Chimeric Antigen Receptor T-Cell Therapies: Improving outcomes, but at what risk?

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PGY2 Oncology Pharmacy Residency Program Director
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Objectives
- Identify currently approved CAR T-cell products and their place in therapy
- Describe cytokine release syndrome (CRS) and neurotoxicity associated with CAR T-cell administration
- Identify appropriate treatment strategies for CRS and neurotoxicity

ARS Question #1
JS is a 40 year old male with acute lymphoblastic leukemia that experienced a CR following an AYA protocol, relapsed and then received blinatumomab with MRD- response. He subsequently relapsed a second time and is inquiring about CAR T-cell therapy. Which of the following is appropriate information for JS?

A. There are no data for CAR T-cell therapy in adult patients with ALL
B. He would not be eligible for tisagenlecleucel, but may be available for a clinical trial
C. He is eligible for treatment with tisagenlecleucel
D. He should not consider CAR T-cell therapy because he is on his second relapse

ARS Question #2
Which of the following CAR construct and time to toxicity are appropriately matched?

A. Tisagenlecleucel → CD28 co-stimulatory domain → faster onset of CRS
B. Axicabtagene ciloleucel → 4-1BB co-stimulatory domain → faster onset of CRS
C. Axicabtagene ciloleucel → CD28 co-stimulatory domain → faster onset of CRS
D. Tisagenlecleucel → 41BB co-stimulatory domain → faster onset of CRS

ARS Question #3
BR, a 55 year old male with multiply-relapsed NHL receives axicabtagene ciloleucel infusion. He tolerates his pre-conditioning chemotherapy and the infusion without many problems. However, on day 2 of his infusion, he develops a fever with a low-flow oxygen requirement. He is slower to arouse than usual, but still wakes when his name is called. This is most likely described and treated by which of the following:

A. Grade 2 CRS with overlapping Grade 1 neurotoxicity → JR should receive a dose of tocilizumab 8 mg/kg.
B. Grade 3 Neurotoxicity → BR should receive dexamethasone 10 mg IV q 6 hours until resolution
C. Grade 1 CRS → BR should receive a dose of siltuximab 11 mg/kg
D. BR is not experiencing any toxicities associated with CAR T-cell therapy

Disclosures
- Advisory Boards
  - Pfizer
  - Amgen
  - Jazz Pharmaceuticals
Need for Additional Therapies in Hematologic Malignancies
Relapsed and refractory disease, following treatment with conventional and targeted therapies or bone marrow transplantation, is associated with a poor prognosis.

Tumor Immune Escape
- Metabolically hostile microenvironment
- Thymic selection
- T-cell anergy
- Impaired tumor MHC antigen presentation
- Increased expression of negative co-stimulatory ligands
- Expansion of Tregs
- Increased production of inhibitory enzymes and cytokines
- Downregulation of NK cells

Harnessing the Immune System
- Stem cell transplant
- Vaccine therapy
- Cytokine therapy
- Immune checkpoint inhibitors
- Adoptive transfer of tumor infiltrating cells
- Bi-specific T-cell engaging antibody (BiTE®) therapy
- Chimeric antigen receptor (CAR) T-cells

Chimeric Antigen Receptor T-Cells (CAR Ts)
- CAR design
  - CD3ζ signaling element
  - Costimulatory receptor
  - Targeted single chain variable fragment
- Major histocompatibility independent mechanism

FDA Approved CAR T Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Co-Stimulatory Domain</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tisagenlecleucel (Kymriah®)</td>
<td>41BB</td>
<td>Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse</td>
</tr>
<tr>
<td>Tisagenlecleucel (Kymriah®)</td>
<td>41BB</td>
<td>Adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy</td>
</tr>
<tr>
<td>Axicabtagene ciloleucel</td>
<td>CD28</td>
<td>Adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy</td>
</tr>
</tbody>
</table>

T-cell Isolation and Gene Transfer

Pre-Conditioning Chemotherapy

- Improves antitumor activity
- Depletion of leukocytes
- Decrease in regulatory T-cells
- Decreased indoleamine production
- Tumor debulking
- Reduction in tumor antigen
- Cyclophosphamide and fludarabine
  - Increase T-cell expansion
  - Improved disease-free survival

Tisagenlecleucel Expansion and Persistence

Case Study #1 ALL

- JS is a 40 year old male with acute lymphoblastic leukemia (ALL) that experienced a CR following an AYA protocol, relapsed and then received blinatumomab with MRD-negative response. He subsequently relapsed a second time and is inquiring about CAR T-cell therapy.

