CAR T-Cell and Other Immunotherapies

Celebrating a Second Chance at Life Survivorship Symposium

July 11-17, 2020

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Celebrating a Second Chance at Life

The Growing Role of CAR T-Cell Therapy

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July 15, 2020
Outline

• Overview of the Immune System
• How the Immune System Fights Cancer
• What is a CAR T-cell?
• Overview of the CAR T-cell Patient Journey
• What happens after CAR T-cells?
  – Side Effects
  – Follow-up/Expectations
• CAR T-cell Trials
Overview of the Immune System
Immune System Basics

Our Immune System is Important

1. Fights off infections (bacteria, parasites, viruses, fungus) and learns from it
2. Helps survey for things that shouldn’t be there, ie. are not “self”
3. Recognizes when “self” may have gone awry, ie. cancer
4. Fights cancer if it is recognized

White Blood Cells
Innate vs Adaptive Immune Response

- The innate immune system helps to recognize foreign invaders and immediately kills them.
- The adaptive immune system is highly targeted but takes time to learn what is good and bad.
- Once the adaptive immune system learns, it can remember what it has seen for the rest of your life.

Adaptive Immune System

- Neutrophil
- Eosinophil
- Basophil
- Monocyte
- T Cell
- B Cell
- Natural killer
- Macrophage
How the Immune System Kills Cancer
Working Together The Innate and Adaptive Immune System Fight Cancer

How the Immune System Fights Cancer

1. Tumor recognition
2. Activation of immune system
3. Destruction of tumor cells

Lymph Node

Tumor

White Blood Cell (T-cell)

Tumor Cell

Courtesy: Juan Carlos Varela
T-cells: The Generals of the Immune System

T-cells Oversee the Immune Response

• T-cells are part of the adaptive immune response
• They talk to the innate immune cells and learn when there are danger signals
• Recognize foreign invaders or abnormal “self” (cancer) and kill off infected/abnormal cells
• When they go awry can cause autoimmune disease or graft vs host disease
How Cancer Evades the Immune System

- Cancer can hide the signals that say it shouldn’t be there.
- Cancer can prevent the immune system from activating.
- Cancer can resist killing by the immune system.
What happens when the immune system doesn’t recognize cancer as bad?

• We have options!
  – Cancer immunotherapies (immune checkpoint blockade, vaccines, etc.)
  – Bone marrow transplant using someone else’s immune system (cell therapy)
  – Re-program the immune system to target what it can't/won’t see (gene therapy)
    • Viruses (adenovirus, lentivirus, retrovirus)
    • Gene editing (CRISPR, TALENs, ZFNs)
    • Transposon systems (ancient viruses hoping around our genome)
    • Temporary expression of new genes
What Are CAR T-Cells?

- **Immunotherapy**: A type of cancer treatment that helps your immune system fight cancer
- **Gene Therapy**: A type of treatment that uses genetic engineering to reprogram cells to do what we want them to
  - CAR = Chimeric Antigen Receptor
- **Cellular Therapy**: A type of cancer therapy that uses a specific kind of immune cells to fight cancer
  - CAR-T = T-cells
What are CAR-T Cells?

Outside (cancer)

Inside (T-cell)

How a CAR-T cell sees

How a CAR-T knows what to do

What are CAR-T Cells?
Approved CAR T-cells

1. Pediatric and young Adult B-ALL
2. Relapsed/refractory diffuse large B-Cell lymphoma

1. Relapsed/refractory diffuse large B-Cell lymphoma
CAR T-Cell Responses - Systemic

Pre-Treatment

Day 30
CAR T-Cells have shown efficacy in SECONDARY CNS lymphoma however are not approved for PRIMARAY CNS lymphoma. Clinical trials are underway.
Cancer Gene Therapy?

What's the deal with this leukemia trial? *Gotta wait and see. Helping the immune system attack tumors has been a longtime research target. Lots of promising leads, often they don't pan out.*

What'd these guys do? They took some of the patient's T-cells and patched their genes so they'd attack the cancer. That hasn't been enough in the past, but their patch also added code to get the T-cells to replicate wildly and persist in the body.

Which worked, but created its own set of problems? How'd you guess? But I think the craziest part is the way they insert the patched genes. How? Well, think—what specializes in invading and modifying T-cells? ...Seriously?

Yup. Must've been a fun conversation.

Ok, so I have blood cells growing out of control, so you're going to give me different blood cells that also grow out of control? Yes, but it's ok, because we've treated this blood with HIV! Are you sure you're a doctor? Almost definitely.
Overview of the CAR T-Cell Patient Journey
Overview of CAR T-Cell Therapy

Clinical Care – Patient Perspective

Manufacturing – Product Preparation

1. Leukapheresis
2. T-cell activation/transduction*
3. Modified T-cell expansion*
4. Chemotherapy
5. Modified T-cell infusion

* Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

Courtesy of Marcela Maus
Leukapheresis

- Process by which we separate the immune cells (T-cells) from a patient's blood
What happens with T-Cell Manufacturing?

