CAR-T Therapy in 2019

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I have no financial disclosures.
CAR-T therapy: Summary

• Introduction.
• CAR-T / Immunology Primer.
• Indications for CAR-T.
• CAR-T Clinical Care. Outcomes. Toxicities.
• Regulatory Aspects: FDA standards. FACT standards.
• CAR-T logistics: Costs, Regulations.
On August 30th, 2017, the FDA approved Kymriah® for treatment of pre-B cell ALL, the 1st FDA approved cellular therapy product

How will this impact our patients, our medical centers, our state.
Cell Therapy: Scope

Much more than just CAR-T cells

Immune Effector Cells

- Derived from Blood or Marrow
  - CAR-T (Chimeric Antigen Receptor T-cells)
  - Dendritic Cells, NK Cells
  - Tumor Vaccines
  - Mesenchymal Cells (MSC)

Tissue Engineered Products

- Tissue / Organ Derived
  - Inducible Pluripotent Stem Cells
  - Embryonal Stem Cells
  - Neural stem cells
  - Adipose derived stem cells
  - Organogenesis. Osteogenesis.
Changing landscape: Scientific Growth


Over 1000+ clinical trials for Cellular Therapy now listed in ClinTrials.gov
Part 1. Hematology and Immunology Primer

Bone Marrow

White Blood Cells

- **L** Lymphocytes: Immune surveillance, Antibody production
- **N** Neutrophils (ANC) Front line defense for infections. Phagocytize (“Pac Man” effect)
- **M** Monocytes: Phagocyte. Seed tissues (“Macrophages”).
- **E** Eosinophils: Phagocyte
- **B** Basophils: Produce histamine

Platelets

Red Blood Cells
Hematology and Immunology Primer

Bone Marrow

White Blood Cells

- Lymphocytes:
  - Born in the Marrow.
  - Go to school in:
    - Thymus (T-cells)
    - Lymph nodes (B-cells)

Platelets

Red Blood Cells

Lymphocytes
- B-cells
- T-cells
- NK cells
Hematology and Immunology Primer

Bone Marrow

White Blood Cells

- L
- N
- M
- B
- E

Platelets

Red Blood Cells

Acute Leukemia

ALL

AML
Hematology and Immunology Primer

Production

Bone marrow

B-cell leukemia
T-cell leukemia

Maturation

Lymph nodes / Thymus

B-cell lymphoma
T-cell lymphoma
Part 2. Hematology and Immunology Primer

- T-cells and Macrophages: “Two Dance partners”

Macrophages activate T-cells.

- TCR = T-cell receptor
- HLA = Human Leukocyte antigen (Our tissue typing genes)

Foreign protein (i.e. Bacteria)

Cytokines: Inflammatory Proteins
- A wave of Cytokines comes out from T-cells.
- Cause Fevers, Shakes, Chills, Headaches, High/Low BP
- Sends signals to other parts of the Immune System.
Part 2. What are CAR-T cells? Re-programming

Viral insertion process:

Step 1: A gene to make a specific receptor is packaged into a virus.
Step 2: The retrovirus is inserted into the T-cell, carrying the new gene with it.
Step 3: The T-cell makes new receptors.

TCR = T-cell receptor
HLA = Human Leukocyte antigen (Our tissue typing genes)

Cytokine release syndrome: Major side effect of CAR-T
Chimeric Antigen Receptor T-cell (CAR-T)

• T-cells: “Self Recognition Cells”
• CAR-T: Genetically Modified T-cells.
• 3 Basic Tenets:
  a. Tumors express a specific antigen.
  b. That antigen is not on normal tissue.
  c. A pre-defined gene can be inserted into a T-cell (...correctly).
There are two commercial CAR-T. What are they?

- Current commercial CAR-T (Kymriah and Yescarta) target CD19+ cells.
- CD-19: Cell surface protein on B-cells (normal and malignant).