Tisagenlecleucel in ALL (ELIANA)

- Single Cohort, Phase II, Multicenter, Global Study
- Secondary Endpoints: CR rates, MRD response, duration of remission, EFS, OS, Kinetics, Safety
- 


CR = complete response/remission
AYA = adolescent young adult
MRD = minimal residual disease

Tisagenlecleucel Toxicity

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Any Grade (N=75)</th>
<th>Grade 3 (N=25)</th>
<th>Grade 4 (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS, N (%)</td>
<td>67 (89)</td>
<td>26 (25)</td>
<td>30 (40)</td>
</tr>
<tr>
<td>Neurologic Event, N (%)</td>
<td>30 (40)</td>
<td>10 (40)</td>
<td>0</td>
</tr>
<tr>
<td>Infection, N (%)</td>
<td>32 (43)</td>
<td>18 (23)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Febrile Neutropenia, N (%)</td>
<td>26 (35)</td>
<td>24 (32)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Extended Cytopenias, N (%)</td>
<td>28 (37)</td>
<td>12 (16)</td>
<td>12 (16)</td>
</tr>
<tr>
<td>Tumor Lysis Syndrome</td>
<td>3 (4)</td>
<td>3 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>

CRS = Complete Remission Syndrome
CRS = CR with incomplete hematologic recovery
DOR = duration of remission
EFS = event-free survival
OS = overall survival

ARS Question #1

JS is a 40 year old male with acute lymphoblastic leukemia that experienced a CR following an AYA protocol, relapsed and then received blinatumomab with MRD- response. He subsequently relapsed a second time and is inquiring about CAR T-cell therapy. Which of the following is appropriate information for JS?

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C. He is eligible for treatment with tisagenlecleucel
D. He should not consider CAR T-cell therapy because he is on his second relapse

CASE Study #2 Relapsed DLBCL

BR, a 55 year old male with multiply-relapsed NHL receives axicabtagene ciloleucel infusion. He tolerates his pre-conditioning chemotherapy and the infusion without many problems. However, on day 2 of his infusion, he develops a fever with a low-flow oxygen requirement. He is slower to arouse than usual, but still wakes when his name is called.

Tisagenlecleucel in Lymphoma (Juliet)

International, Phase II, Multicenter

Leukapheresis → Lymphodepletion → T-Cell Infusion

Primary Endpoint: Best Overall Response Rate

Secondary Endpoints: response duration, OS, safety, cellular kinetics

Tisagenlecleucel Toxicity in Lymphoma

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Any Grade (N=111)</th>
<th>Grade 3/4 (N=111)</th>
<th>Event &gt;8 weeks after infusion (N=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS, N (%)</td>
<td>64 (58)</td>
<td>24 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Neurologic Event, N (%)</td>
<td>23 (21)</td>
<td>13 (12)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Infection, N (%)</td>
<td>38 (34)</td>
<td>22 (20)</td>
<td>37 (39)</td>
</tr>
<tr>
<td>Febrile Neutropenia, N (%)</td>
<td>17 (15)</td>
<td>16 (15)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Extended Cytopenias, N (%)</td>
<td>49 (44)</td>
<td>36 (32)</td>
<td>NA</td>
</tr>
<tr>
<td>Tumor lysis Syndrome, N (%)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Tisagenlecleucel in Lymphoma Results

ORR, % 52
CR, % 40
PR, % 12
Median DOR, months Not reached
Median PFS, months 12 months
OS-12 months, predicted 40%


