Unique Toxicity Profiles of BiTE and Experimental T-cell Therapies: Clinical Presentation and Management

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Disclosure

Ali McBride

Pfizer: Advisory Board; Sandoz: Advisory Board

All other planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.
Question #1

Which of the following biomarkers are associated with T cells?

A. CD20
B. CD3
C. CD147
D. CD19
Adaptive Immune Mechanisms

Humoral immune responses
- B cells and antibodies

Cell mediated immune responses
- Cytotoxic T cell (Tc)
- Helper T cells (Th)
Origin of Cells of the Immune System

• Derived from common progenitor cell in bone marrow
  – Pluripotent hematopoietic stem cell
• Progenitor stem cells
  – Erythroid lineage
  – Myeloid lineage
  – Lymphoid lineage

Available at: https://visualsonline.cancer.gov/retrieve.cfm?imageid=7177&dpi=72&fileformat=jpg
Cells of Innate and Adaptive Immunity

**Innate Immunity**
- “Large Lymphocytes”
- Nonspecific
- Natural Killer cells (CD16, CD56)

**Adaptive Immunity**
- “Small Lymphocytes”
- Specific
- B cells (CD19)
- T cells (CD3, CD4 or CD8)
The Cluster of Differentiation (CD)

- Protocol for identification and investigation of cell surface molecules
- “CD number” assigned on basis of 1 cell surface molecule recognized by 2 specific monoclonal antibodies
- CD nomenclature established in 1982
  - 1st International Workshop and Conference on Human Leukocyte Differentiation Antigens (HLDA)

The Cluster of Differentiation (CD)

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>CD Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocyte</td>
<td>CD45+, CD15+</td>
</tr>
<tr>
<td>Monocyte</td>
<td>CD45+, CD14+</td>
</tr>
<tr>
<td>T lymphocyte</td>
<td>CD45+, CD3+</td>
</tr>
<tr>
<td>T cytotoxic lymphocyte</td>
<td>CD45+, CD3+, CD8+</td>
</tr>
<tr>
<td>B lymphocyte</td>
<td>CD45+, CD19+</td>
</tr>
<tr>
<td>Natural killer cell</td>
<td>CD45+, CD16+, CD56+, CD3-</td>
</tr>
</tbody>
</table>
### Structure of Antibody Molecules

#### Types of Monoclonal Antibodies (mAbs)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Symbol</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murine</td>
<td>Entirely murine amino acids</td>
<td>‘o’</td>
<td>e.g. murmonab</td>
</tr>
<tr>
<td>Chimeric</td>
<td>Human constant (C) + murine variable (V) regions</td>
<td>‘xi’</td>
<td>e.g. rituximab</td>
</tr>
<tr>
<td>Humanized</td>
<td>Murine complimentary determining regions (CDRs)</td>
<td>‘zu’</td>
<td>e.g. alemtuzumab</td>
</tr>
<tr>
<td>Human</td>
<td>Entirely human amino acids</td>
<td>‘u’</td>
<td>e.g. adalimumab</td>
</tr>
</tbody>
</table>
Structure-Function Relationship of Antibody Molecules

Ligand Blockade  
Receptor Blockade  
Receptor Downregulation  
Depletion  
Signaling Induction

Modification of Protein Structure to Enhance Function

Immuno-oncology in Practice

- Bring T cells and cancer cell targets into physical proximity
- Increase numbers of T cells capable of recognizing a tumor antigen
- Modulate T-cell activity once tumor-associated antigen is encountered
- Make tumors more attractive or accessible targets for cytotoxic T cells
- Disable the "brakes" or inhibitory signals limiting magnitude or duration of activity against neoplastic cells following T-cell activation

Cytotoxic T Cells

- T cells are a type of lymphocyte that play an active role in the immune response
- T cells recognize and eliminate foreign or abnormal cells, including cancer cells
- Cancer cells have mechanisms to evade T cell recognition

Bispecific T cell Engager (BiTE) Antibodies

- BiTE antibodies form a link between T cells and tumor cells
- Causes T cells to exert cytotoxic activity on tumor cells, independently of the presence of MHC I or co-stimulatory molecules, initiating apoptosis
- Mimics physiological processes observed during T cell attacks against tumor cells
Bispecific T cell Engager (BiTE) Antibodies

CAR-T Cell Therapies

- Engineered expression of chimeric antigen receptors (CARs) on the surface of T cells
- Enables the redirection of T cell specificity

CAR-T Cell Therapies
Safety and Efficacy of BiTE Antibodies for Hematologic Malignancies
Question #2

Which of the following adverse effects are not associated with blinatumomab?