B-ALL: B-cell Leukemia

DLBCL: B-cell Lymphoma

B-cells

Normal B-cell

Eradicates normal B-cells
CAR-T product design: Everyone is different.

**Targeting site.** Depends upon the cancer. Targets a specific protein (antigen) on a cancer cell.

**T-cell stimulating regions.** Variable. Are often product specific.

**CAR: Modular Design**

- Targeting Element (scFv)
- Spacer
- Transmembrane Domain
- Co-stimulatory Domain (e.g. CD28 or 4-1BB)
- Signaling Domain CD3z
Evolution of CAR-T cells: 2011 to present

First generation
- \( V_H \) and \( V_L \)
- CD3ζ

Second generation
- \( V_H \) and \( V_L \)
- 4-1BB
- CD3ζ

Third generation
- \( V_H \) and \( V_L \)
- CD28
- 4-1BB
- CD3ζ

FDA approved indications
CAR-T
CAR-T therapy: Current FDA approved indications

- **B-cell leukemia in children (tisagenlecleucel / Kymriah®).** FDA criteria:
  Patients up to 25 years of age.
  B-cell ALL that is refractory to front-line therapy (failed two induction attempts)
  B-cell ALL that is in second or later relapse.

- **B-cell lymphoma in adults (axicabtagene/ Yescarta®).** FDA criteria:
  Age ≥ 18 years. No upper age limit.
  Relapsed or refractory disease: Defined as failure to 2 or more lines of therapy
  Includes: Diffuse large B-cell lymphoma (DLBCL),
  Primary mediastinal large B-cell lymphoma.
  DLBCL arising from follicular lymphoma.
  Excluded if primary central nervous system (CNS) lymphoma.
Tip of the Cell Therapy Iceberg

Tissue Regeneration
Gene editing

ALL
Large Cell Lymphoma
Follicular Lymphoma 2020
Multiple Myeloma 2020
Solid Tumors 2020+
Tip of the Cell Therapy Iceberg

Active Clinical Trials
- CNS disorders: Neural stem cells
- Cardiac injury: mesenchymal stem cell
- Retinal epithelial cells
- Osteogenesis
- Cartilage cell transplants

ALL
Large Cell Lymphoma
Follicular Lymphoma 2020
Multiple Myeloma 2020
Solid Tumors 2020+
CAR-T trials: Where are we now

**Cell Therapy**

- **Precision Medicine**
  - Tumor specific targets

- **Adult Cancer**
  - Lung, Pancreatic, Sarcomas,

- **Pediatric Cancers**
  - Brain Tumors, Neuroblastoma

- **Follicular Lymphoma**

- **Multiple Myeloma**

**Acute Lymphoblastic Leukemia**
- #1 leukemia in children.
- FDA approved (Aug 2017)

**Diffuse Large Cell Lymphoma**
- #1 lymphoma in adults.
- FDA approved (Oct 2017)

**Acute Myelogenous Leukemia**
- #1 leukemia in adults.
- Under development

**Nationally**

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CAR-T clinical care
CAR-T Process: Overview

**Apheresis**
- T-Cell Collection
- Unmobilized

**Relapse**

**Manufacture**
- CAR-T product
- 28 day process – Steps:
  a. Expand T-cells.
  b. Transduction (vector).
  c. Product Quality Control

**Re-induction**

**CAR-T admission (General)**
- LD Chemo: 3-4 days
- Goal:
  - Decrease Tumor Load
  - Decrease # normal T-cells

**Infusion**
- Monitor 14D after infusion minimum.
CAR-T Clinical Care: Supportive Care

• **Antimicrobial prophylaxis:**
  - High Risk of Viral, Fungal, Bacterial Infections.
  - Strict antimicrobial regimen required during and after therapy.
  - Immunization (memory B-cells) eradicated.

