Cellular Therapy for Diffuse Large B Cell Lymphoma
Activity Overview
The goal of this activity is to review currently available CAR T Cell therapies for diffuse large B cell lymphoma. Topics to be covered include patient eligibility criteria, complications, outcomes and treatment guidelines.

Target Audience
This activity is intended for medical oncologists, hematologists, and primary care physicians.

Instructions to Receive Credit
To receive credit, read the introductory CME material, watch the webcast, and complete the evaluation, attestation, and post-test, answering at least 70% of the post-test questions correctly.
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Med-IQ requires any person in a position to control the content of an educational activity to disclose all relevant financial relationships with any commercial interest. The ACCME defines “relevant financial relationships” as those in any amount occurring within the past 12 months, including those of a spouse/life partner, that could create a conflict of interest (COI). Individuals who refuse to disclose will not be permitted to contribute to this CME activity in any way. Med-IQ has policies in place that will identify and resolve COIs prior to this educational activity. Med-IQ also requires faculty to disclose discussions of investigational products or unlabeled/unapproved uses of drugs or devices regulated by the US Food and Drug Administration.
The content of this activity has been peer reviewed and has been approved for compliance. The faculty and contributors have indicated the following financial relationships, which have been resolved through an established COI resolution process, and have stated that these reported relationships will not have any impact on their ability to give an unbiased presentation.

Christine Ho, MD, has indicated no real or apparent conflicts.

The peer reviewers and activity planners have no financial relationships to disclose.
Upon completion, participants should be able to:

• Understanding which point in a patient’s treatment, that a cellular therapy option is available

• Identification and treatment plans for complications associated with CAR T cell therapy

• Understand what preliminary outcomes are for this course of treatment
Cellular Therapy for Diffuse Large B Cell Lymphoma
B-Cell Lymphomas

- Non-Hodgkin’s lymphoma (NHL) is the 7th leading cause of new cancer cases in the United States.
- NHL accounts for approximately 3% of cancer-related deaths in the US.
- Subtypes of NHL:
  - Diffuse large B cell lymphoma (DLBCL)- 32.5%
  - Follicular lymphoma (FL)- 17.1%
  - Mantle-cell lymphoma (MCL)- 3-5%
- DLBCL
  - MYC-rearranged DLBCL
  - High-grade B-cell lymphoma with MYC, BCL2 or BCL rearrangements
  - Activated B-cell (ABC) DLBCL
Anatomy of a Chimeric Antigen Receptor (CAR)


A single-chain variable fragment (scFv) is not actually a fragment of an antibody, but instead is a fusion protein of the variable regions of the heavy and light chains of immunoglobulins, connected with a short linker peptide.
Generations of CAR T Cells

First Generation CAR
- scFv
- VH
- VL
- hinge
- CD3ζ

Second Generation CAR
- One Costimulation Domain
- (4-1BB or CD28)
- CD3ζ

Third Generation CAR
- Two costimulation domains
- CD27
- CD28
- ICOS
- 4-1BB
- OX40
CAR T-Cell Therapy Process

1. **T cells are isolated from patient**
2. **T cells are engineered 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**
Cellular Products (as of Feb 2020)

• **Tisagenlecleucel (CTL019, Novartis, Kymriah)**
  – August 2017: Approved for R/R B-cell precursor ALL (pediatric or young adult patient ≤ 25 years old)
  – May 2018: Approved for adult patients with R/R large B-cell lymphoma after ≥ 2 lines of systemic treatment

• **Axicabtagene ciloleucel (KTE-019, KITE, Yescarta)**
  – October 2017: Approved for adult patients with R/R large B-cell lymphoma after ≥ 2 lines of systemic treatment

• **Lisocabtagene maraleucel (JCAR017, BMS)**
  – February 2020: FDA priority review for R/R large B-cell lymphoma
Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

Phase 2 ZUMA-1

Phase 1 (n=7)

- Refractory DLBCL / PMBCL / TFL (n=7)

Phase 2 (n=101)

- Cohort 1: Refractory DLBCL (n=77)
- Cohort 2: Refractory PMBCL/TFL (n=24)

RESULTS:

- Axi-cel could be centrally manufactured and administered safely.
- Overall response seen in 5 patients.
- Complete response seen in 4 patients.
- Ongoing CR seen in 3 patients at 1 year.