A. Cytokine Release Syndrome
B. Hepatotoxicity
C. Seizures
D. Alopecia
Review: 

Acute Lymphoblastic Leukemia (ALL)

- ALL can arise from both T cell and B cell precursors
- B cell ALL is more common (~88% of all cases)
- 95% of B precursor leukemic blasts express the surface antigen CD19
- CD19 is a promising target for immunotherapy
Blinatumomab

- Bispecific T cell engager (BiTE) antibody with dual specificity for CD19 and CD3

- CD19 is a highly specific B-cell marker expressed throughout B-cell development and in >90% of B cell lineage cancers

- FDA Approvals:
  - 2017: Treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children
  - 2014: Treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL

Blinatumomab Mechanism of Action

• Simultaneously binds CD3 positive cytotoxic T cells and CD19 positive B cells, resulting in T cell mediated lysis of normal and malignant B cells

• Engages patients’ endogenous T cells to attack and eradicates B precursor leukemic blasts
Blinatumomab for Relapsed/Refractory B Cell Precursor, Ph-Negative ALL

**Patients**

N = 189

18 years or older, refractory after induction, or relapsed within 12 months of CR1 or HCT or r/r after salvage therapy

**Study Design**

Multi-center, single arm, open label, phase II

Primary endpoint: CR and CRh within the first 2 cycles

**Intervention**

Blinatumomab via continuous intravenous infusion

9 µg/day for 1 week, then 28 µg/day to 4 weeks, then 2 weeks off; up to 5 cycles

ALL, acute lymphoblastic leukemia; CR, complete remission; CR1, first CR; CRh, CR with partial hematologic recovery of peripheral blood counts; HCT, hematopoietic stem cell transplantation; Ph, Philadelphia chromosome

## Blinatumomab in R/R ALL: Efficacy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Patients (N = 189)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR or CRh in first 2 cycles, %</td>
<td>43</td>
</tr>
<tr>
<td>CR in first 2 cycles, %</td>
<td>33</td>
</tr>
<tr>
<td>MRD negativity in first 2 cycles, %*</td>
<td>82</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td></td>
</tr>
<tr>
<td>‧ All patients</td>
<td>6.1</td>
</tr>
<tr>
<td>‧ MRD-negative CR</td>
<td>11.5</td>
</tr>
<tr>
<td>‧ MRD-positive CR</td>
<td>6.7</td>
</tr>
<tr>
<td>Median RFS, mos</td>
<td></td>
</tr>
<tr>
<td>‧ CR + CRh</td>
<td>5.9</td>
</tr>
<tr>
<td>‧ CR</td>
<td>6.9</td>
</tr>
<tr>
<td>‧ CRh</td>
<td>5.0</td>
</tr>
<tr>
<td>Allogeneic HCT, %*</td>
<td>40</td>
</tr>
<tr>
<td>‧ After CR</td>
<td>44</td>
</tr>
<tr>
<td>‧ After CRh</td>
<td>22</td>
</tr>
<tr>
<td>100-day mortality after allogeneic HCT, %</td>
<td>11</td>
</tr>
</tbody>
</table>

ALL, acute lymphoblastic leukemia; CR, complete remission; CRh, CR with partial hematologic recovery of peripheral blood counts; HCT, hematopoietic cell transplant; MRD, minimal residual disease; OS, overall survival; RFS, relapse-free survival.

### Blinatumomab: Safety

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Topp et al $^1$</th>
<th>Topp et al $^{2,3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>2 (9.5%)</td>
<td>15 (7.9%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (4.8%)</td>
<td>30 (15.8%)</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>1 (4.8%)</td>
<td>16 (8.4%)</td>
</tr>
<tr>
<td>Bacterial sepsis</td>
<td>1 (4.8%)</td>
<td>15 (7.9%)</td>
</tr>
<tr>
<td>Bronchopneumonia</td>
<td>1 (4.8%)</td>
<td>17 (8.9%)</td>
</tr>
<tr>
<td>Syncope/convulsion</td>
<td>1 (4.8%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>ND</td>
<td>6 (3.1%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1 (4.8%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1 (4.8%)</td>
<td>13 (6.8%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>ND</td>
<td>10 (5.2%)</td>
</tr>
</tbody>
</table>

Blinatumomab: Adverse Effects

- Cytokine release syndrome
- Infections
- Neurological toxicities
- Tumor lysis syndrome
- Neutropenia
- Elevated liver enzymes
Cytokine Release Syndrome (CRS)

