CAR T-cell Therapy Lymphoma: The Good, the Bad and the Exciting

Celebrating a Second Chance at Life Survivorship Symposium

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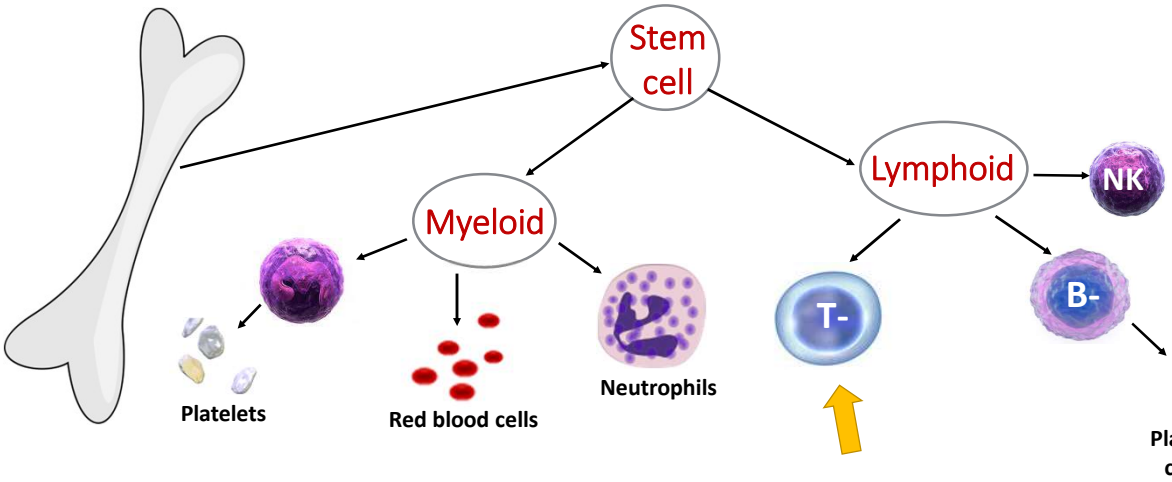
Learning Objectives

- Understand rationale for using CAR T-cell therapy in lymphoma
- Know the steps involved in undergoing CAR T-cell therapy
- Know the short-term side effects/toxicities of CAR T-cell therapy
- Know the impact on quality of life
- Understand the longer-term side effects and outcomes of CAR T-cell therapy

Hematopoiesis = blood cell growth



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Other Treatment: Autologous Stem Cell Transplant

- High dose chemotherapy is the treatment (i.e. BEAM, Melphalan)
- The major side effect of the chemotherapy: it eradicates the hematopoietic stem cells
  - Therefore, we must collect stem cells prior to the treatment
- *Correct term: High dose chemotherapy followed by stem cell rescue*
- What if you didn't respond to chemotherapy to begin with?
- What if you had a recurrence after autologous stem cell transplant?

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Other Treatment: Allogeneic Stem Cell Transplant

- We first eradicate immune system with "conditioning therapy". Depending on intensity of the conditioning, there is added anti-malignancy benefits. Then we infuse donor stem cells into the recipient (the patient)
- Allogeneic transplant = 25% mortality at one year
- What we want: graft vs malignancy (also known as graft vs leukemia or graft vs tumor). We want the donor's immune system to recognize the cancer as foreign/bad
- What we don't want: graft vs host disease (GVHD)
- What is the source of graft vs malignancy (and GVHD): T-cells!

Who gets CAR T-cell therapy?

