CAR T-Cell Therapy and the Pharmacology of Managing Cytokine Release Syndrome

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Learning Objectives

1. Identify patients who meet criteria as candidates for CAR-T therapy
2. Devise strategies to mitigate cytokine release syndrome and other serious side effects with CAR T-cell therapy in concordance with Risk Evaluation Mitigation Strategy (REMS) requirements
Financial Disclosure

• Dr. Park has nothing to disclose.
• Dr. King has served on advisory boards for Genentech.
Design of a Tumor Targeted Chimeric Antigen Receptor (CAR)

Specificity of antibody target recognition + Effector mechanisms of T cell

Graphic courtesy of Memorial Sloan Kettering Cancer Center
Generation of CAR T Cells

1. Construct a CAR
2. Subclone CAR gene into a vector
3. Transduce and expand patient T cells ex vivo

Retroviral vector encoding CAR cDNA

Graphic courtesy of Memorial Sloan Kettering Cancer Center
CAR T Cells as Cancer Therapy

- T cells are isolated from patient
- T cells are engineered to express CARs that recognize cancer cells
- Modified T cells are grown and expanded in culture
- Modified T cells are infused into patient

Graphic courtesy of Memorial Sloan Kettering Cancer Center
Advantages of CAR T-Cell Therapy

- HLA-independent antigen recognition, therefore universal application
- Target antigens include proteins, carbohydrates and glycolipids
- Rapid generation of tumor-specific T cells
- Minimal risk of GvHD
- A living drug: potential for lasting immunity
- Selective modification of specific T-cell subtypes
- Additional modification capability of CAR construct

GvHD = graft-versus-host disease; HLA = human leukocyte antigen.
CD19 as a Target of B-Cell Malignancies

Stem Cell → pro B → pre B → immature B → mature B → plasma cell

CD19 → CD22 → CD20

Pre B-ALL → B-cell lymphomas and leukemias → myelomas
Evolution in CAR Design

First-generation CAR

Second-generation CAR

Third-generation CAR

mAB scFv
TM domain
Hinge
CD3ζ, or FCRy

One co-stimulatory domain (CD28, 4-1BB, OX-40)

Two co-stimulatory domains (CD28, 4-1BB, OX-40)

Timeline of Clinical Development of CD19 CAR-T Cells in Hematologic Malignancies

2007
- First CLL patient treated with CD19 CAR T cells (MSK)
- First report of ALL eradication in mice with CD19 CAR T cells

2010
- More reports of response in CLL patients t/w CD19 CAR T cells

2011
- First report of response in FL patient t/w CD19 CAR T cells

2013
- Reports of CR in ALL patients t/w CD19 CAR T cells

2014
- Phase II trials of CD19 CAR T cells in ALL/NHL

ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia; CR = complete response; FL = follicular lymphoma; NHL = non-Hodgkin lymphoma.
Poor Prognosis of Relapsed ALL in Adults With Chemotherapy

MRC UKALL2/ ECOG2993 Study (n=609)

Outcome of patients after 1st relapse
5-yr OS: 7%

Age 50+: 3%
Age <20: 12%

LALA-94 Study (n=421)

Outcome of patients after 1st relapse
2-yr OS: 11% & 5-yr OS: 8%

A Phase I Trial of 19-28z CAR T Cells in R/R ALL at MSKCC: Study Outcome

- Overall CR rate: 84.6% (44 of 52 pts)
- MRD-CR rate: 66.6% (32 of 48 evaluable pts)

MRD = minimal residual disease.