- Potentially serious complication of non-physiological T cell activation
- Produced by T cell engaging therapies such as bispecific T cell engaging antibodies and chimeric antigen receptor-engineered T cells
- May be caused by abnormal activation of macrophages
Cytokine Release Syndrome

• Occurs during the first cycle of treatment with blinatumomab
• Toxicities: CRS, disseminated intravascular coagulation, and central nervous system events (seizure or encephalopathy)
• Lowering the initial dose of blinatumomab to 5µg/m²/day and the addition of dexamethasone has been shown to reduce the toxicity of the agent

Cytokine Release Syndrome Biomarkers

C-Reactive Protein (CRP)

- Acute phase reactant that is synthesized by the liver in response to elevated IL-6
- CRP level of ≥ 200mg/L is linked to CRS with good sensitivity and specificity

Interleukin-6 (IL-6)

- Rising level of IL-6 is a strong predictor of CRS
- Changes in IL-6 level precede elevation of CRP

Tocilizumab

- Humanized monoclonal antibody against IL-6 receptors
- IL-6 blockade with tocilizumab demonstrated rapid reversal of life-threatening symptoms
- First choice therapy for CRS

# Blinatumomab: Toxicity Management

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRS</strong></td>
<td>3</td>
<td>Withhold until resolved, then restart at 9 mcg/day. Escalate to 28 mcg/day after 7 days if toxicity does not reoccur.</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Discontinue permanently</td>
</tr>
<tr>
<td><strong>Neurologic Toxicity</strong></td>
<td>3</td>
<td>Withhold until resolved to less than Grade 1 for 3 days, then restart at 9 mcg/day. Escalate to 28 mcg/day after 7 days if toxicity does not reoccur. If longer than 14 days to resolve, discontinue permanently.</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Discontinue permanently</td>
</tr>
<tr>
<td>Seizure</td>
<td></td>
<td>If more than one seizure, discontinue permanently.</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>3</td>
<td>Withhold until resolved to less than Grade 1 for 3 days, then restart at 9 mcg/day. Escalate to 28 mcg/day after 7 days if toxicity does not reoccur. If longer than 14 days to resolve, discontinue permanently.</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Consider discontinuing permanently</td>
</tr>
</tbody>
</table>

Key Takeaways

• Immuno-Oncology is changing the current landscape of cancer therapies
• Toxicity of emerging immunotherapy agents is manageable and usually reversible, but can be severe
• Numerous considerations and precautions for monitoring of cytokine release syndrome should be implemented
Safety and Efficacy of CAR-T cells for Hematologic Malignancies
Chimeric Antigen Receptor (CAR)-T Cells

- Genetically programmed to bind to transmembrane glycoproteins
- Major histocompatibility complex independent action
- Targets
  - Limited off target effects
  - Specific to certain types of cancer
- Tisagenlecleucel- 1st FDA approved product

<table>
<thead>
<tr>
<th>Targets Under Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD19</td>
</tr>
<tr>
<td>CD20</td>
</tr>
<tr>
<td>CD33</td>
</tr>
<tr>
<td>B-cell maturation antigen (BCMA)</td>
</tr>
</tbody>
</table>

CAR-T Cell Structure

*Costimulatory domains containing CD27, CD28, 4-1BB (CD137), ICOS, or OX40 (CD134)

CAR-T Cell Production

1. Conditioning regimen
2. CAR-T cell infusion
3. Ex vivo expansion and purification
4. Leukapheresis
5. DNA integration

Conditioning Regimen

- Depletion of leukocytes that may interfere with adoptive T cell activity
- Decrease in regulatory T-cells
  - Increased levels of interleukin (IL)-15 and IL-17
- Tumor debulking- less disease leads to greater persistence of CAR- T cells
- Anti-programmed cell death protein (PD-1) immune checkpoint inhibitor use after CAR-T cell infusion
  - Enhances CAR-T cell expansion, function, and persistence
- Medications
  - Cyclophosphamide
  - Fludarabine

Role of Fludarabine

• Greater CAR-T cell expansion and persistence with fludarabine
  – Fludarabine- reduces reaction to murine single-chain variable fragment on an antibody
  – B-cell acute lymphoblastic leukemia (ALL)- improved disease-free survival
  – Non-hodgkin’s lymphoma- improved progression-free and overall survival
• Juno’s ROCKET phase 2 trial (JCAR015)
  – CAR-T-cell-related encephalopathy syndrome (CRES)- 3 deaths from cerebral edema

