CRS vs. ICANS
What Does This Mean?

ELIZABETH ROGERS, PHARMD, BCPS, BCOP
DUKE UNIVERSITY HOSPITAL
8/7/2020
Disclosures

I have nothing to disclose.
Objectives

• Recognize clinical manifestations of cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS)

• Discuss grading systems for CAR-T cell associated toxicities

• Describe treatment options for patients presenting with CRS and/or ICANS
Outline

- CAR-T Overview
- CAR-T toxicities: CRS & ICANs
- Literature Review
- Grading Systems
- Treatment

CAR-T= Chimeric antigen receptor (CAR) T-cell therapy
CAR-T Overview
What is CAR-T?

• CAR-T= Chimeric antigen receptor (CAR) T-cell therapy
• Genetically modified autologous T-cell immunotherapy
• Targets CD19 on cancerous cells
• Emerging therapy for hematologic malignancies
  • B-cell lymphoma and B-cell leukemia
• Increases T-cell proliferation and cytokine release leading to immune activation
• Cytokine release allows for unique toxicities including cytokine release syndrome (CRS) and neurotoxicity

CAR-T Cell Process

1. Remove blood from patient to get T cells
2. Make CAR T cells in the lab
   - Insert gene for CAR
3. Grow millions of CAR T cells
4. CAR T cells bind to cancer cells and kill them
5. Infuse CAR T cells into patient
Available CAR-T Products

**Tisagenlecleucel (Kymriah)**

- FDA approved for adult patients with relapsed or refractory (r/r) large B-cell lymphoma after 2 or more lines of systemic therapy
- FDA approved for r/r B-cell precursor acute lymphoblastic leukemia (ALL) in 2\textsuperscript{nd} or later relapse in adults up to age 25

**Axicabtagene Ciloleucel (Yescarta)**

- FDA approved for adult patients with r/r large B-cell lymphoma after 2 or more lines of systemic therapy including DLBCL
CAR-T Toxicities
Toxicities of CAR-T

- Cytokine Release Syndrome (CRS)
- Immune effector cell-associated neurotoxicity syndrome (ICANS)
- Late Complications
CAR-T Toxicity Risk Factors

- Age
- Tumor Burden
- Cell Dose
- Chemo Conditioning
- Comorbidities
- Symptom Onset

Cytokine Release Syndrome (CRS)

- Inflammatory response
- Greater severity = higher disease burden
- Typical time to onset = 2 to 3 days
- Typical duration = 7 to 8 days
- Fatal complication of CAR-T
- Mostly reversible complication
- Black box warning

CRS Clinical Manifestations

- Rarely presents beyond 14 days after initiation of therapy

- Fever
- Rigors
- Hypotension
- Hypoxia
- Tachycardia
- Respiratory Failure
- AKI
- Coagulopathy
- Capillary Leak
- Neurologic Manifestations

Toxicities of CAR-T

- Cytokine Release Syndrome (CRS)
- Immune effector cell-associated neurotoxicity syndrome (ICANS)
- Late Complications

Immune Effector Cell Associated Neurotoxicity (ICANS)

- Endothelial activation and blood-brain barrier disruption
- Proinflammatory cytokines
- Elevated levels of glutamate and quinolinic acid in cerebrospinal fluid
- Typical time to onset = 4 to 10 days
- Typical duration = 14 to 17 days
- Fatal complication
- Reversible??
- Black box warning

ICANs Clinical Manifestations

- Delirium
- Encephalopathy
- Aphasia
- Lethargy
- Seizures
- Agitation
- Tremor
- Difficulty Concentrating
- Cerebral Edema (rare)
- Dizziness

Audience response

JM is a 65 year old male who recently received tisagenlecleucel for relapsed or refractory DLBCL. Two days after his infusion, he was noted to have a temperature of 101.5°F with chills and rigors. His vitals included a blood pressure of 96/58 mmHg and heart rate of 145. He subsequently required 4L of oxygen via nasal cannula.
Which of the following is JM likely experiencing?