## CR Rates by Subgroups

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>N</th>
<th>CR Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>53</td>
<td>83.0</td>
</tr>
<tr>
<td><strong>Disease Burden</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>21</td>
<td>95.2</td>
</tr>
<tr>
<td>Morphological</td>
<td>32</td>
<td>75.0</td>
</tr>
<tr>
<td>Pre-CAR HSCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>34</td>
<td>82.4</td>
</tr>
<tr>
<td>Yes</td>
<td>19</td>
<td>84.2</td>
</tr>
<tr>
<td><strong># of Prior Therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>90.5</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>84.6</td>
</tr>
<tr>
<td>&gt;=4</td>
<td>19</td>
<td>73.7</td>
</tr>
<tr>
<td><strong>Ph Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph−</td>
<td>38</td>
<td>78.9</td>
</tr>
<tr>
<td>Ph+</td>
<td>15</td>
<td>93.3</td>
</tr>
<tr>
<td>Conditioning Chemo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cy/Flu</td>
<td>10</td>
<td>80.0</td>
</tr>
<tr>
<td>Cy</td>
<td>43</td>
<td>83.7</td>
</tr>
<tr>
<td><strong>Age Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–30</td>
<td>14</td>
<td>92.9</td>
</tr>
<tr>
<td>30–60</td>
<td>31</td>
<td>80.6</td>
</tr>
<tr>
<td>&gt;60</td>
<td>8</td>
<td>75.0</td>
</tr>
</tbody>
</table>

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Long-Term Outcome: All Patients

Median follow up: 29 months (range, 1 – 65)

Event-Free Survival
Median EFS: 6.1 mo

Overall Survival
Median OS: 12.9 mo

Long-Term Outcome: By Pretreatment Disease Burden

Event-Free Survival
Median EFS: 10.6 vs. 5.3 mo

Overall Survival
Median OS: 20.1 vs. 12.4 mo

Tisagenlecleucel in Children and Young Adults With R/R B-ALL

- **Phase II, global, 25-center study**
  - Primary endpoint: Overall response in 3 months
- **92 pts enrolled → 75 pts (82%) treated**
  - Median age: 11 (range, 3 to 23)
  - Median prior # of tx: 3 (range, 1 to 8)
  - Prior alloHSCT: 61%
- **Conditioning regimen:** Cy and Flu
- **T-cell dose (median):** $3.1 \times 10^6\text{ CAR T cells/kg}$

Cy = cyclophosphamide; Flu = fludarabine; HSCT = hematopoietic stem cell transplantation; R/R = relapsed/refractory.

Tisagenlecleucel in R/R B-ALL: Remission Duration and Survival

- Overall Response Rate: 81% (60% CR + 21% CRi)

Tisagenlecleucel for B-Cell ALL

- FDA approved August 2017 for treatment of patients up to age 25 years with B-cell precursor ALL that is refractory or in second or later relapse
  - First chimeric antigen receptor T-cell immunotherapy approved by FDA
- FDA approved with a Risk Evaluation and Mitigation Strategy
Clinical Course After CD19 CAR

Pediatric ALL

Adult ALL

## Clinical Efficacy of CD19 CAR T Cells in R/R ALL

<table>
<thead>
<tr>
<th>T-Cell Product</th>
<th>Age, med (range)</th>
<th>No. of Pts.</th>
<th>Prior HSCT</th>
<th>T-Cell Dose</th>
<th>CR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-28z (MSKCC)</td>
<td>44 (23-74)</td>
<td>53</td>
<td>36%</td>
<td>1-3x10^6 CAR T cells/kg</td>
<td>85%</td>
<td>Med OS: 13 mo Med EFS: 6.1 mo Post-CAR HSCT: 39%</td>
</tr>
<tr>
<td>19-41BBz (UPenn)</td>
<td>N/A</td>
<td>12</td>
<td>N/A</td>
<td>4x10^7–1x10^9 CAR T cells</td>
<td>89%</td>
<td>N/A</td>
</tr>
<tr>
<td>19-41BBz (FHRC)</td>
<td>40 (20-73)</td>
<td>30</td>
<td>37%</td>
<td>2x10^6–10^7 CAR T cells/kg</td>
<td>100%</td>
<td>31% relapse (17% died in CR) Post-CAR HSCT: 48%</td>
</tr>
<tr>
<td><strong>Peds</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-41BBz (CTL019)**</td>
<td>12 (3-23)</td>
<td>68</td>
<td>61%</td>
<td>0.2–5x10^6 CAR T cells/kg</td>
<td>83%</td>
<td>Med OS: 19 mo 6 mo EFS: 73% Post-CAR HSCT: 12%</td>
</tr>
<tr>
<td>19-28z (NCI)</td>
<td>14 (5-27)</td>
<td>20</td>
<td>38%</td>
<td>1-3x10^6 CAR T cells/kg</td>
<td>70%</td>
<td>6 mo OS: ~65% Post-CAR HSCT: 71%</td>
</tr>
<tr>
<td>19-41BBz (SCRI)</td>
<td>12 (1-25)</td>
<td>45</td>
<td>62%</td>
<td>0.5–10x10^6 CAR T cells/kg</td>
<td>89%</td>
<td>12 mo EFS: 51% (45% relapse) 12 mo OS: 70%</td>
</tr>
</tbody>
</table>