- Available and approved by the FDA:
  - *Refractory acute lymphoblastic leukemia (ALL)*
  - *Multiple myeloma after 4+ of therapy*
  - Diffuse large B-cell lymphoma + other aggressive B-cell lymphomas not responding to first-line therapy (refractory) or relapse of disease within 1 year of first-line therapy = second line therapy
  - Diffuse large B-cell lymphoma + other aggressive B-cell lymphomas in patients who are refractory to 2+ prior lines of therapy
  - Follicular lymphoma after 2+ lines of therapy.
  - Mantle cell lymphoma after 2+ lines of therapy

Lymphoma CAR T-cell Therapies

- **YESCARTA® (axicabtagene ciloleucel or "axi-cel")**
  - Aggressive B-cell lymphomas, follicular lymphoma
- **KYMRIAH® (tisagenlecleucel or "tisa-cel")**
  - Aggressive B-cell lymphomas, follicular lymphoma
- **BREYANZI® (lisocabtagene maraleucel or "liso-cel")**
  - Aggressive B-cell lymphomas*
- **TECARTUS® (brexucabtagene autolecel or "brexu-cel")**
  - Mantle cell lymphoma

Why Get CAR T-cell Therapy?

- Recall:
  - What if you didn't respond to chemotherapy to begin with?
  - What if you had a recurrence after autologous stem cell transplant?
  - Allogeneic transplant = 25% mortality at one year
- In aggressive lymphomas (like DLBCL), an autologous stem cell transplant is not as effective as CAR T-cell therapy when the cancer has returned within 12 months of induction therapy.
- For follicular lymphoma, there are about 20% of patients who have a more active lymphoma, despite being called "indolent". Many times, the treatments become less effective or don't last as long.
- For mantle cell lymphoma, many times, the treatments become less effective or don't last as long.

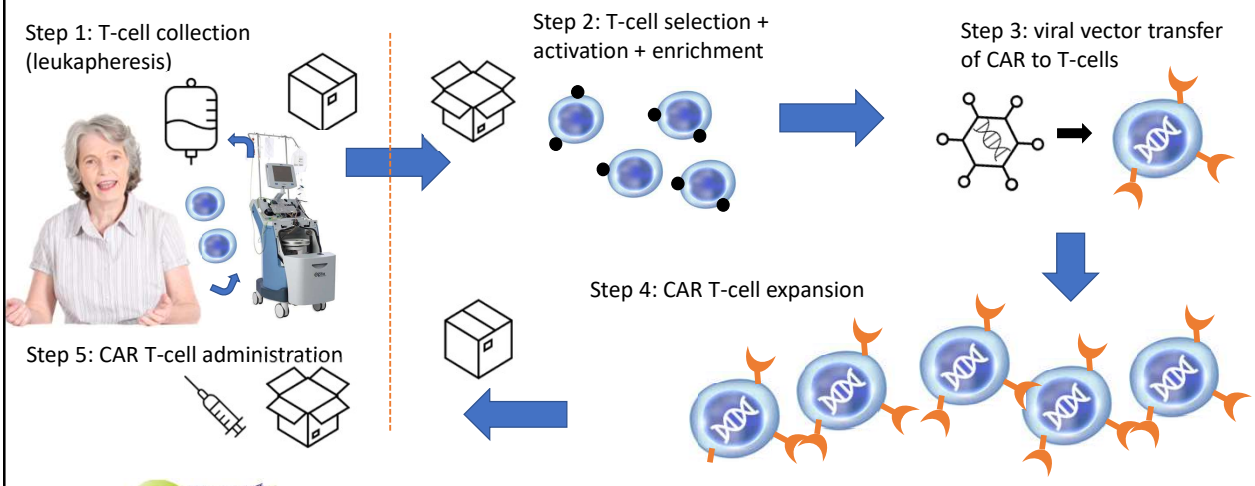
What is the Goal of CAR T-cell Therapy?

- Cure
- Success rate varies based on disease and prior therapies.
- Higher likelihood of longer-term disease-free survival:
  - If you have less disease before CAR T-cell therapy
  - If you a have a complete response by PET/CT scan at D+30
  - If recurrence hasn't occurred by 2 years

What is the Plan with CAR T-cell Therapy?