- Your cells may be further purified
- Your T cells are activated so they start to grow
- The cells are “transduced” to insert the new genetic material into the cells.
- The “transduced cells” start to divide rapidly carrying the new genetic material with them
- The cells are again purified and undergo extensive testing
Lymphodepletion (Low dose chemotherapy)

- Now that we’ve made a new sports car it’s time to clear the highways.
- Lymphodepleting chemotherapy (usually cyclophosphamide and fludarabine) primes your body to receive the CAR T-cells.
- It “depletes” the immune cells in your body as to create more “space” for the CAR T-cells to survive and expand within your body.
- Once infused the CAR T-cells can grow >1,000x inside your body in order to fight the cancer.
- In most cases this involved 3 days of chemotherapy followed by 48 hours of rest before your CAR T-cell infusion.
- The symptoms of your chemotherapy should be mild as these are lower dosages than you have likely received in the past.
- This can be done as an inpatient or outpatient.
CAR T-Cell Infusion

- Your CAR T-cells are usually frozen for transport and are thawed at the treating center.
- They are typically infused via a central line and can be in a bag or a vial.
- Infusions usually take less than 30 minutes.
- CAR T-cell infusions can occur as an inpatient or an outpatient.
WHAT HAPPENS AFTER CAR T-CELL INFUSION?
Cytokine Release Syndrome (CRS)

- Typical onset 2-3 days, typical duration 7-8 days
- Can range in severity from low-grade constitutional symptoms to a high-grade syndrome associated with life-threatening multiorgan system failure.
- On a spectrum of excessive immune system activation and sometimes can be fatal.
- You do not need to have CRS in order to have a response from CAR T-cells.
- Largely driven by proteins in the blood called “cytokines” that are secreted and activate other parts of the immune system.
- The most important cytokine may be IL-6, and we therefore treat patients with a drug that blocks IL-6 called tocilizumab.
Neurotoxicity

- Typical onset 4-6 days, typical duration 14-17
- Toxic “encephalopathy” with symptoms of confusion and delirium, with occasional seizures and even rarer swelling in the brain.
- Some patients may just have headaches. Others may have difficulty speaking and even may enter a coma.
- Some patients need to be put on a ventilator to help them breathe.
- Usually all of these symptoms are reversible.
- This is mainly treated with STEROIDS.
- We do not currently believe that steroids decrease the likelihood of having a response from your CAR-T cells.
Long-Term Side Effects

- **B-Cell Aplasia**
  - Because CD19 is expressed on bad and good B-Cells, the CAR T-cells will get rid of your normal B-Cells
- **Hypogammaglobulinemia**
  - B-cells usually make antibodies (like IgG) and therefore without them you may have low IgG levels
  - This can be treated by giving infusions of IVIG
- **Cytopenias**
  - Some patients also may have prolonged low blood counts from the chemotherapy and side effects of CAR T-cell therapy.
  - Your doctor will monitor these counts
- Because this is a new therapy the FDA requires patients to be followed for upwards of 15 years through a group called the CIBMTR.

Tasian et al. Therapeutic Advances in Hematology, 2015
Expectations after CAR T-Cell Therapy

- After discharge you will be followed as an outpatient.
- You are required to stay within 2 hours of the treating center for at least 30 days following your CAR T-cell treatment.
- You will have blood work and exams performed to determine how well the therapy worked.
- You may have repeat imaging and/or biopsies performed to re-stage your disease.
- You will require medications to prevent infections for 6-12 months.
- You may need blood transfusions and other medications to help your weakened immune system.
Expectations after CAR T-Cell Therapy

- Patients can expect to go back to work/school approx. 1-3 months after their CAR-T cell therapy.

- You may experience fatigue following CAR T-cell therapy which should improve within 3-6 months.

- There are newer CAR T-cell therapies being studied in case the first CAR T-cell therapy does not work. There are also studies looking at combining special medications with CAR T-cells to improve how they work.

- Some patients who received CAR T-cells are now alive and cancer free almost 10 years from their initial treatment.
How Do CAR T-Cells Compare to Transplant?

- The process for CAR T-cell therapy is very similar to an autologous stem cell transplant (transplant using your own cells).
- The side effects differ in that in addition to the side effects from chemotherapy, the CAR T-cells can cause cytokine release syndrome and neurotoxicity.
- Unlike allogeneic stem cell transplants (transplants using donor cells), CAR T-cells do not require long-term immunosuppression, and current versions do not have the risk of graft-vs-host-disease.
- CAR T-cells can be given before or after a patient has had a bone marrow transplant.
- Patients may have a bone marrow transplant after CAR T-cell therapy.
CAR T-Cell Therapy with COVID-19

- You may need to have COVID testing done before your chemotherapy and CAR T-cell infusion
- You may need to be tested for COVID if you have a fever
- You may not be able to have visitors with you in the hospital during your treatment
- You may not be able to bring visitors with you to appointments
- We may try to make as many visits virtual
- You should avoid crowded/public spaces and avoid people with symptoms before, during and after your treatment because of your weakened immune system

Tasian et al. Therapeutic Advances in Hematology, 2015
CAR-T CELL TRIALS
CAR-T Trials across the United States

Total Trials by date:
- 400 – 06/24/20
- 349 – 01/17/19
- 317 – 09/26/18
- 220 – 08/27/17
- 183 – 04/13/17
- 123 – 05/19/16
- 88 – 12/10/15
- 77 – 09/2015
- <5 – 2010

Map as of 09/26/18

Search term: “chimeric antigen receptor”

Jason Carter Clinical Trials Program
Clinicaltrials.gov
Future CAR T-Cells Coming Soon

- Mantle cell lymphoma
- Adult B-ALL
- Multiple Myeloma

- Other types of cell therapies:
  - Solid tumors such as melanoma

Before Cell Therapy

After Cell Therapy

AACR April 2015; Adaptimmune
Questions?

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