Navigating the CAR-T Cell Therapy Landscape in Hematologic Malignancies

Science and Practical Issues in Nursing Care

Meeting space has been assigned to provide a symposium supported by Celgene Corporation and Novartis Pharmaceuticals Corporation during the Oncology Nursing Society’s (ONS) 44th Annual Congress, April 11-14, 2019 in Anaheim, CA. The Oncology Nursing Society’s assignment of meeting space does not imply product endorsement.

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**Susan Blumel, RN, BSN**, has a financial interest/relationship or affiliation in the form of: Consultant and/or Advisor for Evidera; Juno Therapeutics; and Kite Pharma, Inc. Speakers Bureau participant with Kite Pharma, Inc.

Susan Blumel, RN, BSN, does intend to discuss either non–FDA-approved or investigational use for the following products/devices: Different CAR-T cell products in a range of hematologic malignancies.

**Colleen Callahan, RN, MSN, CRNP**, has a financial interest/relationship or affiliation in the form of: Consultant and/or Advisor for Novartis Pharmaceuticals Corporation.

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A Brief Introduction

CAR-T Cell 101—A Rational Target in Cancer Therapy

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Overview of CAR-T Cell Therapy\textsuperscript{1,2}


1. Patient with relapsed/refractory B-cell malignancy

2. T cells taken from cancer patient

3. Leukapheresis

Retroviral or lentiviral vector transduction with anti-CD19 CAR

Preconditioning chemotherapy

Engineered cells given back to the patient, where they often expand in response to exposure to the tumor

T cell infusion

Anti-CD19 CAR

T cells isolated and genetically engineered to express a modified T-cell receptor

Patient with relapsed/refractory B-cell malignancy

Leukapheresis

Retroviral or lentiviral vector transduction with anti-CD19 CAR

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**Anti-CD19 CAR-T Cell Constructs**

- **Tisagenlecleucel (CTL019)**
  - **August 30, 2017**: Approved for R/R B-cell precursor ALL (pediatric or young adult patients aged ≤25 y)
  - **May 1, 2018**: New indication for adult patients with R/R large B-cell lymphoma after ≥2 lines of systemic therapy

- **Axicabtagene ciloleucel (KTE-019)**
  - **October 18, 2017**: Approved for adult patients with R/R large B-cell lymphoma after ≥2 lines of systemic therapy

- **Lisocabtagene maraleucel (JCAR017)**

- **UCART 19 (allogeneic donor)**

**Anti-BCMA CAR-T Cell Constructs**

- bb2121
- JCARH125
- LCAR-B38M (JNJ-68284528)
- MCARH171
- P-BCMA-101
- FCARH143
- ALLO-715 (allogeneic donor)
CAR-T Cell Therapy in Leukemia

Guiding Nurses in Optimal Delivery of a Potential New Option

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Pediatric ALL\textsuperscript{1,2}

- ALL: most common childhood cancer
  - 25% of cancers in children aged <15 y
  - 9% of cancers in adolescents aged 15-19 y
- Survival in 1975 was 31%; increased to >90% in mid 2000s
- 2%-3% of cases are refractory; 10%-15% of patients relapse
  - Chemotherapy resistance and dose-limiting toxicities often make relapse difficult to treat
  - Little improvement over the past 20 y in survival rates for children who relapse

Need novel therapies:
Targeted approach with CAR-T cell therapy

CAR-T Cell Therapy

Patient population

- Majority are in at least a second relapse
- Refractory to initial therapy

Goals for therapy

- Proliferation: high level of in vivo proliferation correlates with high response rates
- Persistence: longer-term persistence may allow longer-term disease control
Eligibility

- Relapsed or refractory CD19+ B-cell precursor ALL
- No curative options for therapy (ie, not eligible for BMT)
- Cannot have rapidly progressing disease
- Must be >6 months from BMT
- No active GVHD or immunosuppression
- Cannot have active uncontrolled infection
Case Study 1: A Young Adult with Relapsed/Refractory ALL in Second Relapse

**Initial Presentation**
- Diagnosed at age 8 y with B-cell ALL

**First relapse**
- 10 mo off therapy at age 13 y (testicular relapse)
  - Testicular radiation and chemotherapy

**Second relapse**
- 4 y off treatment at age 20 y (isolated marrow relapse)
  - Chemotherapy
  - Blinatumomab
  - Moxetumomab
    - Bilateral choroid retinopathy with retinal detachment r/t swelling beneath macula
    - Capillary leak
    - Hemolytic uremic syndrome
- Presents with refractory disease

What are his options?
Case Study 1 (Cont’d)

Initial communication with intake coordinator and nurse navigator

- Education
  - Program
  - Timeline
  - What to expect with first visit

First visit at institution

- Meet with nurse practitioner, oncologist, clinic nurse, social worker, child life specialist, intake coordinator
- Discuss T-cell collection
- Apheresis line planning
- CAR-T cell consent meeting
- Apheresis unit visit; meet with nurses and physicians
- Anesthesia visit
In many cancers, tumor-specific antigens for target are not as well defined, but with ALL, CD19 is a good target.

CD19 is a protein widely expressed on normal and malignant B cells (from early pro-B stage through maturity).

The majority of cases of B-cell ALL are CD19+.

Stem cells do not express CD19.

T Cell

Type of lymphocyte

Has a central role in cell-mediated immunity

Workhorses of the immune system; recognize and attack invading disease cells

CAR

Customized receptors with an extracellular antigen-binding domain targeting antigens expressed on malignant cells, combined with intracellular signaling domains of the T cell

Antigen-binding domain derived from a monoclonal antibody single-chain variable fragment
Lentiviral vector
- A tool used to deliver genetic material into cells
- Uses disabled HIV

Genetic material is the chimeric antigen receptor with specificity for the CD19 antigen

Transduces T cells with lentiviral vector to express the CD19 chimeric antigen receptor

Using gene transfer techniques, the T cells are modified to express antibodies against the CD19 antigen
Redirecting T-Cell Specificity in CAR-T Cells

- CAR-T cells engage an antigen on a tumor cell through the extracellular antibody domain; this activates the T cells.
- Engagement of the CAR-T cell results in intracellular signaling and expansion of the CAR-T cells to induce tumor cell killing.
- CARs link an extracellular antigen recognition domain to intracellular signaling domains of the T cell to:
  - Increase expansion
  - Increase persistence
  - Increase potency
  - Prevent cellular exhaustion
Bridging Chemotherapy

- Often required by patients during the time between T-cell collection, manufacturing, and return for lymphodepleting chemotherapy prior to CAR-T cell infusion
- Frequently used: maintenance-type chemotherapy, methotrexate, etoposide/cyclophosphamide, intrathecal chemotherapy, targeted therapy

Goals

- Prevent disease progression using lowest possible therapy intensity
- Avoid organ toxicity and infections
- Not achieve cure
- Maintain wellness to have patient in best clinical shape prior to infusion and not affect eligibility
## Lymphodepleting Chemotherapy (Pre-Infusion)

### Anti-Leukemia
- T cells expected to start expanding 7-10 days after infusion
  - Need to make sure leukemia is not out of control during that time
- Cannot give chemotherapy once T cells infused

### Lymphodepletion
- Focus on administering CAR-T cells with robust proliferative capacity
- Modulate host immune environment to support expansion and persistence
- Adoptively transferred T cells engraft and expand more efficiently in a lymphopenic host
- Presence of regulatory T cells must be minimized in the patient
Peripheral blasts at start of lymphodepleting chemotherapy