- **T-cells can't recognize the malignancy as "bad",** so let's **re-engineer some** so they know what they need to do: kill the cancer
- CAR = chimeric antigen receptor
  - All approved products for lymphoma are engineered to target CD19, a marker on B-cells
- **Current process for approved CAR T-cell therapies:**
  - Step 1: insurance approval and production request: 10-21 days
  - Step 2: T-cell collection -> growth: 14-42 days
  - Step 3: Low dose (lymphodepleting) chemotherapy: 2-3 days
  - Step 4: CAR T-cell infusion: 1 day
  - Step 5: monitoring for side effects/toxicities: 30 days

Steps to Make CAR T-cells



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While You Are Waiting

- 14 - 42 days for CAR T-cell manufacturing
- May need disease control. This is called bridging therapy
- Then, approximately 4-7 days prior to CAR T-cell infusion, lower dose (lymphodepleting) chemotherapy is necessary
  - Goal is to weaken the immune system in order to accept the CAR T-cells back into the body

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Days 0 - 30

- **CAR T-cell infusion (Day 0)**
  - inpatient versus outpatient
- **Close monitoring for side/effects and toxicities (Days 0 - 30)**
  - infection
  - cytokine release syndrome
  - neurotoxicity
  - if not in hospital, you will stay close to the treatment center

Days 0 – 30: Infection

- Caused by lymphodepleting chemotherapy
- Bacterial and/or fungal infection risk during neutropenia
  - Typically, this is Day 0 through Day 14
- You will be on an anti-viral, antibiotic, and anti-fungal agent
- But a fever might not be infection…

Day 0 – 30: Cytokine release syndrome (CRS)

- As T-cells expand in the body, they release cytokines, which are natural chemicals the immune system uses to communicate
- BIG 3 symptoms:
  - **Fever**
  - Low blood pressure (hypotension)
  - Shortness of breath (hypoxemia)
- Those with a higher tumor burden prior to CAR T-cell therapy have an increased risk of CRS
- Risk also depends on the CAR T-cells used (i.e. axi-cel, liso-cel)

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Day 0 – 30: Cytokine release syndrome (CRS)

- Will you get it? It depends, but likely you will.
  - Diffuse large B-cell lymphoma (DLBCL)/Follicular lymphoma: 20-80%
  - Mantle cell lymphoma: 80%
- CRS grade 1: fever only

- CRS grade 2: fever + low blood pressure and/or low oxygen saturation

- CRS grade 3-4: need blood pressure supporting medications and/or advanced breathing support

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Day 0 – 30: Cytokine release syndrome (CRS)

- Tends to begin on days 3 -5 and last for 5-10 days, but there is wide variability in if and when it presents, how severe it is, and how long it lasts
- Treatment: anti-cytokine therapy (i.e. tocilizumab) and steroids
- CRS is reversible
- There can be secondary effects:
  - low blood pressure can lead to kidney injury
  - steroids can increase the risk of infection
  - deconditioning

Day 0 - 30: Neurotoxicity (ICANS)

- Neurotoxicity is driven by the same process as CRS:
  - cytokines can cross the blood-brain barrier and lead to central nervous system side effects
- ICANS = immune effector cell-associated neurotoxicity syndrome
- Broad signs/symptoms: tremors, forgetfulness, difficulty with comprehension, seizures
- You will get frequent and standardized assessments to monitor for changes

Day 0 - 30: Neurotoxicity (ICANS)

- Will you get it? It depends…
  - Diffuse large B-cell lymphoma (DLBCL): 30-60%
  - Follicular lymphoma: 20-60%
  - Mantle cell lymphoma: 80%

Other Toxicities: Financial

- Cost of the cell product: $400,000 - 500,000
- Cost of the supportive care: > $1,000,000
- Commercial insurance – less of an issue
- Medicare – reimbursement for cost of care is convoluted
- Medicaid – state specific, but generally inconsistent and inadequate reimbursement

Day 30 – 90: Intermediate Term – "Brain Fog"

- Underreported – but mainly this affects concentration, short term memory
- Advised not to drive for 2 months after infusion
- In patients with this "brain fog", returning to work has been difficult
- A newer understanding of a "peripheral" communication between cytokines and the immune cells that cross over the blood-brain barrier
- This tends to resolve

Source: Joly et al, J Natl Cancer Inst 2020.

