Clinical Practice Guideline Webinar – Immune Effector Cell-related Adverse Events

Friday, March 5, 2021
3:00 PM – 4:00 p.m. EST

Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer

This webinar is supported, in part, by independent medical education grant funding from Amgen, AstraZeneca Pharmaceuticals LP, Celgene Corporation and Merck & Co., Inc.
Webinar Agenda

3:00 – 3:05 p.m. ET  Overview: Welcome and Introductions

3:05 – 3:45 p.m. ET  Presentation and discussion of guideline content

3:45 – 3:55 p.m. ET  Question and Answer Session

3:55 – 4:00 p.m. ET  Closing Remarks
How to Submit Questions

• Click the “Q&A” icon located on at the bottom of your Zoom control panel
• Type your question in the Q&A box, then click “Send”
• Questions will be answered in the Question & Answer session at the end of the webinar (as time permits)
Webinar faculty

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

Matthew J. Frigault, MD, MSc
Massachusetts General Hospital

Frederick L. Locke, MD
H. Lee Moffitt Cancer Center & Research Institute

Bianca D. Santomasso, MD, PhD
Memorial Sloan Kettering Cancer
Learning objectives

• Properly monitor patients receiving immune effector cell therapies for treatment-related adverse events and identify those at high risk

• Identify common and uncommon toxicities that may occur with immune effector cell therapies

• Determine appropriate management techniques for common adverse events resulting from immune effector cell therapies
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
Development of the guideline

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


1 Department of Medicine, 2 Department of Biomedical Science, 3 Department of Medicine and University of Delaware, 4 Department of Medicine, 5 Department of Medicine and University of California, 6 Department of Medicine, 7 Department of Medicine, 8 Department of Medicine, 9 Department of Medicine, 10 Department of Medicine, 11 Department of Medicine, 12 Department of Medicine, 13 Department of Medicine, 14 Department of Medicine, 15 Department of Medicine, 16 Department of Medicine, 17 Department of Medicine, 18 Department of Medicine, 19 Department of Medicine, 20 Department of Medicine, 21 Department of Medicine, 22 Department of Medicine, 23 Department of Medicine, 24 Department of Medicine, 25 Department of Medicine, 26 Department of Medicine.
Webinar outline

• Introduction to CAR T therapy
• Screening and selecting patients for IEC therapy
• Common adverse events with IEC therapy
  • CRS – cytokine release syndrome
  • ICANS – immune effector cell-associated neurotoxicity syndrome
  • Cytopenias
CAR T therapy

1. Acquire T cells from blood
2. Create CAR T cells
3. Grow CAR T cells
4. Infuse CAR T cells into patient
5. CAR T cells attack cancer cells

Insert gene for CAR using viral vector

Chimeric antigen receptor (CAR)

Antigen-recognition domain
Signaling domains

Death of cancer cells
Evolution of CAR constructs
## FDA-approved CAR T therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target/co-stimulatory domain</th>
<th>Indication</th>
<th>Dose</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</td>
<td>2 x 10⁶ CAR-positive, viable T cells per kg bodyweight (up to 2x10⁸)</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>
<td>0.2-0.5x10⁶ CAR-positive, viable T cells per kg if under 50 kg 0.1-2.5x10⁸ CAR-positive, viable T-cells if over 50 kg</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>
<td>0.6-6.0 x 10⁸ CAR-positive, viable T cells</td>
</tr>
<tr>
<td>Brexucabtagene autoleucel</td>
<td>CD19/CD28</td>
<td>Adults with mantle cell lymphoma (MCL) who have not responded to or who have relapsed following other treatments</td>
<td>2 x 10⁶ CAR-positive, viable T cells per kg bodyweight (up to 2x10⁸)</td>
</tr>
<tr>
<td>Lisocabtagene maraleucel*</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, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B</td>
<td>50 to 110x10⁶ CAR-positive, viable T cells (consisting of 1:1 CAR-positive viable CD4 and CD8 T cells)</td>
</tr>
</tbody>
</table>

