Conflict of Interest Disclosure
Lori Muffly MD MS

- Consulting Fees: Pfizer, KITE
- Contracted Research: Baxalta, Adaptive, Astellas
- Ownership Interest: Corvus (stock)
Objectives

• Overview of CAR T Cell Therapy

• Common CAR T Cell Toxicities:
  – Cytokine Release Syndrome (CRS)
  – Neurological Toxicity (Neurotox)
  – On target, off tumor side effects
  – Cytopenias and infections

• The Patient Experience
Case Presentation: Mr. W.

- 58 year old rancher diagnosed with B-cell acute lymphoblastic leukemia (ALL) in May, 2018
- Initial remission with chemotherapy quickly followed by relapse in the marrow and skin
- No response to salvage blinatumomab or inotuzumab
- March, 2019: Skin involvement throughout trunk, face, neck; circulating blasts; declining KPS
- Enrolled onto CCT5001: Phase 1 Dose Escalation Study of CART 19-22 in Adults with Relapsed or Refractory Diffuse Large B-cell Lymphoma or Acute Lymphoblastic Leukemia (NCT 03233854)
Refractory Blood Cancers Continue to Have Very Poor Outcomes

The Multinational Association of Supportive Care in Cancer • Annual Meeting 2019 • www.mascc.org/meeting

Success with Targeting Tumor Antigens in Blood Cancers
Structure of CARs and T Cell Receptors

A T-Cell Receptor

B Chimeric Antigen Receptor

Tumor-specific antigen
scFvs
Targeting element
Transmembrane domain
CD28 or 4-1BB (costimulatory domain)
CD3ζ
How CAR T Cells Work

Viral DNA Insertion

Expression of CAR

CAR enables T cell to recognize tumor cell antigen

Antigen

CAR T cells multiply and release cytokines

Tumor cell apoptosis

Tumor cell

T cell

**CAR T Cells Are a Living Therapy!**
CAR T Cell Therapy Delivery

- T cells are isolated from patient
- T cells are engineered to express CARs that recognize cancer cells
- Patient Evaluation & Consent
- Hospitalization
- Toxicities
- Relocation
- Lymphodepletion Chemotherapy
- Modified T cells are grown and expanded in culture
- Modified T cells are infused into patient
- 2-6 weeks Bridging therapy often necessary

Bridging therapy often necessary.
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

In a single-center phase 1–2a study, the anti-CD19 chimeric antigen receptor (CAR) humanized anti-CD19 CAR T cells, 1 received ponatinib, 1 received antithymocyte globulin, and 1 patient for allogeneic stem-cell transplantation during remission (4 received stem-cell transplantation during remission).

The median time to maintenance of B-cell aplasia at 6 months after tisagenlecleucel infusion to the date of death from any cause. Nineteen patients died after tisagenlecleucel infusion; these increases tended to be more common during the cytokine release syndrome than in patients with lower cytokine levels.

Among the 75 patients who received tisagenlecleucel, transient increases in serum interleukin-6, interferon gamma, and ferritin levels occurred during the cytokine release syndrome. Among the 75 patients who received an infusion from the date of tisagenlecleucel to the date of death from any cause. Ten patients were followed for 19 months or more, and 2 patients died with a response to treatment. The probability of B-cell recovery was not reached.

All patients with a response to treatment had maintenance of B-cell aplasia, and most patients in the study received immunoglobulin replacement in accordance with local practice. The median time to maintenance of B-cell aplasia at 6 months after tisagenlecleucel was 60 to 82 and 90% (95% CI, 81 to 95) at 6 months and 50% (95% CI, 37 to 64) at 18 months.
F.D.A. Panel Recommends Approval for Gene-Altering Leukemia Treatment

By DENISE GRADY  JULY 12, 2017

F.D.A. Approves Second Gene-Altering Treatment for Cancer

By DENISE GRADY  OCT. 18, 2017

RELATE COVERAGE

Immune System, Loaded With Remade T-cells, Vanquishes Cancer  SEPTEMBER 12, 2011

A Breakthrough Against Leukemia Using Altered T-Cells  DEC. 9, 2012
**CAR Therapy: Past, Present, Future**

**Development of Chimeric T-cell receptor expressing CTL with antibody specificity**

2. Esshar Z et al; Proc Natl Acad Sci U S A. 1993 Jan 15;90(2):720-4

**Development of scFv CAR against a B-cell lymphoma idiotype**

7. Milone MC et al; Mol Ther. 2009 Aug;17(8):1453-64

**Use of ligands to CD28 & 4-1bb to enhance CTL expansion**

10. Use of scFv CAR against Ovarian Cancer
11. First in-human data for the use of scFv CAR against NHL

**Development of CAR directed against CD19**

12. First in-human data for the use of CAR against CD19 expressing NHL
13. Clinical Evaluation and Approval of Anti-CD19 CAR-T therapy in B-cell malignancies

The Multinational Association of Supportive Care in Cancer • Annual Meeting 2019 • www.mascc.org/meeting
Case Presentation: Mr. W, cont.