Axicabtagene Ciloleucel in Lymphoma (Zuma-1)

International, Phase I, Multicenter

Leukapheresis → Lymphodepletion → T-Cell Infusion 2X10⁶ Cells/Kg

Primary Endpoint: Objective Response

Secondary Endpoints: response duration, PFS, OS, safety, biomarker assessments

Axicabtagene Ciloleucel in Lymphoma Results

<table>
<thead>
<tr>
<th>ORR, %</th>
<th>83</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, %</td>
<td>58</td>
</tr>
<tr>
<td>PR, %</td>
<td>25</td>
</tr>
<tr>
<td>Median time to response, months</td>
<td>1.0</td>
</tr>
<tr>
<td>Median DOR, months</td>
<td>11.1</td>
</tr>
<tr>
<td>Median DOR-CR, months</td>
<td>Not reached</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>5.3</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>NR</td>
</tr>
</tbody>
</table>


Axicabtagene Ciloleucel Toxicity in Lymphoma

N=108 with Toxicity Analysis

<table>
<thead>
<tr>
<th>Worst Grade</th>
<th>Worst Grade</th>
<th>Worst Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2</td>
<td>97 (90)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>3/4</td>
<td>43 (39)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>5</td>
<td>35 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Cytokine Release Syndrome, N (%)</td>
<td>88 (81)</td>
<td>11 (10)</td>
</tr>
</tbody>
</table>


ASCO’s 2018 Advance of the Year

Death from CAR T-Cell Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Malignancy</th>
<th>CAR T-Cell</th>
<th>Day of Death</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morgan 2010</td>
<td>Colon Cancer</td>
<td>HER2-28-ζ</td>
<td>5</td>
<td>ARDS</td>
</tr>
<tr>
<td>Brentjens 2010</td>
<td>CLL</td>
<td>CD19-28-ζ</td>
<td>2</td>
<td>CRS</td>
</tr>
<tr>
<td>Frey 2014</td>
<td>B-ALL</td>
<td>CD19-41BB-ζ (Taageneleucel) (CTL019)</td>
<td>5</td>
<td>CRS (+Influenza)</td>
</tr>
<tr>
<td>15</td>
<td>CRS (+Sepsis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kochenderfer 2015</td>
<td>PMBCL</td>
<td>CD19-28-ζ</td>
<td>16</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Chong 2016</td>
<td>FL</td>
<td>CD19-41BB-ζ</td>
<td>--</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Neelapu (Zuma-1)</td>
<td>DLBCL</td>
<td>CD19-28-ζ Axicabtagene ciloleucel (KTE-C19)</td>
<td>--</td>
<td>HLH</td>
</tr>
</tbody>
</table>

Death from CAR T-Cell Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Malignancy</th>
<th>CAR T-Cell</th>
<th>Day of Death</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locke 2016 (Zuma-1)</td>
<td>NHL</td>
<td>CD19-28-ζ</td>
<td>--</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Turtle 2016</td>
<td>B-ALL</td>
<td>CD19-41BB-ζ</td>
<td>122</td>
<td>CRS Neurotoxicity</td>
</tr>
<tr>
<td>Turtle 2016</td>
<td>NHL</td>
<td>CD19-41BB-ζ</td>
<td>30</td>
<td>CRS (+GI Bleed) Neurotoxicity (+CNS Bleed)</td>
</tr>
<tr>
<td>Rocket 2017</td>
<td>B-ALL</td>
<td>CD19-28-ζ (UCAR015)</td>
<td>--</td>
<td>Cerebral edema X 5</td>
</tr>
<tr>
<td>Zuma-1 (2017)</td>
<td>NHL</td>
<td>CD19-28-ζ</td>
<td>--</td>
<td>Cerebral edema</td>
</tr>
<tr>
<td>Turtle</td>
<td>CLL</td>
<td>CD19-41BB-ζ</td>
<td>11</td>
<td>Cerebral edema</td>
</tr>
</tbody>
</table>

Assessing CAR T-Cell Toxicities

ICANS = immune effector cell-associated neurotoxicity syndrome
CRS Pathophysiology

