</td>
<td>1.90</td>
<td>5.74</td>
<td>2.42</td>
</tr>
<tr>
<td>QALYs (not responding to treatment)</td>
<td>0.33</td>
<td>0.20</td>
<td>0.13</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>TOTAL QALYs</strong></td>
<td><strong>9.28</strong></td>
<td><strong>2.10</strong></td>
<td><strong>5.87</strong></td>
<td><strong>2.48</strong></td>
</tr>
</tbody>
</table>

*B-ALL: B-cell acute lymphoblastic leukemia, QALY: quality-adjusted life year *

*for inpatient therapies, costs associated with adverse events that were expected to increase the length of stay or extend beyond discharge*
ICER Analysis

Base-Case Incremental Results

<table>
<thead>
<tr>
<th>B-ALL</th>
<th>Incremental Costs</th>
<th>Incremental LYs</th>
<th>Incremental QALYs</th>
<th>Incremental CE Ratio per LY</th>
<th>Incremental CE Ratio per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tisagenlecleucel vs. Clofarabine</td>
<td>$329,498</td>
<td>7.91</td>
<td>7.18</td>
<td>$41,642</td>
<td>$45,871</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B-cell Lymphoma</th>
<th>Incremental Costs</th>
<th>Incremental LYs</th>
<th>Incremental QALYs</th>
<th>Incremental CE Ratio per LY</th>
<th>Incremental CE Ratio per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axicabtagene Ciloleucel vs. Chemotherapy</td>
<td>$462,043</td>
<td>4.12</td>
<td>3.40</td>
<td>$112,168</td>
<td>$136,078</td>
</tr>
</tbody>
</table>

- The cost of KYMRIAH is $475,000
- In the United States, thresholds of $100,000 or $150,000 per QALY gained have been suggested as a reasonable upper bound for an intervention to be deemed cost effective
- The cost of YESCARTA is $368,000

Base-case payment for tisagenlecleucel assumes payment only for responders at one month.
Base-case payment for axicabtagene ciloleucel assumes payment at infusion.
CE: cost-effectiveness, LY: life year, QALY: quality-adjusted life year
Outcome-Based Agreement (OBA) for KYMRIA

- Novartis has developed OBA when administered to patients up to 25 years of age diagnosed with B-cell ALL that is refractory or in second or later relapse
- Written agreement between Novartis and participating certified centers
- Applies to patients covered by all forms of insurance, including commercial, Medicaid, Medicare, and other government plans
- Novartis will not charge for the cost of the drug when the patient does not achieve either (28 to 35 days following infusion):
  - Complete remission (CR)
  - Complete remission with incomplete blood count recovery (CRi)
The Future

- With increasing clinical experience and further technical advances with product development, it is likely that the safety profile of these agents will continue to improve with time.
- Efforts are ongoing to make these cells more effective and less toxic.
- Treatment for post-CAR T-cell relapse such as possible reinfusion.
- Donor CAR T-cells for patients who do not have sufficient numbers of cell manufactured?
- How to sustain remission post-CAR T therapy?
- Expanded use for other hematologic malignancies.