Week -1

Treatment

- Cyclophosphamide 500 mg/m² × 2 d
- Fludarabine 30 mg/m² × 4 d
- Nausea/Vomiting
  - Antiemetics
  - Fluid bolus
- Decreased PO intake
- Tumor lysis risk
  - May need daily lysis labs
  - Allopurinol
- Transfusions

Day -1 Procedures

- CSF negative
- MRD 68%
Week 2: CAR-T Cell Infusion

- **CAR-T cell infusion**
  - Pre-medicate (acetaminophen/diphenhydramine) one-half hour prior to infusion
  - Infuse over a few minutes
  - Monitor vital signs 1-2 hours post infusion
    - Acute infusional toxicities are rare
- Educate patients and families regarding reasons to call
- Provide frequent monitoring the week of infusion
Follow Up and Admissions

**Follow Up**
- **Week 3:** Follow-up visits (days 7 and 10)
- **Week 4:** Follow-up visits (days 14 and 17)
- **Week 5:** Follow-up visits (day 21)
- **Week 6:** Day 28 BMA/BX/LP
- **Follow up week after to review results**

**Admissions**
- Expect anytime from infusion day to about day 14
- Admit via clinic Monday to Friday and ED nights and weekends
- Have patient remain admitted until afebrile
- Maintain communication with the PICU
Response

• Rapid onset of action
  – Same as seen with chemotherapy or targeted therapy
  – Expect to see T cells expanding in 7-10 days
• Infusions have resulted in proliferation/expansion of engineered T cells to 100-100,000 times after infusion into the patient
• CAR-T cells have been found in marrow and CSF, even when patients did not have CNS disease
# CAR-T Constructs in Adult/Pediatric Relapsed/Refractory B-Cell Precursor ALL

<table>
<thead>
<tr>
<th>Construct</th>
<th>Tisagenlecleucel (CTL-019)(^1)</th>
<th>NCI CD19-28z(^2)</th>
<th>Axicabtagene Ciloleucel (KTE-019)(^3)</th>
<th>FHCR CD19-4-1BB(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Phase 1/2a</td>
<td>—</td>
<td>ZUMA-3</td>
<td>PLAT-02</td>
</tr>
<tr>
<td>N</td>
<td>60</td>
<td>51</td>
<td>44</td>
<td>43</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>CR: 56 pts (93%)</td>
<td>CR: 31 pts (60.8%)</td>
<td>CR/CRI: 69%</td>
<td>MRD-negative CR: 40 (93%)</td>
</tr>
<tr>
<td></td>
<td>100% CNS remission</td>
<td>MRD negative: 28 pts</td>
<td>100% responders MRD negative</td>
<td>MRD-negative CR: 40 (93%)</td>
</tr>
<tr>
<td></td>
<td>12-mo RFS: 60%</td>
<td>Median leukemia-free</td>
<td>12-mo EFS: 50.8%</td>
<td>MRD-negative CR: 40 (93%)</td>
</tr>
<tr>
<td></td>
<td>24-mo RFS: 53%</td>
<td>survival in MRD-</td>
<td>11 pts underwent HSCT</td>
<td>MRD-negative CR: 40 (93%)</td>
</tr>
<tr>
<td></td>
<td>7 pts underwent HSCT</td>
<td>negative pts: 18 mo</td>
<td></td>
<td>MRD-negative CR: 40 (93%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21 pts received HSCT</td>
<td></td>
<td>MRD-negative CR: 40 (93%)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Severe CRS: 27%</td>
<td>Grade ≥3 CRS: 7 pts</td>
<td>Grade ≥3 CRS: 10 pts (23%)</td>
<td>23% pts had reversible severe CRS and/or neurotoxicity</td>
</tr>
<tr>
<td></td>
<td>(13.5%)</td>
<td>(13.5%)</td>
<td>Grade ≥3 neurologic events: 17 pts (39%)</td>
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</tr>
<tr>
<td></td>
<td>Grade 3 neurotoxicity: 3 pts</td>
<td></td>
<td>Grade 5 AEs: 2</td>
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</tbody>
</table>

Phase 2 ELIANA: Global/Multicenter Trial of Tisagenlecleucel in Pediatric R/R ALL\(^1\)

- First global, multicenter trial of CAR-T cell therapy (25 sites)
  - 11 countries across North America, Europe, Asia, and Australia
  - Manufacturing at a centralized facility
  - 75 patients infused
  - Overall remission rate within 3 mo: 81%
  - EFS at 6 mo: 73%; EFS at 12 mo: 50%

Phase 2 ELIANA: Safety Outcomes

- CRS occurred in 77% of patients
  - 48% of those received tocilizumab
- Neurologic events occurred in 40% of patients
  - Managed with supportive care
  - No cerebral edema reported

Tisagenlecleucel (Commercialized CAR-T Cells): FDA Label¹

• Indicated for patients ≤25 y with B-cell precursor ALL (refractory or in second or later relapse)
• Requires lymphodepleting chemotherapy with cyclophosphamide and fludarabine
• Delay infusion if patient has any unresolved toxicities from prior therapy
  – Pulmonary toxicity
  – Cardiac toxicity
  – Hypotension
  – Active GVHD
  – Active uncontrolled infection
  – Worsening leukemia burden following lymphodepleting chemotherapy

CAR-T Cell Therapy Side Effects

- CRS
- Neurologic
- Tumor lysis syndrome
- GVHD
- B-cell aplasia
Cytokine Release Syndrome

- Constellation of inflammatory symptoms related to T-cell engagement and expansion
  - Severity related to disease burden; correlates with T-cell proliferation
  - Can be mild to severe, leading to multisystem organ failure
  - Typically occurs 1-14 days after CAR-T cell infusion
  - Elevation in inflammatory markers, with a massive elevation in IL-6
Cytokine Release Syndrome: Management¹

- **Goal:** Want to prevent multisystem organ failure but do not want to stop the CAR-T cells from working
  - Treatment
    - Supportive care
    - Tocilizumab: Monoclonal antibody to IL-6 receptor; blocks IL-6–mediated inflammatory effects
    - Steroids (if no improvement with tocilizumab)

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Following CAR-T infusion

**Day 2**
Admitted for fever

**Day 3**
- Developed headaches
- CRP, 11.6; ferritin, 366

**Day 5**
- Hypotensive (40-50s/20s)
- IV boluses, blood products, norepinephrine, dopamine
- $O_2$ requirement, chest x-ray, pulmonary edema
- Mild AKI
- Early DIC; no signs of bleeding
- CRP: 34; ferritin, 14,100
- Tocilizumab
Neurotoxicity

- Cause: unclear
  - Cytokine mediated
  - T-cell mediated
- Risk factors: unclear
  - High disease burden
  - Concurrent CRS
- Treatment
  - Supportive care
  - Levetiracetam

Case Study 1 (Cont’d):
Days 7 to 28

Following CAR-T infusion

Day 7
- Still has O₂ requirement (HFNC)
- Remains on dopamine; norepinephrine weaned
- CRP, 15; ferritin, 20,400
- Confusion

Day 8
- Hypotensive (77/44);
- Norepinephrine added back, dopamine ↑, tocilizumab #2, methylprednisolone
- CRP, 6.5; ferritin, 23,500
- Increased confusion, trouble finding word