References:
Axicabtagene Ciloleucel in R/R DLBCL [ZUMA-1]: Overall Response

- Overall response rate: 82% (54% CR + 28% PR)

DLBCL = diffuse large B-cell lymphoma; PR = partial response.

Axicabtagene in R/R DLBCL: Remission Duration and Survival

Median F/u: 15.4 months
OS at 18 months: 52%

CD19 CARs Approved for Large B-Cell Lymphoma

- FDA approved axicabtagene October 2017 for treatment of adult patients with relapsed or refractory large B-cell lymphoma after ≥2 lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and diffuse large B-cell lymphoma arising from follicular lymphoma.
- FDA approved tisagenlecleucel May 2018 for treatment of adult patients with relapsed or refractory large B-cell lymphoma after ≥2 lines of systemic therapy, including DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
- FDA approved with a Risk Evaluation and Mitigation Strategy.
Timeline of Clinical Development of CD19 CAR T Cells in Hematologic Malignancies

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- First CLL patient treated with CD19 CAR T cells (MSK)
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2011
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2013
- Phase II trials of CD19 CAR T cells in ALL/NHL

2014
- Approval of CD19 CAR T cells in ALL & NHL

2017
- Trials of
  1) “Armored” CAR T cells,
  2) Bi-specific or novel target CAR T cells
  3) Combination with immunomodulators

2018-9
- Phase II trials of 1) “Armored” CAR T cells, 2) Bi-specific or novel target CAR T cells, 3) Combination with immunomodulators
CD19 and CD22-Bispecific CAR T Cells

Universal or “off-the-shelf” CAR T Cells

Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells

Waseem Qasim,1,2# Hong Zhan,1 Sujith Samarasinghe,2 Stuart Adams,2 Persis Amrolia,1,2 Sian Stafford,1 Katie Butler,1 Christine Rivat,1 Gary Wright,2 Kathy Somana,2 Sara Ghorashian,1 Daniella Pinner,2 Gul Ahsan,2 Kimberly Gilmour,2 Giovanna Lucchini,2 Sarah Inglett,2 William Mifsud,2 Robert Chiesa,2 Karl S. Peggs,2 Lucas Chan,4 Farzin Farzaneh,4 Adrian J. Thrasher,1 Ajay Vora,4 Martin Pule,4 Paul Veyts1

Study Updates

PALL study of pediatric ALL:
- 5 children treated
- CRS: 1 Gr1, 3 Gr2 and 1 Gr3
- 4/5 pts w/ viral complications
- Response: 5/5 CRi → alloHSCT → 2 relapse, 1 death in CR and 2 alive in CR

CALM study of adult ALL:
- 6 adults treated (4 MRD+ pts)
- CRS: 1 Gr1, 4 Gr2, 1 Gr4 → 1 death on D15
- Response: 4/6 Cri → alloHSCT → 1 relapse, 1 death in CR and 2 alive in CR

Qasim W et al. ASH 2017, Abstract 1271; Graham C et al. ASH 2017, Abstract 887

Disruption of CD52 gene & TRAC (loss of TCRαβ)