• **Impact of B-cell aplasia:**
  - Intravenous Immune Globulin (IVIG) replacement.
  - IVIG given monthly post-CAR-T therapy. Cost $10K/infusion.
CAR-T Clinical Care:
Cytokine Release Syndrome (CRS)

- Median Onset 3-5 days
- IL-6
- Tociluzimab
- Fevers
- Hypotension
- Hypoxia
- Edema
- Myalgias
- Chills
- Rashes
Clinical Care: CAR-T Neurotoxicity

- Confusion
- Seizures
- Tremors
- Loss of Consciousness
- Aphasia
- Headaches
- Stroke

Neurotoxicity
CAR-T therapy: Toxicities

Acute Toxicities
- Cytokine Release Syndrome (CRS)
- Neurologic Risks
- Cytopenia (low blood counts)
- Infectious Risks

Chronic Toxicities
- Chronic Immuno-deficiency (B-cell Aplasia)
- Off-Target effects
Potential Long Term Toxicities

FDA requirement: All CAR-T cell recipients should be followed for a minimum of 15 years post-infusion

- We do not yet know the long term effects of CAR-T therapy.
- We do not yet know possible latent effects of from the virus used to transduce (create) the CAR-T cells.
- Risk of insertional mutagenesis (inserting a gene in a “wrong place” in your genome) and risk of secondary cancers.
CAR-T therapy outcomes

Acute lymphoblastic Leukemia
Diffuse Large Cell Lymphomas
Acute lymphoblastic leukemia and Diffuse Large B-Cell Lymphoma

**Acute Lymphoblastic Leukemia (ALL):**
- #1 malignancy of childhood. 3000 cases/year in children.
- Tisagenlecleucel (Kymriah®): 83% complete remission rate in ALL.

**Diffuse large B-cell lymphoma (DLBCL):**
- 4% of US cancers. 72,000 new cases annually, 823 in Michigan.
- Axicabtagene (Yescarta®): 51% complete remission rate in DLBCL.
CAR-T cells in Acute Lymphoblastic Leukemia

Maude S, NEJM 2018

Overall Survival 90% at 6 months post-therapy

73% Event Free Survival (EFS) at 6-months
CAR-T cells in Acute Lymphoblastic Leukemia

Maude S, NEJM 2018

Duration of Remission

No. of patients, 61
No. of events, 17
Median duration of remission, not reached
**CAR-T Toxicity: High Risk in Leukemia**

### Licensing Trial

<table>
<thead>
<tr>
<th>AEs of Special Interest</th>
<th>ELIANA (B2202)(^1)</th>
<th>ENSIGN (B2205J)(^2)</th>
<th>Pedi-CART (CHP-959)(^3)</th>
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<tbody>
<tr>
<td><strong>Cytokine release syndrome (CRS)</strong></td>
<td>N = 68</td>
<td>N = 29</td>
<td>N = 59</td>
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<tr>
<td></td>
<td>78%</td>
<td>90%</td>
<td>88%</td>
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<td><strong>ICU admission</strong></td>
<td>46%</td>
<td>46%</td>
<td>NR</td>
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<td><strong>Anti-cytokine therapy</strong></td>
<td>38%</td>
<td>27%</td>
<td>27%</td>
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<tr>
<td><strong>Cytopenias not resolved by day 28</strong></td>
<td>37%</td>
<td>31%</td>
<td>NR</td>
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<tr>
<td><strong>Infections</strong></td>
<td>43%</td>
<td>48%</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Neurological toxicities</strong></td>
<td>44%</td>
<td>31%</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Tumor lysis syndrome</strong></td>
<td>4%</td>
<td>NR</td>
<td>NR</td>
</tr>
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</table>

CAR-T cells in Large Cell Lymphoma

Neelapu, NEJM 2017

N = 111 patients

Overall Survival

Months
CAR-T therapy: Logistics and Costs
Building a Clinical CAR-T Program: Components

Order Process

- Pharmacy
- Social work
- Medical Team
- Contract Office
- Insurers / Payers
- Finance
- Education certification
- Practice Guidelines
Cell Therapy: It’s a sea of icebergs

- Complexity of Technology
- Promote Cost Efficiency
- Ensure Patient Access
- Regulatory Standards
Cell Therapy: Regulatory Standards

**Food and Drug Administration**
- Oversees product manufacturing
- Established Risk Evaluation and Mitigation Strategies (REMS) program to deliver product.