*not approved at time of guideline development*
Clinical trials of CAR T therapies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Indication</th>
<th>Treatment</th>
<th>ORR</th>
<th>Landmark OS</th>
<th>Grade 3+ toxicity rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZUMA-2</td>
<td>R/R mantle cell lymphoma</td>
<td>Brexucabtagene autoleucel (KTE-X19)</td>
<td>86%</td>
<td>1-year: 86%</td>
<td>CRS: 18% ICANS: 46%</td>
</tr>
<tr>
<td>ZUMA-1</td>
<td>Refractory large B cell lymphoma</td>
<td>Axicabtagene ciloleucel</td>
<td>83%</td>
<td>2-year: 50%</td>
<td>CRS: 11% ICANS: 32%</td>
</tr>
<tr>
<td>JULIET</td>
<td>R/R diffuse large B cell lymphoma</td>
<td>Tisagenlecleucel</td>
<td>52%</td>
<td>1-year: 49%</td>
<td>CRS: 22% ICANS: 12%</td>
</tr>
<tr>
<td>ELIANA</td>
<td>R/R B cell acute lymphoblastic leukemia</td>
<td>Tisagenlecleucel</td>
<td>82%</td>
<td>18-month: 70%</td>
<td>CRS: 48% ICANS: 13%</td>
</tr>
<tr>
<td>TRANSCEND</td>
<td>R/R diffuse large B cell lymphoma</td>
<td>Lisocabtagene maraleucel</td>
<td>73%</td>
<td>1-year: 57%</td>
<td>CRS: 4% ICANS: 12%</td>
</tr>
</tbody>
</table>

Webinar outline

• Introduction to CAR T therapy
• Screening and selecting patients for IEC therapy
• Common adverse events with IEC therapy
  • CRS – cytokine release syndrome
  • ICANS – immune effector cell-associated neurotoxicity syndrome
  • Cytopenias
Patient selection considerations

• Treatment decisions should be **risk-adapted** to take into account characteristics of individual patients and products.

• Patients who have previously undergone allo-HSCT, BiTE therapy, anti-CD19 mAb therapy, and other mAb therapy may be treated with CAR T, provided the patient’s disease **still expresses the target antigen**.

• Toxicity and timing of toxicities **may vary for different products**, depending on costimulatory or other structural domains.
Patient selection considerations

• Patients with **higher pre-treatment disease burden** are at increased risk of toxicity.

• **ECOG performance status** should be taken into account, due to the high risk of toxicity.

• **CAR T therapy** may be appropriate for patients with **stable disease or in CR** with high relapse risk.

• Some **CAR T products** can be given in outpatient setting, but **admission should be considered** at first signs of toxicity.
Pre-treatment evaluations

• Similar to auto-SCT
• Pre-treatment tests should include:
  • C-reactive protein (CRP)
  • Ferritin
  • Lactate dehydrogenase (LDH)
  • Complete blood count
  • Comprehensive metabolic panel
  • Transthoracic echocardiogram or multigated acquisition scan
  • Neurological evaluation
  • Disease burden assessment
Considerations during the COVID-19 pandemic

• Treatment plans for cancer patients must take into account potential limitations in hospital resources
• Delaying CAR T may not be an option in some cases
• Make sure tocilizumab is readily available
• Ensure adequate staffing and supportive care

