CAR T-Cell Therapy: The Good, the Bad and the Long Term

Celebrating a Second Chance at Life Survivorship Symposium

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CAR T-Cell Therapy: the good, the bad, and the long term

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Learning Objectives

- Share what CAR T-cell therapy is and why it's used
- Explain the short term side effects/toxicities of CAR T-cell therapy
- Understand the longer term side effects of CAR T-cell therapy

Hematopoiesis  *blood cell growth*

- Stem cell
  - Myeloid
    - Platelets
    - Red blood cells
    - Neutrophils
  - Lymphoid
    - NK cells
    - T-cells
    - B-cells
    - Plasma cells
Autologous Stem Cell Transplant

- High dose chemotherapy is the treatment (i.e. BEAM, Melphalan)
- Major side effect of the chemotherapy: 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?

Allogeneic Stem Cell Transplant

- First, we eradicate immune system with “conditioning therapy”. Depending on intensity of the conditioning, there is added anti-malignancy benefits
- 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).
  - Currently used to achieve disease control, then proceed to allogeneic stem cell transplant
- 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.
- Multiple myeloma after 4+ of therapy.

Who gets CAR T-cell therapy?

In April 2022:
- Diffuse large B-cell lymphoma as second line therapy
  - For patients who have relapsed within 1 year of initial therapy or are refractory to first line therapy.
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 key…(we have a way to go):
  - Myelodysplastic syndrome (MDS)
  - Acute Myeloid Leukemia (AML)
  - Other myeloid disease (i.e. myelofibrosis)
  - Other "solid" tumors

So What is CAR T-cell Therapy?

- T-cells can’t recognize the malignancy as "bad", so let's re-engineer some so they know what they needs to do: **kill the cancer**

- Current process:
  - Step 1: insurance approval and production request: 10-21 days
  - Step 2: T-cell collection - > growth: 14-21 days
  - Step 3: low dose chemotherapy followed by CAR T-cell infusion: 5-7 days
  - Step 4: monitoring for side effects/toxicities: 28 days
What is CAR T-cell Therapy?

- Step 1: T-cell collection (leukapheresis)
- Step 2: T-cell selection + activation + enrichment
- Step 3: viral vector transfer of CAR to T-cells
- Step 4: CAR T-cell expansion
- Step 5: CAR T-cell administration

While waiting for CAR T…

- 14 - 21 days for CAR T-cell manufacturing
- Disease control = bridging therapy
- Then, approximately 5 days prior to CAR T-cell infusion, lower dose chemotherapy is necessary
  - Need to weaken the immune system in order to accept the CAR T-cells back into the body
  - Called lymphodepleting chemotherapy
**Days 0 - 28**

- **CAR T-cell infusion (Day 0)**
  - inpatient versus outpatient
- **Close monitoring for side/effects and toxicities (Days 0 - 28)**
  - infection
  - cytokine release syndrome
  - neurotoxicity
  - if not in hospital, you will stay close to the treatment center

**Day 0 – 28: 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
- After neutrophils recover, you will continue on an anti-viral medication
**Day 0 – 28: 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 cell product used (i.e. axi-cel, cilta-cel).

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**Day 0 – 28: Cytokine release syndrome (CRS)**

- Will you get it? It depends, but likely yes.
  - Acute lymphoblastic leukemia (ALL): 80-90%
  - Diffuse large B-cell lymphoma (DLBCL)/Follicular lymphoma: 40-80%
  - Mantle cell lymphoma: 80%
  - Multiple myeloma: 80-90%*
- **CRS grade 1:** fever only
- **CRS grade 2:** fever + low blood pressure and/or low oxygen saturation
- **CRS grade 3-4:** need blood pressure medications and/or advanced breathing support.
Day 0 – 28: Cytokine release syndrome (CRS)

- Tends to begin on days 3-5 and last for 5-10 days
- 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 - 28: Neurotoxicity (ICANS)

- Neurotoxicity is driven by the same process as CRS: cytokines
  - Cross the blood-brain barrier and can 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 standardized and frequent assessments
Day 0 - 28: Neurotoxicity

- Will you get it?
- It depends…
  - Acute lymphoblastic leukemia (ALL): 60-80%
  - Diffuse large B-cell lymphoma (DLBCL): 30-60%
  - Mantle cell lymphoma: 80%
  - Multiple myeloma: rare, can see Parkinsonian-like symptoms rarely

Day 0 - 28: Neurotoxicity

- Tends to begin on days 6 – 9
- Tends to last 11-20 days (about 3-4 days for patients with multiple myeloma)
- There is a wide variability of if/when it presents, how severe it is, and how long it lasts
- Treatment: steroids
- Neurotoxicity is almost always reversible
- There can be secondary effects: deconditioning
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
  - In Colorado, “covered” but not reimbursed

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
- Resolves!

Day 30+: Late Effects – Blood Counts

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

Day 30+: Late Effects – Risk of 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 in order to fight infection
  - 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
  - Also see this in BCMA-directed CAR T-cell therapy patients
- 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 for the first year 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


Decreasing Toxicity

- Decreasing both the short term and the late side effects, is important
- Available options:
  - Outpatient versus inpatient
  - Prophylactic steroids on Days 0-2 of CAR T-cell therapy
    - Has been shown to reduce severity of CRS in lymphoma
  - Clinical trials
The Future: When CARs Fly…

- Internal CAR T-cell production
- CAR NK cell therapy
- CAR monocyte therapy
- Other 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

“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 get 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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