**REMS:**
- Mandatory education program.
- Mandates 15 year patient follow-up.
- REMS: Not comprehensive.
- Does **not** ensure quality of care.

**FAC-T (Voluntary)**
- Establishes a Bench-Mark for Excellence in Care.
- Given complexity of therapy, mandatory FAC-T accreditation is being considered by insurers, state legislatures.
Cell Therapy: Regulatory Standards

The Impact of “FACT” standards.

• Foundation for Accreditation of Cellular Therapy (FACT)
• FACT standards established in 1997 for Hematopoietic Stem Cell products.
• Goal: To ensure quality for a service. FACT does not examine cost or access.
• In 2017: FACT standards extended to Immune Cell Therapy Products.
• By 2020’s: Expansion of regulations to Regenerative Medicine Products.
• FAC-T is a voluntary organization though. No Federal Mandate. Insurers may mandate.
Cell Therapy: Costs of commercial CAR-T

**Acute Care:** $500,000 to $750,000/case

- Apheresis: $10-20,000
- CAR-T ("Drug") costs:
  - For leukemia: $475,000
  - For lymphoma: $373,000
- Hospitalization (2-4 weeks): $100-250K

**Chronic Care:** IVIG monthly ($10K / mo)

**Insurance issues:** CMS (August 2019):

- Instituted broad **coverage** policy.
- Has not instituted broad **reimbursement** policy.
- To address this, CMS (April 2019) increased “new technology add-on payment (NTAP)” to 65% of drug charges.
- Leaves hospitals with short-fall.
# Michigan Medicine Data: Referrals, Insurance Status, Coverage

<table>
<thead>
<tr>
<th></th>
<th>Leukemia Referrals</th>
<th>Leukemia treated</th>
<th>Lymphoma Referrals</th>
<th>Lymphoma treated</th>
<th>Total Tx / Referral</th>
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<tbody>
<tr>
<td>Referrals (2017-2019)</td>
<td>14</td>
<td>5</td>
<td>41</td>
<td>18</td>
<td>55</td>
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<tr>
<td>Insurance</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Medicaid</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>4</td>
<td>5/9</td>
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<tr>
<td>Medicare</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>9</td>
<td>9/18</td>
</tr>
<tr>
<td>VA/Humana</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1/1</td>
</tr>
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<td>Tri-Care</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<td>BCBS</td>
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<td>1</td>
<td>5</td>
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<td>4/6</td>
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<td>Self-pay</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0/1</td>
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<tr>
<td>Other Commercial</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>4/13</td>
</tr>
</tbody>
</table>
On Sept 19th, 2019, the CON established new standards for cell therapy products in MI. What did they focus on?

- CAR-T (Chimeric Antigen Receptor T-cells)
- Dendritic Cells, NK Cells
- Tumor Vaccines
- Mesenchymal Cells (MSC)

Michigan CON (9.19.19)
Established standards for IECT.
To Ensure Access. Ensure Quality.
- No limit to number of sites in the state that can offer IECT.
- IECT are not restricted to BMT centers.
- However, the CON will require sites to have FACT accreditation within 3 years of application.
Changing landscape: Impact on one patient

M’s story

• Diagnosed Acute Leukemia, February 2011. Age 4 years.
Must be ready to face the challenges:

- **Friday, Oct 6th, 2017**
  - Patient relapses (Out-of-state)

- **Oct 6th**
  - BMT Intake Coordinator
  - Organizes Transfer.
  - Insurance approval initiated.
  - Apheresis Scheduled (Collect T-cells).