- Refractory disease = progressive or stable disease as the best response to most recent chemo or disease progression or relapse within 12 mos after ASCT
- Conditioning regimen of Fludarabine 30mg/m2 and Cyclophosphamide 500mg/m2 on Days -5, -4, and -3.
- Axi-cel administered at a target dose of $2 \times 10^6$/kg on Day 0.
A total of 111 patients were enrolled.

Axi-cel was manufactured for 110 patients (99%).

Axi-cel was administered to 101 patients (91%).

Reasons patients did not receive the product:
- Unsuccessful manufacture (n=1)
- Adverse events (n=4)
- Died from disease progression (n=1)
- Unmeasurable disease (n=2)
- Sepsis (n=1)
- Death, multifactorial (n=1)

Median time from leukapheresis to delivery of Axi-cel to treatment facility was 17 days.
Endpoints

• Primary endpoint:
  – Rate of objective response (combined rates of complete response and partial response).

• Secondary endpoints included:
  – Duration of response
  – Progression-free survival
  – Overall survival
  – Incidence of adverse events
  – Blood levels of CAR T cells and serum cytokines

• Cytokine release syndrome was graded by the Lee criteria.
• Median follow up was 15.4 months.
Results (at a minimum of 6 months of f/u)

- At a minimum of 6 months of follow up:
  - Objective response rate = 82%
  - Complete response rate = 52%
  - Median time to response = 1 month (range 0.8-6)
  - Median duration of response = 8.1 months

- Response rates were consistent across key covariates:
  - Age, disease stage, IPI score, presence or absence of bulky disease, COO subtype, use of tocilizumab or steroids
Results (at a minimum of 1 year of f/u)

- ORR = 82%
- CR = 58%
- Median DOR = 11.1 months (95% CI, 3.9 to could not be estimated)
- Median duration of PFS = 5.8 months (95% CI, 3.3 to could not be estimated)
- Median OS = not reached (95% CI, 12.0 months to could not be estimated)
## Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 1 or 2</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td>number of patients (percent)</td>
<td>number of patients (percent)</td>
</tr>
<tr>
<td>Any</td>
<td>101 (100)</td>
<td>5 (5)</td>
<td>96 (95)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>86 (85)</td>
<td>72 (71)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>85 (84)</td>
<td>6 (6)</td>
<td>79 (78)</td>
</tr>
<tr>
<td>Anemia</td>
<td>67 (66)</td>
<td>24 (24)</td>
<td>43 (43)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>60 (59)</td>
<td>46 (46)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>59 (58)</td>
<td>21 (21)</td>
<td>38 (38)</td>
</tr>
<tr>
<td>Nausea</td>
<td>59 (58)</td>
<td>59 (58)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>52 (51)</td>
<td>50 (50)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>50 (50)</td>
<td>48 (48)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Headache</td>
<td>47 (47)</td>
<td>46 (46)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>43 (43)</td>
<td>39 (39)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>41 (41)</td>
<td>40 (40)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>40 (40)</td>
<td>34 (34)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Chills</td>
<td>39 (39)</td>
<td>39 (39)</td>
<td>0</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>39 (39)</td>
<td>37 (37)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>35 (35)</td>
<td>4 (4)</td>
<td>31 (31)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>34 (34)</td>
<td>13 (13)</td>
<td>21 (21)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>59 (58)</td>
<td>21 (21)</td>
<td>38 (38)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34 (34)</td>
<td>33 (33)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>33 (33)</td>
<td>30 (30)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Hyponatrema</td>
<td>33 (33)</td>
<td>23 (23)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Constipation</td>
<td>31 (31)</td>
<td>31 (31)</td>
<td>0</td>
</tr>
<tr>
<td>White-cell count decreased</td>
<td>31 (31)</td>
<td>2 (2)</td>
<td>29 (29)</td>
</tr>
</tbody>
</table>
Cytokine Release Syndrome and Neurotoxicity

CRS:
- The most common symptoms of CRS of ≥grade 3 were pyrexia (11%), hypoxia (9%), and hypotension (9%).
- The median time to resolution of CRS was 8 days.
- All events of CRS resolved except for one event of grade 5 HLH and one event of grade 5 cardiac arrest.

