Webinar Agenda

5:30 – 5:35 p.m. ET  Overview: Welcome and Introductions
5:35 – 6:10 p.m. ET  Presentation and Discussion
6:10 – 6:25 p.m. ET  Question and Answer Session
6:25 – 6:30 p.m. ET  Closing Remarks
Webinar faculty

Stephen Grupp, MD, PhD – Children’s Hospital of Philadelphia and University of Pennsylvania

Sattva Neelapu, MD – The University of Texas MD Anderson Cancer Center

Jorg Dietrich, MD, PhD – Massachusetts General Hospital
Learning objectives

• Appropriately manage CAR T and immune effector cell-associated toxicities
• Outline risk factors for IEC-associated toxicities
• Describe ongoing studies for the management of IEC-related toxicities
Development of the guideline

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events
Development of the guideline

• Panel of 26 members, including physician, nursing, and patient advocacy perspectives

• Representatives from several organizations participated:
  • American Society of Hematology (ASH)
  • American Society for Transplantation and Cellular Therapy (ASTCT)
  • Foundation for the Accreditation of Cellular Therapy (FACT) at the University of Nebraska Medical Center
  • Emily Whitehead Foundation

• All recommendations based on literature where available, and panel experience and consensus where applicable
### FDA-approved CAR T therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target/co-stimulatory domain</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axicabtagene ciloleucel</td>
<td>CD19/CD28</td>
<td>Adults with R/R large B-cell lymphoma, including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma, after 2+ therapies</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>CD19/4-1BB</td>
<td>Patients ≤25 yr with refractory B-cell acute lymphoblastic leukemia or in 2+ relapse</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>CD19/4-1BB</td>
<td>Adults with R/R large B-cell lymphoma after 2+ therapies Including DLBCL, high-grade B-cell lymphoma, DLBCL arising from follicular lymphoma</td>
</tr>
<tr>
<td>Brexucabtagene autoleucel</td>
<td>CD19/CD28</td>
<td>Adults with R/R mantle cell lymphoma</td>
</tr>
<tr>
<td>Lisocabtagene maraleucel*</td>
<td>CD19/4-1BB</td>
<td>Adults with R/R large B-cell lymphoma, including diffuse large B-cell lymphoma not otherwise specified (including arising from indolent lymphoma), high-grade B-cell lymphoma, PMBCL and follicular lymphoma grade 3B, after at least 2 prior therapies</td>
</tr>
<tr>
<td>Idecabtagene vicleucel*</td>
<td>BCMA/4-1BB</td>
<td>Adults with R/R multiple myeloma after 4+ prior therapies</td>
</tr>
</tbody>
</table>

*not approved at the time of Guideline publication*
Webinar outline

• Management, risk factors and future directions for:

• CRS and related toxicities
  • Cardiovascular events
  • HLH/MAS

• Neurologic toxicities
  • ICANS
  • Cerebral edema
Cytokine release syndrome

**Constitutional**
- Fever +/- rigors
- Malaise/fatigue
- Myalgias
- Arthralgias
- Headache

**Gastrointestinal**
- Nausea/vomiting
- Diarrhea
- Anorexia

**Skin**
- Rash

**Respiratory**
- Tachypnea
- Hypoxia
- Pulmonary edema

**Cardiovascular**
- Tachycardia
- Hypotension
- Capillary leak
- Widened pulse pressure
- Increased cardiac output (early)
- Potentially diminished cardiac output (late)

**Hepatic dysfunction**
- Transaminitis
- Hyperbilirubinemia

**Coagulation**
- Elevated D-dimer
- Hypofibrinogenemia +/- bleeding

**Renal function**
- Azotemia
### ASTCT CRS grading

<table>
<thead>
<tr>
<th>CRS parameter</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>&gt; 38°C</td>
<td>&gt; 38°C</td>
<td>&gt; 38°C</td>
<td>&gt; 38°C</td>
</tr>
<tr>
<td>with</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>None</td>
<td>Not requiring vasopressors</td>
<td>Requiring a vasopressor with or without vasopressin</td>
<td>Requiring multiple vasopressors (excluding vasopressin)</td>
</tr>
<tr>
<td>and/or</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxia</td>
<td>None</td>
<td>Requiring low-flow nasal cannula or blow-by</td>
<td>Requiring high-flow nasal cannula, face mask, non-rebreather mask or venturi mask</td>
<td>Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)</td>
</tr>
</tbody>
</table>

