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

Celebrating a Second Chance at Life Survivorship Symposium

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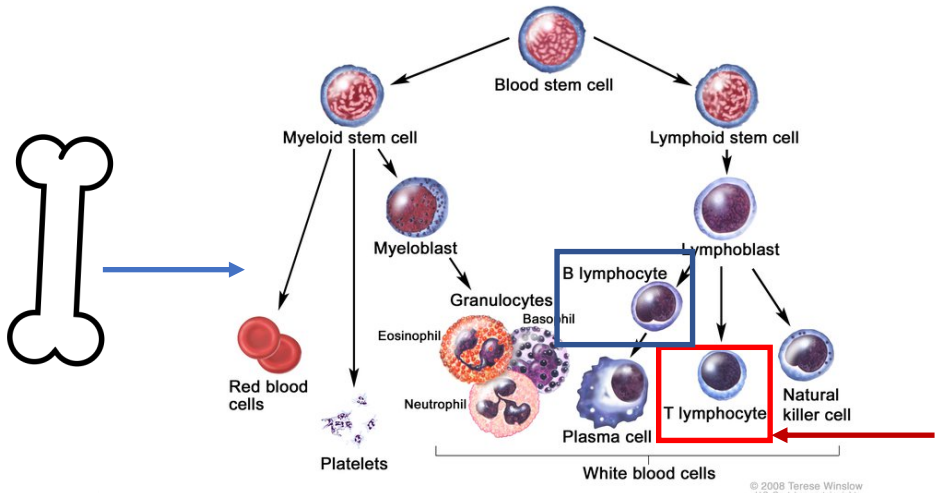
Learning Objectives

- 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

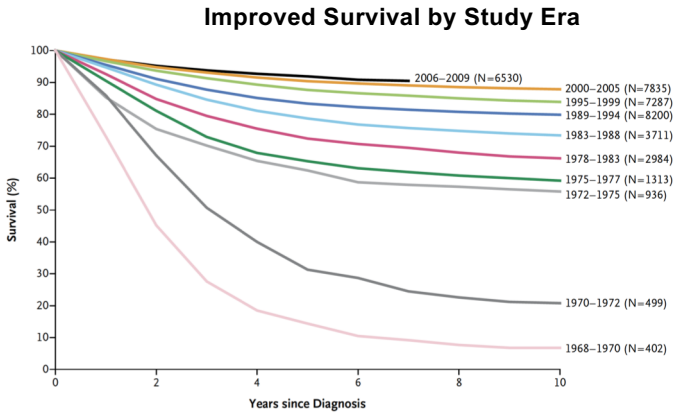
BMTinfonet.org 30 YEARS EMPOWERING PATIENTS
2023 SURVIVORSHIP SYMPOSIUM

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



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

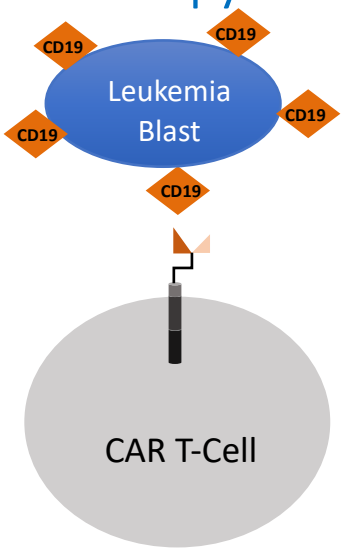
- Pediatric ALL patients receive chemotherapy for 2.5 years
- Adult ALL patients receive chemotherapy
- Bone marrow transplant may be indicated for high-risk patients after chemotherapy
- Newer immunotherapies moving more into upfront settings:
  - blinatumomab (Blincyto®) (targets CD19)
  - inotuzumab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