Neurotoxicity:
- The most common neurotoxicity events of ≥grade 3 were encephalopathy (21%), confusional state (9%), aphasia (7%), and somnolence (7%).
- The median time to resolution was 17 days after infusion.
- All neurologic events resolved except for 4 events.

### CRS:
<table>
<thead>
<tr>
<th>Study</th>
<th>Z UMA-1 (Locke, 2018)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No patients enrolled [treated]</td>
<td>111 [101]</td>
</tr>
</tbody>
</table>

**Cytokine-release syndrome**:  
- Time to onset, median, range  
  - Duration, median, range 2 days [1–12]  
  - Grade 1:  
  - Grade 3 or 4: 8 days [NR]  
  - Tocilizumab use: 93%  
  - Vasopressors use: 13%  
  - Steroid treatment: 63%  
  - ICU admission: 17%  
  - 27%

**Infections**  
- All grades: 35%  
- Grade 3 or 4: 31%

**Neurotoxicity**:  
<table>
<thead>
<tr>
<th>Study</th>
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</thead>
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<td>No patients enrolled [treated]</td>
<td>111 [101]</td>
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</table>

- Time to onset, median (range) 5 days [1–17]  
- Duration, median, range 17 days [NR]  
- All grades: 64%  
- Grade 3 or 4: 28%
Expansion and Biomarkers

- CAR T levels peaked in the peripheral blood within 14 days of infusion.
- CAR T cells were detectable in most patients at 180 days after infusion.
- Expansion was significantly associated with response (P<0.001).
- Peak expansion was significantly associated with neurologic events ≥grade 3 but not with CRS.
- Serum biomarkers associated with neurotoxicity and CRS included IL-6, IL-10, IL-15, and granzyme B.
Conclusions

1. Responses were ongoing in 42% of patients, including in 40% with a CR with a median follow up of 15.4 months.

2. Some patients converted to a CR as late as 15 months after treatment.

3. Ongoing durable remissions were observed as far out as 24 months.

4. The overall survival rate was 52% at 18 months although the median overall survival had not been reached.

5. CRS and neurotoxicity were generally reversible.

6. The use of tocilizumab or steroids did not affect overall responses.

7. Axi-cel is an effective and safe treatment option for patients with relapsed or refractory large B cell lymphoma after at least 2 prior therapies.
Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Stephen J. Schuster, M.D., Michael R. Bishop, M.D., Constantine S. Tam, M.D., Edmund K. Waller, M.D., Ph.D., Peter Borchmann, M.D., Joseph P. McGuirk, D.O., Ulrich Jäger, M.D., Samantha Jaglowski, M.D., Charalambos Andreadis, M.D., Jason R. Westin, M.D., Isabelle Fleury, M.D., Veronika Bachanova, M.D., Ph.D., S. Ronan Foley, M.D., P. Joy Ho, M.B., B.S., D.Phil., Stephan Mielke, M.D., John M. Magenau, M.D., Harald Holte, M.D., Ph.D., Serafino Pantano, Ph.D., Lida B. Pacaud, M.D., Rakesh Awasthi, Ph.D., Jufen Chu, Ph.D., Özlem Anak, M.D., Gilles Salles, M.D., Ph.D., and Richard T. Maziarz, M.D., for the JULIET Investigators*
Eligibility Criteria:
• Previously received at least two lines of therapy including Rituxan and an anthracycline
• Patients had either had a relapse after or were ineligible for autologous transplant
• Relapsed/refractory DLBCL, DLBCL transformed from follicular lymphoma, high-grade B-cell lymphoma with MYC rearrangement plus rearrangement of BCL2, BCL6, or both genes

Exclusion:
• Primary mediastinal DLBCL
• Prior treatment with CD19-directed therapy, prior allo transplant
• Active CNS disease

* Fludarabine/cyclophosphamide or Bendamustine
Patient Characteristics

- Prior to infusion, 92% of the patients received bridging chemotherapy.
- 73% received Fludarabine/Cyclophosphamide
- 20% received Bendamustine
- 111 patients received an infusion of Tisa-cel
Endpoints