- Immune effector cell-associated neurotoxicity syndrome (ICANS)
- Cytokine release syndrome (CRS)
- CAR-related encephalopathy syndrome (CRES)
- Fever neutropenia
Literature Review
# Landmark Trials

<table>
<thead>
<tr>
<th>Study Design:</th>
<th>JULIET Trial (N = 111)</th>
<th>ZUMA-1 Trial (N = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective:</td>
<td>Evaluate safety and efficacy of tisagenlecleucel in adult patients with r/r DLBCL</td>
<td>Evaluate the safety and efficacy of axicabtagene ciloleucel in adult patients with r/r DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma</td>
</tr>
<tr>
<td>Lymphodepleting Regimen:</td>
<td>- Fludarabine 25 mg/m² + cyclophosphamide 250 mg/m² for 3 days OR - Bendamustine 90 mg/m² for 2 days</td>
<td>Fludarabine 30 mg/m² + cyclophosphamide 500 mg/m² for 3 days (day -5, -4, -3)</td>
</tr>
<tr>
<td>Safety Outcomes:</td>
<td>Most common AE were CRS, anemia, pyrexia, cytopenias and diarrhea</td>
<td>Most common AE of any grade were pyrexia, neutropenia, CRS and anemia</td>
</tr>
</tbody>
</table>


# Landmark Trials

<table>
<thead>
<tr>
<th>Study Design:</th>
<th>Multicenter, pivotal phase 1 study</th>
<th>Single cohort, multicenter, phase 2 study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective:</td>
<td>To determine the safety and efficacy of lisocabtagene maraleucel in patients with r/r large B-cell NHL</td>
<td>To determine the safety and efficacy of tisagenlecleucel in pediatric and young adult patients with CD19+ r/r B-cell ALL</td>
</tr>
<tr>
<td>Lymphodepleting Regimen:</td>
<td>Fludarabine 30 mg/m2 + Cyclophosphamide 300 mg/m2 for 3 days</td>
<td>96% of patients received lymphodepleting chemotherapy prior to tisagenlecleucel infusion - unclear of specific regimens received</td>
</tr>
<tr>
<td>Safety Outcomes:</td>
<td>Most common AE of any grade were cytopenias (anemia, thrombocytopenia, neutropenia) and CRS</td>
<td>Most common AE of any grade were CRS, pyrexia, decreased appetite, fever neutropenia, and headache</td>
</tr>
</tbody>
</table>

*Data from DLBCL cohort

# Literature Comparison: CRS

<table>
<thead>
<tr>
<th></th>
<th>JULIET N = 111</th>
<th>ZUMA-1 N = 101</th>
<th>TRANSCEND* N = 268</th>
<th>ELIANA N = 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS- any grade; (%)</td>
<td>64 (58)</td>
<td>94 (93)</td>
<td>113 (42)</td>
<td>58 (77)</td>
</tr>
<tr>
<td>CRS- grade ≥ 3; (%)</td>
<td>24 (22)</td>
<td>13 (13)</td>
<td>6 (2)</td>
<td>35 (47)</td>
</tr>
<tr>
<td>Median time from infusion to onset</td>
<td>3 days</td>
<td>2 days</td>
<td>5 days</td>
<td>3 days</td>
</tr>
<tr>
<td>Median duration of CRS</td>
<td>7 days</td>
<td>8 days</td>
<td>-</td>
<td>8 days</td>
</tr>
<tr>
<td>Tocilizumab use; (%)</td>
<td>15 (14)</td>
<td>48 (43)</td>
<td>(19)</td>
<td>28 (37)</td>
</tr>
<tr>
<td>Tocilizumab + glucocorticoid use; (%)</td>
<td>11 (10)</td>
<td>30 (27)</td>
<td>(21)</td>
<td>-</td>
</tr>
<tr>
<td>Grading System</td>
<td>University of Penn</td>
<td>Lee</td>
<td>Lee</td>
<td>Univ of Penn</td>
</tr>
</tbody>
</table>