Qasim et al. Sci Transl Med 2017
Common Toxicities of CD19 CAR T cells

<table>
<thead>
<tr>
<th>Cytokine Release Syndrome (CRS) Clinical Spectrum</th>
<th>Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Delirium</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Global encephalopathy</td>
</tr>
<tr>
<td>Capillary leak</td>
<td>Aphasia</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>Seizure, seizure-like activity</td>
</tr>
<tr>
<td>Hyperferritinemia/MAS</td>
<td>Tremor/myoclonus</td>
</tr>
<tr>
<td>Coagulopathy/DIC</td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>“CAR T cell related encephalopathy syndrome (CRES)”</td>
</tr>
<tr>
<td>Symptoms rapidly resolve with IL-6R blockade</td>
<td>Rapid onset cerebral edema</td>
</tr>
<tr>
<td></td>
<td>Severe symptoms do not resolve with IL-6R blockade</td>
</tr>
</tbody>
</table>
### CD19 CAR Associated CRS and NTX Incidences

<table>
<thead>
<tr>
<th>T Cell Product</th>
<th>Disease</th>
<th>No. of Patients</th>
<th>CRS, All grades (%)</th>
<th>≥Gr3 CRS (%)</th>
<th>≥Gr3 NTX (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-28z (MSK)</td>
<td>ALL</td>
<td>53</td>
<td>85</td>
<td>26</td>
<td>41</td>
</tr>
<tr>
<td>KTE-C19 (ZUMA-3)</td>
<td>ALL</td>
<td>29</td>
<td>93</td>
<td>28</td>
<td>52</td>
</tr>
<tr>
<td>KTE-C19 (ZUMA-1)</td>
<td>DLBCL</td>
<td>101</td>
<td>93</td>
<td>13</td>
<td>28</td>
</tr>
<tr>
<td>CTL019 (JULIET)</td>
<td>DLBCL</td>
<td>99</td>
<td>58</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>JCAR017 (TRANSCEND)</td>
<td>DLBCL</td>
<td>55</td>
<td>35</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>CTL019 (ELIANA)</td>
<td>ALL</td>
<td>75</td>
<td>77</td>
<td>47</td>
<td>13</td>
</tr>
<tr>
<td>JCAR017 (PLAT-02)</td>
<td>ALL</td>
<td>43</td>
<td>93</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>19-28z (NCI)</td>
<td>ALL</td>
<td>21</td>
<td>76</td>
<td>29</td>
<td>5</td>
</tr>
</tbody>
</table>

CRS Is Associated With Elevated Proinflammatory Cytokines

High Tumor Burden and Greater in vivo T-Cell Expansion Correlate With CAR-Associated Toxicity

Muller K et al. Blood 2017;130(21):2317-2325
Severity of CRS Correlates With CAR T-Cell Dose in ALL

**CTL019 in Adult Patients with R/R B-ALL**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose</th>
<th>Schedule</th>
<th>N</th>
<th>CRS ≥ Gr 3, %</th>
<th>Response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>High dose (5 x 10⁸)</td>
<td>Split</td>
<td>15</td>
<td>66</td>
<td>86 (0 TRM)</td>
</tr>
<tr>
<td>2</td>
<td>High dose (5 x 10⁸)</td>
<td>Single</td>
<td>6</td>
<td>100</td>
<td>100 (3 TRM)</td>
</tr>
<tr>
<td>3</td>
<td>Low dose (5 x 10⁷)</td>
<td>Split</td>
<td>6</td>
<td>66</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>Low dose (5 x 10⁷)</td>
<td>Single</td>
<td>3</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>---</td>
<td>---</td>
<td>30</td>
<td>75</td>
<td>72 (3 TRM)</td>
</tr>
</tbody>
</table>

Frey N et al. ASCO 2016 Annual Meeting. Abstract 7002
CRS Is Abrogated by IL-6 Blockade
Santomasso B & Park J et al. Cancer Discovery 2018

Neurotoxicity in Relation to CRS

A

Gr 1-2 NTX

Gr 3-4 NTX

0 7 14 21 28

first fever median (D2)

first sNTX median (D9)