Lee, Santomasso, Biol Blood Marrow Transpl 2018
Monitoring for CRS

• Events requiring physician notification include:
  • Deviations from baseline systolic blood pressure
  • Heart rate >120 or <60 bpm
  • Arrhythmia
  • Respiratory rate >25 or <12 breaths/minute
  • Arterial oxygen saturation <92% on room air
  • Upward trend in blood creatinine or liver function tests
  • Tremors or jerky movements in extremities
  • Altered mental status
  • Temperature ≥ 38°C
Management of CRS

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Tocilizumab-unresponsive</th>
<th>Tocilizumab + steroids-unresponsive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Close monitoring and supportive care</td>
<td>Consider tocilizumab</td>
<td>Tocilizumab</td>
<td>Tocilizumab + steroids</td>
<td>If CRS does not respond to 1 dose of tocilizumab, combine steroids + tocilizumab</td>
<td>Options include: Anakinra, siltuximab, HD methylprednisolone</td>
</tr>
</tbody>
</table>

- For **elderly patients or those with significant co-morbidities**, tocilizumab should be considered earlier in the treatment course.
- If CRS does not improve after tocilizumab + steroids, **infections** should be considered and managed appropriately.
- If steroids are used, a **rapid taper** should be employed once symptoms begin to improve.
Risk factors for CRS

• High disease burden
• CD28 costimulatory domains in the CAR T product
• High dose of CAR T cells
• Pre-existing cardiac risk factors
• Baseline inflammatory state
CRS and high baseline tumor burden
## Trials for prevention/treatment of CRS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study</th>
<th>Status</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02906371</td>
<td>A Two Cohort Pilot Study of Tocilizumab Optimization Timing for CAR-T19-Associated CRS Management in Pediatric Patients With CD19 Expressing Relapsed/Refractory B-cell ALL</td>
<td>Active, not recruiting Two cohorts, open-label, phase 1/2 study</td>
<td>Pediatric patients aged 1–24 years with CD19 expressing relapsed/refractory B-cell ALL</td>
<td>Two cohorts defined based upon pre-infusion high versus low tumor burden: 1. High tumor burden cohort (high risk of severe CRS) to receive earlier administration of tocilizumab for CRS 2. Low tumor burden cohort (low risk of severe CRS) to receive standard timing of tocilizumab for CRS</td>
</tr>
<tr>
<td>NCT04048434</td>
<td>Effectivity of Extracorporeal Cytokine Adsorption (Cytosorb) as Additive Treatment of CAR-T Cell-Associated Cytokine Release (CRS) Syndrome and Encephalopathy Syndrome (CRES)</td>
<td>Not yet recruiting</td>
<td>Patients aged 18 or older who develop severe CRS (&gt;3)/severe CRES (&gt;3) and CRS/CRES onset &lt;6 hrs.</td>
<td>Patients with severe CAR-T cell-associated CRS (defined as vasopressor dependent) will be treated with standard of care + cytokine adsorption (6 hourly for 24 hrs.).</td>
</tr>
<tr>
<td>NCT03696784</td>
<td>A Phase I Study of Autologous Activated T-cells Targeting the CD19 Antigen and Containing Inducible Caspase 9 Safety Switch (iC9-CAR19) in Subjects With Relapsed/Refractory B-cell Lymphoma</td>
<td>Recruiting Phase I</td>
<td>Patients aged 18 or older with relapsed or refractory B-cell Lymphoma</td>
<td>Patients who develop grade 4 CRS or grade ≥3 CRS or who develop grade ≥3 CRES or grade 2 CRES that is unresponsive to standard of care interventions will be given Rimiducid at 0.4 mg/kg.</td>
</tr>
<tr>
<td>NCT04071366</td>
<td>A Study of Itacitinib for the Prevention of Cytokine Release Syndrome Induced by Immune Effector Cell Therapy</td>
<td>Study to open in January 2020 Phase 2</td>
<td>Patients 12 years and older eligible to receive either tisagenlecleucel or axicabtagene ciloleucel for approved hematologic indications</td>
<td>Oral administration of itacitinib 200 mg once daily for 30 days for the prevention of CRS</td>
</tr>
</tbody>
</table>

