Disclosure

• I do not have (nor does any immediate family member have) a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

• I will be discussing investigational products.
Objectives

• Review the role of the immune system in the treatment of cancer
• Describe the use of CAR T-cells as immunotherapy in hematologic malignancies
• Outline the prevention and management of adverse effects associated with CAR T-cell therapy
The Cancer Immunity Cycle

The “3 Es” of Cancer Immunoediting

- Immunosurveillance works to identify and **eliminate** cells undergoing malignant transformation.
- If a cancer cell is not destroyed, it enters a period of **equilibrium** where outgrowth is prevented by immunologic mechanisms.
- Unfortunately, some cancer cells cannot be controlled and **escape** the immune system leading to clinically apparent disease.

![Diagram of the 3 Es of Cancer Immunoediting](image)

Genetic instability/tumor heterogeneity

Major Mechanisms of Tumor Escape

Reduced Immune Recognition & Stimulation

Establishment of an Immunosuppressive Tumor Microenvironment

Upregulation of Resistance Mechanisms or Increased Expression of Prosurvival / Growth Factor Genes

Therapeutic Approaches to Overcome Immune Tolerance to Cancer

Using the Immune System to Treat Cancer

- Immune Checkpoint Modulators
  - **Immune Cell Therapy**
    - Tumor infiltrating lymphocytes (TILs)
    - T-cell receptor (TCR) therapy
    - **Chimeric antigen receptor (CAR) T cells**
  - Therapeutic Antibodies
  - Cancer Treatment Vaccines
  - Immune System Modulators
The Immune System is Tumor Blind
Chimeric Antigen Receptor (CAR) T-cells

- Type of autologous cellular therapy
- Engineer patients’ own T-cells to recognize and attack cancer cells
- The receptor created on the T-cells is called a chimeric antigen receptor (CAR)
- These T-cells now specifically target antigens expressed by the patient’s cancer cells
- CAR T-cell therapy against CD19+ B-cell malignancies is currently the most developed

Chimeric Antigen Receptor (CAR)

Monoclonal Antibody

Light chain

Heavy chain

T-Cell Receptor Complex

Advancements in CAR Development

1. **Antigen Binding Domain**
   - Recognizes CD19 antigen on B cell

2. **Costimulatory Domain**
   - Increases T-cell activation and enhances cytolytic function of T-cells

3. **CD3-zeta chain signaling domain**
   - Induces T-cell activation

---

**First Generation CAR**
- Antigen Binding Domain
- CD3ζ

**Second Generation CAR**
- Antigen Binding Domain
- One costimulatory domain (4-1BB or CD28)
- CD3ζ

**Third Generation CAR**
- Antigen Binding Domain
- Two costimulatory domains (CD27, CD28, ICOS, 4-1BB, OX40)
- CD3ζ

Advantages of CAR T-cells

**NORMAL T-CELL**

- T-cell receptor
- Peptide
- MHC
- B2-microglobulin

**Tumor**

**CAR T-CELL**

- CAR
- CD19

**Tumor**

**Rationale & Advantages for T-cell Engineering**

- Overcome immune tolerance
- HLA independent antigen recognition
- Target both CD4 and CD8 cells to the tumor
- T cell reactivity to carbohydrates, glycolipids and proteins
- Augment T-cell potency
- Control T-cell longevity
- Minimal risk of autoimmunity or graft-versus-host disease (GVHD)
- Single drug infusion
LYMPHODEPLETING CONDITIONING

1

T-CELLS ARE ISOLATED FROM PATIENT

2

T-CELLS ARE ENGINEORED TO EXPRESS CARs THAT RECOGNIZE CANCER CELLS

3

MODIFIED T-CELLS ARE GROWN AND EXPANDED IN CULTURE

4

MODIFIED T-CELLS ARE INFUSED INTO PATIENT

5

The First 30 Days in the Life of CAR-T

Apheresis
-5 -4 -3

Lymphodepletion (varies)

