Nursing Management for the Successful Application of the Chimeric Antigen Receptor (CAR) T Cell Immunotherapy

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Disclosure

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• Kevin J. Curran, MD
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• Off Label Use
  – CD19-specific CAR T cells
• Video

Overview
• The “3 E’s” of Cancer Immunotherapy
• Describe CARs and their role in treatment of CD19+ B cell leukemia
• Describe the screening and collection process
• Describe the infusion procedure
• Review toxicities and management
• Study overview and case study presentations
What is Immunotherapy?

“Immunotherapy, also called biologic therapy, is a type of cancer treatment that boosts the body’s natural defenses to fight the cancer. It uses substances made by the body or in a laboratory to improve or restore immune system function.” (Cancer.Net 2017)

Cancer and Immune Escape – “The 3 E’s”

Blood Cells of the Immune System

[Diagram showing blood cells and their development stages]

[Links to images and resources]

- Blood Cells of the Immune System
- Platelets
- White blood cells
- Red blood cells
- Myeloid stem cell
- Lymphoid stem cell
- Myeloblast
- Lymphoblast
- Granulocytes
- Basophils
- Eosinophils
- B lymphocyte
- T lymphocyte
- Natural killer cell

[Additional information and references]
Chimeric Antigen Receptor (CAR)

1. Construct a chimeric antigen receptor (CAR)

2. Subclone CAR gene into a retroviral vector (SFG)

3. Transduce and expand T cells \textit{ex vivo}

4. 19-28z+ T cells eradicate CD19+ tumor cells
Expression of B cell markers

- **Stem Cell**
- **pro B**
- **pre B**
- **immature B**
- **mature B**
- **plasma cell**

**Expression of B cell markers**

- **CD19**
- **CD22**
- **CD20**

**Clinical Application: An Overview**

1. **Apheresis**
2. **CD3/CD28 selection and activation with Clinivaive MFC**
3. **Gon Transfert using viral vector**
4. **Expansion on WAVE Bioreactor**
5. **Wash and formulate with Cellmune**
6. **Infusion**

*Individual with relapsed/refractory B-ALL*
Targeting Expansion Tumor Lysis

Screening for Collection

- CD19 + B ALL
- < 26 years old
- VHR, relapsed or refractory disease
- Performance status >60%
- No concurrent active malignancies
- No active infectious diseases: HIV, Hepatitis B or C
- Not currently pregnant
- ALC >0.5
- 6 months from allo-HSCT
- Off any immune suppressive therapy
- No GVHD
Collection

- Peripheral/Central access for collection
  - PIV if large veins
  - Leukophereses catheter placement
  - For <35Kg: 1 unit PRBC for priming PBMC collection

Numbness/tingling
Pain and bruising at IV insertion site
Lightheadedness
Nausea
Fatigue
Low platelets

Treatment Schema

VHR CD19 + B ALL
Relapse/Refractory B- ALL
Leukophereses
Salvage Chemotherapy
Cyclophosphamide & Fludarabine
T cell infusion
Disease and Safety Assessment
Infusion

• Premedication prior to infusion
• Double check CART cell label against the patient’s wristband
• Confirm blood return
• Attach 3-way stop cock at closest port
• Attach NS line to straight hub
• Spike T cell bag, prime line and attach to side hub

Infusion

• The Research RN/NP remains at the bedside to manage infusion reactions
• Infuse over 30-minutes to 1 hour
• Agitate cells every 15 minutes
• Monitor vital signs
CAR T Cell Toxicity

 Toxicity & Management
Cytokine Release Syndrome (CRS)

Likely
- High Fever
- Malaise
- Fatigue
- Myalgia
- Nausea/Anorexia
- Tachycardia
- Hypotension

Less Likely
- Respiratory Distress
- Capillary Leak
- Cardiac Dysfunction
- Renal Impairment
- Hepatic Failure
- Disseminated Intravascular Coagulation

Correlates with Tumor Burden
# Toxicity & Management

**Fever**
- Tmax of **106.9 F (41.6 C)**
- As early as Day 0 – more commonly Day +2 to +5.
- Lasting as late as Day 15
- Acetaminophen and Celebrex PRN

**Hypotension**
- NS/LR bolus: average from 1-7
- Vasopressor

**Hypoxia**
- Oxygen
- Ventilator Support

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**Toxicity & Management**

**Tocilizumab**
- *Monoclonal antibody - IL-6 receptor antibody*
- Administer over 1 hour
- Fever and hypotension often resolve within a few hours
- Does not appear to have an effect on CAR T cells
- Effect on neurologic sequela unknown

**Corticosteroids**
- Thought to be more efficacious for Neurotoxicity
- Prolonged use of high dose steroids has resulted in ablation of CART cell population
Cytokine Release Syndrome (CRS) Management Algorithm