- 58 year old man with relapsed B-ALL, enrolled on clinical trial of CART 19-22
- Lymphodepletion followed by infusion of CART 3x10^6/kg April 10, 2019 (Day 0)
- Day +4: febrile with hypoxemia requiring high flow oxygenation consistent with Grade 3 CRS
- Received tocilizumab 8mg/kg IV x 1 and dexamethasone 10mg IV x 1
Cytokine Release Syndrome (CRS)

- **CRS**: Supraphysiologic response following immunotherapy- clinically presents as fever, hypotension, capillary leak

Associated with rise in IFN-, IL-6, IL-10, IL-2, others
## CRS Grading Scale

### American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading System

<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>Temperature ≥38°C</td>
<td>Temperature ≥38°C</td>
<td>Temperature ≥38°C</td>
<td>Temperature ≥38°C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>With</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>Hypoxia</td>
<td>None</td>
<td>Requiring low-flow nasal cannula or blow-by</td>
<td>Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask</td>
<td>Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)</td>
</tr>
</tbody>
</table>

- CRS is common after CAR T cell therapy (50-95% incidence)
- Grade 3-4 CRS occurs in 5-30%
**CRS Management**

<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>Temperature ≥ 38°C</td>
<td>Temperature ≥ 38°C</td>
<td>Temperature ≥ 38°C</td>
<td>Temperature ≥ 38°C</td>
</tr>
<tr>
<td>Hypotension</td>
<td>None</td>
<td>Not requiring vasopressors</td>
<td>Requiring a vasopressor with or without vasopressor</td>
<td>Requiring multiple vasopressors (excluding vasopressor)</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, facemask, nonrebreather mask, or Venturi mask</td>
<td>Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)</td>
</tr>
</tbody>
</table>

**Supportive Care**
**Tocilizumab +/- Steroids**
**Tocilizumab + Steroids (Dex q6)**
**Solumedrol 1 gm x 3**
**Alert ICU**
**ICU Care**

**Tocilizumab:** IL6 receptor antagonist, FDA approved for the treatment of CAR T associated CRS in Aug, 2017

**Additional agents under investigation for CRS:**
- **Anakinra:** IL1 receptor antagonist (FDA Indication: Rheumatoid arthritis)
- **Siltuxumab:** IL6 antibody (FDA Indication: Castleman’s disease)
Case Presentation: Mr. W, cont.

- 58 year old man with relapsed B-ALL, enrolled on clinical trial of CART 19-22
- Lymphodepletion followed by infusion of CART 3x10^6/kg April 10, 2019 (Day 0)
- Day +4: developed **Grade 3 CRS**. Received Tocilizumab + dexamethasone
- Day +6: declining neurological status, ICE score 1/10 consistent with **Grade 3 Neurotox**.
- Started on dexamethasone 10mg q6, increased Keppra to 1000mg BID, continuous EEG
- Day +7: somnolent, ICE score 0/10, Transferred to ICU and intubated for airway protection. Now consistent with **Grade 4 Neurotox**.
- Solumedrol 1 gram x 3 days ordered. No seizure activity noted.
# Immune Effector-Cell Associated Neurotoxicity (ICANS)

Table 3

Neurologic and Psychiatric Adverse Reactions Reported with Approved CAR T Products