*Data from DLBCL cohort*
## Literature Comparison: Neurotoxicity

<table>
<thead>
<tr>
<th></th>
<th>JULIET N = 111</th>
<th>ZUMA-1 N = 101</th>
<th>TRANSCEND* N = 268</th>
<th>ELIANA N = 75</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurotoxicity- any grade; (%)</strong></td>
<td>23 (21)</td>
<td>65 (64)</td>
<td>80 (30)</td>
<td>30 (40)</td>
</tr>
<tr>
<td><strong>Neurotoxicity- grade ≥ 3; (%)</strong></td>
<td>13 (12)</td>
<td>28 (28)</td>
<td>27 (10)</td>
<td>10 (13)</td>
</tr>
<tr>
<td><strong>Median time from infusion to onset</strong></td>
<td>6 days</td>
<td>5 days</td>
<td>9 days</td>
<td>-</td>
</tr>
<tr>
<td><strong>Median duration of neurotoxicity</strong></td>
<td>14 days</td>
<td>17 days</td>
<td>-</td>
<td>10 days</td>
</tr>
<tr>
<td><strong>Concurrent CRS + neurotoxicity</strong></td>
<td>9 (8)</td>
<td>-</td>
<td>-</td>
<td>26 (35)</td>
</tr>
<tr>
<td><strong>Grading System</strong></td>
<td>CTCAE v4.03</td>
<td>CTCAE v4.03</td>
<td>CTCAE v4.03</td>
<td>CTCAE v4.03</td>
</tr>
</tbody>
</table>

*Data from DLBCL cohort

Grading Systems
Grading Systems Available

- CTCAE v4.03
- CTCAE v5.0
- Penn Criteria
- MSKCC Criteria
- Lee Criteria
- CARTOX Criteria
- ASTCT

## CRS Grading System

<table>
<thead>
<tr>
<th>Grade</th>
<th>CTCAE v4.03</th>
<th>CTCAE v5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>-Mild reaction&lt;br&gt;-Infusion interruption not indicated&lt;br&gt;-Intervention not indicated</td>
<td>-Fever with or without symptoms</td>
</tr>
<tr>
<td>Grade 2</td>
<td>-Therapy interruption indicated but <strong>responds to symptomatic treatment</strong>&lt;br&gt;-Prophylactic medications indicated for &lt; 24 hours</td>
<td>-<strong>Hypotension</strong> responding to fluids&lt;br&gt;-<strong>Hypoxia</strong> responding to &lt; 40% FiO2</td>
</tr>
<tr>
<td>Grade 3</td>
<td>-Prolonged recurrence of symptoms following initial improvement&lt;br&gt;-<strong>Hospitalization indicated</strong></td>
<td>-Hypotension managed with <strong>1 pressor</strong>&lt;br&gt;-Hypoxia requiring &gt; 40% FiO2</td>
</tr>
<tr>
<td>Grade 4</td>
<td>-Life-threatening consequences&lt;br&gt;-<strong>Pressor or ventilatory support indicated</strong></td>
<td>-Life-threatening consequences&lt;br&gt;-Urgent intervention needed</td>
</tr>
</tbody>
</table>

National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v4.03.
National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v5.0.
## CRS Grading System

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>MSKCC Criteria</th>
<th>CARTOX Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Mild symptoms requiring observation or supportive care only</td>
<td>-Temperature &gt; 38°C</td>
<td></td>
</tr>
<tr>
<td>-Grade 1 organ toxicity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 2</th>
<th>MSKCC Criteria</th>
<th>CARTOX Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Hypotension + vasopressors &lt; 24 hours</td>
<td>-Hypotension responding to IV fluids or low dose vasopressor</td>
<td></td>
</tr>
<tr>
<td>-Hypoxia + supplemental oxygen &lt; 40%</td>
<td>-Hypoxia requiring FiO2 &lt; 40%</td>
<td></td>
</tr>
<tr>
<td>-Grade 2 organ toxicity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3</th>
<th>MSKCC Criteria</th>
<th>CARTOX Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Hypotension + vasopressors ≥ 24 hours</td>
<td>-Hypotension + multiple vasopressors</td>
<td></td>
</tr>
<tr>
<td>-Hypoxia + supplemental oxygen ≥ 40%</td>
<td>-Hypoxia requiring FiO2 &gt; 40%</td>
<td></td>
</tr>
<tr>
<td>-Grade 3 organ toxicity or grade 4 transaminitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 4</th>
<th>MSKCC Criteria</th>
<th>CARTOX Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Life-threatening symptoms</td>
<td>-Life-threatening hypotension</td>
<td></td>
</tr>
<tr>
<td>-Hypotension refractory to high dose vasopressors</td>
<td>-Requires ventilator support</td>
<td></td>
</tr>
<tr>
<td>-Hypoxia requiring mechanical ventilation</td>
<td>-Grade 4 organ toxicity except for grade 4 transaminitis</td>
<td></td>
</tr>
</tbody>
</table>