- Most common toxicity of cellular immunotherapy
- Triggered by activation and expansion of T cells
- Complex pathophysiology
  - IL-2, soluble IL-2Rα, INFγ, IL-6, soluble IL-6R, and GM-CSF
  - Monocyte and macrophage activation
  - Dendritic cell activation

Clinical Symptoms

**Clinical Signs and Symptoms Associated with CRS**

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Constitutional</th>
<th>Gastrointestinal</th>
<th>Respiratory</th>
<th>Cardiovascular</th>
<th>Coagulation</th>
<th>Renal</th>
<th>Hepatic</th>
<th>Neurologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever, rigors, malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache</td>
<td>Nausea, vomiting, diarrhea</td>
<td>Tachypnea, hypoxemia</td>
<td>Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), diminished cardiac output (late)</td>
<td>Elevated D-dimer, hyprofibrinogenemia, bleeding</td>
<td>Headache, mental status changes, confusion, delirium, word finding difficulty, aphasia, hallucinations, tremor, dysmetria, altered gait, seizure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**ASBMT CRS Grading Consensus Guidelines**

<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>Temp ≥ 38°C</td>
<td>Temp ≥ 38°C</td>
<td>Temp ≥ 38°C</td>
<td>Temp ≥ 38°C</td>
</tr>
<tr>
<td>Hypotension</td>
<td>None</td>
<td>Not requiring vasopressors</td>
<td>Requiring one vasopressor</td>
<td>Requiring multiple vasopressors</td>
</tr>
<tr>
<td>Hyposia</td>
<td>None</td>
<td>Low-flow oxygen</td>
<td>High-flow oxygen</td>
<td>Positive pressure</td>
</tr>
</tbody>
</table>


**Diffculty Developing “Universal Guidelines”**

- Different CAR T-cell constructs
  - Different magnitude and timing of toxicity
- Different disease states
  - NHL
  - AML
- Patient characteristics
  - Age
  - Comorbidities
  - Prior therapy
  - Cytokine response
  - Variability in biomarker utilization/reliability
- Inpatient versus outpatient
- Dose, timing, and choice of corticosteroids
- Dose, timing, and choice of anti-IL6 blockade


**Biomarkers for CRS**

- Barriers to biomarker utilization
  - Assays are not readily available
  - Severity of CRS is not predicted by cytokine levels
  - Panels need to measure multiple cytokines
- C-reactive protein (CRP)
  - Acute phase reactant
  - Produced in response to IL-6 production
  - Lag time is 1-2 days
  - Peak levels and fold increase in CRP may be predictive
- Ferritin is not predictive of CRS development but may indicate severity
- Hypofibrinogenemia

Variability in Cytokine Response

- Baseline cytokines are variable based on age, gender and ethnicity
- Disease burden
- Type of malignancy
- Relative and absolute changes in cytokine must be considered
- Presence of inflammatory disease
- Infection


Tocilizumab

- Humanized mAB targeting IL-6R
- Inhibits IL-6 binding to both membrane-associated and soluble IL-6Rs
- Inhibiting classical and proinflammatory trans-signaling
- Side effects: transaminitis, thrombocytopenia, hyperlipidemia, and an increased risk of infection
- Effective treatment for CRS
- Symptoms begin to clear within hours
- Cytokines return to normal within 48 hours
- Dose: 8 mg/kg IV once and may be repeated up to 4 doses
- Must keep 2 doses per patient available per REMS for approved CAR T-cell therapies