Day 30+: Late Effects – Low Blood Counts

- "Real world data" demonstrate nearly 30% of patients have prolonged cytopenia (low blood counts)
- *Maybe* with CAR T-cell persistence
- Resolves over time

Day 30+: Late Effects – Infection

- "**Prolonged infection risk**
  - Unique to CD19-directed CAR T-cell therapies
  - CD19 is also located on memory B-cells
  - Lack of memory B-cells weakens the immune system to fight infection
  - *May be* associated with the persistence of CAR T-cells after therapy

Day 30+: Late Effects – Prevent Infection

- **Shingles (VZV):** continue on an anti-viral through at least 12 months post-CAR T-cell therapy
- **Pneumocystis pneumonia (PJP):** continue on antibiotic through at least 12 months post-CAR T-cell therapy
- **Low immunoglobulins (IgG)** = hypogammaglobulinemia
  - Increases risk of respiratory viral infections
  - IVIG can be administered
- **Decreased neutrophil count** = neutropenia
  - G-CSF can be administered

Day 30+: Vaccinations

- COVID re-vaccination(s) is advised
- All other vaccinations: institution-specific
- If re-vaccination is advised, the immune system may be too compromised early after the treatment to adequately mount a response for immunization

Day 30+: Other Late Effects

- **Second Malignancies**
  - To date, most patients have required multiple lines of chemotherapy prior to CAR T-cell therapy
  - 7% risk of skin cancers (non-melanoma)
  - 5% risk of myelodysplastic syndrome (MDS)
- **Neurologic**
  - Rare, and not clear if reported events are truly associated with therapy
  - In a small number of patients, neurotoxicity from initial therapy has reported to last months

Quality of Life

- **Like many therapies, there will be a short-term impact on your quality of life**
  - Hospitalizations and/or daily clinic visits
  - Blood product transfusions
  - Infections and infection risk reduction
  - Toxicity (i.e. CRS and/or neurotoxicity
- **Intermediate/longer term**
  - Infections and infection risk
  - Psychosocial
  - Neurological

Decreasing the Side Effects

- Decreasing both the short term and the late side effects is important
  - Outpatient versus inpatient
  - Prophylactic steroids on Days 0-2 of CAR T-cell therapy
    - Has been shown to reduce severity of CRS/ICANS in lymphoma
  - Education
  - Clinical trials

Where is the CAR Driving to Next?

- **Almost there…**
  - Chronic lymphocytic leukemia/Small lymphocytic leukemia (CLL/SLL)
  - Hodgkin lymphoma
  - ”Solid” tumors: glioblastoma, hepatocellular carcinoma, prostate cancer
- **Lost the CAR keys…*(we still have a way to go):***
  - Myelodysplastic syndrome (MDS)
  - Acute Myeloid Leukemia (AML)
  - Other myeloid diseases (i.e. myelofibrosis)
  - Other “solid” tumors

The Future: When CARs Fly…

- Within-patient CAR T cell expansion
- CAR NK cell therapy
- CAR monocyte therapy
- Newer CAR T or NK cell cancer targets
- ”off-the-shelf” (allogeneic) CAR T-cell or NK-cell therapy
- Gene re-engineering to remove the unnecessary drivers of toxicity

Not So Fast: "Solid" Tumors and CAR T-cell Therapy

- Some targets for CAR T-cell therapy may not be unique to a cancer cell, these are termed "off-target" effects.
- Different diseases have different supporting cells that allow it to grow. This is called the tumor microenvironment and is unfriendly to immune cells.
- The CAR T-cells need to survive the environment while also not getting exhausted in the process.
- Need the right target, need the environment more welcoming, and need the T-cells to stick around and not get tired.

Thanks!

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QUESTIONS?

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