Grade 1
• Supportive care
• Antipyretics, fluid resuscitation, antibiotics
• Persistent or refractory fever consider Tocilizumab

Grade 2
• Consider: Tocilizumab, vasopressors, ICU transfer, Oxygen
• Rapid deterioration consider steroids

Grade 3
• Consider Steroids. ICU transfer

Grade 4
• HD Steroids, ventilation and vasopressors

CRS Monitoring Grading

Table 2. CRS revised grading system

<table>
<thead>
<tr>
<th>Grade</th>
<th>Toxicty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Symptoms are not life threatening and require symptomatic treatment only, eg. fever, nausea, fatigue, headache, myalgia, malaise</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Symptoms require and respond to moderate intervention, Oxygen requirement &lt;40% or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Symptoms require and respond to aggressive intervention, Oxygen requirement ≥40% or Hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening symptoms, Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death</td>
</tr>
</tbody>
</table>

• Lee et. al. Blood. 2014 Jul 10;124(6):188-195
### Toxicity & Management

#### Neurological Toxicities

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>Typically reversible</td>
</tr>
<tr>
<td>Delirium</td>
<td>Levetiracetam prophylaxis</td>
</tr>
<tr>
<td>Expressive aphasia</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Neuro evaluations</td>
</tr>
<tr>
<td>Seizure-like activity</td>
<td>MRI/EEG/LP as needed</td>
</tr>
<tr>
<td>Obtundation</td>
<td></td>
</tr>
</tbody>
</table>

### Neurological Toxicities

#### Management Algorithm

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>- Supportive Care&lt;br&gt;- EEG, Neuro consult, Q4 hr neuro checks</td>
</tr>
<tr>
<td>2</td>
<td>- Consider: ICU, neuro check Q1hr, LP, Brain MRI&lt;br&gt;- Consider steroids for seizure like activity or dysphasia</td>
</tr>
<tr>
<td>3</td>
<td>- ICU transfer&lt;br&gt;- Steroids around the clock, repeat imaging, neuro consult</td>
</tr>
<tr>
<td>4</td>
<td>- HD Steroids, consider intubation and hypertonic saline</td>
</tr>
</tbody>
</table>

Tocilizumab: indicated for CRS
Utilizing CTCAE

- Common Terminology Criteria for Adverse Events CTACE
  - Definition: An objective and consistent method for measuring side effects includes:
    - AE term
    - Standardized description of each grade
  - Available online as a searchable PDF

- Grading
  1. Grade 1 - Mild
  2. Grade 2 - moderate
  3. Grade 3 - severe
  4. Grade 4 - life threatening
  5. Grade 5 - fatality

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>1</td>
</tr>
<tr>
<td>Agitation</td>
<td>Mild mood alteration</td>
</tr>
</tbody>
</table>

Definition: A disorder characterized by a state of restlessness associated with unpleasant feelings of irritability and tension.

Toxicity & Management

- B cell aplasia
  - CD19 therapy also targets normal B cells
  - Hypogammaglobulinemia may limit the patient’s ability to produce antibodies
  - Serum immunoglobulins are checked prior to as well as 1, 3, and 6 months following treatment.
  - IVIG may be given as needed
Toxicity & Management

Less Likely Side Effects

- Allergic reaction to modified T cells
- Cerebral edema
- Immune reaction
- Secondary cancers
- Graft versus Host Disease (GVHD)
- Cardiac Disorder
- Death

Preventing Toxicity

- Tumor de-Bulking
  - Re-induction and conditioning chemotherapy
- Levetiracetam Prophylaxis
  - Unclear benefit
- Prophylactic Tocilizumab
- Suicide or Elimination Gene
Toxicity Management


Research Blood Sample Monitoring

- Blood samples are collected at several time points to:
  - Make sure there is no functional virus present (RCR)
  - To see whether the modified T cells are present
  - To assess the loss of normal B cells
  - To see whether modified T cells have changed the immune system to better kill tumor cells
  - Blood is also stored in the bank for 15 years
Study Overview

- Enrolled (n=49)
- Leukapheresis completed (n=48)
- Cells generated (n=3)
- Cell infused (n=23)
- Treated under SPU (n=2)
- Leukapheresis not obtained (n=1)
  - Low ALC counts (n=1)
- CAR T cells not generated (n=16)
  - No evidence of disease (n=12)
  - Insufficient T cells collected (n=2)
  - Withdrew consent (n=2)
- CAR T cells not infused (n=9)
  - No evidence of disease (n=5)
  - Not eligible for treatment due to infection (n=4)
- Included in Study Analysis (n=25)