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Cytokine release syndrome

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

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

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

**Skin**
- Rash

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

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

**Hepatic dysfunction**
- Transaminitis
- Hyperbilirubinemia

**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
  • Arrythmia
  • 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 methylprednisone</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.
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  • Cytopenias
<table>
<thead>
<tr>
<th>Neurotoxicity domain</th>
<th>Grade 1 (ICE score)</th>
<th>Grade 2 (score)</th>
<th>Grade 3 (score)</th>
<th>Grade 4 (description)</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>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>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><strong>ICE score (age ≥12 years)</strong></td>
<td>7–9</td>
<td>3–6</td>
<td>0–2</td>
<td>0 (patient is unarousable)</td>
</tr>
<tr>
<td><strong>CAPD score (age &lt;12 years)</strong></td>
<td>1–8</td>
<td>1–8</td>
<td>≥9</td>
<td>Unable to perform CAPD</td>
</tr>
<tr>
<td><strong>Depressed level of consciousness</strong></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><strong>Seizure (any age)</strong></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><strong>Motor weakness (any age)</strong></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><strong>Elevated ICP/cerebral edema (any age)</strong></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*
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
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  • CRS – cytokine release syndrome
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  • Cytopenias
Cytopenias with CAR T therapy

- Short-term cytopenias are expected with lymphodepletion
- Timing and persistence of cytopenias may vary by product
- Important to consider myelodysplastic syndromes in differential diagnosis
- Risk factors include high disease burden, prior HSCT and high grade CRS

Monitoring & management of cytopenias

• For cytopenias occurring within first 28 days, CBC may be adequate for follow-up

• For cytopenias persisting >28 days, bone marrow biopsy and aspiration should be performed

• Patients should be hospitalized if they develop active infections or febrile neutropenia

• Consider holding growth factors until day 14 from CAR T infusion, or once CRS has resolved

• Growth factors should be considered for persistent cytopenias

Maus, J Immunother Cancer 2020
Infection precautions and prophylaxis

- Any bacterial or fungal infections should be treated and CAR T held until infections are controlled
- All patients should undergo pneumocystis pneumonia prophylaxis
- The decision for antibacterial, antiviral and/or antifungal prophylaxis should be risk-adjusted by patient characteristics
- For patients with high-risk historical features, antibacterial/antifungal prophylaxis should be strongly considered
- Patients with persistent neutropenia should receive antibacterial/antifungal prophylaxis
Additional toxicities with CAR T therapies

• HLH/MAS
• Cerebral edema
• Cardiac toxicities
• On-target toxicities: Hypogammaglobulinemia
• Tumor lysis syndrome

These toxicities will be discussed in the upcoming “Practical management pearls for immune effector cell-related adverse events” webinar.
Conclusions

• High disease burden correlates with higher likelihood of adverse events
• Most common IEC-related adverse events include CRS, ICANS and cytopenias
• Incidence, timing and severity of adverse events varies by product and patient characteristics
How to Submit Questions

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CME Credit Now Available for JITC Reviewers

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To learn more about the benefits of serving as a JITC manuscript reviewer and to volunteer visit: sitcancer.org/jitc
Upcoming Webinar:

Advances in Cancer Immunotherapy™ Webinar – Clinical Updates from SITC 2020
Tuesday, March 30 at 4 – 5 p.m. ET

Faculty:
Jason Luke, MD – University of Pittsburgh Medical Center
Diwakar Davar, MD – University of Pittsburgh Medical Center
Karl Lewis, MD – University of Colorado
Ignacio Melero, MD, PhD – Fundación para la Investigación Médica Aplicada
Hussein Tawbi, MD, PhD – MD Anderson Cancer Center

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The 2020–2021 Advances in Cancer Immunotherapy™ educational series is supported, in part, by independent medical education grants from Amgen, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Exelixis, Inc., and Merck & Co., Inc.
Advances in Cancer Immunotherapy™
Virtual Programs

Saturday, March 20
Thursday, April 8
Tuesday, April 27

- Learn about how to treat patients with FDA-approved immunotherapies
- Available for CME, CPE and CME credits and MOC points
- **Free** for healthcare professionals, students, patient or patient advocates

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Continuing Education Credits

- Continuing Education Credits are offered for Physicians, PAs, NPs, RNs and Pharmacists
- You will receive an email following the webinar with instructions on how to claim credit
- Questions and comments: connectED@sitcancer.org

Thank you for attending the webinar!

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Acknowledgements

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