Day 10
- Off all pressors
- CRP, 3.5; ferritin, 27,500

Day 16
- Confusion resolved
- Transferred out of PICU

Day 21
- Discharged home

Day 28
- CSF and MRD negative
Tumor Lysis and GVHD

**Tumor Lysis**
- Concern in patient with high blast load
- Monitor electrolytes and uric acid
- Allopurinol as needed

**GVHD**
- Concern in patient who received a previous HSCT
- CAR-T cells are most likely donor T cells
- Activated T cells can cause GVHD

B-Cell Aplasia (On-Target, Off-Tumor Toxicity)\textsuperscript{1-3}

- CART19 cells target and kill any cells expressing the CD19 antigen; normal B cells express the CD19 antigen
- **Hypogammaglobulinemia related to B-cell aplasia**
  - B cells are an important part of the immune system
    - Produce immunoglobulins
    - Inability to produce immunoglobulins increases risk of viral and bacterial infection
    - Scheduled immunoglobulin replacement: IV or subcutaneous
- B-cell aplasia correlates with CAR-T cell persistence

# Relapse Post–CAR-T Cell Therapy

## CD19 positive

- Short persistence of CAR-T cells
- Evidenced by normal B-cell recovery
- Immune-mediated rejection?
- Starting T-cell quality; T-cell exhaustion

## CD19 negative

- Caused by antigen escape
- Is CD19 deleted/mutated/no longer expressed?
- Can happen even if CAR-T cells still detected on research labs and with persistent B-cell aplasia
Psychosocial Aspects of CAR-T Cell Therapy

- Long oncology journey
  - Multiple relapses
  - Inability to get into remission
  - Maybe only chance of cure
- Separation from family and support system
- Travel/Lodging
- Medically well educated
- Social media
Patient and Family Education

- **Multiple opportunities for education**
  - First contact with institution
  - T-cell collection
  - Consent meeting
  - Chemotherapy and infusion visits
- Majority of patients and families come with some knowledge of the therapy
- Many patients and families are very well educated, owing to the number of years they have been dealing with ALL
  - This is a new therapy that is different from anything they have experienced in the past
MasterClass 2
Optimizing the Application of CAR-T Cell Therapy in Lymphoma
Defining the Nurse’s Role

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Lymphoma Clinical Research Nurse Coordinator
Fred & Pamela Buffett Cancer Center
Department of Internal Medicine
University of Nebraska Medical Center
Omaha, Nebraska

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# Summary of Key CAR-T Cell Trials in Lymphoma

<table>
<thead>
<tr>
<th>CAR-T Cell Product</th>
<th>Dose Details</th>
<th>Enrolled Patients</th>
<th>Infused Patients</th>
<th>Additional Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Axicabtagene ciloleucel</strong>&lt;br&gt;<strong>ZUMA-1</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2 × 10&lt;sup&gt;6&lt;/sup&gt; cells/kg</td>
<td>99%</td>
<td>91%</td>
<td>Successfully manufactured, dosed</td>
</tr>
<tr>
<td><strong>Tisagenlecleucel</strong>&lt;br&gt;<strong>JULIET</strong>&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>1 to 5 × 10&lt;sup&gt;8&lt;/sup&gt; cells/kg</td>
<td>69%</td>
<td>90%</td>
<td>Infused, received bridging therapy and lymphodepleting chemotherapy</td>
</tr>
<tr>
<td><strong>Lisocabtagene maraleucel</strong>&lt;br&gt;<strong>TRANSCEND</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>- <strong>NHL-001</strong>&lt;br&gt; 1 × 10&lt;sup&gt;8&lt;/sup&gt; cells (pivotal cohort)&lt;br&gt; 99% patients had product&lt;br&gt; 85% were dosed</td>
<td>- <strong>CLL-004</strong>&lt;br&gt; 5 × 10&lt;sup&gt;7&lt;/sup&gt; or 1 × 10&lt;sup&gt;8&lt;/sup&gt; cells</td>
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Phase 2 ZUMA-1: Axicabtagene Ciloleucel in Refractory Large B-Cell Lymphoma

- 108 patients with refractory large B-cell lymphoma after failure of conventional therapy
  - ORR: 82%; CR: 54%
  - Higher CAR-T cell levels in blood associated with response
  - OS at 18 months: 52%

- Grade 3 or higher CRS and neurologic events in 13% and 28% of the patients, respectively

**Take Homes**
- Axicabtagene ciloleucel associated with high levels of durable response
- FDA approved for R/R DLBCL after ≥2 prior therapies

---

*P < .0001*  
Phase 2 JULIET: Tisagenlecleucel in Relapsed/Refractory DLBCL or Transformed FL

- 111 patients infused; N = 93 assessed for efficacy; median FU: 14 mo
- Primary endpoint met: 52% (CR: 40%; PR: 12%)

- Median DOR = not reached
- Estimated 12-mo RFS rate: 65%
- Estimated 12-mo PFS rate: 83%
- Median OS = 12 mo for all infused patients
  - Estimated 12-mo OS rate: 49%
- Median PFS and OS not reached for patients in CR
- No patients proceeded to HSCT while in remission
- Grade ≥3 CRS and neurologic events in 22% and 12% of the patients, respectively
- Cytopenias ≥28 d: 32%

Take Homes
- Tisagenlecleucel effective, with durable response
- FDA approved for R/R DLBCL after ≥2 prior therapies

In total, 37 patients with R/R DLBCL received the pivotal dose of lisocabtagene maraleucel: single dose of $1 \times 10^8$ cells
- ORR at 6 months was 49%, with 46% CR
- Toxicities were well managed
- At this dose level, no patients experienced grade 3 or 4 CRS; 8% experienced grade 3 or 4 neurotoxicity

**Take Homes**
- **Lisocabtagene maraleucel shows durable responses in pts with heavily pretreated R/R DLBCL**
- **Observed acute toxicities have been manageable at all dose levels tested**

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Phase 1 TRANSCEND CLL 004: Lisocabtagene Maraleucel in R/R CLL/SLL

16 patients received therapy

**Efficacy**
- Best ORR: 81% (44% CR/CRi; 37.5% PR/nPR)
- uMRD4 (blood): 73%; uMRD (BM): 87.5%
- ORR 3 mo post-therapy: 80% (50% CR/CRi; 30% PR/nPR)
- uMRD in blood at d 30: 73%

**Safety**
- Grade 3 CRS in 1 patient
- Grade 3 neurologic events in 3 patients
- Tocilizumab or dexamethasone use: 69%
- Grade 3 TLS in 2 patients

**Take Homes**
- *Lisocabtagene maraleucel* shows deep and durable responses in R/R CLL/SLL
- Observed acute toxicities have been manageable at all dose levels tested

Practical Considerations
CAR-T Cell Administration, Dosing, and Safety Management

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Case Study 2: A 55-Year-Old Woman with Relapsed DLBCL

October 2015 – Initial Presentation

- 55-year-old woman initially presented to her PCP with acute left arm swelling
- On work-up, found to have large (10 cm) mediastinal mass with left brachiocephalic vein compression, left paratracheal, axillary, and right retrocrural regions
- Biopsy showed DLBCL
- Received 6 cycles of R-CHOP with persistent mediastinal mass
- Referred for possible AuPSCT, and received 3 cycles of RICE without response
- Then received 4 cycles of rituximab/gemcitabine/oxaliplatin with progression of disease

October 2016

- Referred for CAR-T cell therapy
- Enrolled in a clinical trial
Keys to Success of the CAR-T Approach

- Establish processes and role responsibilities
- Maintain team collaboration and communication
Who Is Your Team?