- Primary endpoint:
  - Best overall response rate (combined percentage of patients who had a CR or PR)
- Secondary endpoints:
  - Response duration
  - Overall survival
  - Safety
  - Cellular kinetics
- Exploratory analysis:
  - Evaluation of biomarkers
Results

- 93 patients were included in the efficacy analysis.
- These patients had ≥3 months of follow up.
- Best overall response rate = 52%
  - Complete response = 40%
  - Partial response = 12%
- A conversion from partial to complete response occurred in 54% of patients (some occurring 15-17 months after the initial response).
- Among the patients who were in CR at 3 months, the estimated probability of remaining in CR at 12 months was 81%.
- Response rates did not differ across major demographic or prognostic subgroups.
Results

- Median duration of response = not reached.
- Durable responses were observed for up to 18.4 months after infusion.
- Median PFS =
  - Not reached for patients in CR
  - Estimated rate of PFS at 12 months was 83% for pts who had a CR or PR at 3 months
- Median OS = 12 months
- Estimated probability of survival at 12 months was 49% for all pts and 90% for pts in CR.
• Persistent CAR transgene levels were detected for up to 2 years after infusion in patients with durable responses.

• Clinical responses were observed across various doses.

• For both responders and non-responders, expansion, concentration and median time to maximum transgene levels were similar.
Safety

- Most common AEs of any grade was CRS (58%), anemia (48%), fever (35%).
- Median time from infusion to onset of CRS was 3 days. Median duration was 7 days.
  - Pts were treated with tocilizumab or toci + steroids.
- Neurotoxicity occurred in 21% of pts. Median duration was 14 days.
  - 9 pts with grade 3 or 4 neuro events had concurrent CRS.
  - Treatment = supportive + steroids

### Table 1. Overall Safety of Tisagenleculocyt

<table>
<thead>
<tr>
<th>Type of Adverse Event</th>
<th>Patients with Any Event (N = 211)</th>
<th>Patients with Events Starting ≤ 6 Wk after Infusion (N = 111)</th>
<th>Patients with Events Starting &gt; 6 Wk after Infusion (N = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>111 (100%)</td>
<td>111 (100%)</td>
<td>69 (72%)</td>
</tr>
<tr>
<td>Adverse event suspected to be related to study drug</td>
<td>96 (86%)</td>
<td>46 (41%)</td>
<td>46 (41%)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>55 (50%)</td>
<td>30 (27%)</td>
<td>25 (28%)</td>
</tr>
<tr>
<td>Serious adverse event suspected to be related to study drug</td>
<td>46 (41%)</td>
<td>30 (27%)</td>
<td>16 (18%)</td>
</tr>
<tr>
<td>Grade 3 or 4 adverse event</td>
<td>94 (85%)</td>
<td>47 (42%)</td>
<td>47 (47%)</td>
</tr>
<tr>
<td>Grade 3 or 4 adverse event suspected to be related to study drug</td>
<td>64 (58%)</td>
<td>21 (22%)</td>
<td>21 (22%)</td>
</tr>
</tbody>
</table>

- Adverse events of special interest:
  - Cytokine release syndrome:
    - Any grade: 64 (58)
    - Grade 3: 15 (14)
    - Grade 4: 9 (8)
  - Infection:
    - Any grade: 30 (27)
    - Grade 3: 13 (14)
    - Grade 4: 2 (2)
  - Neutropenia not resolved by day 28:
    - Any grade: 49 (44)
    - Grade 3: 18 (16)
    - Grade 4: 18 (16)
  - Neurologic event:
    - Any grade: 23 (21)
    - Grade 3: 8 (7)
    - Grade 4: 5 (5)
  - Febrile neutropenia:
    - Any grade: 17 (15)
    - Grade 3: 14 (13)
    - Grade 4: 2 (2)
  - Tumor lysis syndrome:
    - Any grade: 1 (1)
    - Grade 3: 1 (1)
    - Grade 4: 0 (0)
Conclusions