Days post CAR

NTX Gr 0
NTX Gr 1
NTX Gr 2
NTX Gr 3
NTX Gr 4
Death

Santomasso B & Park J et al. Cancer Discovery 2018
NTX Correlates With T-Cell Expansion and CSF Protein

Santomasso B & Park J et al. Cancer Discovery 2018
Pharmacotherapy in Cytokine Release Syndrome

Supportive Care Modalities:
Fever
Hypotension
Supportive Care Pharmacotherapy: Fever

- Antipyretics (e.g., acetaminophen)
- Broad-spectrum antibiotics
  - Blood cultures, radiographic studies, frequent vital sign checks
- Consideration of G-CSF (e.g., filgrastim) if neutropenic

Supportive Care Pharmacotherapy: Hypotension

- **Fluid boluses**
  - 0.9% normal saline recommended
  - 500–1000 mL
  - Escalate to vasopressors, tocilizumab, and/or glucocorticoids after failure of response

- **Vasopressors**
  - Escalation to high dose or multiple pressors → tocilizumab and/or glucocorticoids

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<table>
<thead>
<tr>
<th>Vasopressor</th>
<th>High Dose Equivalents (must be on ≥3 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>≥ 20 µg/kg/min</td>
</tr>
<tr>
<td>Dopamine</td>
<td>≥ 10 µg/kg/min</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>≥ 200 µg/kg/min</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>≥ 10 µg/kg/min</td>
</tr>
<tr>
<td>Norepinephrine + vasopressin</td>
<td>≥ 10 µg/kg/min</td>
</tr>
<tr>
<td>Combo vasopressin (non-vasopressin)</td>
<td>≥ 20 µg/kg/min of norepinephrine equiv.</td>
</tr>
</tbody>
</table>

Pharmacotherapy in Cytokine Release Syndrome

Tocilizumab
**IL-6 (Interleukin-6)**

- Correlation between severity of CRS and serum IL-6 levels
- IL-6 can signal multiple ways:
  - Direct binding to membrane bound IL-6R and gp130 complex (classic signaling)
  - Direct binding to soluble IL-6R → interaction with membrane bound gp130 (trans-signaling)

*Gp130 – glycoprotein 130*

Tocilizumab

• Interleukin-6 receptor antagonist (IL-6R Antagonist)
• Available as subcutaneous (SC) or intravenous (IV) injection
  • Intravenous recommended for cytokine release syndrome (CRS)
• FDA approved
  • CRS:
    • Patients $\geq$ 2 years of age after CAR-T cell induced CRS (severe or life-threatening)
Tocilizumab: IL-6

- Tocilizumab binds to both soluble and membrane-bound IL-6 receptors
- Mitigates downstream activation of JAK/STAT pathway/pro-inflammatory effects
- Serum IL-6 levels have been shown to increase after doses
  - IL-6 displaced by tocilizumab at receptor
  - Concern for increased risk of neurotoxicity
    - Potential increased uptake of IL-6 into CNS

Tocilizumab: Administration

- Dosing based on weight (cap at 800 mg per infusion):
  - >30 kilograms: 8 mg/kg intravenously
  - <30 kilograms: 12 mg/kg intravenously
- Infusion over 60 minutes
  - Prepared in 0.45% or 0.9% normal saline
- If no clinical improvement tocilizumab may be re-dosed
  - Minimum 8-hour interval between doses
  - Limit to a maximum of 4 total doses
- Commercial CAR T cell products (REMS requirement):
  - At least two doses of tocilizumab required on site per CAR T-cell patient
Tocilizumab: Pharmacokinetics

- Onset (CRS): Median time to defervescence = 4 hours
- Renal: No adjustment required for mild or moderate dysfunction
  - Minimal clinical data for creatinine clearance (CrCl) <50 mL/min
- Hepatic: Caution if baseline AST/ALT >1.5 x ULN
  - The decision to administer in CRS should take into account risk vs. benefit profile
- Drug-Drug Interactions:
  - IL-6 elevation may lead transient inhibition of various CYP enzymes
    - Function restored in vitro with tocilizumab administration
  - Recommended therapeutic monitoring with high-risk medications
  - Sensitive drug substrate concentrations may increase or decrease
## Tocilizumab: Adverse Effects