T-cell manufacturing, transduction, preservation, etc

Cell infusion
-2 -1 0

Possible bridging chemotherapy

Hospitalization
(Not all patients are hospitalized and length of hospitalization varies)

Patient stays within a certain radius of site until ~day 30
The Role of Lymphodepletion in CAR-T Expansion

• Several factors contribute to CAR T-cell expansion and persistence
• There appears to be a link between adequate lymphodepletion and T-cell expansion
• Fludarabine and cyclophosphamide is a potent lymphodepleting regimen commonly used prior to CAR T-cell infusion

APC: antigen presenting cell
Fludarabine is Associated with Higher T-cell Expansion


Graph credit: clinicaloptions.com
The B-cell Surface Protein CD19 is an Ideal Target

- CD 19 is expressed throughout B-cell development; therefore it is expressed on the surface of most B cell malignancies.
- Additionally, expression is restricted to B cells and not expressed on pluripotent bone marrow stem cells.

# CD19 CAR-T cell Products

<table>
<thead>
<tr>
<th></th>
<th>Tisagenlecleucel (CTL019) Novartis</th>
<th>Axicabtagene Ciloleucel (KTE-C19) Kite Pharma</th>
<th>JCAR 017 Juno Therapeutics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAR Type</strong></td>
<td>CD19/4-1BB/CD3z</td>
<td>CD19/CD28/CD3z</td>
<td>CD19/4-1BB/CD3z</td>
</tr>
<tr>
<td><strong>Costimulatory Domain</strong></td>
<td>4-1BB (CD 137)</td>
<td>CD28</td>
<td>4-1BB (CD 137)</td>
</tr>
<tr>
<td><strong>scFv</strong></td>
<td>FMC63</td>
<td>FMC63</td>
<td>FMC63</td>
</tr>
<tr>
<td><strong>Vector Delivery</strong></td>
<td>Retrovirus</td>
<td>Retrovirus</td>
<td>Lentivirus</td>
</tr>
<tr>
<td><strong>Defined cells</strong></td>
<td>No</td>
<td>No</td>
<td>CD4:CD8</td>
</tr>
<tr>
<td><strong>Trials</strong>*</td>
<td>ALL (ELIANA)</td>
<td>NHL (ZUMA 1)</td>
<td>NHL (TRANSCEND)</td>
</tr>
<tr>
<td></td>
<td>NHL (JULIET)</td>
<td>ALL (ZUMA 3, ZUMA 4)</td>
<td></td>
</tr>
</tbody>
</table>

*not a complete list

There is an Unmet Need in Pediatric & Young Adult B-Cell Acute Lymphoblastic Leukemia

• B-cell acute lymphoblastic leukemia (ALL) is the most common malignancy diagnosed in children
  • 5 year survival 85%

• Despite current treatment options, ~15% pediatric/young adult patients with ALL experience relapsed/refractory (R/R) disease and 10% die
  • Prognosis is very poor with available treatment: clofarabine, blinatumomab, allogeneic hematopoietic stem cell transplant (HSCT)
  • Patients with ALL who relapse post allogeneic HSCT have a 2-year overall survival rate of ~15%

ELIANA: CAR T-cell Therapy in ALL

- Multicenter, open-label, single arm phase II trial of CAR T-cell therapy: tisagenlecleucel (CTL019)
- 63 pediatric/young adult patients (age 3-23) with relapsed/refractory CD19+ B-cell acute lymphoblastic leukemia (ALL)
  - 6 (10%) had primary refractory disease
  - 38 (60%) received ≥3 prior regimens
  - 30 (48%) had one prior hematopoietic stem cell transplant (HSCT), 5(8%) had two HSCTs

- Patients with B-cell ALL
- ≥ 5% BM lymphoblasts;
- No isolated extramedullary disease relapse, prior CD19-directed therapy, or prior gene therapy (N = 88)

- Single-Dose CTL019 (N = 63*)
  - Fludarabine
    - 30 mg/m² IV daily x 4 doses
  - Cyclophosphamide
    - 500 mg/m² IV daily x 2 doses