FDA Approval of Tocilizumab for CAR T Associated CRS

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Retrospective, pooled analysis of prospective clinical trials involving CT019 and KTE-C19 in hematologic malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary objective</td>
<td>Characterize resolution of CRS (grade 3 or higher)</td>
</tr>
<tr>
<td>Responders defined</td>
<td>No fever or vasopressors required within 14 days of tocilizumab administration</td>
</tr>
<tr>
<td></td>
<td>No more than 2 doses of tocilizumab required</td>
</tr>
<tr>
<td></td>
<td>No drugs other than tocilizumab or corticosteroids used for treatment</td>
</tr>
<tr>
<td>Results</td>
<td>CT019, N=45</td>
</tr>
<tr>
<td>Response Rate</td>
<td>69%</td>
</tr>
<tr>
<td>Median time to tocilizumab (days)</td>
<td>4</td>
</tr>
<tr>
<td>Median doses of tocilizumab</td>
<td>1</td>
</tr>
<tr>
<td>Median time to response (days)</td>
<td>4.5</td>
</tr>
</tbody>
</table>


Tocilizumab-Refractory CRS

- Tocilizumab refractory CRS may emerge as a distinct pathophysiological entity
- All patients had ALL treated with anti-CD22 CAR T cells
- 10 subjects evaluated: 7 developed CRS
- One patient developed grade 4 CRS with manifestations of HLH that was unresponsive to tocilizumab
- Higher IL-2 (35 pg/mL) versus median 6.1 pg/mL
- GM-CSF level higher at 12 hours (28 pg/mL) versus median 1 pg/mL
- No rise in IL-6
- Ultimately had CR


HLH/MAS: A Complication of CAR T-Cells

- Constellation of symptoms
  - High fevers, hepatosplenomegaly, hepatic dysfunction, coagulopathy, hypofibrinogenemia and hyperferritinemia
  - IL-2R, MCP-1 and MIP1B and other proinflammatory cytokine production
  - Leads to immune activation and excessive inflammation
  - Lymphocytic tissue infiltration
  - Hemophagocytosis present in bone marrow
  - Multisystem organ failure may result
  - Tocilizumab is treatment of choice
  - Some may choose HLH directed treatment with etoposide


ARS Question #2

- Which of the following CAR construct and time to toxicity are appropriately matched?
  A. Tisagenlecleucel → CD28 co-stimulatory domain → faster onset of CRS
  B. Axicabtagene ciloleucel → 4-1BB co-stimulatory domain → faster onset of CRS
  C. Axicabtagene ciloleucel → CD28 co-stimulatory domain → faster onset of CRS
  D. Tisagenlecleucel → 41BB co-stimulatory domain → faster onset of CRS


hs = hemophagocytic lymphohistiocytosis
MAS = macrophage activation syndrome
Other Alternatives for Prevention and Treatment of CRS

- Prophylactic tocilizumab?
- CAR T-cell dose refinement
- Siltuximab binds IL-6
- Anakinra IL-1 receptor antagonist
- Point of care cytokine measurement
- Incorporation of suicide genes


Assessing CAR T-Cell Toxicities

- Determine CAR T-Cell Toxicity
  - CRS
    - Fever
    - Hypotension
    - Hypoxia
    - Organ Toxicity
  - ICANS
    - CARTOX-10
    - Seizure
    - Increased ICP
    - Motor Weakness

- Manage according to grade of CRS
- Manage according to grade of ICANS

Pathophysiology of ICANS

- Passive diffusion of cytokines into the brain
- High serum levels of IL-6 and IL-15 associated with severe neurotoxicity
- Trafficking of T cells into the CNS
- Presence of CAR T-cells in cerebrospinal fluid from patients with neurotoxicity
- Disruption of blood brain barrier
- Elevated protein levels
- Secondary cortical irritation
- Diffuse generalized slowing consistent with encephalopathy on EEG
- Seizure activity
- MRI and CT scans are usually negative
- Exceptions: cerebral edema


Characterization of ICANS

- Typically manifests as toxic encephalopathy
  - Earliest signs are diminished attention, language disturbance, impaired handwringing
  - Severe ICANS (Immune effector cell-associated neurologic symptoms) is associated with seizures, mental obtundation, increased ICE and cerebral edema
  - May be biphasic
    - Phase I: typically within first 5 days
      - Fever and other CRS symptoms present
      - Typically shorter duration and lower grade
      - Responsive to anti-IL-6 therapy
    - Phase II: delayed neurotoxicity occurring during weeks 3-4 after CAR T-cell therapy
      - Longer duration and higher grade neurotoxicity
      - Anti-IL-6 therapy is not effective!