### Non-CRS Population

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>Dizziness, headache</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea/vomiting, diarrhea</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Hepatitis, increased ALT/AST/bilirubin</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Local irritation/rash (2%)</td>
</tr>
<tr>
<td>Renal</td>
<td>Nephrolithiasis (&lt;2%)</td>
</tr>
<tr>
<td>Infection</td>
<td>Upper respiratory tract infection, herpes simplex</td>
</tr>
</tbody>
</table>

### CRS Population

- Retrospective analysis
  - Adult and pediatric patients
- No adverse effects independently attributable to tocilizumab (intravenous)
  - No differences in adults vs. pediatrics

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Le, et al. The Oncologist. Aug 2018;23(8)
Genentech Inc. Actema (tocilizumab) package insert. San Francisco, CA 2017
Tocilizumab: Clinical Evidence

Pooled retrospective analysis from CTL019 and KTC-C19 trials

- Open-label; multicenter phase II trial
- N= 60
- Received tocilizumab for life threatening or severe CRS
- Primary objective:
  - Characterize CRS resolution

**Intervention**
- Tocilizumab 8 mg/kg (adults)
- Tocilizumab 12 mg/kg (peds)

**CRS resolution:** Absence of fever and off vasopressors for at least 24 hours

**Responders:**
- CRS resolved within 14 days of first dose
- ≤2 doses of tocilizumab
- Assessments at 2, 7, and 21 days post first dose

# Tocilizumab: Clinical Evidence (Demographics)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>CTI019 CAR-T</th>
<th>KTC-C19 CAR-T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of age (range)</td>
<td>12 (3-23)</td>
<td>60 (9-75)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>24 (53.3%)</td>
<td>10 (66.7%)</td>
</tr>
<tr>
<td>F</td>
<td>21 (46.7%)</td>
<td>5 (33.3%)</td>
</tr>
<tr>
<td>Underlying Malignancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>45 (100%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>DLBCL</td>
<td>0</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>PMBCL</td>
<td>0</td>
<td>1 (6.7%)</td>
</tr>
</tbody>
</table>

PMBCL = primary mediastinal B-cell lymphoma.

Le, et al. The Oncologist. Aug 2018;23(8)
Tocilizumab: Clinical Evidence (Demographics)

<table>
<thead>
<tr>
<th>Characteristics and treatment</th>
<th>CTL019 CAR-T</th>
<th>KTC-C19 CAR-T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CRS grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>10 (22.2%)</td>
<td>14 (93.3%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>35 (77.8%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Baseline CRS duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4 days</td>
<td>23 (51.5%)</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>4+ days</td>
<td>22 (48.9%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Doses of tocilizumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>25 (55.5%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>2</td>
<td>13 (28.9%)</td>
<td>5 (33.3%)</td>
</tr>
<tr>
<td>3+</td>
<td>7 (15.6%)</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td>Initial dose of tocilizumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 mg/kg</td>
<td>38 (84.4%)</td>
<td>15 (100%)</td>
</tr>
<tr>
<td>12 mg/kg</td>
<td>7 (15.6%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Le, et al. The Oncologist. Aug 2018;23(8)
# Tocilizumab: Clinical Evidence (Results)

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>CTL019 CAR-T n (%, 95% CI)</th>
<th>KTC-C19 CAR-T n (%, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response by D14</td>
<td>31 (68.9%, 53.4 – 81.8)</td>
<td>8 (53.3%, 26.6 – 78.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional Outcomes</th>
<th>CTL019 CAR-T n (%, 95% CI)</th>
<th>KTC-C19 CAR-T n (%, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response by D2</td>
<td>9 (20%, 9.6-34.6)</td>
<td>3 (20%, 4.3-48.1)</td>
</tr>
<tr>
<td>Response by D7</td>
<td>26 (57.8%, 42.2 – 72.3)</td>
<td>8 (53.3%, 26.6 – 78.7)</td>
</tr>
<tr>
<td>Response by D21</td>
<td>31 (68.9, 53.4 – 81.8)</td>
<td>8 (53.3%, 26.6-78.7)</td>
</tr>
</tbody>
</table>
Tocilizumab: Clinical Evidence (Safety)