- *16 pts discontinued before infusion: disease (n=9), manufacturing failures (n=7).
  - Have not reached 3 month follow-up or pending infusion at data cutoff (n=9)

**ELIANA: CAR T-cell Therapy in ALL**

- **Primary endpoint**: Overall Remission Rate (ORR) \( [\text{complete remission (CR)} + \text{CR with incomplete blood count recovery (CRi)}] \) within 3 months of infusion

<table>
<thead>
<tr>
<th>Results</th>
<th>N = 63</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR within 3 months</strong></td>
<td></td>
</tr>
<tr>
<td>CR/CRi</td>
<td>52 (83%)</td>
</tr>
<tr>
<td>95% CI (0.71-0.91), ( p&lt;0.0001 )</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>40 (63%)</td>
</tr>
<tr>
<td>CRi</td>
<td>12 (19%)</td>
</tr>
</tbody>
</table>

**Relapse Free Rates**

- 6 months: 75%
- 12 months: 64%

CR: complete remission
CRi: complete remission with incomplete blood count recovery

Overall Survival

- 89% at 6 months
- 79% at 12 months

Comparison of Available Treatments for Pediatric and Young Adult R/R B-cell ALL

<table>
<thead>
<tr>
<th></th>
<th>Clofarabine (Monotherapy)</th>
<th>Blinatumomab</th>
<th>Inotuzumab ozogamicin</th>
<th>Tisagenlecleucel (CAR-T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled Patients</td>
<td>61</td>
<td>70</td>
<td>109</td>
<td>68</td>
</tr>
<tr>
<td>Prior HSCT</td>
<td>29.5%</td>
<td>57.1%</td>
<td>16%</td>
<td>56.5%</td>
</tr>
<tr>
<td>&gt;3 prior regimens</td>
<td>62.3%</td>
<td>11.4%</td>
<td>1%</td>
<td>60.3%</td>
</tr>
<tr>
<td>ORR (CR + CRi)</td>
<td>19.7%</td>
<td>38.6%</td>
<td>80.7%</td>
<td>82.5%</td>
</tr>
<tr>
<td>Median Overall Survival</td>
<td>3 months</td>
<td>7.5 months</td>
<td>7.7 months</td>
<td>16.6 months</td>
</tr>
<tr>
<td>12 month Overall Survival</td>
<td>20%</td>
<td>38%</td>
<td>41% (15 month)</td>
<td>79.2%</td>
</tr>
</tbody>
</table>

There is an Unmet Need in Diffuse Large B-Cell Lymphoma (DLBCL)

- DLBCL is the most common form of adult non-Hodgkin Lymphoma (NHL) accounting for ~25% of newly diagnosed cases
  - 5 year survival 62%, up to 50% of patients relapse depending on disease factors
  - 30-40% respond to salvage chemo and undergo autologous HSCT
  - 50% of patients relapse post autologous HSCT
- SCHOLAR-1 study retrospectively evaluated outcomes in refractory DLBCL
  - 636 patients from 4 trials
  - ORR 26%, CR 7%
  - Median overall survival 6.3 months

ZUMA-1: CAR T-cell Therapy in NHL

- Multicenter phase II trial in two cohorts of CAR T-cell therapy: *axicabtagene ciloleucel* (KTE 019, AXI-CEL) in 101 patients with relapsed or refractory aggressive non-Hodgkin lymphoma
  - Cohort 1: refractory diffuse large B-cell lymphoma (DLBCL, n=77)
  - Cohort 2: primary mediastinal B-cell lymphoma/transformed follicular lymphoma (PMBCL/TFL, n=24)
  - Median age 58 years old (range 23-76), 85% stage III/IV
  - 77% refractory to ≥ 2nd line of therapy, 21% relapsed ≤ 12 months after auto HSCT

- No response to previous chemotherapy or relapse within 12 months of auto HSCT.
- Prior treatment with anthracycline and anti-CD20 mAB
- ECOG PS ≤1

---

**Fludarabine**  
30 mg/m² IV daily x 3 doses  
+  
**Cyclophosphamide**  
500 mg/m² IV daily x 3 doses  

---

**Single-Dose KTE019**  
(N = 101)

---

ZUMA-1: CAR T-cell Therapy in NHL

- Primary endpoint: Objective Response Rate (ORR) in the combined DLBCL, PMBCL, and TFL population.