- CAR-T MD
- CAR-T nurse coordinator
- Financial services
- Social work
- Education specialist

Consultation and workup

- CAR-T MD
- Manufacture
- Apheresis
- Cell therapy lab
- Outpatient nurses and infusion center

Pre-treatment

- CAR-T MD and coordinator
- Manufacturers
- Cell therapy lab
- Outpatient nurses and infusion center

Follow-up

- CAR-T inpatient team
- Pharmacists
- Cell therapy lab
- Inpatient and outpatient nurses
- Neurology, CCM, ED
- Nutrition, PT

Infusion and first 30 days

Research
- Sponsors and affiliates
- PI
- Nurse coordinator
- CRA
- Data
- Regulatory

Other
- Schedulers
- Lodging
- Data: FACT, CIBMTR

Referring MD/staff

- CAR-T MD
- CAR-T nurse coordinator
- Outpatient nurses
- Referring MD/staff
Essential Communications: Team

- Initial and ongoing education of team
  - Live meetings, presentations, tumor board
  - Protocol or REMS training
  - Include ancillary teams: neurology, cardiology, emergency department, infectious disease
- Biweekly CAR-T meeting
  - Determine appropriate treatment plan: commercial versus clinical trial
  - Track patient status
  - Maintain listing of all patients
- Timed communications to team members by phase of treatment
  - Product-specific tools
  - Email distribution list for patient milestone updates, upcoming apheresis procedures, upcoming admissions
- **Utilize the electronic medical record**
  - Flags, documentation aids, order sets, treatment plans, links to essential documents
Case Study 2 (Cont’d):
CAR-T Cell Infusion

November 2016

• Patient received lymphodepleting chemotherapy (cyclophosphamide + fludarabine) followed by CAR-T cell infusion on 11/22/16
• Prophylactic fluconazole, acyclovir, trimethoprim/sulfamethoxazole, levetiracetam initiated

Infusion Day

• Baseline MMSE 28/30
• Bag break during thaw
• Product rebagged; gram-negative; cultures pending
• Risk/benefit analysis by team
• Began piperacillin/tazobactam and vancomycin
• Product infused
Case Study 2 (Cont’d): Days 1-3

Day 1
- Temperature: 39.4°C
- Infection workup initiated
- Oncology ID consulted

Day 2
- Fevers continue
- Prophylactic tocilizumab administered 800 mg × 1

Day 3
- No fevers for 24 h
- All cultures negative
- ANC 0.0
- De-escalated to prophylactic levofloxacin
- MMSE 29/30
Case Study 2 (Cont’d):
Manifestation of CRS

Day 5

- Temp 39.9° C
- Intermittent nausea, fatigue, mild hypotension; responded well to IV fluid bolus
- O₂ saturation: 87%, requiring O₂ 1 L via nasal cannula
- Cultures obtained
- Placed on cefepime
- MMSE 30/30

Grade 2 CRS
# CAR-T Cell Approach: Key Toxicities¹

<table>
<thead>
<tr>
<th><strong>Axicabtagene Ciloleucel</strong>&lt;sup&gt;a&lt;/sup&gt; and Tisagenlecleucel&lt;sup&gt;b&lt;/sup&gt;</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>CRS</strong></td>
<td></td>
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<tr>
<td>• Typical time to onset: 2-3 d</td>
<td></td>
</tr>
<tr>
<td>• Typical duration: 7-8 d</td>
<td></td>
</tr>
<tr>
<td>• Manifestation may include fever, hypotension, tachycardia, hypoxia, and chills; may be associated with cardiac, hepatic, and/or renal dysfunction</td>
<td></td>
</tr>
<tr>
<td>• Serious events may include atrial fibrillation and ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis /macrophage activation syndrome (HLH/MAS)</td>
<td></td>
</tr>
<tr>
<td><strong>Neurologic toxicity</strong></td>
<td></td>
</tr>
<tr>
<td>• Typical time to onset: 4-10 d</td>
<td></td>
</tr>
<tr>
<td>• Typical duration: 14-17 d</td>
<td></td>
</tr>
<tr>
<td>• The most common neurologic toxicities include encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia, anxiety, and autonomic neuropathy; agitation, hyperactivity, or signs of psychosis can also occur</td>
<td></td>
</tr>
<tr>
<td>• Serious events including seizures, as well as fatal and serious cases of cerebral edema, have occurred</td>
<td></td>
</tr>
<tr>
<td><strong>HLH/MAS</strong></td>
<td></td>
</tr>
<tr>
<td>• Criteria for considering HLH/MAS</td>
<td></td>
</tr>
<tr>
<td>– Rapidly rising and high ferritin (&gt;5,000 ng/mL) with cytopenias in the context of CRS, especially if accompanied by any of the following:</td>
<td></td>
</tr>
<tr>
<td>➢ Grade ≥3 increase in serum bilirubin, AST, ALT</td>
<td></td>
</tr>
<tr>
<td>➢ Grade ≥3 oliguria or increase in serum creatinine</td>
<td></td>
</tr>
<tr>
<td>➢ Grade ≥3 pulmonary edema</td>
<td></td>
</tr>
<tr>
<td>• Presence of hemophagocytosis in bone marrow or organs based on histopathologic assessment of cell morphology and/or CD68 IHC</td>
<td></td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>• Patients may exhibit cytopenias for weeks to months following lymphodepleting chemotherapy and CAR-T cell therapy infusion</td>
<td></td>
</tr>
<tr>
<td>• Long-term B-cell aplasia and hypogammaglobulinemia can occur in patients with a CR after CAR-T cell therapy infusion</td>
<td></td>
</tr>
</tbody>
</table>

¹ Median time to CRS onset of 2 d (range: 1-12 d), median duration of 7 d (range: 2-48 d); median time to neurotoxicity onset of 4 d (range 1-43 d), median duration of 17 d. 
² Median time to CRS onset of 3 d (range: 1-51 d), median duration of 8 d (range: 1-36 d); median time to neurotoxicity onset of 6 d (range: 1-359 d); median duration of 14 d.

Prompt and urgent intervention to prevent progression of CRS is required; however, other causes of systemic inflammatory response should be ruled out, including infection and malignancy progression; empiric treatment for infection is warranted in the neutropenic patient; organ toxicities associated with CRS may be graded according to CTCAE v5.0, but they do not influence CRS grading.

Fever is defined as temperature >38°C not attributable to any other cause; in patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is not longer required to grade subsequent CRS severity; in this case, CRS grading is driven by hypotension and/or hypoxia.