Murthy, Immunotargets Ther 2019
Cardiovascular toxicities

• Common events include:
  • Hypotension; heart failure (new or worsening); arrhythmias
• Baseline evaluation of cardiac function is important
  • TTE, serum troponin, and NT-proBNP/BNP
• Risk factors for cardiac events include:
  • Prior therapies (anthracycline)
  • Prior cardiac insult
  • Low ejection fraction
  • Arrhythmias
Management of cardiovascular events

• Any evidence of cardiac toxicity should warrant escalation of treatment (IL-6 blockade, steroids)
• High-risk patients should receive in-patient treatment
• Can continue treatment with: beta blockers, angiotensin II receptor blockers, calcium channel blockers, ACE inhibitors
• Should discontinue antiplatelet agents if possible
HLH/MAS

- Hemophagocytic lymphohistiocytosis / macrophage activation syndrome
- Appears to be more common with certain CAR T products
- Substantial overlap with CRS symptoms
- Late onset and tocilizumab refractoriness may indicate HLH/MAS

Symptoms:
- High fever, elevated ferritin and liver enzymes, pancytopenias
- Elevated serum IFNγ, IL-10, sIL-2Rα, IL-6, IL-8, GM-CSF
- Hepatosplenomegaly, lymphadenopathy, hemophagocytosis
Management of HLH/MAS

- Tocilizumab
- Anakinra or steroids
- Etoposide
Webinar outline

• Management, risk factors and future directions for:
  
  • CRS and related toxicities
    • Cardiovascular events
    • HLH/MAS
  
  • Neurologic toxicities
    • ICANS
    • Cerebral edema
# ASTCT ICANS grading - adults

<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 is unarousable)</td>
</tr>
<tr>
<td>Depressed level of consciousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Awakens spontaneously</td>
<td></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>Any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention</td>
<td>Life-threatening prolonged seizure (&gt;5 min), repetitive clinical or electrical seizures without return to baseline in between</td>
</tr>
<tr>
<td>Motor findings</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</td>
<td>Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing’s triad</td>
</tr>
</tbody>
</table>

Lee, Santomasso, Biol Blood Marrow Transpl 2018
# ASTCT ICANS grading - pediatric

<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 (age ≥12 years)</td>
<td>7–9</td>
<td>3–6</td>
<td>0–2</td>
<td>0 (patient is unarousable)</td>
</tr>
<tr>
<td>CAPD score (age &lt;12 years)</td>
<td>1–8</td>
<td>1–8</td>
<td>≥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>Unarousable or requires vigorous or repetitive tactile stimuli to arouse</td>
</tr>
<tr>
<td>Seizure (any age)</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Life-threatening prolonged seizure (&gt;5 min), repetitive clinical or electrical seizures without return to baseline in between</td>
</tr>
<tr>
<td>Motor weakness (any age)</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 (any age)</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, cranial nerve VI palsy, papilledema, or Cushing’s triad</td>
</tr>
</tbody>
</table>
Immune effector cell-associated encephalopathy (ICE) score

- **Orientation**: Orientation to year, month, city, hospital: 4 points (1 point each)
- **Naming**: Name 3 objects (e.g., clock, pen, button): 3 points (1 point each)
- **Following commands**: (e.g., Show me 2 fingers or close your eyes and stick out your tongue): 1 point
- **Writing**: Ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point
- **Attention**: Count backwards from 100 by 10: 1 point
- **Total scale**: 0-10
Monitoring for ICANS

• Altered mental status defines the onset of ICANS
• Work-up should include:
  • CRP
  • CBC
  • CMP
  • Fibrinogen
  • Prothrombin time test
  • PT/INR
• Head CT, EEG, and brain MRI may be considered
Management of ICANS

• **4-1BB** CAR T agents: consider steroids at grade 2 ICANS; administer steroids for grades 3-4 ICANS

• **CD28** CAR T agents: administer steroids for grades 2-4 ICANS

• Management of neurotoxicity may take precedence over low-grade CRS, due to possibility of tocilizumab worsening ICANS
  • For example: in the case of a patient with concomitant grade 1 CRS (fever) and grade 2 ICANS, steroids should be given. This does not apply to higher-grade CRS.