Results from Phase 2 Zuma-1 in NHL

- Objective Response Rate: 82%
- Complete Response: 54%
- Partial Response: 28%

6 months

- Objective Response Rate: 41%
- Complete Response: 36%

Zuma-1 Meets Primary Endpoint of ORR

CAR-T Improves Overall Survival Compared to Standard of Care in NHL

CAR-T Toxicities

Cytokine Release Syndrome (CRS)

Neurological Toxicity

“On-target, Off-tumor”

- Tumor Lysis Syndrome
- Infection
- Prolonged Cytopenias

Other:

Cytokine Release Syndrome (CRS) is the Most Common Toxicity of Cellular Immunotherapy

- Potentially life threatening toxicity associated with cellular therapies
- Caused by immune activation of T-cells resulting in elevated inflammatory cytokines and activation of other immune cells
  - Including IL-6, IFN-Ɣ, IL-10 and others
- Onset usually occurs within the first week after CAR T-cell infusion and typically peaks within 1-2 weeks
- Patients at high risk of severe CRS: high disease burden, high T-cell dose, rapid and high T-cell expansion
- Goal of management with CAR T-cell therapy is to prevent life threatening complications while preserving the antitumor effects


IL-6: interleukin-6; IL-10: interleukin-10; IFN-Ɣ: interferon gamma
# Clinical Signs & Symptoms Associated with CRS

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Fever, rigors, malaise, fatigue, anorexia, myalgias, arthralgias</td>
</tr>
<tr>
<td>Skin</td>
<td>Rash</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tachypnea, hypoxemia</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, hypotension, changes in cardiac output</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Elevated D-dimer, hypofibrinogenemia, bleeding</td>
</tr>
<tr>
<td>Renal</td>
<td>Azotemia</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Transaminitis, hyperbilirubinemia</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Headache, mental status changes, confusion, delirium, aphasia, hallucinations, tremor, altered gait, seizures</td>
</tr>
</tbody>
</table>

CRS is Associated with Elevated Proinflammatory Cytokines

CRP May be a Predictive Biomarker for CRS

**Targeted Immunosuppressive Therapy Against CRS**

- **Tocilizumab**
  - FDA approval for CAR T-cell induced severe or life threatening CRS in August 2017
  - Recombinant humanized monoclonal antibody
  - IL-6 receptor antagonist

- **Corticosteroids**
  - Suppress inflammatory responses
  - Dexamethasone 10 mg q6h or methylprednisolone 1mg/kg q12h followed by rapid taper

Tocilizumab Induces Reversal of Cytokine Release Syndrome

- IL-6 blockade demonstrates rapid reversal of CRS symptoms in most patients
  - 8 mg/kg IV over one hour (max dose 800 mg)
    - Patients <30 kg: 12 mg/kg
  - If no response in 24-48 hours consider a second dose of tocilizumab or initiation of steroids
    - Minimum of 8 hours between consecutive doses of tocilizumab

Tocilizumab and Steroids are Effective in Reversing CRS

CORTICOSTEROIDS MAY DIMINISH CAR T-CELLS

TOCILIZUMAB DOES NOT DECREASE EXPANSION OF CAR T-CELLS

**Grade 1 CRS:**
Fever, constitutional symptoms

**Grade 2 CRS:**
- Hypotension responds to fluids or 1 low dose vasopressor
- Hypoxia responds to < 40% O₂
- Grade 2 organ toxicity

**Grade 3 CRS:**
- Hypotension requires multiple or high dose pressor
- Hypoxia requires ≥ 40% O₂
- Grade 3 organ toxicity or grade 4 transaminitis