## Efficacy and Safety: B Cell ALL

<table>
<thead>
<tr>
<th>CAR-T Cells (Institution)</th>
<th>Product</th>
<th>No.</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTL019 (CHOP)</td>
<td>Anti-CD19 CD3 zeta, 4-1BB</td>
<td>63 Children</td>
<td>CR 83%</td>
<td>Cytokine release syndrome (CRS) Grade ≥3 47%</td>
</tr>
<tr>
<td>19-28Z CAR (MSKCC)</td>
<td>Anti-CD19 CD3 zeta, CD28</td>
<td>51 Adults</td>
<td>CR 84%</td>
<td>Not reported</td>
</tr>
<tr>
<td>CD4⁺:CD8⁺ (FHCRC)</td>
<td>Anti-CD19 CD3-zeta, CD137, and EGFRt</td>
<td>36 Adults</td>
<td>CR 94%</td>
<td>Reported in aggregate with other B-cell malignancies</td>
</tr>
</tbody>
</table>

## Efficacy and Safety: B Cell Lymphoma (BCL)

<table>
<thead>
<tr>
<th>Study (Manufacture)</th>
<th>Product</th>
<th>No.</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axicabtagene ciloleucel</td>
<td>Anti-CD19 CD3 zeta, CD28</td>
<td>101</td>
<td>CR 54%</td>
<td>CRS Grade ≥3 13% Febrile neutropenia 31% 3 deaths</td>
</tr>
<tr>
<td>(ZUMA1, KITE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTL019 (JULIET, Novartis)</td>
<td>Anti-CD19 CD3 zeta, 4-1BB</td>
<td>85</td>
<td>CR 43%</td>
<td>CRS 57% 3 deaths*</td>
</tr>
<tr>
<td>JCAR017 (TRANSCEND, Juno)</td>
<td>Anti-CD19 CD3 zeta, 4-1BB</td>
<td>28</td>
<td>CR 60%</td>
<td>CRS Grade 1-2 36% 4 deaths*</td>
</tr>
</tbody>
</table>

*Disease progression not attributed to therapy

Patient Case

JW is a 40 year old male with past medical history of stage IV refractory B cell lymphoma, hypertension, and seasonal allergies with no known drug allergies.

Past treatment:
- R-CHOP x 6 cycles
- R-ICE x 3 cycles
- Autologous stem cell transplantation

<table>
<thead>
<tr>
<th>Home medications</th>
<th>Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loratadine 10 mg PO daily</td>
<td>WBC 3,000/mm3</td>
</tr>
<tr>
<td>Lisinopril 20 mg PO daily</td>
<td>ANC 1,500/mm3</td>
</tr>
<tr>
<td>Multivitamin 1 tablet PO daily</td>
<td>Hgb 10.1 g/dL</td>
</tr>
<tr>
<td>Hydrochlorothiazide 12.5 mg PO daily</td>
<td>Platelets 150,000/mm3</td>
</tr>
</tbody>
</table>
The treatment team wants to initiate anti-CD19 CAR-T cell treatment for JW. What would you inform him about CAR-T cell therapy?

A. Complete response rates are similar to conventional chemotherapy
B. Conditioning chemotherapy enhances CAR-T cell expansion and persistence
C. Cytokine release syndrome is a rare complication of CAR-T cell therapy
D. Deaths from toxicities was greater than disease progression in clinical trials
# Efficacy and Safety: Chronic Lymphocytic Leukemia (CLL)

<table>
<thead>
<tr>
<th>Study (Institution)</th>
<th>Product</th>
<th>No.</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTL019 (UPenn)</td>
<td>Anti-CD19 CD3 zeta, 4-1BB</td>
<td>35</td>
<td>CR 23%</td>
<td>CRS any Grade 54%, Grade ≥3 20%</td>
</tr>
<tr>
<td>CD4⁺:CD8⁺ (FHCRC)</td>
<td>Anti-CD19 CD3-zeta, CD137, and EGFRt</td>
<td>13</td>
<td>CR 50%</td>
<td>Reported in aggregate with other B-cell malignancies</td>
</tr>
</tbody>
</table>