• If **steroids** are used, administer at least two doses and employ a fast taper

• **Levetiracetam** is recommended for management of seizures
Risk factors for ICANS

- High tumor burden
- High CAR T dose
- High ferritin and cytokine levels
- Low platelet level
- High-grade CRS
- Pre-existing neurologic comorbidities
- Early fever after CAR T dosing
Risk factors for ICANS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Grade 0</th>
<th>Grade 1-2</th>
<th>Grade 3-5</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>41</td>
<td>37</td>
<td>22</td>
<td>0.094</td>
<td></td>
</tr>
<tr>
<td>40-60 years</td>
<td>66</td>
<td>13</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>64</td>
<td>17</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pre-existing neurologic comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>45</td>
<td>28</td>
<td>28</td>
<td>0.0059</td>
<td>0.0023</td>
</tr>
<tr>
<td><strong>Marrow disease %</strong></td>
<td>Median (range)</td>
<td>0.6 (0-97)</td>
<td>0.4 (0-93)</td>
<td>25.8 (0-97)</td>
<td>0.072</td>
</tr>
<tr>
<td><strong>Lymphodepletion regimen</strong></td>
<td>Cy/Flu</td>
<td>56</td>
<td>22</td>
<td>22</td>
<td>0.11</td>
</tr>
<tr>
<td>Non-Cy/Flu</td>
<td>76</td>
<td>7</td>
<td>17</td>
<td>&lt;0.0001</td>
<td>0.0009</td>
</tr>
<tr>
<td><strong>CAR T cell dose</strong></td>
<td>2x10^5 cells/kg</td>
<td>57</td>
<td>29</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>2x10^6 cells/kg</td>
<td>64</td>
<td>17</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2x10^7 cells/kg</td>
<td>42</td>
<td>0</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cytokine release syndrome</strong></td>
<td>None (Grade 0)</td>
<td>88</td>
<td>13</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>57</td>
<td>25</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>6</td>
<td>6</td>
<td>88</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values as percent of patients unless otherwise indicated.
ICANS, steroid use and outcomes

• High-grade ICANS with prolonged steroid use >10 days appears to be a negative prognostic factor

Karschnia, Blood 2019
Cerebral edema

• Unclear whether ICANS and edema arise from distinct pathophysiology
• Disruption of the blood-brain barrier likely cause with capillary leakage syndrome
• Patients with suspected cerebral edema should be immediately referred to intensive care

June CH et al., Science, 2018
Management of cerebral edema

- Intensive Care Unit management
- Frequent Neuro checks
- Respiratory support
- Mannitol / Hyperventilation / Dexamethasone / hypertonic saline
- Consider EVD for ICP monitoring
Case: Fatal cerebral edema

21 M with relapsed B-cell ALL

- Cyclophosphamide/Fludarabine → CD-19 CAR-T
- Day 1: CRS grade 2 (fevers, tachycardia)
- Day 2: High-dose dexamethasone
- Day 4: Neuro exam abnormal with wordfinding difficulty → lethargic → unresponsive
- → intubated → Mannitol, Hyperventilation, Decadron → Repeated head CT
- Day 5: Declared brain death

Torre M et al, J Neuropath Exp Neurol, 2018
Conclusions

• The field of IEC toxicity management is rapidly changing, and guidelines may change accordingly

• Guidelines will be updated following new FDA approvals

• These guidelines can provide help for patient management, but clinical situations should include physician discretion

• Both CRS and ICANS can occur in the majority of patients, so familiarity with their presentation and management are important for all members of the cancer care team

• Prophylactic strategies are being explored in clinical trials
Case Studies in Immune Effector Cell-related Adverse Events
October 13, 2021, 5:30–6:30 p.m. ET

Immune Checkpoint Inhibitor-related Adverse Events Guideline Overview
August 13, 2021, 10–11 a.m. ET

CME-, CNE-, CPE-certified

Learn more and register at: https://www.sitcancer.org/research/cancer-immunotherapy-guidelines/webinars
Targets for Cancer Immunotherapy: A Deep Dive Seminar Series

Eight online seminars will address key questions in the field of cancer immunotherapy drug development

SEMINARY 4: ADENOSINE – August 24, 2021, 11:30 a.m. - 1:30 p.m. ET

SEMINARY 5: MACROPHAGE BIOLOGY FOR ANTI-TUMOR IMMUNITY – October 7, 2021, 10:30 a.m. - 12:30 p.m. ET

Learn more and register at: https://www.sitcancer.org/education/deepdive
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September 15, 2021, 12 – 4:10 PM ET

CME-, CPE-, CNE-, MOC-certified

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Acknowledgements

• Some figures created using biorender.com
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Questions or comments: connectED@sitcancer.org

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