**Grade 4 CRS:**
Mechanical ventilation required
Grade 4 organ toxicity, excluding transaminitis

**Vigilant supportive care**
Assess for infection
Treat fever and neutropenia, if present
Monitor fluid balance
Antipyretics and analgesics, as needed

**Vigilant supportive care**
Multiple comorbidities or older age?

- Yes
  - **Vigilant supportive care**
    - Monitor cardiac and other organ function closely

- No
  - **Vigilant supportive care**
    - Tocilizumab ± Corticosteroids

Neurotoxicity is the Second Most Common Toxicity Associated with CAR T-cell Therapy

- Symptoms: diminished attention, language disturbance, confusion, disorientation, agitation, aphasia, tremors, seizures, encephalopathy
- Pathophysiology remains unclear; however is likely still related to T-cell activation
- Neurotoxicity and CRS follow a different course of onset and resolution
- Onset varies and can be biphasic
  - Early – Symptoms occur concurrently with CRS symptoms (~within first 5 days)
  - Late – Begins after CRS symptoms have resolved
  - Delayed – Neurotoxicity has occurred 3-4 weeks after cell infusion (seizures, episodes of confusion)

Grading of CAR T-cell related Encephalopathy Syndrome (CRES)

<table>
<thead>
<tr>
<th>Symptom/ sign</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic Assessment Score</td>
<td>7-9 (mild)</td>
<td>3-6 (moderate)</td>
<td>0-2 (severe)</td>
<td>Critical / obtunded, cannot perform assessment of tasks</td>
</tr>
<tr>
<td>Raised intracranial pressure</td>
<td>NA</td>
<td>NA</td>
<td>Stage 1-2 papilloedema or CSF opening pressure &lt; 20 mmHg</td>
<td>Stage 3-5 papilloedema or CSF opening pressure ≥20 mmHg or cerebral edema</td>
</tr>
<tr>
<td>Seizure or motor weakness</td>
<td>NA</td>
<td>NA</td>
<td>Partial seizure; non-convulsive seizures on EEG responding to benzodiazepine</td>
<td>Generalized seizures; convulsive or non-convulsive status epilepticus; new motor weakness</td>
</tr>
</tbody>
</table>

10-point neurological assessment (score of 10 = normal)
- Orientation to year, month, city, hospital, President = 5 points
- Name 3 objects (point to clock, pen, button) = 3 points
- Ability to write a standard sentence = 1 point
- Count backwards from 100 by tens = 1 point

Tocilizumab Has No Benefit for the Treatment of Neurotoxicity

- No clear clinical standard for managing neurotoxicity
- Corticosteroids are the preferred agent for treatment of severe symptoms
  - No evidence tocilizumab is of benefit as it does not cross the blood-brain barrier and not all neurotoxicity has responded
  - Tocilizumab may be used if experiencing concurrent CRS
- Seizure prophylaxis is commonly used for the first 30 days
- Appears to be self limiting and the majority of patients recover without long term neurologic deficits

ELIANA: Safety of Tisagenlecleucel in ALL

<table>
<thead>
<tr>
<th></th>
<th>N = 68*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytokine Release Syndrome</strong></td>
<td>54 (79)</td>
</tr>
<tr>
<td>Median time to onset of CRS, days (range)</td>
<td>3 (1-22)</td>
</tr>
<tr>
<td>Median duration of CRS, days (range)</td>
<td>8 (1-36)</td>
</tr>
<tr>
<td>Admitted to ICU, n (%)</td>
<td>31 (46)</td>
</tr>
<tr>
<td><strong>Systemic anti-cytokine therapy, n (%)</strong></td>
<td>27 (38)</td>
</tr>
<tr>
<td>High dose vasopressors, n (%)</td>
<td>17 (25)</td>
</tr>
<tr>
<td>Intubation, n (%)</td>
<td>10 (15)</td>
</tr>
<tr>
<td>Deaths within 30 days, n (%)</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

*68 patients treated and included in the safety analysis. 63 patients were evaluable for efficacy.