# Efficacy and Safety: Multiple Myeloma

<table>
<thead>
<tr>
<th>Study (Manufacture/ Institution)</th>
<th>Product</th>
<th>No.</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bb2121 (CRB-401, Bluebird Bio)</td>
<td>Anti-BCMA CD3 zeta, 4-1BB</td>
<td>11</td>
<td>CR 50%*</td>
<td>CRS Grade 1-2 73%</td>
</tr>
<tr>
<td>CTL019</td>
<td>Anti-CD19 CD3-zeta and 4-1B</td>
<td>10</td>
<td>PFS 60%</td>
<td>CRS Grade 1 10%</td>
</tr>
<tr>
<td>LCAR-B38M (Nanjing Legend Biotech)</td>
<td>Anti-BCMA Domains not reported</td>
<td>35</td>
<td>CR 94%</td>
<td>CRS Grade 1-4 85% Grade ≥3 6%</td>
</tr>
</tbody>
</table>

* Of evaluable pts

Key Takeaways

• Studies are showing promising results in heavily pretreated patients

• More studies are needed to determine the optimal:
  – CAR-T cell dose
  – Target
  – Co-stimulatory domain
  – Conditioning regimen
Presentation and Management of CAR-T cell Toxicities
Immunotherapy Toxicity

- Cytokine-associated toxicity
  - CRS and CRES
  - Non-antigen specific
  - High-level of immune activation

- Autoimmune toxicity
  - Antigen-specific attack of host tissue
  - On target, off-tumor toxicity
  - Antigen expression on non-malignant tissue

CAR-T Cell Toxicities

- Rates vary across studies
  - Different products
  - Cell dose
  - Disease state
  - Patient population

- Onset varies with product

<table>
<thead>
<tr>
<th>Toxicity (Grade ≥3)</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>66%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>44%</td>
</tr>
<tr>
<td>Anemia</td>
<td>43%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>31%</td>
</tr>
<tr>
<td>Neurologic</td>
<td>28%</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>21%</td>
</tr>
<tr>
<td>CRS</td>
<td>13%</td>
</tr>
</tbody>
</table>

Pathophysiology of CRS/CRES

- Excretion of endogenous cytokines
- Cell dose: response relationship and onset dependent on specific product
- Risk factors
  - Large tumor burden
  - Early onset CRS
  - Multiple co-morbidities
  - Older age
  - Elevated C reactive protein (CRP) prior to CAR-T cell infusion

<table>
<thead>
<tr>
<th>Cytokine Elevations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF alpha</td>
</tr>
<tr>
<td>IFN gamma</td>
</tr>
<tr>
<td>IL-1 beta</td>
</tr>
<tr>
<td>IL-2</td>
</tr>
</tbody>
</table>
CRS and CRP

Reprinted with permission from AAAS.
CRS (Occurring during the first 3 weeks after CAR-T cell infusion)

- Hypotension (systolic blood pressure < 90 mmHg)
- Organ toxicity
  - Neurotoxicity
  - Cardiac
  - Gastrointestinal
  - Hepatic/renal
  - Dermatologic
  - Coagulopathy
- Fever (temperature ≥ 38°C)
- Hypoxia (O₂ saturation < 90% on room air)

CRES

Seizures

Neurologic assessment
- Orientation/alertness
- Name objects
- Writing
- Counting

Motor weakness

Increased ICP

## Grading of CRS/CRES

<table>
<thead>
<tr>
<th>CRS/CRES Grade</th>
<th>Criteria</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Non-life threatening symptoms requiring symptomatic treatment • Constitutional symptoms</td>
<td>• Fever- supportive care acetaminophen +/- hypothermia blanket • Assess and treat infection(s)/seizures • Consider tocilizumab or siltuximab for refractory fevers</td>
</tr>
</tbody>
</table>

## Grading of CRS/CRES

<table>
<thead>
<tr>
<th>CRS/CRES Grade</th>
<th>Criteria</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Symptoms require and respond to moderate intervention</td>
<td>• Manage similar to grade 1</td>
</tr>
<tr>
<td></td>
<td>• Oxygen requirement &lt; 40%</td>
<td>• Monitor for cardiac and other organ dysfunction</td>
</tr>
<tr>
<td></td>
<td>• Hypotension responsive to fluids or low dose vasopressor</td>
<td>• Fluid bolus, may repeat if SBP less than 90 mmHg</td>
</tr>
<tr>
<td></td>
<td>• Grade 2 organ toxicity</td>
<td>• +/- *tocilizumab/ siltuximab, *dexamethasone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Supplemental oxygen</td>
</tr>
</tbody>
</table>

