CAR T-Cell Therapy: Acute Lymphoblastic Leukemia - A Drive through the Past, Present and Future

Celebrating a Second Chance at Life Survivorship Symposium
April 29 – May 5, 2023

Haneen Shalabi, DO
National Cancer Institutes of Health, Pediatric Oncology Branch

Learning Objectives

• Discuss why people may need CAR T-cell therapy for leukemia
• Talk about steps involved in making a CAR T-cell product
• Share short and long-term side effects associated with CAR T-cell therapy
• Review outcomes after CAR T-cell therapy
Blood Cell Growth Occurs in the Bone Marrow

Childhood Acute Lymphoblastic Leukemia (ALL)

- Most common cancer diagnosed in children
  - 30 cases/million in children aged < 20 years
  - 25% of all new cancer diagnoses
  - 85-90% of patients will be cured

Improved Survival by Study Era

Mullighan et al. NEJM 2015
Acute Lymphoblastic Leukemia in Adults

• Rare diagnosis in adults
• Second most commonly diagnosed acute leukemia
  • 6,500 cases/year
  • Only 40-50% of adults will achieve long term durable remissions

Overview of Standard Leukemia Treatment

• Pediatric ALL patients receive chemotherapy for 2.5 years
• Adult ALL patients receive chemotherapy
• Bone marrow transplant may be indicated for high-risk patients after chemotherapy
• Newer immunotherapies moving more into upfront settings:
  • blinatumomab (Blincyto®) (targets CD19)
  • inotuzumab (Besponsa®) (targets CD22)
Approach to the Relapsed/Refractory Patient

- Curative options for relapsed/refractory disease is a therapeutic challenge
  - Particularly poor outcomes for adults and adolescent young adult (AYA) population
  - Toxicity from cumulative therapies limits treatment options
  - Novel treatments are needed

Chimeric Antigen Receptor (CAR) T-cell Therapy

- Normally, T-cells cannot recognize cancer cells
- CAR T-cells use T-cells from the body and re-engineer them so that a T-cell can recognize cancer cells
  - Goal is to kill cancer cells
  - CAR T-cells combine the recognition properties from a B-cell, and the keeps the functionality of a T-cell
Making a CAR T-cell Product

1. Apheresis
2. Stimulation/Activation
3. Transduction
4. Expansion
5. Lymphodepleting Chemotherapy
6. CAR T-cell Infusion

CAR T-cells in Leukemia

- CAR T-cell therapy is typically for patients who have relapsed or refractory (R/R) ALL that did not respond, or came back after chemotherapy and/or transplant.

- Pediatric CAR T-cell product tisagenlecleucel (Kymriah®) received FDA approval in 2017
  - For patients < 25 years old

- Adult CAR T-cell product brexucabtagene autoleucel (Tecartus®) received FDA approval in 2021
  - For patients > 18 years old
Tisa-Cel Demonstrated Remarkable Response Rates in Pediatric B-ALL

• Global Registration trial (25 centers participated)
• 75 patients were infused, with > 80% complete remission rates
• 12-month event free survival was 50%
• 12-month overall survival was 75%

Brexu-Cel is Effective at Treating Adults with B-ALL

• Multi Site Study in the US (19 hospitals)
• 45 patients received CAR T-cells
• 69% of patients achieved complete remission
• Median duration of remission was 7 months
Process of Receiving CAR T-cells for Treatment for R/R ALL

- Insurance approval for one of the FDA approved products (2-3 weeks)
- Referral to CAR T-cell Center
- Apheresis (T-cell collection) (2-3 weeks to grow cells)
- Chemotherapy followed by CAR T-cell infusion (4-5 days)
- Monitoring for side effects and toxicities (1 month)

Non-FDA Approved CAR T-cell Products

- Several clinical trials for pediatric and adult patients with r/r ALL
- Clinicaltrials.gov
- Typically phase I or phase II trials evaluating novel CAR T-cell therapies or alternate targeting strategies
- Eligibility criteria differs per trial
Interim Chemotherapy

• While CAR T-cells are being manufactured (14-21 days) you may receive chemotherapy to:
  • keep leukemia disease controlled
  • decrease leukemia burden
• Recent studies have demonstrated that patients with higher disease burden before receiving CAR T-cells:
  • can have more severe side effects
  • lower chances of getting into a remission

CAR T-cell Infusion

• About 5 days before CAR T-cell infusion, lower dose chemotherapy, usually with Fludarabine and Cyclophosphamide, is given to:
  • prepare body to receive CAR T-cells
  • create “space” for CAR T-cells to grow using cytokines in your body
  • disease control
• CAR T-cell infusion (Day 0)
  • Given inpatient or outpatient depending on center
• Side effect monitoring (Day 0-28)
Cytokine Release Syndrome (CRS) is most Common Side Effect

• Constellation of symptoms due to higher than normal cytokine production
  • >80% of patients will get CRS
• Onset occurs within hours to days post-infusion
• Most common symptoms include
  • Fever
  • Low blood pressure
  • Difficulty breathing/shortness of breath

CRS Severity Depends on Patient and Product Characteristics

• Patients with higher tumor burden and increased cell dose have increased risk of more severe CRS
• Some may products may have increased risk of CRS
• Timing of CRS varies but is usually within first 2 weeks after CAR T-cell infusion
  • Symptoms vary, not all patients get everything
CRS Grading and Treatment

