CAR T-cell therapy

Chimeric Antigen Receptor T-cell Therapy for Multiple Myeloma

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Chimeric antigen receptors (CARs)


CARs

Chimeric Antigen Receptors (CARs)

Kochenderfer and Rosenberg, Nature Reviews Clinical Oncology 2015
CAR T-cell toxicities

CAR T cells can cause severe but reversible toxicities

- Cytokine release syndrome (“CRS”)
  - Symptoms similar to sepsis due to infection or severe flu-like syndrome
  - High fevers
  - Tachycardia
  - Hypoxia
  - Hypotension
  - Decrease in liver or kidney function
  - Prolonged PTT, PT, DIC and risk of bleeding
  - Patients frequently require ICU admission
  - Usually occur in first 2 weeks but may occur a month following cell infusion
  - Can give IL-6 receptor antagonist tocilizumab +/- steroids
Neurological toxicities

CAR T cells can cause severe toxicities

- Neurologic Toxicities
  - Confusion
  - Somnolence
  - Tremors
  - Gait instability
  - Aphasia, other difficulties speaking
  - Seizures
  - Myoclonus and other focal motor defects
  - Cerebral edema on MRI → patient deaths
  - **Neurologic toxicities may occur separately from CRS**
  - Steroids are first line therapy
Toxicity grading system

**CAR T-cell Toxicity Grading Systems**

- Historically, there has been no universal grading system for CRS
  - NIH system
  - University of Pennsylvania system
  - MSKCC system
  - MD Anderson system
  - Difficult to compare toxicities between cell products
- Neurotoxicity has been graded with the CTCAE system
- Recent attempt at a universal system for CRS and neurotoxicity (ASBMT committee)
  - Lee et al., Biol Blood Marrow Transplant 2018

Guideline

*ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells*

# Supportive care

## Supportive Care for CAR T-cell Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Preventive/supportive measure</th>
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<tbody>
<tr>
<td>FEVERS</td>
<td>• Acetaminophen</td>
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<tr>
<td></td>
<td>• Cooling blankets</td>
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<tr>
<td></td>
<td>• Avoid NSAIDs, steroids and mepivacaine</td>
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<tr>
<td>Cardiovascular</td>
<td>• At least q 4 hour vitals, q 2 if HR &gt; 115</td>
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<td></td>
<td>• IV fluid boluses for hypotension if SBP &lt; 80% baseline and &lt; 100 mm Hg, or if SBP &lt; 90.</td>
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<tr>
<td></td>
<td>• IVF to replace insensible losses; keep not positive</td>
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<tr>
<td></td>
<td>• ECG, troponin, and Echo if patients require &gt; 1 fluid bolus for hypotension or are in the ICU</td>
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<tr>
<td>ID</td>
<td>• PCP and HSV/VZV prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• Pan-culture for any fever</td>
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<tr>
<td></td>
<td>• Pan-culture and broad spectrum antibiotics for neutropenic fever</td>
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<tr>
<td>Hemo</td>
<td>• Allopurinol for tumor lysis syndrome prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• Goals: Hb &gt; 8, platelets &gt; 20, ANC &gt; 500 (with filgrastim)</td>
</tr>
<tr>
<td></td>
<td>• Goals: PTT normal; give FFP if &gt; 1.5 x ULN; give cryoprecipitate for goal fibrinogen &gt; 100.</td>
</tr>
<tr>
<td>Neurologic</td>
<td>• Neurology consult for all patients</td>
</tr>
<tr>
<td></td>
<td>• Brain MRI and lumbar puncture whenever possible</td>
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Tocilizumab

Toxicity Management: Indications for Tocilizumab

- Tocilizumab is an IL-6 receptor antagonist used in rheumatologic disorders.
- Tocilizumab is the first-line agent for CRS at the NCI.
- Dose is 8 mg/kg IV infused over 1 hour, not to exceed 800 mg.
- List of criteria for tocilizumab use on the adult service at NCI in the “CAR T-cell toxicity guidelines”
- **No universal agreement on indications for tocilizumab**
- Generally, consider tocilizumab for
  - Toxicities necessitating intensive care
  - Hypotension requiring vasopressors
  - Hypoxia requiring more than a nasal cannula, or significantly increased work of breathing
  - Consider for certain lab/study abnormalities: significant cardiac ejection fraction decrease, renal or hepatic failure, hyponatremia, coagulopathy, creatine kinase increase, etc.
Indications for corticosteroids