<table>
<thead>
<tr>
<th>Tisagenlecleucel (Kymriah)</th>
<th>Axicabtagene ciloleucel (Yescara)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Encephalopathy:</strong> includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, somnolence, and automatism</td>
<td><strong>Encephalopathy:</strong> includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbed attention, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor</td>
</tr>
<tr>
<td><strong>Delirium:</strong> includes delirium, agitation, hallucination, hallucination visual, irritability, restlessness</td>
<td><strong>Delirium:</strong> includes agitation, delirium, delusion, disorientation, hallucination, hyperactivity, irritability, restlessness</td>
</tr>
<tr>
<td><strong>Headache:</strong> includes headache and migraine</td>
<td><strong>Headache</strong></td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td><strong>Dizziness:</strong> includes dizziness, presyncope, syncope</td>
</tr>
<tr>
<td><strong>Sleep disorder:</strong> includes sleep disorder, insomnia, nightmares</td>
<td><strong>Aphasia:</strong> includes aphasia, dysphasia</td>
</tr>
<tr>
<td></td>
<td><strong>Motor dysfunction:</strong> includes muscle spasms, muscular weakness</td>
</tr>
<tr>
<td></td>
<td><strong>Tremor</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Ataxia</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Seizure</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Dyscalculia</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Myoclonus</strong></td>
</tr>
</tbody>
</table>
# Immune Effector Cell-Associated Encephalopathy Score (ICE)

<table>
<thead>
<tr>
<th>ICE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Orientation</strong>: orientation to year, month, city, hospital: 4 points</td>
</tr>
<tr>
<td><strong>Naming</strong>: ability to name 3 objects (eg, point to clock, pen, button): 3 points</td>
</tr>
<tr>
<td><strong>Following commands</strong>: ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”): 1 point</td>
</tr>
<tr>
<td><strong>Writing</strong>: ability to write a standard sentence (eg, “Our national bird is the bald eagle”): 1 point</td>
</tr>
<tr>
<td><strong>Attention</strong>: ability to count backwards from 100 by 10: 1 point</td>
</tr>
</tbody>
</table>

---

Day 4, MMSE 29/30

I love Shawnee, KS.

Day 5, MMSE 27/30

Day 6, MMSE 29/30

I miss my kids.
# ICANS Consensus Grading

ASTCT ICANS Consensus Grading for 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 isunarousable and unable to perform ICE)</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 nonconvulsive seizures on EEG that resolve with intervention</td>
<td>Life-threatening prolonged seizure (&gt;5 min); or 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; or cranial nerve VI palsy; or papilledema; or Cushing’s triad</td>
</tr>
</tbody>
</table>

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

N/A indicates not applicable.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.
**Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)**

### Grade 1
*Some or all of the following:*
- Spontaneous awakening
- Mild Confusion
- Word-finding difficulty
- Tremor
- No clinical seizures

**ICE 7-9**

- Monitor for progression
- Evaluate/treat other causes of encephalopathy
- Document neurologic exam
- Consult psycho- oncology

### Grade 2
*Some or all of the following:*
- Awakening to voice
- Moderate Confusion
- Expressive aphasia
- Perseveration
- No clinical seizures

**ICE 3-6**

- Notify Neurology consultant
- Discuss imaging with neurology
- Order neuro checks q2h
- Discuss with MICU

### Grade 3
*Some or all of the following:*
- Awakening to tactile stimulus
- Global aphasia
- Myoclonus
- Clinical seizure
- Brief electrographic seizures

**ICE 0-2**

- ICE score with neuro checks
- Telemetry and continuous O2
- Notify Crisis RN
- Pupillometry with neuro checks
- Consult psycho-oncology

### Grade 4
*Some or all of the following:*
- Coma/posturing
- Focal weakness
- Status epilepticus
- Pupillary/CN abnormalities
- Diffuse cerebral edema
- ICE 0

**ABC's; stabilize patient**
- Emergent CT head when stable to travel
- Order neuro checks qhour pending ICU transfer

---

**BMT Physician**

- Monitor for progression
- Evaluate/treat other causes of encephalopathy
- Document neurologic exam
- Consult psycho-oncology

- Consult Neurology
- Consider neuro checks q2h

- Notify Neurology consultant
- Discuss imaging with neurology
- Order neuro checks q2h
- Discuss with MICU

- Neuro checks q2h
- ICE score with neuro checks
- Notify Crisis RN
- Telemetry and continuous O2
- Notify Crisis RN
- Pupillometry with neuro checks
- Consult psycho-oncology

- Consider CT head if focal symptoms
- Consider EEG
- Follow up EEG read in 1h
- Consider empiric increase in AED regimen

- Consider urgent imaging
- Consider EEG
- Follow up EEG read in 1h if ordered
- Consider empiric increase in AED regimen
- Consider possibility of diffuse cerebral edema
- Discuss with Neurocritical Care

- Neuro checks qhour while awaiting ICU transfer
- ICE score with neuro checks
- Notify Crisis RN
- Pupillometry with neuro checks
- Telemetry and continuous O2
- Give handoff to E2 RN