*High-risk patients/CRES
<table>
<thead>
<tr>
<th>CRS/CRES Grade</th>
<th>Criteria</th>
<th>Management</th>
</tr>
</thead>
</table>
| 3             | Symptoms require and respond to aggressive intervention  
• Oxygen requirement ≥ 40%  
• Hypotension requiring high-dose or multiple vasopressors  
• Grade 3 organ toxicity or Grade 4 elevation in AST/ALT | • Manage similar to grade 2  
• ICU transfer  
• Supplemental oxygen, non-invasive positive pressure ventilation  
• Consider tocilizumab/ siltuximab +/- dexamethasone |
| 4             | Life-threatening symptoms –  
• Ventilator support  
• Grade 4 organ toxicity (excluding elevation in AST/ALT) | • Manage similar to grade 3  
• High-dose corticosteroids |
### Treatment of CRS/CRES

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 receptor antagonist</td>
<td>Tocilizumab 8 mg/kg (maximum 800 mg/dose) IV</td>
</tr>
<tr>
<td></td>
<td>- Dose may be repeated</td>
</tr>
<tr>
<td></td>
<td>Siltuximab 11 mg/kg IV x 1 dose</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Dexamethasone 10-20 mg IV every 6 hours</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone 1 g/day IV followed by a rapid taper</td>
</tr>
<tr>
<td></td>
<td>(severe grade 4 toxicity)</td>
</tr>
</tbody>
</table>


Patient Case

- JW is a 40 year old male with past medical history of stage IV refractory B cell lymphoma, hypertension, and seasonal allergies with no known drug allergies.
- He is day +4 of anti-CD19 CAR-T cells he developed:
  - Fever (temp 39°C)
  - Headache
  - Hypotension (SBP 84 mmHg).
- The team ordered blood cultures, x-ray, and 500 mL IV NS bolus. SBP improved to 88 mmHg, temp 38.8°C, and A&O x 3.

<table>
<thead>
<tr>
<th>Current Scheduled Medications</th>
<th>Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keppra 750 mg PO every 12 hours</td>
<td>WBC 700/mm3</td>
</tr>
<tr>
<td>Filgrastim 480 mcg SubQ daily</td>
<td>ANC 300/mm3</td>
</tr>
<tr>
<td>Cefepime 2 g IV every 8 hours</td>
<td>Hgb 7.9 g/dL</td>
</tr>
<tr>
<td>Vancomycin 1.5 g IV every 12 hours</td>
<td>Platelets 25,000/mm3</td>
</tr>
</tbody>
</table>
Question #4

What interventions are appropriate for JW at this time?

A. Repeat fluid bolus, acetaminophen, and neurology consult
B. Repeat fluid bolus, cooling blanket, and acetaminophen
C. Tocilizumab 8 mg/kg, repeat fluid bolus, and acetaminophen
D. Dexamethasone 10 mg IV q6h and acetaminophen
Other CRS Related Organ Toxicity

- Cardiac - tachycardia, arrhythmias, heart block, heart failure
- Respiratory - tachypnea, pulmonary edema, pleural effusions
- Gastrointestinal - nausea, vomiting, diarrhea
- Hepatic - increase in AST/ALT or bilirubin
- Renal - decreased urine output, increased serum creatinine
- Coagulopathy - disseminated intravascular coagulation
- Hemophagocytic lymphohistiocytosis
- Dermatologic - rash

Short-term Adverse Effects

- Infusion reactions - pre-medicate
- Tumor lysis syndrome - allopurinol
- Hematologic
  - Neutropenia - neupogen
  - Thrombocytopenia - platelet transfusions
  - Anemia - red blood cell transfusions
- Fever - cultures and antibiotics
- Headache
- Nausea and vomiting

Intermediate to Long-term Adverse Effects

- Monitor for infections
- Hypogammaglobulinemia
  - Monitor IgG levels and give IVIG for low IgG levels
- Hematologic toxicities

Interventions

• Avoid medications causing central nervous system depression
• Assess for drug interactions or excluded medications
  – Avoid corticosteroids as pre-medications for transfusions
  – Avoid non-steroidal anti-inflammatory medications NAIDS
• Prophylaxis
  – Varicella-zoster virus- continue acyclovir or valacyclovir for 1 year
  – Seizure
  – Pneumocystis pneumonia
  – Stress ulcer

Key Takeaways

• CAR-T cell toxicities have a unique presentation compared to traditional chemotherapy
• Training on the recognition, treatment, and monitoring of CRS/CRES is essential to decrease treatment related morbidity and mortality
• Interdisciplinary teams are necessary to optimally care for patients undergoing CAR-T cell therapy