• CRS grade 1: fever only
• CRS grade 2: fever with low blood pressure +/- low oxygen
• CRS grade 3/4: fever with need for blood pressure supportive medications or more oxygen support- *ICU level care*
• First line treatment is supportive care + anti-cytokine therapy with tocilizumab (Actemra®)
  - Steroids are used for more severe cases
• Generally reversible with little long term toxicity although data is limited

Neurotoxicity (ICANS)

• Considered the “black box” warning for CAR T-cell therapy
  - *ICANS* = immune effector cell associated neurotoxicity syndrome
  - Varying rates of neurotoxicity: 30-87% in pivotal trials
• Multiple reasons why neurotoxicity occurs
  - Cytokines
  - Blood brain barrier disruption
  - On target/ off tumor
Symptoms of Neurotoxicity

- Disorientation (confusion)
- Difficulty writing, speaking, or following commands
- Severe neurotoxicity, in up to 30% of cases e.g.
  - Seizures
  - Encephalopathy (altered mental state)
  - Cerebral edema (brain swelling)
- Typically occurs after CRS has started, wide variability in presentation and duration of symptoms

Diagnosis and Assessment of ICANS

- Frequent assessments including daily exams and standardized questionnaires pre- and post-infusion
- For adults, 5 questions with a handwriting sample
- For pediatric patients < 12 years, observational assessments
- Additional work up depending on symptoms may include:
  - CT or MRI brain/spine
  - Lumbar puncture
  - EEG

**Adult Questionnaire**

<table>
<thead>
<tr>
<th>Field</th>
<th>Suggested Assessment</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation</td>
<td>Orientation to year, month, city, hospital</td>
<td>4 points</td>
</tr>
<tr>
<td>Naming</td>
<td>Name 3 objects (e.g., point to clock, pen, button)</td>
<td>3 points</td>
</tr>
<tr>
<td>Following Commands</td>
<td>E.g. show 2 fingers or close your eyes and stick out your tongue</td>
<td>1 point</td>
</tr>
<tr>
<td>Writing</td>
<td>Ability to write a standard sentence (e.g. It is a sunny day)</td>
<td>1 point</td>
</tr>
<tr>
<td>Attention</td>
<td>Count backwards from 100 by 10</td>
<td>1 point</td>
</tr>
</tbody>
</table>
ICANS Grading

- Grading incorporates a composite score of encephalopathy (altered mental state) and signs/symptoms of four global domains
  - **ICANS grade 1:** minimal symptoms (e.g. confusion)
  - **ICANS grade 2:** moderate symptoms (e.g. depressed level of consciousness)
  - **ICANS grade 3/4:** more severe signs/symptoms; may need **ICU level care**
    - Seizures
    - Edema (brain swelling)
    - weakness or difficulty moving limbs

ICANS Treatment

- First line treatment is supportive care
  - More frequent assessments
  - Anti-seizure medications
- Steroids are given for more severe cases
- Ongoing studies evaluating anti-cytokine therapy and/or spinal taps with steroids +/- chemotherapy
- Generally reversible however long-term effects are not well defined
Low Blood Counts (Cytopenias)

- Low blood counts including platelets, neutrophils, and red blood cells can occur post-CAR due to:
  - Lymphodepleting chemotherapy
  - CAR T-cell induced inflammation
- Most patients generally recover within 30 days post-CAR T-cell therapy
  - Supportive care including transfusions and GCSF
- Risk factors associated with prolonged cytopenias > 3 months include:
  - Baseline low blood counts, severity of CRS, prior therapies

Infections and CAR

- CAR therapy is often administered to highly immunocompromised patients
- Lymphodepleting chemotherapy can contribute to risk of infection
- Infections can occur both early (< 30 days post infusion) and late (>30 days)
- Generally, patients receive anti-viral, anti-fungal, +/- antibacterial therapy to reduce the risk of infections.
- For B-cell ALL or lymphoma, healthy B cells can be decreased so IVIG may administered for at least 3 months post CAR T-cell infusion
Infection Prevention Post-CAR T-cell Therapy

• Potential risk of long-term infectious complications if CD19 CAR T-cells persist
• Continue anti-viral, anti-fungal, and anti-bacterial prophylaxis (institution specific)
• Vaccination strategies are institution specific

Patient Reported Outcomes and CAR T-cell Therapy

• A decline in quality of life (QoL) and an increase in symptom burden correlated with CRS
• CAR T-cell patients had less decline in QoL, physical, and functional well-being as compared to patients who received bone marrow transplant
• Pediatric patients had improvement 3-12 months after CAR T-cell therapy in:
  • Emotional health
  • Social functioning
  • School functioning
  • Physical health
  • Psychosocial health

Sidana et al. TCT 2022
Laetsch et al. Lancet Oncol 2019
Late Effect Considerations

Image courtesy of NIH medical arts

Will CARs Be “THE” Answer?

Future Directions

- Novel CAR Constructs For Other Disease Subtypes
- Optimization of CAR T-cells
- Reducing Toxicity Profile
- Monitoring Long Term Outcomes
- Improving Access

Thank you for your attention!

Questions/Comments: haneen.shalabi@nih.gov
QUESTIONS?

Haneen Shalabi, DO
National Cancer Institutes of Health, Pediatric Oncology Branch

LET US KNOW HOW WE CAN HELP YOU

Visit our website: bmtinfonet.org

Email us: help@bmtinfonet.org

Phone: 888-597-7674 or 847-433-3313

Find us on:

Facebook, facebook.com/bmtinfonet

Twitter, twitter.com/BMTInfoNet