## CRS Grading System

<table>
<thead>
<tr>
<th>Grade</th>
<th>Penn Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>-Mild reaction treated with <strong>supportive care</strong> including antipyretics or antiemetics</td>
</tr>
</tbody>
</table>
| Grade 2 | -Moderate reaction including some **signs of organ dysfunction** related to CRS  
-Hospitalization for management of CRS related symptoms |
| Grade 3 | -More severe reaction where **hospitalization is required**  
-Hypotension treated with **multiple fluid boluses or low dose vasopressors**  
-Coagulopathy requiring FFP, cryoprecipitate or fibrinogen concentrate  
-Hypoxia requiring supplemental oxygen |
| Grade 4 | -Life-threatening complications including hypotension **requiring high dose vasopressors**  
-Hypoxia requiring **mechanical ventilation** |

## CRS Grading System

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>-Symptoms are not life threatening and require <strong>symptomatic treatment only</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>-Symptoms require and respond to <strong>moderate intervention</strong> (Oxygen requirement &lt; 40% FiO2, or hypotension responsive to IV fluids or a low dose vasopressor, or grade 2 organ toxicity)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>-Symptoms require and respond to <strong>aggressive intervention</strong> (oxygen requirement &gt; 40% FiO2, or hypotension require high dose or multiple vasopressors, or grade 3 organ toxicity or grade 4 transaminitis)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>-<strong>Life-threatening symptoms</strong> (requirement of ventilator support or grade 4 organ toxicity excluding transaminitis)</td>
</tr>
</tbody>
</table>

Neurotoxicity Grading Systems

- **CTCAE v5.0**: Grades neurotoxicity domains from 1 to 4 for the following adverse event terms:
  - Encephalopathy, seizure, dysphasia, tremor, headache, confusion, depressed level of consciousness, and cerebral edema
  - Progress from mild → moderate → severe → life-threatening symptoms
  - Encompasses self-care activities of daily living (ADL) and instrumental ADL

- **CARTOX Criteria**:

<table>
<thead>
<tr>
<th>Adverse Event Term</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 (CARTOX-10)</td>
<td>7 to 9 (mild impairment)</td>
<td>3 to 6 (moderate impairment)</td>
<td>0 to 2 (severe impairment)</td>
<td>Patient in critical condition and/or obtunded and cannot perform assessment of tasks</td>
</tr>
<tr>
<td>Elevated ICP</td>
<td>N/A</td>
<td>N/A</td>
<td>Stage 1 to 2 papilledema or CSF opening pressure &lt; 20 mmHg</td>
<td>Stage 3 to 5 papilledema or CSF opening pressure ≥ 20 mmHg or cerebral edema</td>
</tr>
<tr>
<td>Seizures or motor weakness</td>
<td>N/A</td>
<td>N/A</td>
<td>Partial seizure or nonconvulsive seizures on EEG with response to benzodiazepine</td>
<td>Generalized seizures or convulsive or non-convulsive status epilepticus or new motor weakness</td>
</tr>
</tbody>
</table>

New Standard Grading System

- Numerous grading systems available with overlapping assessments
  - Varies widely across institutions
- Toxicity comparisons between products and trials are difficult
- Lack of objectivity in grading systems
- ASTCT recognized the need for clear and accurate consensus guidelines
  - Experts met June 20-21, 2018 to discuss harmonization of guidelines
  - Agreed CRS is the most appropriate term for symptoms occurring after CAR-T
  - Redefined neurotoxicity complication following CAR-T with term ICANS
New Standard Definitions: ASTCT

- **CRS:**
  - “A supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction”

- **ICANS:**
  - “A disorder characterized by a pathologic process involving the CNS following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema”

# CRS Grading System: New Standard

<table>
<thead>
<tr>
<th>Grade</th>
<th>ASTCT Criteria</th>
</tr>
</thead>
</table>
| Grade 1 | - Fever (> 38°C) with or without constitutional symptoms (ie. Myalgia, arthralgia and malaise)  
-No hypoxia or hypotension present |
| Grade 2 | - Fever (> 38°C) with hypotension not requiring vasopressors  
-Hypoxia requiring the use of oxygen via low flow nasal cannula (< 6 L/min) |
| Grade 3 | - Fever (> 38°C) with hypotension requiring 1 vasopressor with or without vasopressin  
-Hypoxia requiring high flow nasal cannula (> 6 L/min), facemask, nonrebreather mask or venturi mask not attributable to any other cause |
| Grade 4 | - Fever (> 38°C) with hypotension + multiple vasopressors (excluding vasopressin)  
-Hypoxia requiring positive pressure (ie. CPAP, BiPAP, mechanical ventilation and intubation) |