1. Durable responses were seen with the use of tisagenlecleucel for adults with relapsed or refractory DLBCL.

2. Best overall response rate was 52%.

3. Long-term persistence of tisa-cel was present for up to 2 years.

4. Tisa-cel is an effective and safe treatment option for patients with relapsed or refractory large B cell lymphoma after at least 2 prior therapies.
## Comparison: Characteristics of Cellular Products

<table>
<thead>
<tr>
<th></th>
<th>Axicabtagene ciloleucel</th>
<th>Tisagenlecleucel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US FDA indication</strong></td>
<td>DLBCL, including DLBCL NOS, PMBCL, high-grade B cell lymphoma, DLBCL arising from FL</td>
<td>DLBCL</td>
</tr>
<tr>
<td><strong>Costimulatory domain</strong></td>
<td>CD28</td>
<td>4-1BB</td>
</tr>
<tr>
<td><strong>Vector delivery</strong></td>
<td>Retrovirus</td>
<td>Lentivirus</td>
</tr>
<tr>
<td><strong>Defined cells</strong></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>CAR T dose</strong></td>
<td>$2 \times 10^6$/kg (max $2 \times 10^8$)</td>
<td>$0.6 - 6 \times 10^8$</td>
</tr>
<tr>
<td><strong>Lymphodepleting chemotherapy</strong></td>
<td>Flu 30 mg/m², Cy 500 mg/m²</td>
<td>Flu 30 mg/m², Cy 500 mg/m², Or Bendamustine 90 mg/m²</td>
</tr>
<tr>
<td><strong>Bridging therapy</strong></td>
<td>None</td>
<td>Allowed</td>
</tr>
</tbody>
</table>

**Chemotherapy**
- Flu: 30 mg/m²
- Cy: 500 mg/m²

**Note:**
- DLBCL: Diffuse Large B-Cell Lymphoma
- PMBCL: Primary Mediastinal B-Cell Lymphoma
- FL: Follicular Lymphoma
Comparison: Axi-cel (ZUMA-1) vs. Tisa-cel (JULIET)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ZUMA-1 (Neelapu et al.)</th>
<th>JULIET (Borchmann et al.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled (infused), n</td>
<td>111 (101)</td>
<td>165 (111)</td>
</tr>
<tr>
<td>Evaluable patients, n</td>
<td>101</td>
<td>93</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>58 (23–76)</td>
<td>56 (22–76)</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>24%</td>
<td>23%</td>
</tr>
<tr>
<td>Lymphoma subtypes</td>
<td>DLBCL, TFL, PMBCL</td>
<td>DLBCL, TFL</td>
</tr>
<tr>
<td>Double-hit lymphoma</td>
<td>NR</td>
<td>27%</td>
</tr>
<tr>
<td>≥ 3 lines of therapy</td>
<td>69%</td>
<td>51%</td>
</tr>
<tr>
<td>Primary refractoriness</td>
<td>26%</td>
<td>NR</td>
</tr>
<tr>
<td>Refractory to last therapy</td>
<td>77%</td>
<td>54%</td>
</tr>
<tr>
<td>Prior autologous HCT</td>
<td>21%</td>
<td>49%</td>
</tr>
</tbody>
</table>
### Comparison: Axi-cel (ZUMA-1) vs. Tisa-cel (JULIET)

<table>
<thead>
<tr>
<th>Variables</th>
<th>ZUMA-1 (Locke et al.(^2))</th>
<th>JULIET (Schuster et al.(^3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled (treated), n</td>
<td>111 (101)</td>
<td>165 (111)</td>
</tr>
<tr>
<td>Median follow up</td>
<td>27.1 months</td>
<td>19.3 months(^1)</td>
</tr>
<tr>
<td>Costimulatory domain</td>
<td>CD28</td>
<td>4-1BB</td>
</tr>
<tr>
<td>CAR T dose (range)</td>
<td>(2.0 \times 10^6) cells/kg</td>
<td>Median, (3.1 \times 10^6) cells</td>
</tr>
<tr>
<td>Lymphodepleting regimen</td>
<td>Flu 30 mg/m² x 3 days</td>
<td>Flu 25 mg/m² x 3 days</td>
</tr>
<tr>
<td></td>
<td>Cy 500 mg/m² x 3 days</td>
<td>Cy 250 mg/m² x 3 d or B 90 mg/m² x 2 days</td>
</tr>
</tbody>
</table>