Response

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response /Complete Response- incomplete count recovery (CR/CRi)</td>
<td>75% (18/24)</td>
</tr>
<tr>
<td>MRD-negative</td>
<td>89% (16/18)</td>
</tr>
<tr>
<td><strong>Response/Conditioning Chemotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>High Dose Cyclophosphamide (HD-Cy)</td>
<td>94% (15/16)</td>
</tr>
<tr>
<td>Low Dose Cyclophosphamide (LD-Cy)</td>
<td>38% (3/8)</td>
</tr>
<tr>
<td><strong>Response/Pre-Treatment Disease Burden</strong></td>
<td></td>
</tr>
<tr>
<td>Morphologic Disease (≥5% BM blasts)</td>
<td>50% (5/10)</td>
</tr>
<tr>
<td>MRD (&lt;5% BM blasts)</td>
<td>93% (13/14)</td>
</tr>
</tbody>
</table>

CR – Complete Remission
CRi - Complete Remission with incomplete count recovery
MRD – minimal residual disease
HD – high dose (>1500mg/m²)
LD – low dose (≤1500mg/m²)

Curran K, unpublished
**Overall Survival**
(Responding patients offered allo-HSCT if eligible)

![Graph showing overall survival based on dose of Cyclophosphamide prior to infusion](image1)

![Graph showing overall survival based on pretreatment disease burden](image2)

Figure 1: Overall survival based on dose of Cyclophosphamide prior to infusion

Figure 2: Overall survival based on pretreatment disease burden

**Case Presentation #1**

- M.W. - 4 y/o male with refractory pre-B cell ALL
  - MRD Cohort (BMA - 0.41%)
  - Conditioning Chemotherapy + 19-28z CAR T cells
    - Cyclophosphamide (1500mg/m²/dose daily x 2 days)
    - Fludarabine (25mg/m²/dose given daily x 3 days)
- **Day +3** – Fever
- **Day +4** – Compensated shock → IVF only (PICU transfer)
- **Day +5** – Dizziness; Right sided weakness + Seizure/post-ictal
  - Lorazepam, increased levetiracetam
  - Tocilizumab
  - CT negative
  - VEEG – diffuse cerebral dysfunction (no focal epileptiform activity)
  - Seizure #2 in the afternoon – Dexamethasone + Valproate
- **Day +6** – MRI + Diffuse supratentorial white matter vasogenic edema
  - Improving Neuro Sx - +Left hemiparesis
Vasogenic Edema (FLAIR)

Baseline

Day +6

Case Study

- **Day +7** – Improving neurologic symptoms but Left hemiparesis still present; speaking

- **Day +9** – Transfer to Floor (5 day steroid pulse completed)

- **Day +14** – Discharged from hospital
  - MRI: *improvement in diffuse supratentorial white matter signal abnormality and diffuse cerebral edema*
  - BMA - MRD negative CR

- **Day +47** – Received a 9/10 MUD T cell depleted transplant
Vasogenic Edema (FLAIR)

Baseline

Day +6

Day +14

Day +32

Case Presentation #2

- E.M. 8 y.o. male with relapsed pre-B ALL
  - MRD Cohort (BMA - 1.2%)
- Conditioning Chemotherapy + 19-28z CART cells
  - Cyclophosphamide (1500mg/m²/dose daily x 2 days)
  - Fludarabine (25mg/m²/dose given x 1 dose)
- **Day +5** Intermittent mild headaches
- **Day + 6** Fever/Mild Hypotension– Bolus x 1 and transfer to PICU for observation
- **Day + 7** Neck pain and emesis
- **Day + 8** Tremor/Ataxia
- **Day + 14** Discharged from hospital
- **Day + 16 & Day + 43** BMA -MRD neg CR
- **Day + 57** Started conditioning for transplant
Fever Curve for E.M.

Day 0

Day 6

Day 7

Tmax 40.3

Day 11 resolved

Inflammatory Markers E.M.

Day 7

Day 8

Day 10
Future Directions

- Hematologic Malignancies
  - CAR T cell FDA approval for B-ALL and NHL
  - Replace allo-HSCT

- Solid Tumors
  - Successfully target/eradicate solid tumors
  - Combination with check-point blockade

Conclusions

- Immunology and CAR T cells
  - B & T cells play an integral role in our immune system
  - Autologus cells are sent to the lab for genetic modification
  - Autologus CAR T cells can identify and destroy the CD19 protein on B cells

- Collection
  - Rapid coordination
  - Multidisciplinary approach
  - Organized with referring institution, donor room, lab and patient’s family

- Infusion
  - Timing of infusion involves multiple staff members
  - Close monitoring is imperative

- Treatment/Toxicity Management
  - Patient’s require complex nursing care
  - Nursing plays an important role in monitoring and recognizing immunotherapy related toxicities
  - Prompt response to neurological and vital sign changes
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• The incredible children that continue to have the ability to amaze all of us
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Questions ?

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References


