CAR T-Cell Therapy: It's Role after Transplant

Celebrating a Second Chance at Life Survivorship Symposium

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It’s Role After Transplant
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4/22/21
Disclosures

<table>
<thead>
<tr>
<th>Research Support</th>
<th>BMS/Celgene; Curis;</th>
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<tbody>
<tr>
<td>Consultancy</td>
<td>Acrotech; ADC Therapeutics; AstraZeneca; BeiGene, BMS/Celgene/Juno; Diiachi Sankyo; Janssen/Pharmacyclics; Karyopharm; Kite/Gilead; Legend; Morphosys; Myeloid Therapeutics; Novartis; Spectrum; TG Therapeutics, Verastem</td>
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<tr>
<td>Employment</td>
<td>NONE</td>
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<td>Major Stockholder</td>
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<td>Speakers Bureau</td>
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Objectives

- Discuss how the immune system and CAR-T share a common theme
- Discuss where CAR T-cell therapy plays a role in the treatment of patients with blood disorders
- Discuss the evaluation process for candidacy for CAR T-cell therapy
- Discuss the CAR-T journey for patients and their family before, during and after the procedure
- Discuss the potential toxicities and impact on quality of life long-term
Our Immune System

STEM CELLS

- CLP
- CMP
- Self-renewal

COMMITTED PROGENITORS

- Pre-T cell
- Pre-B cell
- BFU-E
- CFU-E
- Meg-CFC
- Mast-CFC
- Eo-CFC
- GM-CFC
- M-CFC
- Oc-CFC (?)

MATURE CELLS

- T-Lymphocyte
- B-Lymphocyte /Plasma cell
- Erythrocyte
- Megakaryocyte /Platelets
- Basophil /Mast cell
- Eosinophil
- Neutrophil
- Monocyte /Macrophage /Kupffer cell
- Langerhans cell
- Dendritic cell
- Osteoclast

How T-cells Fight Cancer

1. Recognition of cancer cells (immune and cancer cells)
2. Release of cancer cell antigens (cancer cell death)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (immune and cancer cells)

Chen DS, Mellman I. Immunity, 2013:39:1-10
T-cells To CAR-T cells

Geyer et al. Cytotherapy 2016

TAA= Tumor associated antigen

Geyer et al. Cytotherapy 2016
Where does CAR T-cell Currently Fit?

Courtesey of Susan Blumel

FDA Approved

<table>
<thead>
<tr>
<th>CAR-T cell</th>
<th>Disease approved</th>
<th>Target</th>
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<tbody>
<tr>
<td>Axi-cel (Yescarta)</td>
<td>LBCL; MCL; FL</td>
<td>CD19</td>
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<tr>
<td>Tisa-cel (Kymriah)</td>
<td>LBCL; ALL</td>
<td>CD19</td>
</tr>
<tr>
<td>Liso-cel (Breyanzi)</td>
<td>LBCL</td>
<td>CD19</td>
</tr>
<tr>
<td>Ide-cel (Abecma)</td>
<td>MM</td>
<td>BCMA</td>
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**Indications:**

- LBCL; MCL; FL → After at least two prior lines of therapy
- ALL → Up to age 25 that is refractory or in 2nd relapse or later
- MM → After 4 prior lines of therapy (specific drugs must have exposure)
The Journey To

Consultation

• Disease type
  • LBCL; MCL, FL, MM
• Prior Treatments
  • Appropriate exposure pre-CAR-T
• Tolerance to prior treatments
  • Intensity of past therapies
  • Transplant

• Disease status
  • Relapse
    • Duration of remission
  • Refractory
  • Never in remission
Workup

- Disease Burden
  - Physical exam
  - Imaging
- Cardiac function
  - Echocardiogram
- Infectious disease
  - HIV; Hep B; Hep C

- Laboratory
  - Bone marrow reserve
  - CBC
  - Hepatic reserve
  - LFTs/Bilirubin
  - Renal reserve
  - CrCl
  - Pulmonary reserve
  - Pulse Ox

Brain to Vein Time

- Insurance
  - Private vs Public
- Prior Authorization
  - On label
- Single case agreement
  - Payment for the product
  - Payment for the care post infusion

- Pre-apheresis treatment
  - Disease burden
  - Disease velocity
  - Anticipated time to T-cell removal (apheresis)
Vein to Vein Time

What you’re doing post-apheresis
- Monitor fitness
- Monitor for infections
- Bridging treatment:
  - Steroids
    - Distance from infusion
  - Radiation
    - Problem locations
    - Low risk locations
  - Low dose chemotherapy
    - Distance from lymphodepleting chemotherapy

Lymphodepleting (LD) Chemo
- Fludarabine/Cyclophosphamide
  - Most common LD chemotherapy
  - Doses differ depending on the CAR-T construct
  - 3 days of treatment
  - At least 2 days of rest prior to infusion
- Bendamustine
  - Only available with Tisa-cel (Kymriah)
  - Two days of treatment
- No LD chemo
  - Only available with Tisa-cel (Kymriah)
The Infusion

1. Where is it done?
   - Often in the patients room or in the infusion center if being administered in out-patient.

2. How long does is last
   - Minutes but depending on product
   - Some products are a single bag or multiple
   - Some products are in vials (Liso-cel)

3. What does it feel like?
   - Painless
   - Odor (DMSO) that the family may smell but not the patient
     - Same smell as transplant infusion

Management of Toxicity: Experience Matters
Management of Cytokine Release Syndrome (CRS)

Fever
Fatigue
Nausea/Vomit

Grade
Tocilizumab—IL-6 receptor mAB

Low blood pressure
Low oxygenation
Organ dysfunction

Management of ICANS

Shake of the Hand

Tremor
Agitation
Word finding
Weakness

Grade
ICANS = Immune effector cell-associated neurotoxicity syndrome

Coma
Seizure
Brain swelling
Post Infusion Monitoring Days 1-14

- Cytokine release syndrome (CRS) and immune cytokine associated neurotoxicity syndrome (ICANS)
  - Availability of at least 2 doses of tocilizumab per CAR-T patient
  - Steroid
    - Dose based on severity of ICANS
- Infections
  - Prophylactic medications
    - Short term: Antibiotics & antifungals
    - Long term: Antiviral & Anti-PJP (PCP)
- Blood transfusions
  - Red blood cell and platelets
- Replacement of electrolytes
- Intravenous fluid

Post Discharge Monitoring Days 15-28

- Count recovery post flu/cy
  - Red blood cell and platelets transfusion less frequent
- Double dip
  - Growth factor use for sporadic neutropenia
  - Possibly more common after CRS/ICANS
- Remain in close proximity to CAR-T center
  - 24/7 caregiver
  - Monitor for recurrence of CRS/ICANS
  - Multiple visits per week
Days 29 and Beyond

- Returning home
  - Discussion with local Oncologist (if necessary)
  - Cytopenias (low blood counts) may persist but transfusion less frequent
  - Sporadic neutropenia (low white blood cells) may return
  - Slow return to work
- Monitor for recurrent infections
  - B-cell aplasia = low immunoglobulins → IVIG use
- Response evaluation around D=100
  - Potentially before if concern for progression
  - No driving for 8 weeks
    - Includes heavy machinery
    - Return to side streets or rural road first

Summary

- Use of CAR-T has been an effective therapy in difficult-to-treat situations with prospect of prolonged disease free survival
- No head to head trials in LBCL to determine safest or most effective CAR-T
  - Individual discussion with CAR-T team
- CAR-T access may be limited by Brain to Vein time
- Half the battle is getting to CAR-T
- Toxicity management has improved with time
Questions?

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