**Toxicity Management: Indications for Corticosteroids**

- In some studies, high dose corticosteroids were thought to decrease the activity of CAR T cells. For this reason, corticosteroids are reserved for refractory CRS and for neurologic toxicities.
- Dexamethasone 10 mg IV q 6 hours for severe neurologic toxicity
- Methylprednisolone: doses range from 50 mg IV q 6 hours to 1000 mg IV for refractory CRS
- No universal agreement on thresholds to give corticosteroids
Toxicity factors

Factors Associated with Toxicity

**Lab Values that reflect severity of toxicity**
- CRP
- LDH
- Ferritin
- DIC markers

**Possibly Contributing Inflammatory Cytokines**
- Interferon-gamma
- IL-1
- IL-2, sIL-2-alpha
- IL-4
- IL-6
- IL-8
- IL-10
- IL-15
- TNF-alpha
- Granzyme B
- GM-CSF
- MIP-1-alpha
- MCP-1

Higher peak blood levels of CAR T cells associated with more severe toxicity.
Risk factors

**Toxicity Risk Factors**

- Disease type: ALL vs NHL (possibly ALL more risk)
- Bone marrow involvement (higher → more risk)
- Burden of disease (higher → more risk)
- Type of lymphodepletion chemo (fludarabine → more risk? Or just better lymphodepletion → more risk?)
- Cell dose (higher → more risk)
- Costimulatory domain?/structure of CAR/antigen target (complex)
- Baseline markers of endothelial activation? (von Willebrand factor, ANG-2)
Infection risk

CAR T-cell Infection Risk

- CAR T-cell therapy patients may have a higher risk of infection within the first 30 and 100 days of therapy.
- Underlying malignancy, # of prior lines of therapy, infections before infusion and presence of F&N post infusion were associated with a higher risk of infection.

103 INFECTIONS IN 58 PATIENTS ACROSS 4 TRIALS

Mikkilineni et al ASH 2019
Severe toxicity
NIH specific thresholds

Management of Severe CRS and Neurologic Toxicity following CAR T-cell infusion

Do the patient have any of the following?
- Hypotension with vasopressor requirement of > 5 mcg/min norepinephrine or equivalent vasopressor to maintain systolic blood pressure > 90 mm Hg
- Hypotension with vasopressor requirement of > 5 mcg/min norepinephrine or equivalent vasopressor lasting > 36 hours since first administration of vasopressor
- Hyponatremia requiring FIO2 > 40% to maintain oxygen saturation > 92%
- Significant subjective diplopia with a respiratory rate > 25 breaths/minute for > 2 hours.
- Left ventricular ejection fraction < 45%
- Creatinine increased more than 2-fold over baseline
- PT or INR > twice the upper limit of normal
- Hemorrhagic event possibly related to cytokine release syndrome
- CRP elevation > 5 times upper limit of normal

No: Aggressive supportive care
Yes: Continue to monitor CRS and neurologic toxicity

For refractory toxicity, methylprednisolone 1000 mg IV can be given

These are NIH-specific.

Thresholds to Give Immunosuppression Differ Among Institutions and the Landscape is Ever-Changing.
B cell maturation antigen

B-Cell Maturation Antigen a Target for
CAR T-cell Therapy of Multiple Myeloma
Multiple myeloma

Arrows indicate plasma cells

Bone marrow with multiple myeloma

Sclerotic lesions of bones
Multiple myeloma
Protocol design

Anti-BCMA CAR clinical protocol design

Days -5 to -3 fludarabine administration

Days -5 to -3 cyclophosphamide administration

Day 0 infusion of anti-BCMA-CAR transduced T cells

Cyclophosphamide: 300 mg/m² daily for 3 days

Fludarabine: 30 mg/m² daily for 3 days
B-cell maturation antigen

Development of the first CAR targeting B-cell maturation antigen (BCMA)

- BCMA (CD269) is a member of the TNF superfamily.