ASBMT ICANS Grading Consensus Guidelines

<table>
<thead>
<tr>
<th>Domain</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICE</td>
<td>7-9</td>
<td>3-6</td>
<td>0-2</td>
<td>Unable to perform</td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td>Awakens spontaneously</td>
<td>Awakens to voice</td>
<td>Awakens with tactile stimulus</td>
<td>Unarousable</td>
</tr>
<tr>
<td>Seizure</td>
<td>N/A</td>
<td>N/A</td>
<td>Seizure resolving with intervention</td>
<td>Life-threatening or recurring seizure</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>Increased ICP/cerebral edema</td>
<td>N/A</td>
<td>N/A</td>
<td>Focal/Local Edema</td>
<td>Diffuse cerebral edema, Papilledema</td>
</tr>
</tbody>
</table>

ICE = immune effector cell-associated encephalopathy


Management of ICANS

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Supportive care, IV fluids, Management of agitation, Neurology consult, papilledema assessment, lumbar puncture, MRI, EEG</td>
</tr>
<tr>
<td></td>
<td>If associated with CRS, consider anti-IL-6 therapy</td>
</tr>
<tr>
<td>2</td>
<td>Dexamethasone 20 mg IV daily or methylprednisolone 1 mg/kg IV q12h if refractory to anti-IL-6 therapy, or for CRS without concurrent CRS</td>
</tr>
<tr>
<td></td>
<td>Consider transfer to ICU</td>
</tr>
<tr>
<td>3</td>
<td>Transfer to ICU, Corticosteroids, continue until grade 1 CRS then taper Acetazolamide</td>
</tr>
<tr>
<td></td>
<td>Consider mechanical ventilation, Seizure management, High dose corticosteroids, Management of increased ICP and papilledema</td>
</tr>
</tbody>
</table>

ARS Question #3

BR, a 55 year old male with multiply-relapsed NHL receives axicabtagene ciloleucel infusion. He tolerates his pre-conditioning chemotherapy and the infusion without many problems. However, on day 2 of his infusion, he develops a fever with a low-flow oxygen requirement. He is slower to arouse than usual, but still wakes when his name is called. This is most likely described and treated by which of the following:

A. Grade 2 CRS with overlapping Grade 1 neurotoxicity → JR should receive a dose of tocilizumab 8 mg/kg.
B. Grade 3 Neurotoxicity → BR should receive dexamethasone 10 mg IV q 6 hours until resolution
C. Grade 1 CRS → BR should receive a dose of siltuximab 11 mg/kg
D. BR is not experiencing any toxicities associated with CAR T-cell therapy

Ongoing Trials: Axicabtagene Ciloleucel (Zuma-3)

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Phase I/II trial of KTE-C19 for r/r ALL</th>
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<tbody>
<tr>
<td>Patients, N=35</td>
<td>≥ 18 yo  &gt;5% bone marrow blasts  Could have received prior CD19 targeted therapy (blinatumomab)</td>
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<td>Primary Endpoint</td>
<td>Safety</td>
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<tr>
<td>Secondary Endpoints</td>
<td>Incidence and time to onset of adverse events  Rates of undetectable MRD remission in bone marrow  KTE-C19 expansion and persistence</td>
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<tr>
<td>Results</td>
<td>2 grade 5 events: cerebral infarction; CRS  ≥ Grade 3 CRS (26%); onset 5 days  ≥ Grade 3 neurotoxicity (46%); onset 7 days  MRD negative 78%  Expansion occurred across all dosing groups</td>
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Conclusions

- Treatment options for r/r ALL and lymphoma include conventional combination chemotherapy and novel targeted therapies including CAR T-cells.
- CRS and ICANS are common and significant toxicities associated with CAR T-cell therapy.
- A multidisciplinary approach is required to manage patients that receive CAR T-cell therapies.

Chimeric Antigen Receptor T-Cell Therapies: Improving outcomes, but at what risk?

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