**Neurotoxicity all grades**: 65%

**Neurologic events >3% within 8 weeks**: Confusional state, Encephalopathy, Delirium, Agitation, Tremor, Irritability

ZUMA-1: Safety of Axicabtagene Ciloleucel in NHL

- **CRS** any grade: 93%
- **Neurotoxicity** any grade: 64%
- Treatment with tocilizumab and steroids did not decrease efficacy of axicabtagene ciloleucel
- 43 patients received tocilizumab: ORR 84%
- 27 patients received steroids: ORR 78%
- 3 deaths: 2 CRS and 1 pulmonary embolism

---

**Grade 3 Adverse Events**

- Neutropenia 66%
- Leukopenia 44%
- Anemia 43%
- Febrile Neutropenia 31%
- Thrombocytopenia 24%
- Encephalopathy 21%

---

What about JCAR017?

• JCAR015 was a CD19 CAR-T product studied in ALL
  • July 2016 – FDA placed a clinical hold on the Phase II ROCKET trial following 3 patient deaths resulting from cerebral edema. Hold was lifted within one week and the trial resumed
  • March 2017 – After 5 total deaths, development of JCAR015 ceased, study permanently halted.

• JCAR017 is the newer version studied in both NHL and ALL
  • TRANSCEND trial (NHL): ORR 76%, CR 52%
  • PLAT-02 trial (ALL): 93% CR

<table>
<thead>
<tr>
<th></th>
<th>JCAR015</th>
<th>JCAR017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costimulatory domain</td>
<td>CD28</td>
<td>4-1BB</td>
</tr>
<tr>
<td>scFv</td>
<td>SJ25C1</td>
<td>FMC63</td>
</tr>
<tr>
<td>Vector Delivery</td>
<td>Retroviral</td>
<td>Lentiviral</td>
</tr>
<tr>
<td>Defined cells</td>
<td>No</td>
<td>CD4:CD8 fixed ratio</td>
</tr>
</tbody>
</table>

Additional Toxicities Associated with CAR T-cells

- B cell aplasia
  - “On target, off tumor” toxicity of successful CD19 CAR T-cell therapy
  - Hypogammaglobulinemia
  - IVIG replacement may be used to mitigate risk of infection

- Infections (opportunistic)
- Prolonged Cytopenias
- Tumor Lysis Syndrome
- Infusion-related immune reactions
Premedications and Prophylaxis Considerations

- Cell-infusion premedications: acetaminophen & diphenhydramine
  - NO steroids
- No steroids from at least the start of lymphodepleting chemotherapy
- Infection prophylaxis
  - Acyclovir x 12 months
  - Antifungal and fluoroquinolone during neutropenic period
  - TMP/SMX starting D+30 and continue x 6 months or CD4 $\geq 200$ cells/mm$^3$
- Seizure prophylaxis: levetiracetam 500-750 mg PO BID day -1 to day 30

First Gene Therapy Approval: Tisagenlecleucel

- FDA approved for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
- Approved based on a biologic license application by the FDA
- Based on data from ELIANA trial
- Cell dose based on patient weight
  - ≤50 kg: 0.2 to 5.0 x 10^6 cells/kg
  - >50 kg: 0.1 to 2.5 x 10^8 cells
- Black box warning for CRS and neurotoxicity
# Treatment of CRS Related to Tisagenlecleucel