• No reports of adverse drug reactions attributable to tocilizumab

• Even number of deaths in both CTL019 and KTC-C19
  • 5 deaths in each group within 30 days of first tocilizumab

• Pharmacokinetic data supports safety of dosing range of up to 4 doses given 8 hours apart

Tocilizumab: Concerns With Efficacy?

- Tocilizumab has NOT been demonstrated to blunt efficacy of CAR T-cell therapy
- Axicabtagene ciloleucel trial
  - Rates of overall response did not differ (subgroup analysis) among tocilizumab users

<table>
<thead>
<tr>
<th>Tocilizumab Use</th>
<th>Patient Events</th>
<th>Objective Response Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>36 events out of 43 evaluable pts</td>
<td>0.84 (26.6–78.7)</td>
</tr>
<tr>
<td>No</td>
<td>47 events of out 58 evaluable pts</td>
<td>0.81 (0.69–0.90)</td>
</tr>
</tbody>
</table>

Tocilizumab: Clinical Evidence (Summary)

• Only FDA-approved agent for CRS management
• Strongly recommend for patients if progression despite supportive care modalities (e.g., grade 2 and beyond)
• FDA approval based on pooled retrospective series
  • Appropriate based on population/severity of illness
  • Studies not powered to specifically assess for tocilizumab toxicity or efficacy
• Unlikely to diminish efficacy of CAR-T cells based on currently available data
• More studies/real world experience needed to elucidate best practices for use of tocilizumab
Pharmacotherapy in Cytokine Release Syndrome (CRS)

Siltuximab
Siltuximab

- Interleukin-6 antagonist (IL-6 antagonist)
  - Chimeric monoclonal antibody
- Available as intravenous (IV) injection only
- Expert opinion:
  - Consider for salvage treatment of CRS refractory to tocilizumab/corticosteroid
Siltuximab: Mechanism

- Siltuximab binds directly to IL-6
- Prevents binding of IL-6 to both soluble and membrane-bound IL-6 receptors
- Lowers serum IL-6 levels

Siltuximab: Administration

- Dosing based on weight (*no known dose cap*):
  - 11 mg/kg
  - Dosing extrapolated from use in Castleman’s disease
- Infusion over 60 minutes
  - Prepared in 250 mL of D5W
  - Must be administered within 4 hours of reconstitution
- No data available re: dosing intervals
Siltuximab

• Routine first line use is NOT generally recommended
  • Absence of published data
• Mechanism of action suggests less risk of “IL-6 flare” seen with tocilizumab
• Strongly consider for refractory CRS when:
  • Suboptimal response after tocilizumab + glucocorticoid
  • Concern for overlapping neurotoxicity
• Studies ongoing to establish role of siltuximab in CRS management

Pharmacotherapy in Cytokine Release Syndrome (CRS)

Glucocorticoids
Glucocorticoids: Mechanism

- Decreases inflammation by suppression of neutrophil migration
- Decreased transcription of:
  - IL-1, IL-2, IL-6
  - TNF-a
  - Bradykinin
- Increases transcription of:
  - IL-1 receptor antagonist
  - Secretory leukocyte inhibitory protein

Glucocorticoids: Selected Agents

Dexamethasone
- Long-acting (t(1/2) = 36-72h)
- Five times the potency of methylprednisolone
- Partial metabolism in choroid plexus
  - CNS Penetration
- Proposed dosing
  - Dexamethasone 0.5 mg/kg (max 10 mg/dose) followed by taper