- By flow cytometry, BCMA is expressed on the myeloma cell surface by almost all cases of multiple myeloma.

- 34 different tissues were assessed by immunohistochemistry, BCMA was only expressed by plasma cells and a small fraction of B cells.

- We designed and tested the first series of anti-BCMA CARs

T cells can be genetically engineered to express an anti-BCMA chimeric antigen receptor

- We designed an anti-BCMA CAR and ligated it into a gamma-retroviral backbone.
- T cells were stimulated with the anti-CD3 monoclonal antibody OKT3 before transduction and cultured for 9 days before infusion.
- We initiated the first-in-humans clinical trial of an anti-BCMA CAR in 2014
Patient characteristics

Baseline characteristics of patients

- 24 patients treated on study; 2 patients received 2 cell infusions
- Median of 9.5 prior lines of therapy
- 6/15 evaluable patients (40%) with high risk cytogenetics, 5/15 (33%) with deletion 17p
- 10/16 patients (63%) refractory to last treatment regimen
- Patients treated on lower dose levels had very similar baseline characteristics as patients treated on highest dose level.
Multiple myeloma reduction

Multiple myeloma that made up more than 90% of Patient 10’s bone marrow cells was eliminated after CAR T-cell infusion.
Patient 14 attained VGPR of heavily pretreated extramedullary light chain myeloma

- 65 year old male with extramedullary λ light chain multiple myeloma
- Received 16 prior lines of therapy, including 2 autologous stem cell transplants
- He had a rapid decrease of λ light chains after CART-cell infusion
- His response was a VGPR that lasted 54 weeks.

Brudno et al. Journal of Clinical Oncology 2018
### Summary of responses of anti-BCMA CAR T at all dose levels

<table>
<thead>
<tr>
<th>CAR T-cell dose/kg</th>
<th>Response (duration in weeks, + means ongoing)</th>
</tr>
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<tbody>
<tr>
<td>0.3x10^6</td>
<td>PR (2), SD (6), SD (6)</td>
</tr>
<tr>
<td>1x10^6</td>
<td>SD (12), SD (4), SD (2)</td>
</tr>
<tr>
<td>3x10^6</td>
<td>SD (7), VGPR (8), SD (16), SD (2)</td>
</tr>
<tr>
<td>9x10^6</td>
<td>Stringent CR (17), VGPR (66), VGPR (29), VGPR (84), SD (2), VGPR (11), Stringent CR (69), VGPR (34), PR (31), VGPR (82), PD, VGPR (11), sCR (88), PR (2^*), PR (29), SD (1)</td>
</tr>
</tbody>
</table>

Patients received no anti-myeloma therapy after infusion of CAR T cells until progression occurred.

*Lost to follow-up*
Anti-BCMA CAR T cells

Toxicity of anti-BCMA CAR T cells: cytokines and myeloma burden

Cytokine release syndrome (CRS) on highest dose level (n=16):
- 2 patients with Grade 4
- 4 patients with Grade 3
- 10 patients with <Grade 3 CRS

Immunosuppression for CRS management:
- 5 patients (31%) received tocilizumab for CRS management
- 4 of the patients who received tocilizumab also received corticosteroids for CRS management or adrenal insufficiency

P=0.04
Anti-BCMA CAR T-cell summary

Summary of anti-BCMA CAR T cells at NCI single-center study

- Only 2/10 objective responses on dose levels 1-3

- 13/16 objective responses at optimal dose of 9x10^6/kg (81% ORR)

- 5 of 16 patients on the optimum dose level have had durations of response of >1 year; 9/16 patients on the optimal dose had responses of >6 months