**Cytokine Release Syndrome**

<table>
<thead>
<tr>
<th>Grade 2</th>
<th>Fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula or blow-by</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tocilizumab 8 mg/kg IV over 1 h (not &gt;800 mg/dose); repeat in 8 h if no improvement; no more than 3 doses in 24 h, with a max of 4 doses total</td>
</tr>
<tr>
<td>For persistent refractory hypotension after 1-2 doses of anti–IL-6 therapy:</td>
<td>Dexamethasone 10 mg IV every 6 h (or equivalent)</td>
</tr>
<tr>
<td></td>
<td>• IV fluid bolus as needed</td>
</tr>
<tr>
<td></td>
<td>• For persistent refractory hypotension after two fluid boluses and anti–IL-6 therapy: Start vasopressors, consider transfer to ICU, consider EEG, and initiate other methods of hemodynamic monitoring</td>
</tr>
<tr>
<td></td>
<td>• Manage per grade 3 if no improvement within 24 h after starting anti–IL-6 therapy</td>
</tr>
<tr>
<td></td>
<td>• Symptomatic management of organ toxicities</td>
</tr>
</tbody>
</table>

Essential Communications With Patient/Caregiver on Prevention/Management of AEs

- Risks of treatment
  - CRS, neurological effects, cytopenias, etc
  - Expected timeframe of concern for and management of AEs
- Patient/caregiver requirements and expectations
  - Must stay in close proximity of the treating facility for 1 month following infusion
  - Recognize and report symptoms immediately
    - Fever, chills
    - Mental changes
    - Dizziness
    - Difficulty breathing
    - Fast or irregular heartbeat
  - Must have caregiver present at all times for 1 month following infusion
  - May not drive for 8 weeks following infusion
  - Must carry wallet card
Case Study 2 (Cont’d): Days 6-7
Follow-Up on Toxicities

**Day 6**

Grade 2 CRS continues; slowed responses and unable to recall where she lives; MMSE 20/30; follows commands; no focal deficits

Grade 2 neurotoxicity as disorientation limits ADLs

- Levetiracetam increased to 1,000 mg by mouth twice daily
- Tocilizumab 8 mg/kg administered
- Neurology consult
  - MRI of brain—no acute pathology
  - EEG—no seizures or acute brain changes noted
- Lumbar puncture at bedside unsuccessful
- Patient monitored closely

**Day 7**

Progressed to grade 3 neurotoxicity; had tremors, lethargy, aphasia, urinary incontinence; MMSE 0/30; arousable and alert, but unable to respond to questions; able to follow simple commands; fevers resolving

- Tocilizumab administered
- Methylprednisolone 1 mg/kg initiated
- Lumbar puncture with IT cytarabine and hydrocortisone in fluoroscopy
- Negative cultures; West Nile virus, enterovirus, meningitis, AFB, HPV, and silver stain all negative
- Continue close monitoring
CAR-T Cell Related Neurotoxicity¹

Assessment and Supportive Care Recommendations (All Grades)
• Neurologic assessment and grading at least twice a day to include cognitive assessment and motor weakness
• MRI of the brain with and without contrast (or brain CT if MRI is not feasible for grade ≥2 neurotoxicity)
• Neurology consultation at first sign of neurotoxicity
• Conduct EEG for seizure activity for grade ≥2 neurotoxicity
• Aspiration precautions: IV hydration
• Use caution when prescribing medications that can cause CNS depression (aside from those needed for seizure prophylaxis/treatment)

| Grade 3 | • ICU care is recommended  
• Dexamethasone 10 mg IV every 6 h or methylprednisolone 1 mg/kg IV every 12 h  
• Consider repeat neuroimaging (CT or MRI) every 2-3 d if patient has persistent grade ≥3 neurotoxicity | Anti–IL-6 therapy as per grade 1 |

Case Study 2 (Cont’d): Days 9-15
Follow-Up

Day 9

Patient much improved and was sitting up in her chair eating breakfast
  • Alert and oriented × 3
  • MMSE 30/30
  • Afebrile
  • Steroids and levetiracetam were tapered

Day 15

Patient continued to improve over the next few days and was safe to discharge on d 15 under her brother’s care
  • Had some weakness/deconditioning during hospital stay
  • Was working with physiotherapist and improving strength daily
  • Continued with outpatient physical therapy
Processes That Promote Safe Care

• Formal patient/caregiver education model
  – Provide handouts and web-based materials, schedule with educator, review requirements for treatment and discharge instructions

• Triage plan for toxicities
  – Have CAR-T-trained staff take calls
  – Explain who and when to call
  – Admit through the ED

• Team communications
• Adequate supply of tocilizumab
• Inpatient versus outpatient infusion
  – Understand eligibility parameters, care model
Triage Plan for Managing Toxicities: Process Map

- **Patient is unwell**
  - **Monday-Friday 8 AM-4:30 PM:** Patient/caregiver calls nurse case manager.
  - **Weekends, after hours, and holidays:** Patient/Caregiver calls the CAR-T provider on call.

- **Call is triaged**
  - **Outpatient evaluation in clinic or infusion center**
  - **Inpatient admission to special care unit or oncology ICU**
  - **No immediate clinical evaluation indicated; follow-up as medically indicated**

- **Patient presents at ED with wallet card**
  - **CAR-T provider on call is notified, and standard emergency treatment is initiated**
  - **CAR-T provider on call meets patient in ED for evaluation; administer tocilizumab, steroids as indicated**

- **Process applicable to outpatients and those who have been discharged from the hospital after the initial safety follow-up period**

---

**Outpatient evaluation in clinic or infusion center**

**Inpatient admission to special care unit or oncology ICU**

**No immediate clinical evaluation indicated; follow-up as medically indicated**

---

**Inpatient admission to special care unit or oncology ICU**

---

**PeerView.com**
Nursing Perspectives: CAR-T Cell Therapy in Lymphoma

- CAR-T approach is patient-specific
  - Patient characteristics affect ability to generate cells and are likely important in the development of toxicity
- Current products and those under development for NHL are quite different, and this may translate into clinical effectiveness and toxicity
  - Have different biologic characteristics (CD28 vs 4-1BB)
  - Contain different mixtures of T-cell subsets
  - Are grown and produced using different technology
  - May be administered at different doses
- CRS and Neurotoxicity management is product specific with consensus efforts in progress
  - REMS program required for both FDA-approved agents
- Requires administration and management in specialized centers with experience
MasterClass 3

The Promise of CAR-T Cell Therapy in Myeloma
An Oncology Nursing Perspective

Gina Martin, BSN, RN
Clinical Research Nurse II
Clinical Trials Office, Cellular Therapy
Winship Cancer Institute of Emory University
Atlanta, Georgia
Mechanisms of Action for BCMA

- BCMA: Uniformly expressed on differentiated B cells; requisite for long-lived plasma cells’ survival
- BCMA: Broadly expressed on malignant plasma cells
- BCMA levels correlate with disease burden

Four MOAs
1. Antibody–drug conjugate
2. Antibody-dependent cellular cytotoxicity
3. Immunogenic cell death
4. BCMA receptor–signaling inhibition