- **Referral #2**

- **Oct 9th**
  - Transfer to UM.
  - Patient critically ill on transfer
  - Patient Febrile, Multi-organ dysfunction.
  - Aggressive management to get to apheresis.

- **Apheresis**
  - Oct 9th
  - 1 day collection. 5 hour procedure.

- **Oct 10th**
  - Transfer back (Out-of-state)

- **Cells sent to Novartis for CAR-T manufacturing:**
  - 28 days.
# CAR-T Cell Therapy in Large cell lymphoma

<table>
<thead>
<tr>
<th>Product</th>
<th>Tisagenlecleucel (Kymriah™)</th>
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</thead>
<tbody>
<tr>
<td>Approved indication</td>
<td>ALL (up to age 25)</td>
</tr>
<tr>
<td></td>
<td>DLBCL (≥18)</td>
</tr>
<tr>
<td>Trial</td>
<td>JULIET (DLBCL)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>n=81 (JULIET)</td>
</tr>
<tr>
<td>Cytokine Release Syndrome</td>
<td>Total=58%</td>
</tr>
<tr>
<td></td>
<td>Severe=23%</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>Total=58%</td>
</tr>
<tr>
<td></td>
<td>Severe=12%</td>
</tr>
<tr>
<td>Response Rate</td>
<td>Response at 3 mos: 52%</td>
</tr>
<tr>
<td>Survival (at 2 years)</td>
<td>~60%</td>
</tr>
<tr>
<td>Complete Remission at 2 years</td>
<td>~40%</td>
</tr>
</tbody>
</table>

- Not FDA approved yet

Trial: JULIET (DLBCL), ZUMA-1 (DLBCL), TRANSCEND (DLBCL)

Number of patients: n=81 (JULIET)

Cytokine Release Syndrome: Total=58%, Severe=23%

Neurotoxicity: Total=58%, Severe=12%

Response Rate: Response at 3 mos: 52%

Survival (at 2 years): ~60%

Complete Remission at 2 years: ~40%
CAR-T clinical care: Selecting Patients

Evaluate disease status.
Leukemia: Bone marrow aspirate/biopsy, Spinal tap, possible head MRI
Lymphoma: FDG-PET (lymphoma) and/or CT scan, Spinal tap (if +prior history), possible MRI.
Greater the tumor load, more CRS.

Recent History: Determine
Most recent chemotherapy? Are they on immune suppressant drugs? Recent Transplant?
No chemo within 7 days. No immune suppressants within 14-28 days.

Concurrent issues:
Any active infections? Recent Infections. Check Viral assays (PCR).
Should be afebrile, with no active infections. MUCH higher risk of CRS.
Assess Cardiac, Pulmonary, Hepatic, Renal function.
Pregnancy Testing (if applicable). Getting pregnant while on CAR-T therapy may carry risks.
CAR-T cells in Non-Hodgkin's Lymphoma

Schuster SJ, NEJM 2017

**Duration of Remission**

**C** Diffuse Large B-Cell Lymphoma, Response Duration

- Median, not reached; 86% had response at median follow-up of 28.6 mo

**D** Follicular Lymphoma, Response Duration

- Median, not reached; 89% had response at median follow-up of 28.6 mo
CAR-T cells in Acute Lymphoblastic Leukemia

Maude S, NEJM 2018

Duration of Remission

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Any</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS</td>
<td>77%</td>
<td>46%</td>
</tr>
<tr>
<td>Neurologic</td>
<td>40%</td>
<td>13%</td>
</tr>
<tr>
<td>Infection</td>
<td>43%</td>
<td>24%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35%</td>
<td>35%</td>
</tr>
</tbody>
</table>

CRS, cytokine release syndrome
Neurologic headaches, seizures, coma, aphasia

No. of patients, 61
No. of events, 17
Median duration of remission, not reached