Approach to the Relapsed/Refractory Patient

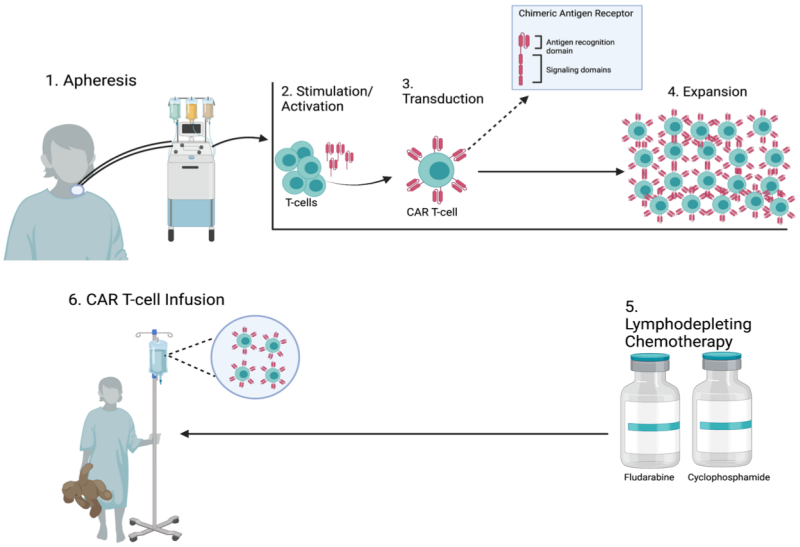
- Curative options for relapsed/refractory disease is a therapeutic challenge
  - Particularly poor outcomes for adults and adolescent young adult (AYA) population
- Toxicity from cumulative therapies limits treatment options
- Novel treatments are needed

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



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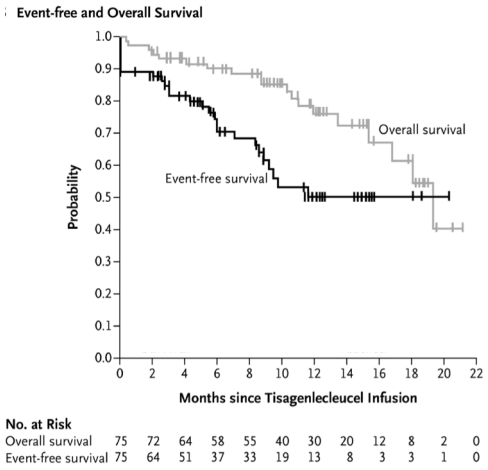
CAR T-cells in Leukemia

- 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

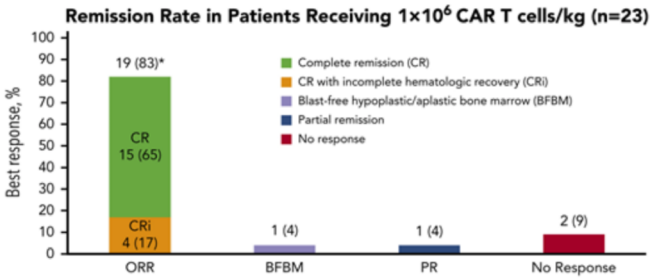
- Global Registration trial (25 centers participated)
- 75 patients were infused, with > 80% complete remission rates
- 12-month event free survival was 50%
- 12-month overall survival was 75%



Maude et al NEJM 2018

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



Shah et al J Blood 2021

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

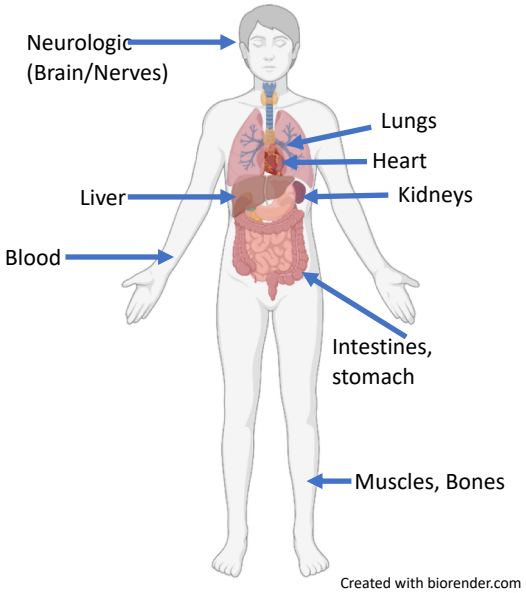
- While CAR T-cells are being manufactured (14-21 days) you may receive chemotherapy to:
  - keep leukemia disease controlled
  - decrease leukemia burden
- Recent studies have demonstrated that patients with higher disease burden before receiving CAR T-cells:
  - can have more severe side effects
 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