## ICANS Encephalopathy Assessment Tools

<table>
<thead>
<tr>
<th></th>
<th>CARTOX-10</th>
<th>ICE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Orientation</strong></td>
<td>Orientation to year, month, city, hospital, president</td>
<td>Orientation to year, month, city, hospital</td>
</tr>
<tr>
<td></td>
<td>- 5 points</td>
<td>- 4 points</td>
</tr>
<tr>
<td><strong>Naming</strong></td>
<td>Ability to name 3 objects</td>
<td>Ability to name 3 objects</td>
</tr>
<tr>
<td></td>
<td>- 3 points</td>
<td>- 3 points</td>
</tr>
<tr>
<td><strong>Following Commands</strong></td>
<td>N/A</td>
<td>Ability to follow simple commands</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1 point</td>
</tr>
<tr>
<td><strong>Writing</strong></td>
<td>Ability to write a standard sentence</td>
<td>Ability to write a standard sentence</td>
</tr>
<tr>
<td></td>
<td>- 1 point</td>
<td>- 1 point</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td>Ability to count backwards from 100 by 10</td>
<td>Ability to count backwards from 100 by 10</td>
</tr>
<tr>
<td></td>
<td>- 1 point</td>
<td>- 1 point</td>
</tr>
<tr>
<td><strong>Scoring</strong></td>
<td>7 - 9 = Grade 1 ICANS</td>
<td>0 - 2 = Grade 3 ICANS</td>
</tr>
<tr>
<td></td>
<td>3 - 6 = Grade 2 ICANS</td>
<td>0 = Grade 4 ICANS</td>
</tr>
</tbody>
</table>

## ICANs Grading System: ASTCT

<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</td>
<td>7-9</td>
<td>3-6</td>
<td>0-2</td>
<td>0 (patient unarousable)</td>
</tr>
<tr>
<td>CAPD score for children age &lt; 12</td>
<td>1-8</td>
<td>1-8</td>
<td>&gt; 9</td>
<td>Unable to perform CAPD</td>
</tr>
<tr>
<td>Depressed level of consciousness</td>
<td>Awakens spontaneously</td>
<td>Awakens to voice</td>
<td>Awakens only to tactile stimulus</td>
<td>Patient is unarousable or requires vigorous tactile stimuli to arouse</td>
</tr>
<tr>
<td>Seizure</td>
<td>N/A</td>
<td>N/A</td>
<td>Any clinical seizure (focal, generalized, or nonconvulsive) that resolves with intervention</td>
<td>Life-threatening prolonged seizure (&gt; 5 min) or repetitive seizures without return to baseline</td>
</tr>
<tr>
<td>Motor findings</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Deep focal motor weakness</td>
</tr>
<tr>
<td>Elevated ICP/cerebral edema</td>
<td>N/A</td>
<td>N/A</td>
<td>Focal/local edema on neuroimaging</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>


CAPD= Cornell Assessment of Pediatric Delirium
Which of the following grading systems were developed in 2018 with the goal of harmonization and standardization in identification of toxicities related to immune effector cell therapies?
Which of the following grading systems were developed in 2018 with the goal of harmonization and standardization in identification of toxicities related to immune effector cell therapies?

- Lee Guidelines
- University of Pennsylvania Guidelines
- ASTCT Guidelines
- CTCAE Guidelines
CRS & ICANs Management
ASTCT CRS Management

**Grade 1**
- Antipyretics and IV hydration
- Diagnostic work-up to rule out infection
- Consider growth factors and antibiotics if neutropenic

**Grade 2**
- Antipyretics and IV hydration
- Supplemental O2
- Tocilizumab +/- dexamethasone or its equivalent methylprednisolone

ASTCT CRS Management

Grade 3
- Antipyretics and IV hydration
- Consider ICU monitoring
- Vasopressor support and/or supplemental O2
- Tocilizumab + dexamethasone 10-20 mg IV q6h or its equivalent methylprednisolone