# Anti-BCMA CAR-T Cells in Relapsed/Refractory Multiple Myeloma

<table>
<thead>
<tr>
<th>Construct</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>bb2121(^1)</td>
<td>Lentivirus; murine scFv; 4-1BB</td>
</tr>
<tr>
<td>bb21217(^2)</td>
<td>bb2121 cultured with the PI3K inhibitor bb007</td>
</tr>
<tr>
<td>LCAR-B38M(^3)</td>
<td>Lentivirus; llama heavy chain; 4-1BB</td>
</tr>
<tr>
<td>JCARH125(^4)</td>
<td>Lentivirus; fully human svFc; 4-1BB</td>
</tr>
<tr>
<td>P-BCMA-101(^5)</td>
<td>Nonviral delivery; piggyBac™ DNA Modification System; fully human Centyrins; 4-1BB</td>
</tr>
<tr>
<td>MCARH171(^6)</td>
<td>Retrovirus; 4-1BB</td>
</tr>
<tr>
<td>FCARH143(^7)</td>
<td>Lentivirus; fully human svFc; 4-1BB; defined composition of CD8+ and CD4+ T cells</td>
</tr>
</tbody>
</table>

bb2121: Phase 1 CRB-401 Study Design¹


**Dose Escalation (N = 21)**
- ≥ 50% BCMA expression

- Dose range: 50 x 10⁶, 150 x 10⁶, 450 x 10⁶, 800 x 10⁶

**Dose Expansion (N = 22)**
- <50% BCMA expression (n = 10)
- ≥50% BCMA expression (n = 12)

- Dose range: 150-450 x 10⁶ CAR+ cells

- Manufacturing success rate: 100%

**Timeline**
- Screening
- Leukapheresis
- bb2121 manufacturing (10 days) + release
- bb2121 infusion
- Sample collections for T-cell expansion and cytokines
- First response assessment (week 4)

**Protocol Details**
- Flu 30 mg/m²
- Cy 300 mg/m²
- Days -5, -4, -3
- BM BX (week 2)
- BM BX (week 4)
Study participants were heavily pretreated

- ~8 prior lines of therapy (range, 3-23)
- 1/3 penta-refractory (refractory to lenalidomide, bortezomib, pomalidomide, carfilzomib, and daratumumab)
- Majority had received a stem cell transplant
- MM tends to occur more aggressively with each relapse, leading to decreased duration of response with next line of therapy

Anti-BCMA CAR-T (bb2121): Efficacy Outcomes\textsuperscript{1,a}

- **mPFS**: 11.8 mo at active doses (≥150 × 10\textsuperscript{6} CAR-positive T cells) in 18 subjects in dose-escalation phase
- **mPFS**: 2.7 mo at inactive doses (50 × 10\textsuperscript{6} CAR-positive T cells)
- **mPFS**: 17.7 mo in 16 responding subjects who are MRD negative

\textsuperscript{1} Data cutoff: March 29, 2018. \textsuperscript{a} Patients with ≥2 months of response data or PD/death within <2 months. ORR is defined as attaining sCR, CR, VGPR, or PR, including confirmed and unconfirmed responses. Low BCMA is <50% bone marrow plasma cells expression of BCMA; high BCMA is defined as ≥50%.

Anti-BCMA CAR-T (bb2121): Safety Outcomes\textsuperscript{1,a}

### CAR-T Treatment-Emergent Adverse Events in All Infused Patients (N = 43)

<table>
<thead>
<tr>
<th>TEAE, n (%)</th>
<th>Overall</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS</td>
<td>27 (63)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Neurotoxicity\textsuperscript{b}</td>
<td>14 (33)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35 (81)</td>
<td>34 (79)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26 (61)</td>
<td>22 (51)</td>
</tr>
<tr>
<td>Anemia</td>
<td>24 (56)</td>
<td>19 (44)</td>
</tr>
<tr>
<td>Infection</td>
<td>26 (61)</td>
<td>9 (21)</td>
</tr>
</tbody>
</table>

- No grade 4 CRS events
- No fatal CRS or neurotoxicity events

\textsuperscript{a} Data cutoff: March 29, 2018. \textsuperscript{b} Patients with ≥2 months of response data or PD/death within <2 months. ORR is defined as attaining sCR, CR, VGPR, or PR, including confirmed and unconfirmed responses. Low BCMA is <50% bone marrow plasma cells expression of BCMA; high BCMA is defined as ≥50%.

## Clinical Outcomes With Other Anti-BCMA CAR-T Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Phase</th>
<th>(N)</th>
<th>Dose Description</th>
<th>Events</th>
<th>ORR (%)</th>
<th>CR/CRs (%)</th>
<th>VGPR (%)</th>
<th>Pts with Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LCAR-B38M</strong></td>
<td>1b/2</td>
<td>74/57</td>
<td>0.5 x 10^6 cells/kg</td>
<td>4/57 (7%) grade ≥3 CRS, 1 grade 1 neurotoxicity</td>
<td>88%</td>
<td>39/57 (68%)</td>
<td>3/57 (5%)</td>
<td>36/57 (63%)</td>
</tr>
<tr>
<td><strong>P-BCMA-101</strong></td>
<td>1</td>
<td>21</td>
<td>48-430 x 10^6 cells</td>
<td>9.5% grade 1 or 2 CRS</td>
<td>100%</td>
<td>3/3 (100%)</td>
<td>27%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>JCARH125</strong></td>
<td>1/2 EVOLVE</td>
<td>44</td>
<td>9% grade ≥3 CRS, 7% grade ≥3 neurotoxicity</td>
<td>82% ORR ≥ VGPR 48%; CR/CRs 27%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MCARH171</strong></td>
<td>1 Study</td>
<td>11</td>
<td>72-818 x 10^6 cells</td>
<td>2/11 grade 3 CRS, 1 grade 2 neurotoxicity</td>
<td>64%</td>
<td>27%</td>
<td>46%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>FCARH143</strong></td>
<td>1 Study</td>
<td>11</td>
<td>5 x 10^7 cells/kg</td>
<td>0 grade ≥3 CRS, 1 pt with neurotoxicity</td>
<td>100%</td>
<td>3/3 (100%)</td>
<td>46%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>bb21217</strong></td>
<td>1 CRB-402</td>
<td>12</td>
<td>150 x 10^6 cells</td>
<td>1 pt with grade 3 CRS, 25% pts with neurotoxicity</td>
<td>83.3%</td>
<td>3/5 (25%)</td>
<td>50%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Nursing Perspectives: A Patient’s Journey With CAR-T Cell Therapy in Multiple Myeloma Management
Case Study 3: 
A Patient with Refractory Multiple Myeloma

12/08
Diagnosed with high-risk IgA FLLC smoldering myeloma
• 1/29/13: C1D1 on the PVX-410 vaccine clinical trial for high-risk smoldering myeloma

1/7/14
Diagnosed with symptomatic MM
• 1/13/14: RVD induction; s/p 4 cycles → ASCT conditioned with melphalan 200 mg/m² → d 100 in CR and started on maintenance lenalidomide 10 mg; PD with rise in FLC and PET 9/16
• 10/2016: IRd; PD 12/16 after 2 cycles
• 1/11/17: Pomalidomide/dexamethasone; PD after 2 cycles
• 3/14/17: Carfilzomib/cyclophosphamide/dexamethasone; PD after 2 cycles
• 5/24/18: V-DCEP; PD after 2 cycles
• 7/10/18: Elotuzumab/pomalidomide/dexamethasone; PD after 2 cycles

9/18
Referred from UPMC to Emory for CAR-T trial options; found to be a good candidate for the bb2121-MM-001 study (KarMMA) and signed consents 9/11/18
Case Study 3 (Cont’d): Screening and Enrollment

Several days of tests and procedures to confirm eligibility
• Labs
• Echo
• ECG
• PET/CT
• BMBX
• Apheresis orientation (assess veins for collection)

Nursing Considerations
• Identified caregiver
• Provided tour of Emory to familiarize patient with our processes
• Gave patient a detailed calendar of appointments and directions for each day
• Educated patient and caregiver on clinical trial, expectations, leukapheresis, lymphodepleting chemotherapy, and bb2121 therapy
• Consulted social worker to assist patient with travel/lodging
Patient successfully completed leukapheresis, but, because of aggressive disease, required bridging therapy during manufacturing period