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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

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

Lee et al, Bio Blood Marrow Transplant 2018

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

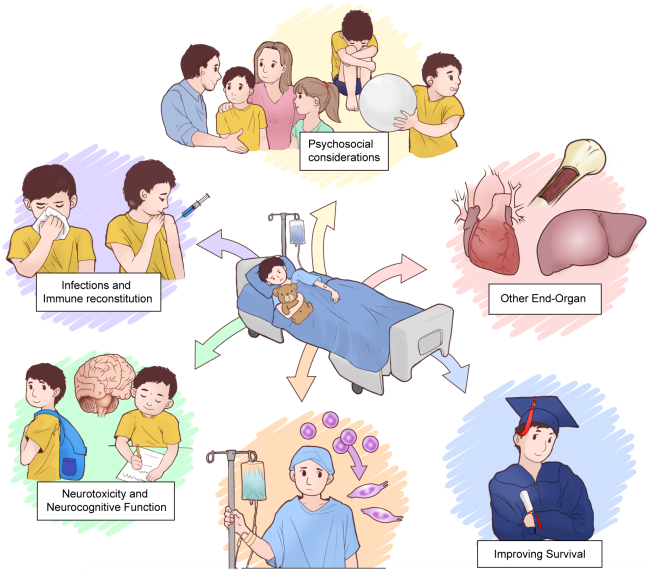
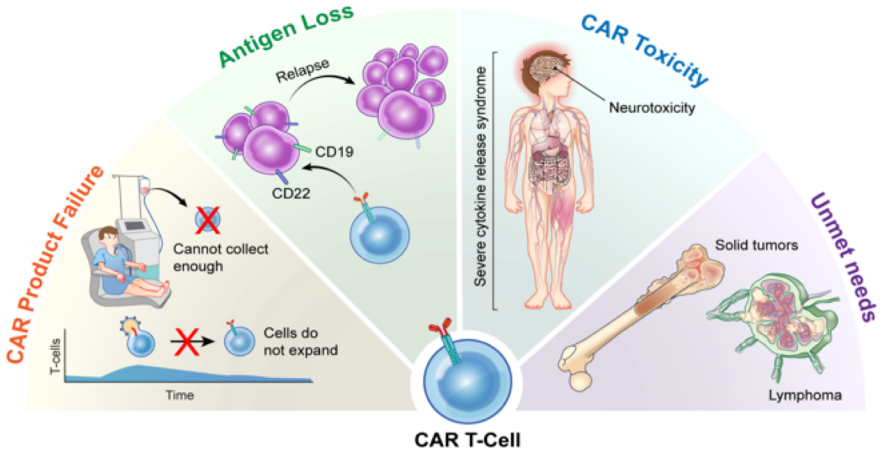


Image courtesy of NIH medical arts

Will CARs Be "THE" Answer?



Shah NN, et al. Nat Rev Clin Oncol 2019

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:
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QUESTIONS?

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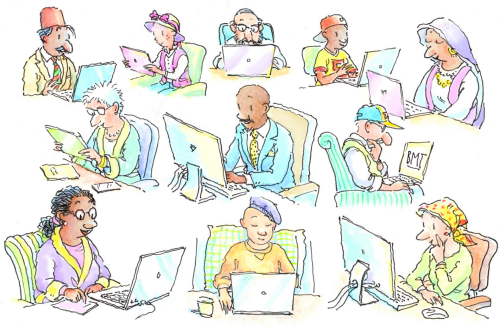
LET US KNOW HOW WE CAN HELP YOU



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