Grade 4
- Antipyretics and IV hydration
- ICU monitoring
- Vasopressor support and/or supplemental O2 via positive pressure ventilation (CPAP, BiPAP, intubation or mechanical ventilation)
- Tocilizumab + methylprednisolone 1000 mg/day
ASTCT Treatment Stepwise Approach: CRS

Grade 1
- IV fluids
- Antipyretics

Grade 2
- O2 support
- Steroids
- Tocilizumab

Grade 3
- ICU care
- Vasopressors
- Steroids + Tocilizumab

Grade 4
- ICU care required
- Ventilation

Continued & escalated as needed through all grades

ASTCT ICANS Management

Grade 1

- Aspiration precautions and IV hydration
- Seizure prophylaxis with levetiracetam
- EEG monitoring, brain imaging
- Consider tocilizumab if concurrent CRS

Grade 2

- Supportive care from grade 1
- Consider steroids (dexamethasone or methylprednisolone)
ASTCT ICANS Management

Grade 3

- Supportive care from grade 1
- Dexamethasone 10-20 mg IV q6h
- Seizure management with benzodiazepines for short-term control, levetiracetam +/- phenobarbital and/or lacosamide
- Methylprednisolone 1000 mg/day for local edema

Grade 4

- Supportive care from grade 1
- Methylprednisolone 1000 mg/day
- Seizure management with benzodiazepines for short-term control, levetiracetam +/- phenobarbital and/or lacosamide
- Lower ICP by hyperventilation, hyperosmolar therapy with mannitol, hypertonic saline
ASTCT Treatment Stepwise Approach: ICANS

Grade 1
- IV fluids
- Seizure ppx
- Tocilizumab if CRS + ICANS

Grade 2
- Steroids

Grade 3
- Advanced seizure management

Grade 4
- ICP reductive therapies

Continued & escalated as needed through all grades
Role of Anti IL-6 Therapy

**Tocilizumab**
- FDA approved for cytokine release syndrome
- Dosing based on weight
  - < 30 kg = 12 mg/kg
  - > 30 kg = 8 mg/kg
- Max dose = 800 mg IV over 60 minutes
- If no clinical improvement, may give 3 additional doses at least 8 hours apart

**Siltuximab**
- Not FDA approved for CRS or ICANs
- Dosing: 11 mg/kg IV over 60 minutes

Siltuximab (Sylvant) [package insert]. Hemel Hempstead, Hertfordshire, UK. Eusa Pharma, Inc; 2020.
Resolution of CRS and ICANS

• Once patients meet criteria for CRS and/or ICANs, patients are said to have CRS and/or ICANs until all signs and symptoms leading to diagnosis of CRS and/or ICANs have resolved

• CRS and ICANs can be downgraded in patients as symptoms improve

• Goal = patient returns to baseline or grade 1 toxicity

• Individualized approach given various patient situations
Audience response

SD is a 71 year old female with history of r/r DLBCL. She recently underwent CAR-T cell infusion with axicabtagene ciloleucel 8 days ago. Overnight, patient had a generalized seizure, and it was determined that she is experiencing an ICANS grade 3 toxicity. SD already has levetiracetam prophylaxis on board as part of the standard protocol for CAR-T patients at your institution.
Which of the following would be the most appropriate option for further management of her grade 3 ICANS toxicity?

- Tocilizumab 8 mg/kg
- Advanced seizure management with benzodiazepines for short-term control, increased levetiracetam +/- phenobarbital and/or lacosamide
- Dexamethasone 10 mg q6h
- IV hydration
Future Considerations

Ongoing Studies
- Over 500 CAR-T cell therapies are under development
- ZUMA-3
- ZUMA-7

Future Indications
- Solid tumors
- Multiple Myeloma
- Allogeneic chimeric antigen receptors
- New antigen targets

Education
- Multidisciplinary education
- Providers, nursing, pharmacy
- Protocol development
Summary

- CRS and ICANs are serious complications of CAR-T cell therapy
- Prompt identification and management is essential
- New standard of care grading system available
- Management of CRS and ICANs is a stepwise approach
Thank You!

Acknowledgements:
- LeAnne Kennedy
- Sally Barbour
- Erin Kennedy
- Entire Duke University Hospital Team!
CRS vs. ICANS
What Does This Mean?

ELIZABETH ROGERS, PHARMD, BCPS, BCOP
DUKE UNIVERSITY HOSPITAL
8/7/2020