9/14/18
Started on daratumumab/carfilzomib/cyclophosphamide/dexamethasone

9/26/18
Rapid progression causing ARF (cr: 11); admitted to hospital; started on HD; given salvage V-DCEP

10/22/18
ARF resolved; HD stopped; baseline assessments completed to determine lymphodepleting chemotherapy eligibility

Lymphodepleting chemotherapy (fludarabine 30 mg/m² + cyclophosphamide 300 mg/m²)
- Given 10/31/18-11/2/18; tolerated well
- Started on acyclovir for shingles prophylaxis and sulfamethoxazole + trimethoprim every Monday, Wednesday, and Friday for pneumocystis prophylaxis
- Standing order for IVIG if IgG <400 mg/dL
Case Study 3 (Cont’d): bb2121 Infusion

- 11/4/18: Patient admitted
- 11/5/18: bb2121 infusion (day +0)
  - Premedications, including acetaminophen 650 mg and diphenhydramine 25 mg, given 30 min prior to infusion
  - Patient tolerated infusion well; no infusion reactions noted

Nursing Considerations

- Nurse coordinator reviewed orders w/ inpatient nurse educator on BMT unit to address any concerns/questions
- Email sent to interdisciplinary team outlining required labs, vital signs, prohibited meds, CRS/neurotoxicity management guidelines, contact info for medical monitor/PI/CRN
- Nurse coordinator present during infusion to ensure protocol followed
- Institutional standard: Assess CARTOX-10 every 4 h
- MMSE performed every other day
- Close monitoring for CRS/neurotoxicity
## CRS Grading Scale

<table>
<thead>
<tr>
<th>Symptoms/Signs</th>
<th>CRS Grade 1 (Mild)</th>
<th>CRS Grade 2 (Moderate)</th>
<th>CRS Grade 3 (Severe)</th>
<th>CRS Grade 4 (Life-Threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever ≥38.5°C</td>
<td>Yes</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Hypotension (SBP ≤90 mmHg)</td>
<td>N/A</td>
<td>Improvement with IV fluids or single low-dose vasopressor</td>
<td>Needs high-dose or multiple vasopressors</td>
<td>Life-threatening</td>
</tr>
<tr>
<td>Hypoxia requiring supplemental O₂ to maintain SaO₂ &gt;90%</td>
<td>N/A</td>
<td>FiO₂ &lt;40%</td>
<td>FiO₂ ≥40%</td>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>Organ toxicity</td>
<td>N/A</td>
<td>Grade 2</td>
<td>Grade 3, or grade 4 transaminitis</td>
<td>Grade 4 (excluding transaminitis)</td>
</tr>
</tbody>
</table>

---

*a CRS grade is determined by the most severe symptom (excluding fever).

CAR-T cell infusion

**Monitoring:** Hospitalization for 14 d post infusion to monitor for CRS/NT

---

If **rapid onset of CRS** (fever ≥38.5°C <72 h post-infusion) or any signs or symptoms of CRS as grade ≥2, initiate first line treatment

---

If no improvement with first-line treatment within 24 h or rapid progression of CRS, initiate second-line treatment

---

If no improvement with second-line treatment within 24 h or rapid progression of CRS, initiate third-line treatment

---

If no improvement despite third-line treatment, initiate fourth-line treatment

---

If **slow onset of fever** (≥38°C ≥72 h) post infusion

**Monitoring:** Continue close monitoring for organ function CRP, ferritin, and coagulation panel

---

If clinical progression of CRS or rapid deterioration, initiate first-line treatment

---

If no improvement with second-line treatment within 24 h or rapid progression of CRS, initiate third-line treatment

---

If no improvement despite third-line treatment, initiate fourth-line treatment

---

1. Based on KarMMa Study Protocol.
## CRS Treatment Algorithm: Recommendations by Treatment Line

<table>
<thead>
<tr>
<th>First Line</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>• Slow onset (≥72 h): Symptomatic treatment</td>
<td>• Slow onset (≥72 h): Give tocilizumab 8 mg/kg IV ± dexamethasone 10 mg every 24 h</td>
<td>Give tocilizumab 8 mg/kg IV <strong>AND</strong> dexamethasone 10 mg IV every 12 h</td>
<td>Give tocilizumab 8 mg/kg IV <strong>AND</strong> dexamethasone 20 mg IV every 6 h</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>• Rapid onset (&lt;72 h): Recommend tocilizumab 8 mg/kg IV ± dexamethasone 10 mg every 12-24 h</td>
<td>• Rapid onset (&lt;72 h): Give tocilizumab 8 mg/kg IV <strong>AND</strong> dexamethasone 10 mg every 12-24 h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

1. Based on KarMMa Study Protocol.
### CRS Treatment Algorithm:
#### Second- to Fourth-Line Recommendations

<table>
<thead>
<tr>
<th>Second Line</th>
<th>Third Line</th>
<th>Fourth Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Give second dose of tocilizumab 8 mg/kg IV <strong>AND</strong> dexamethasone 20 mg IV every 6-12 h</td>
<td>• Methylprednisolone 2 mg/kg IV once, then 2 mg/kg divided 4 x d</td>
<td>Recommend giving immunosuppressive therapies (eg, cyclophosphamide 1.5 mg/m²)</td>
</tr>
<tr>
<td>• Consider other non-CRS causes clinical deterioration (eg, sepsis, ARDS, cardiogenic shock)</td>
<td>• Consider other anti–IL-6 agents (eg, siltuximab)</td>
<td></td>
</tr>
</tbody>
</table>

#### Supportive Care/Other Recommendations

- **Grade 1**: Recommend seizure prophylaxis and provide symptomatic support (antipyretics, analgesics, empiric antibiotics if neutropenic)
- **Grade 2**: Frequent monitoring and symptom management (seizure prophylaxis, aggressive electrolyte and fluid replacement, supplemental O₂, low-dose vasopressor support); cardiac monitoring, EEG if concurrent with NT
- **Grade ≥3**: Transfer patient to higher level of care (eg, ICU) for monitoring and management of symptomatic, hemodynamic, and respiratory support

---

1. Based on KarMMa Study Protocol.
Neurotoxicity Treatment Algorithm

1. Based on KarMMa Study Protocol.
# Neurotoxicity Treatment Algorithm: Recommendations by Treatment Line

<table>
<thead>
<tr>
<th>First-Line</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early Onset</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td><strong>Late Onset</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Grade 1: Recommend dexamethasone 10 mg every 8-12 h</td>
<td>Grade 1: Observation</td>
<td>↑ dose and/or frequency of dexamethasone</td>
</tr>
<tr>
<td>Grade 2: Give dexamethasone 10 mg every 8-12 h</td>
<td>Grade 2: Recommend dexamethasone 10 mg every 12-24 h</td>
<td>Recommend methylprednisolone 2 mg/kg loading dose, followed by 2 mg/kg divided into 4 doses per day for life-threatening complications; taper slowly over 7 days</td>
</tr>
<tr>
<td>Grade 3: Give dexamethasone 20 mg every 6-8 h</td>
<td>Grade 3: Give dexamethasone 10-20 mg every 8-12 h (not recommended for isolated grade 3 headache)</td>
<td></td>
</tr>
<tr>
<td>Grade 4: Give dexamethasone 20 mg every 6 h</td>
<td>Grade 4: Give dexamethasone 10-20 mg every 6-8 h (↑ dose/↓ interval for events requiring respiratory support or seizures)</td>
<td>↑ dose and/or frequency of dexamethasone</td>
</tr>
</tbody>
</table>

<sup>a</sup> Initiate seizure prophylaxis.