**Interventions**

- **Steroids**
  - Continue Keppra 500 mg BID prophylactically
  - Reconcile medications to identify other potential contributors
  - Delirium precautions

- **Continue increasing Keppra to 1000 mg BID empirically**
  - Dexamethasone 10mg IV q6-12h depending on CAR-T product
  - Tocilizumab 8mg/kg if concurrent CRS
  - Consider melatonin at bedtime

- Adjust antiepileptic drugs based on EEG and discussion with NCC
- Methylprednisolone 1g IV daily; reassess daily, taper when able
- Tocilizumab 8mg/kg if CRS, not to exceed 3 doses in 24 hours
- Consider Anakinra
CAR T Neurotoxicity: CRS, Cytokines, and Vascular Endothelial Activation
Why Did Mr. W Develop Grade 3-4 CRS/Neurotoxicity?

Day 8 CAR T expansion by FACS in Our Patient
Case Presentation: Mr. W, cont.

- 58 year old man with relapsed B-ALL, enrolled on clinical trial of CART 19-22
- Lymphodepletion followed by infusion of CART $3 \times 10^6$/kg April 10, 2019 (Day 0)
- Day +4: **Grade 3 CRS**
- Day +7 to D+10: Intubated in ICU with **Grade 4 Neurotoxicity**
- Day +11: neuro status improving, extubated transferred to floor
- Day +26: Discharged to local housing with ongoing transfusion needs due to **prolonged severe pancytopenia**.
Other CAR T Related Side Effects

• Pancytopenia- often prolonged

• On target/off tumor effects
  – Example: hypogammaglobulinemia following CD19 CART

• Infections

• Delirium, cognitive decline, debilitation
CAR T Cell Therapy: The Patient Experience??

Patient-Reported Outcomes with Chimeric Antigen Receptor T Cell Therapy: Challenges and Opportunities

Rajshekhar Chakraborty\textsuperscript{1}, Surbhi Sidana\textsuperscript{3}, Gunjan L. Shah\textsuperscript{2}, Michael Scordo\textsuperscript{2}, Betty K. Hamilton\textsuperscript{1} Navneet S. Majhail\textsuperscript{1,\*}

\textsuperscript{1} Taussig Cancer Center, Cleveland Clinic, Cleveland, Ohio
\textsuperscript{2} Adult Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, New York
\textsuperscript{3} Division of Hematology, Mayo Clinic, Rochester, Minnesota
CAR T Cell Therapy: Patient and Societal Financial Toxicity?

Patient costs:
- Travel, co-pays
- Local housing (often extended)
- Mandatory caregiver
- Numerous follow-ups
- Outpatient Physical Therapy
- Skilled Nursing Facility
The Reason to Continue On...

• 58 yo with refractory B-ALL, enrolled on clinical trial of CART 19-22
• No other treatment options at the time
• Received CAR T cells on April 10, 2019
• Day 28 evaluation showed a complete remission, MRD-negative
• Month 2 evaluation:
  
  **SAMPLE-LEVEL MRD RESULT**
  
  **No Residual Sequence Detected**
  ESTIMATED MRD VALUE:
  0 residual clonal cells (Range: 0 - 2) **
  Sequence determining MRD result: IGH Sequence A

• Mr. W. is now at home with his family, mostly independent
CAR T Cell Therapy Toxicity: Summary

- CAR T Cell therapy represents an exciting “living” cancer immunotherapy now available to patients commercially and through clinical trials.

- CRS and neurological toxicity are common and can be severe; grading and management require multidisciplinary expertise.

- Mainstay of therapy is currently tocilizumab (CRS) and steroids (CRS, neurotoxicity).

- Additional work is required to understand the impact of CAR T on patient-reported symptoms and functioning over time.
Stanford CAR T Team

Crystal Mackall – Director

David Miklos - Clinical Ops
  Lori Muffy, Kara Davis, Liora Schultz
  Jay Spiegel, Matt Frank, Nash Hossain
  Janet McDowell, Juliana Craig, Jenny Yoon, Sharan Craig

Steve Feldman – Manufacturing
  Matt Abramian, Shabnum Patel

Sharon Mavroukakis – Regulatory
  Emily Egeler

Bita Sahaf - Correlative Science
  Sean Bendall

Pathology: Jean Oaks
  Eric Yang, Michael Ozawa
  Katie Kong

CIRM
California's Stem Cell Agency