Methylprednisolone
- Intermediate-acting (t(1/2)= 8-12h)
- Poor CNS penetration
- Proposed dosing
  - 2 mg/kg/day followed by taper

Glucocorticoids: Adverse Effects

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Hypertension, tachycardia, thromboembolism, fluid retention</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Depression, emotional lability, euphoria</td>
</tr>
<tr>
<td>Endocrine/metabolic</td>
<td>Hyperglycemia, adrenal suppression, hypokalemia</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Peptic ulcers, GI hemorrhage, increased appetite, esophagitis</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Lymphopenia</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Acne vulgaris, hyperpigmentation, skin atrophy, cataracts</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>Opportunistic, fungal, and viral infection</td>
</tr>
</tbody>
</table>

Glucocorticoids: Concerns With Efficacy?

- Diminish the expansion and persistence of T cells → concern of limiting of effectiveness of CAR-T cells
  - Attempt to reserve use only when CRS is refractory to tocilizumab/other intervention
- Axicabtagene ciloleucel trial
  - Rates of overall response did not differ (subgroup analysis) among glucocorticoid users

<table>
<thead>
<tr>
<th>Glucocorticoid Use</th>
<th>Patient events</th>
<th>Objective Response Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>27 events out of 21 evaluable pts</td>
<td>0.78 (26.6 – 78.7)</td>
</tr>
<tr>
<td>No</td>
<td>74 events of out 62 evaluable pts</td>
<td>0.84 (0.69-0.90)</td>
</tr>
</tbody>
</table>

Glucocorticoids: Clinical Evidence (Summary)

- Suppress inflammatory response
  - Strongly consider for CRS that is refractory to tocilizumab
- Dexamethasone and methylprednisolone are drugs of choice
  - Dosing range varies based on grade of CRS and concern for overlapping neurotoxicity
- Some data suggest steroids may not mitigate response to CAR-T cells
  - More prospective/controlled data needed to assess true steroid effect
- Concerns for decreased T-cell expansion/decreased efficacy require caution with routine glucocorticoid use

Case Study

AK is a 24-year-old female with R/R B-cell ALL who is day +2 of anti-CD19 CAR-T therapy. The RN pages you to report a fever ($T_{\text{max}}$ 101.3F) and hypotension (BP: 89/70). Patient is A&O x4 after exam. Which of the following the most appropriate intervention for AK at this current time?

A. NS fluid bolus of 1L, antipyretics, broad spectrum antibiotics, blood cultures, chest x-ray
B. NS fluid bolus of 1L, dexamethasone, norepinephrine, blood cultures, chest x-ray,
C. Tocilizumab, blood cultures, chest x-ray, broad spectrum antibiotics
D. NS fluid bolus of 1L, dexamethasone, broad spectrum antibiotics
You are called to bedside about 1 hour after your previous intervention. AK is now persistently febrile with a SBP of 80/60. The ICU is consulted, and she is started on low-dose vasopressors. Patient remains alert and oriented upon exam but is visibly diaphoretic and is still febrile; blood cultures return negative. What agent is most appropriate to consider at this time?

A. Vancomycin  
B. Tocilizumab  
C. Dexamethasone  
D. Siltuximab
Case Study (continued)

AK’s symptoms resolve within 3 hours after receipt of tocilizumab. Unfortunately, AK experiences a resurgence of febrile episodes and hypotension. She is transferred to the ICU for further management. After 3 doses of tocilizumab and high-dose vasopressors, she remains hypotensive, febrile, and is now only minimally responsive. What agent is most appropriate to consider at this time?

A. Additional dose of tocilizumab (patient has not reached max dose recommendation)
B. Siltuximab
C. Dexamethasone
D. Methylprednisolone
Future Directions

- Role of prophylactic tocilizumab for at risk patients
- Role of siltuximab in the treatment or prevention of CRS
- Other anti-inflammatory therapies
  - Anakinra
- Formal consensus guidelines for CRS management
  - Which agents?
  - When to use?
  - When to combine?
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Our Patients!!!
Thank You for Your Attention!

Please email with any questions:
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