1. Based on KarMMa Study Protocol.
Neurotoxicity Treatment Algorithm: Other Guidance

- Supportive care/nursing considerations
  - Initiate seizure precautions for patients experiencing NT or those at high risk
  - MRI or CT scan, EEG, and LP should be done at onset of NT and repeated if symptoms progressing or no clinical improvement; consult neurology
  - ICU monitoring may be indicated for rapid or progressive NT
  - If both CRS and NT present, treat CRS per CRS algorithm, and NT per NT algorithm

Cerebral edema: Give high-dose methylprednisolone 1-2 g; repeat every 24 h as needed

1. Based on KarMMa Study Protocol.
<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/6/18</td>
<td>Less than 24 h after infusion, patient spiked fever of 39.8°C; c/o headache and chills; ↑ ferritin: 1,418; ↑ D-dimer: 2,015; ↑ CRP 154; alert and oriented × 4; BP: 108/64; HR: 107; RR: 20; SpO₂: 96% on room air</td>
</tr>
<tr>
<td>11/11/18</td>
<td>Grade 1 CRS, treated with acetaminophen as needed for fevers; blood culture peripheral and IV; started on empiric cefepime until blood culture negative for 48 h</td>
</tr>
</tbody>
</table>
Summary: CAR-T Cell Therapy for Multiple Myeloma

- Anti-BCMA CAR-T therapy is promising for MM patients
- No CAR-T for MM is currently FDA approved, so patients have access only via clinical trials
- Side effects are managed with supportive care, and it is important to educate the patient and family on the signs and symptoms of CRS/neurotoxicity
- Patients are immunocompromised for an extended period after CAR-T cell therapy, so providers must ensure that patients have prophylactic coverage (acyclovir, sulfamethoxazole and trimethoprim, and monthly IVIG as needed)
ADL: activities of daily living
AFB: acid-fast bacilli
ALL: acute lymphocytic leukemia
AKI: acute kidney injury
ANC: absolute neutrophil count
ARDS: acute respiratory distress syndrome
ARF: acute renal failure
ASCT: autologous stem cell transplant
AuPSCT: autologous peripheral stem cell transplant
BCMA: B-cell maturation antigen
BM: bone marrow
BMA: bone marrow aspiration
BMT: bone marrow transplantation
BX: biopsy
CAR: chimeric antigen receptor
CAR-T: chimeric antigen receptor-T
CARTOX: CAR-T cell therapy–associated TOXicity
CCM: certified case manager
CD: cluster of differentiation
CIBMTR: Center for International Blood and Marrow Transplant Research
CLL: chronic lymphocytic leukemia
c/o: complains of
CR: complete response
CRA: clinical research associate

CRi: complete remission with incomplete hematologic recovery
CRN: clinical research nurse
CRP: C-reactive protein
CRS: cytokine-release syndrome
CTL: cytotoxic T lymphocyte
Cy: cytarabine
DIC: disseminated intravascular coagulation
DLBCL: diffuse large B-cell lymphoma
DOR: duration of response
EEG: electroencephalogram
EFS: event-free survival
FACT: Foundation for the Accreditation of Cellular Therapy
FiO_2: fraction of inspired oxygen
FLC: serum free light chain
FLLC: follicular lymphoma-like cells
Flu: fludarabine
FU: follow-up
GVHD: graft-vs-host disease
HD: hemodialysis
HFNC: high-flow nasal cannula
HSCT: hematopoietic stem cell transplantation
IL-6: interleukin 6
IgA: immunoglobulin A
IgG: immunoglobulin G
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRd</td>
<td>ixazomib-lenalidomide-dexamethasone</td>
</tr>
<tr>
<td>IT</td>
<td>intrathecal</td>
</tr>
<tr>
<td>IVIG</td>
<td>intravenous immunoglobulin</td>
</tr>
<tr>
<td>LD</td>
<td>lymphodepleting</td>
</tr>
<tr>
<td>LOC</td>
<td>level of consciousness</td>
</tr>
<tr>
<td>LP</td>
<td>lumbar puncture</td>
</tr>
<tr>
<td>nPR</td>
<td>nodular PR</td>
</tr>
<tr>
<td>mDOR</td>
<td>median duration of response</td>
</tr>
<tr>
<td>MM</td>
<td>multiple myeloma</td>
</tr>
<tr>
<td>MMSE</td>
<td>mini mental status exam</td>
</tr>
<tr>
<td>MOA</td>
<td>mechanism of action</td>
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<tr>
<td>mPFS</td>
<td>median progression-free survival</td>
</tr>
<tr>
<td>MRD</td>
<td>minimal residual disease</td>
</tr>
<tr>
<td>NHL</td>
<td>non-Hodgkin lymphoma</td>
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<tr>
<td>NT</td>
<td>neurotoxicity</td>
</tr>
<tr>
<td>ORR</td>
<td>objective response rate</td>
</tr>
<tr>
<td>PD</td>
<td>progressive disease</td>
</tr>
<tr>
<td>PI</td>
<td>principal investigator</td>
</tr>
<tr>
<td>PICU</td>
<td>pediatric intensive care unit</td>
</tr>
<tr>
<td>PI3K</td>
<td>phosphatidylinositol 3’ kinase</td>
</tr>
<tr>
<td>PO</td>
<td>by mouth</td>
</tr>
<tr>
<td>PR</td>
<td>partial response</td>
</tr>
<tr>
<td>PT</td>
<td>physical therapist</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone</td>
</tr>
<tr>
<td>REMS</td>
<td>Risk Evaluation and Mitigation Strategy</td>
</tr>
<tr>
<td>RICE</td>
<td>rituximab, ifosfamide, carboplatin, and etoposide</td>
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<tr>
<td>RFS</td>
<td>recurrence-free survival</td>
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<tr>
<td>R/R</td>
<td>relapsed/refractory</td>
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<tr>
<td>RVD</td>
<td>lenalidomide, bortezomib, and dexamethasone</td>
</tr>
<tr>
<td>SA0₂</td>
<td>oxygen saturation</td>
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<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
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<tr>
<td>scFv</td>
<td>single-chain variable fragment</td>
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<tr>
<td>sCR</td>
<td>stringent complete response</td>
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<tr>
<td>SCT</td>
<td>stem cell transplantation</td>
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<tr>
<td>SLL</td>
<td>small lymphocytic lymphoma</td>
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<tr>
<td>SP0₂</td>
<td>peripheral capillary oxygen saturation</td>
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<tr>
<td>TCR</td>
<td>T-cell receptor</td>
</tr>
<tr>
<td>TLS</td>
<td>tumor lysis syndrome</td>
</tr>
<tr>
<td>uMRD</td>
<td>undetectable minimal residual disease</td>
</tr>
<tr>
<td>V-DCEP</td>
<td>bortezomib with dexamethasone, cyclophosphamide, etoposide, and cisplatin</td>
</tr>
<tr>
<td>VGPR</td>
<td>very good partial response</td>
</tr>
</tbody>
</table>
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Thank you, and good day.