### Efficacy

<table>
<thead>
<tr>
<th></th>
<th>ZUMA-1</th>
<th>JULIET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best ORR (CR)</td>
<td>82% (54%)</td>
<td>52% (40%)</td>
</tr>
<tr>
<td>6-month ORR (CR)</td>
<td>41% (36%)</td>
<td>33% (29%)</td>
</tr>
<tr>
<td>Ongoing ORR (CR)</td>
<td>39% (37%)</td>
<td>NR</td>
</tr>
<tr>
<td>mDOR</td>
<td>11.1 months</td>
<td>Not reached</td>
</tr>
<tr>
<td>12-month PFS</td>
<td>44%</td>
<td>66%</td>
</tr>
<tr>
<td>18-month PFS</td>
<td>40%</td>
<td>64%</td>
</tr>
<tr>
<td>12-month OS</td>
<td>59%</td>
<td>49%</td>
</tr>
<tr>
<td>18-month OS</td>
<td>53%</td>
<td>43%</td>
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</tbody>
</table>
Comparison: Axi-cel (ZUMA-1) vs. Tisa-cel (JULIET)

<table>
<thead>
<tr>
<th>Study</th>
<th>ZUMA-1 (Locke, 2018)</th>
<th>JULIET (Schuster)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No patients enrolled</td>
<td>111 (101)</td>
<td>165 (111)</td>
</tr>
</tbody>
</table>

**Cytokine-release syndrome**

<table>
<thead>
<tr>
<th>Time to onset, median, range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade (all)</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Tocilizumab use</td>
</tr>
<tr>
<td>Vasopressors use</td>
</tr>
<tr>
<td>Steroid treatment</td>
</tr>
<tr>
<td>ICU admission</td>
</tr>
</tbody>
</table>

**Infections**

| All grades | 35%³ | 34% |
| Grade 3 or 4 | 31%³ | 20% |

**Neurotoxicity**

<table>
<thead>
<tr>
<th>Time to onset, median, range</th>
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<tr>
<td>Grade (all)</td>
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<tr>
<td>Grade 3 or 4</td>
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</table>

³ Data from Locke, 2018 | ² Data from Schuster
Areas of Ongoing Research

• Comparative outcome analysis of Axi-cel versus Tisa-cel
• Clinical outcomes between patients who are transplant naïve versus post-transplant
• Infectious complications/patterns with CAR T treatment
• Prolonged Cytopenias with CAR T treatment
• Toxicities: Risk factors and management
• Etc…
Complications of CAR T-Cell Therapy

• Cytokine Release Syndrome

• Neurotoxicity
• Most common toxicity in adoptive T cell therapy
• Typically occurs within a few days to a few weeks post T cell infusion
  – Incidence, time of onset, and severity vary between different T cell products
• Pathophysiology: Triggered by T cell activation along with the activation of other immune cells such as macrophages and dendritic cells
• Elevations in cytokines
  – IL-6, IL-2, soluble IL-2Ra, IFNγ, soluble IL-6R, GM-CSF
  – Ferritin, C-reactive protein (CRP)
• Risk factors for severe CRS:
  – Disease burden
Cytokine Release Syndrome

- Presentation: Can range from mild constitutional symptoms, such as fever, malaise, myalgias, anorexia to more severe life-threatening symptoms such as circulatory shock requiring pressor support, disseminated intravascular coagulation, acute respiratory distress syndrome
- Can affect any organ system: cardiovascular, respiratory, renal, hematologic, gastrointestinal, nervous system
- Correlation between the development of CRS and clinical parameters is imperfect
  - Need to identify predictive biomarkers
- There does not seem to be a correlation between the severity of CRS to clinical response.
Tocilizumab is currently the 1\textsuperscript{st} line agent used in the treatment of CRS.

Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor.

IL-6 has been shown to be elevated in the serum of patients with CRS and is a main driver of manifestation of CRS.

Tocilizumab has been shown to effectively abrogate CAR T cell induced cytokine release syndrome without impairing the activity and efficacy of the T cells.

Tocilizumab dosing and timing of administration varies between centers.
Systemic steroids can also effectively alleviate symptoms of CRS.