<table>
<thead>
<tr>
<th>CRS Severity</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prodromal Syndrome:</strong></td>
<td>Rule out infection</td>
</tr>
<tr>
<td>• Low-grade fever, fatigue, anorexia</td>
<td>Symptomatic support</td>
</tr>
<tr>
<td><strong>Overt CRS</strong> (one or more of the following):</td>
<td>Administer antipyretics, oxygen, IV fluids and/or low-dose vasopressors as needed</td>
</tr>
<tr>
<td>• High fever, hypoxia, mild hypotension</td>
<td></td>
</tr>
<tr>
<td><strong>Severe or Life-Threatening CRS</strong> (one or more of the following):</td>
<td>Administer high dose/multiple vasopressors, O₂, mechanical ventilation and/or supportive care as needed</td>
</tr>
<tr>
<td>• Hemodynamic instability despite IV fluids and vasopressor support</td>
<td></td>
</tr>
<tr>
<td>• Worsening respiratory distress, ↑ O₂ requirement (high flow O₂ and/or ventilation)</td>
<td></td>
</tr>
<tr>
<td>• Rapid clinical deterioration</td>
<td>Administer tocilizumab</td>
</tr>
</tbody>
</table>

**Resistant CRS:**

• No clinical improvement in 12-18 hours or worsening at any time, despite prior management

As above + methylprednisolone 2mg/kg, then 2mg/kg per day until vasopressors and high-flow O₂ are no longer needed, then taper quickly

If no response to steroids within 24 hrs, repeat tocilizumab.

If no response to 2nd dose within 24 hours, consider a 3rd dose or alternative measures
Tisagenlecleucel is Restricted to Certified Healthcare Facilities

- The tisagenlecleucel product is only available under a Risk Evaluation and Mitigation Strategy (REMS)
- Certified facilities must ensure that healthcare providers who prescribe, dispense or administer are trained in the management of CRS and neurological toxicities.
- Requires immediate access to tocilizumab including 2 doses for each patient within 2 hours of the infusion if needed.

Tisagenlecleucel Price Tag of $475,000... A Bargain?

- Outside estimates prior to approval ranged as high as $700,000
- Price tag understates the total per-patient cost
  - Does not include costs for: pre-infusion treatment, drug administration, hospitalization, or costs associated with adverse events, follow-up, etc.
  - Tocilizumab 800 mg is ~$4800/dose
- The manufacturer has announced:
  - A plan to enter into outcomes-based contracts where it would not charge for the product if the patient does not respond within 30 days
  - Future indications will be priced differently, so the same drug will have more than one price in the marketplace

Tisagenlecleucel: Large Promise at an Enormous Price?

• The Institute for Clinical and Economic Review (ICER) will review CAR-T cost-effectiveness to provide an estimate of the appropriateness of the price : clinical benefit (due 3/16/18)

• Issues to consider
  • Evaluation of CAR-T as an independent treatment vs bridge to HSCT?
  • Comparing CAR-T to HSCT
    • Autologous: median cost within first 100 days $100,000
    • Allogeneic: median cost within first 100 days $200,000; within 1 year $500,000
    • 75% of cost during the initial transplant hospitalization
  • Comparing CAR-T to other drugs
    • Blinatumomab: $178,000 for a 6 week treatment cycle (typically multiple cycles per patient)

Future Directions

**CAR Structure**
Optimal costimulatory signaling domain?

**Optimal Vector**

**Composition & Dose**
Defined Ratio?
Optimal amount of cells?
Multiple infusions?

**Conditioning**
Best lymphodepleting regimen?

**Toxicity**
- Reduce the incidence of CRS
- Pathophysiology of neurotoxicity
  - Optimal treatment

**Sustain Remission**
- Is persistence the goal?
- Independent treatment vs Bridge to HSCT
- Multiple CAR-T infusions
- CD19 negative progression

**Relapse**
?
Conclusions

• CAR-T therapy has demonstrated rapid response rates and improved survival in heavily pretreated patients offering a promising approach for the treatment of refractory malignancies.

• This immunotherapy is associated with unique acute toxicities that require specialized monitoring and management.

• Initial efficacy data needs validation in long term follow up and multicenter clinical trials.

• The final role of CAR T-cells and place in therapy is still to be determined...

Hartmann J, et al.
Emily Whitehead
First CAR-T recipient

THANK YOU

Generating super-soldiers
the production of CAR-T cells

T-cell

CAR-T cell

Chimeric Antigen Receptor

retroviral vector

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