- Responses allowed patients to be off-therapy for many months

- Multiple myeloma is difficult to treat because of its phenotypic heterogeneity
bb2121 Anti-BCMA CAR T-cell therapy in patients with relapsed/refractory multiple myeloma: updated results from a multicenter phase I study CRB401

- The CAR used in bb2121 had the same 11D5-3 scFv as the previously mentioned CAR used at the NCI.
- The bb2121 CAR had a 4-1BB costimulatory domain and was encoded by a lentivirus

![Study CRB401 Diagram]
Bb2121 responses

Raje et al. The New England Journal of Medicine, 2019
Progression-free survival

Bb2121 progression-free survival

- Cytokine-release syndrome was relatively mild; 2 of 33 patients had Grade 3, and none had Grade 4 CRS
- Only 1 of 33 patients had Grade 3 or 4 neurologic toxicity
- 7 patients received tocilizumab and 4 received corticosteroids

Raje et al. The New England Journal of Medicine, 2019
Room for improvement:

Development of Fully-Human, Heavy-Chain Only anti-BCMA CAR T-cell Therapy
Potential advantages of CARs with heavy-chain-only binding domains led us to develop fully-human heavy-chain-only CARs targeting BCMA.

- **FHvH**: Fully-human heavy chain variable domain generated in a transgenic rat by TeneoBio, Inc.
- Because the heavy-chain-only domains do not have linkers, immune responses directed at linkers and junctions between the linker and variable domains are eliminated.
- Heavy-chain-only binding domains are smaller (good for bispecific CARs).
- In vitro, FHvH33-CD8BBZ function was equivalent to function of a CAR with the 11D5-3 murine scFv used in several clinical trials.
Clinical trail of FHVH33-CD8BBZ T cells

Eligibility

- Enrolling relapsed multiple myeloma
- Patients need normal cardiac ejection fraction, no history of cardiac problems
- Creatinine maximum 1.5 mg/dL
- Platelets minimum 55/μL
- Must have measurable multiple myeloma and at least 3 lines of prior therapy

Trial design

- Dose escalation
- Conditioning regimen of 300 mg/m² cyclophosphamide and 30 mg/m² fludarabine daily for 3 days
- One infusion of anti-BCMA CART cells 3 days after the chemotherapy ends
## Demographics

### FH-BCMA Demographics

#### Demographics of Treated Patients

<table>
<thead>
<tr>
<th></th>
<th>N or median</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>15</td>
<td></td>
</tr>
<tr>
<td><strong>Age, median (range)</strong></td>
<td>64 (41-71)</td>
<td></td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>9</td>
<td>60%</td>
</tr>
<tr>
<td>High risk feature- (t(4;14))</td>
<td>6</td>
<td>40%</td>
</tr>
<tr>
<td>High risk feature- (t(14;16))</td>
<td>1</td>
<td>7%</td>
</tr>
<tr>
<td>High risk feature- del17p or TP53</td>
<td>5</td>
<td>33%</td>
</tr>
<tr>
<td>(\geq 2) high risk features</td>
<td>4</td>
<td>27%</td>
</tr>
<tr>
<td>Prior lines of therapy</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Extramedullary disease at baseline</td>
<td>7</td>
<td>47%</td>
</tr>
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Summary

Summary of responses of anti-BCMA CAR T at all dose levels

![Graph showing duration of response to CAR T-cell Therapy](Image)
Out of the 7 patients who have relapsed, 2 patients had evidence of BCMA negative myeloma in the bone marrow and 1 patient had BCMA negative myeloma detected in a new soft-tissue plasmacytoma.
Future plans

Summary and future plans for CAR T-cell therapies of multiple myeloma

- Anti-BCMA CAR T cells have powerful activity against multiple myeloma.

- Anti-BCMA CAR T cells are in international phase II clinical trials, but multiple myeloma is phenotypically heterogeneous, so targeting more than 1 antigen is important.

- More multiple myeloma antigens are needed in addition to BCMA

- Currently at the NCI, we have an actively-recruiting trial of an anti-BCMA CAR with a heavy-chain-only antigen recognition domain.
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Patients and their families