There is theoretical evidence that indicates that steroids may interfere with the activity of the T cells especially when given prior to T cell infusion.

Our practice is to utilize steroids with persistent signs/symptoms of CRS while receiving tocilizumab.
• Early management of CRS is crucial for preventing progression to severe, life-threatening CRS.

• Tocilizumab is the 1st line agent used to treat CRS.

• Systemic steroids can also be administered if not responsive to tocilizumab.
Neurotoxicity

• Neurologic toxicities can occur concurrently with CRS or can occur alone.

• Pathophysiology is unclear. Hypotheses include:
  – Trafficking of T cells into the CNS (detection of CAR T cells in the CSF in the absence of CNS disease)
  – Diffusion of cytokines into the brain

• Neurotoxicity can occur shortly following T cell infusion or a few weeks afterwards. Duration can also vary from a few hours to a few weeks.

• Management of neurotoxicity differs from that of CRS.

• Therapeutic agents should be able to effectively penetrate the blood brain barrier.
  – Monoclonal antibodies, such as tocilizumab, may not have any beneficial effect.
  – Dexamethasone is often the agent of choice, given its effective CNS penetration.
### Neurotoxicity: Signs and Symptoms

Typically manifests as a toxic encephalopathy.

<table>
<thead>
<tr>
<th>Attention deficits</th>
<th>Aphasia</th>
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<tbody>
<tr>
<td>Language disturbances</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Impaired handwriting</td>
<td>Seizures</td>
</tr>
<tr>
<td>Confusion</td>
<td>Mental obtundation</td>
</tr>
<tr>
<td>Disorientation</td>
<td>Cerebral edema</td>
</tr>
<tr>
<td>Agitation</td>
<td></td>
</tr>
</tbody>
</table>
# Neurotoxicity: Grading

<table>
<thead>
<tr>
<th>Neurotoxicity Domain</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICE score&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7-9</td>
<td>3-6</td>
<td>0-2</td>
<td>0 (patient is unarousable and unable to perform ICE)</td>
</tr>
<tr>
<td>Depressed level of consciousness&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Awakens spontaneously</td>
<td>Awakens to voice</td>
<td>Awakens only to tactile stimulus</td>
<td>Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma</td>
</tr>
<tr>
<td>Seizure</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Life-threatening prolonged seizure (&gt;5 min); or Repetitive clinical or electrical seizures without return to baseline in between</td>
</tr>
<tr>
<td>Motor findings&lt;sup&gt;2&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Deep focal motor weakness such as hemiparesis or paraparesis</td>
</tr>
<tr>
<td>Elevated ICP/cerebral edema</td>
<td>N/A</td>
<td>N/A</td>
<td>Focal/local edema on neuroimaging&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing’s triad</td>
</tr>
</tbody>
</table>

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

N/A indicates not applicable.

<sup>a</sup> A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

<sup>1</sup> Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

<sup>2</sup> Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

<sup>3</sup> Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Neurotoxicity: Work-up

- MRI/CT Brain
- CSF analysis
- EEG (with initiation of antiepileptic)
- Neurology consult
- ICU consult
Neurotoxicity: Management

- Tocilizumab treatment may not have any beneficial effect.
- Dexamethasone is recommended for neurotoxicity treatment.
- Steroids can be tapered with improvement/resolution of neurotoxicity.
- The optimal duration of steroid treatment is unknown.
- Even with resolution of symptoms, patients should be monitored very closely for recurrence of neurotoxicity symptoms during steroid taper.
- Additional agents for neurotoxicity treatment if not responding to dex or flare with dex taper:
  - Siltuximab (off-label use)
    - Has CNS penetration
  - Anakinra (off-label use)
    - Has CNS penetration
CAR T Cells: Key Points

- CAR T cell therapy is an exciting new treatment.

- Must be able to recognize and promptly treat the unique toxicities of CAR T cell therapy.

- Multidisciplinary approach to management of CAR T cell toxicities is important.

- As we gain more experience with the use of T cell therapy, it is very likely that our treatment regimens as well as algorithms for the treatment of T cell toxicities will continue to evolve and improve.


References


Thank You!

Questions?