Nursing Considerations for Universal CAR-T Cell Therapy in Pediatrics

COLLEEN CALLAHAN MSN, CRNP

Disclosures

Colleen Callahan, MSN, CRNP, has a financial interest/relationship or affiliation in the form of: Consultant and/or Advisor for Novartis Pharmaceuticals Corporation.

T Cell Quality

Quality of collected T cells for manufacture is critical

- Naïve and early memory T cells in the apheresis product correlates with successful CAR-T cell performance in pediatric ALL

Cumulative chemotherapy cycles deplete naïve and stem cell memory T cells reducing expansion potential

- Early collection of high-risk patients may be beneficial
- Concern with infants especially young age at diagnosis→T cells won't be healthy enough to grow and yield an infusible product
- Naïve T cell deficits can be seen at diagnosis—implies that immune deficits exist prior to chemotherapy (many patients with solid tumors had low numbers of naïve T cells prior to any therapy)

T Cell Quality

Optimal timing of collection is important

- Factors to consider
  - Circulating blasts
  - Heavy pretreatment leads to impaired T cell function and therefore manufacturing issues
  - Severe lymphopenia
  - Infants

Timing for T cell collection is a fine balance between waiting for healthy new T cells (ALC recovery) and administering chemotherapy

Auto CAR-T Cell Challenges

Heavy pre-treatment/intensive chemotherapy

- Impaired T cell function
- Lymphopenia

T cells intrinsically bad as a result of the cancer

- Immune suppression from tumor microenvironment
- T cell dysfunction not r/t chemo
  - Lymphoma/CLL: proliferate less

Disease progression/complications

Infants

Memory phenotype

Need apheresis slot

Need manufacturing slot

Cost

Product variability

Cell number

Collection and manufacturing failures (7.6%)

Phase 2 Tisagenlecleucel trial 18.5% did not received CAR-T cells due to disease complications or manufacturing failure

Universal CAR-T Cell Therapy

Some patients unable to receive auto CAR-T cell therapy due to inability to collect cells or failure of in vitro expansion

Universal CAR-T cell therapy

- Off the shelf product
- Standardized manufacturing
- Available for immediate use
- Allogeneic donors
- GVHD risk
- More cost effective
- Unlikely to produce long term efficacy due to CAR cells eventually being rejected by the host

Universal CAR-T Cell Challenges

Rejection of UCAR-T cells

- Patient's own T cells will recognize infused UCAR-T cells as foreign
- Condition the recipient's immune system to minimize rejection
  - Intensification of lymphodepletion may help allow UCAR-T cells to expand
    - Increased risk of infection
    - Expected to have short persistence due to eventual immune rejection
- Need to make donor UCAR-T cells resistant to the lymphodepleting agents (anti-CD52 alemtuzumab)

Universal CAR-T Cell Challenges

Graft vs Host Disease

- UCAR-T cells see the host as “foreign”
- Need to prevent GVHD to be safe
- Knock out the T cell receptor (TCR) via gene editing. Not 100%. Small numbers still remain.

Infection Risk

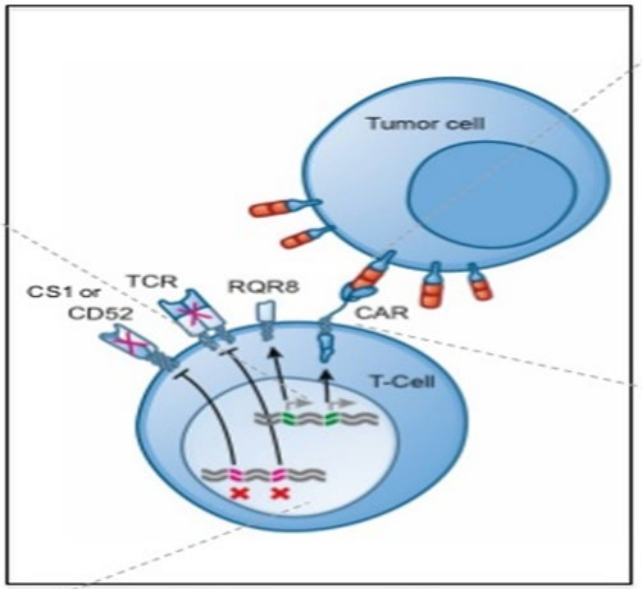
Need for lymphodepletion and host immunosuppression leads to infection risk

- Marrow suppression
- Prolonged cytopenias
- Leading to potential viral re-activation

Universal CAR-T Cell Gene Editing

Gene editing adds to complexity of manufacturing

- High degree of complexity of genetic manipulation
  - Knock out genes encoding the TCR (T cell receptor) to reduce risk of GVHD
  - Engineer UCAR-T cells to be resistant to lymphodepleting medications
    - Knock out genes encoding CD52 so UCAR-T cells are resistant to alemtuzumab



BENJAMIN ET AL, THE LANCET, DECEMBER 12, 2020;
IMAGE: CELLECTIS

Universal CAR-T Cells

Free of exposure to chemotherapy agents

Manufacture not affected by patient specific factors

Prepare in advance so readily available

Cost advantage

Standardized manufacturing

Multiple doses made from one collection

Universal CAR-T Cell Trial (CALM; PALL)

June 2016-October 2018

Ages 9 months to 62 yrs

- 7 children
- 14 adults

62% prior allo SCT

Exclusions

- Active CNS disease
- Extramedullary disease
- Active infection

7 days lymphodepletion (promotes engraftment and expansion, reduce rejection)

81%: Cyclophosphamide, fludarabine, alemtuzumab (effects last for weeks, can lead to viral reactivation)

19% Cyclophosphamide, fludarabine without alemtuzumab due to concerns of viral infection

- 4 patients did not receive alemtuzumab and showed no UCART expansion

MG: Case Presentation

2/2018 diagnosis at birth with Infant ALL (MLLr)

- WBC 192,000; CNS 2b
- Hyperbilirubinemia
- Treated on AALL15P1
  - Sepsis
  - Seizure
  - Leukoencephalopathy
  - Feeding issues
  - Chemotherapy delays d/t prolonged count recovery

12/2018 began maintenance therapy

MG: Case Presentation

3/2019 Relapse (marrow and CNS); has a matched sibling donor

- Thrombus
- Cardiac dysfunction (concern for handling severe CRS)
- Nutrition/feeding difficulties requiring TPN
- C-diff, norovirus
- 5/2019 MRD 2.6%
- Too sick to travel for collection
- ALC slow to recover and concerns for keeping her off chemotherapy too long

Transfer to CHOP

- Cardiac evaluation
  - Cleared by Cardiology

MG: Case Presentation

Infant ALL

- Concern that T cells won't be healthy enough to grow

Maximize chance by collecting before chemo but only if feasible from a safety standpoint

- She was too sick to collect prior to starting re-induction chemo

Post re-induction

- 6/2019 MRD 76%
- ALC too low for collection

MG: Case Presentation

Alemtuzumab, fludarabine, cyclophosphamide

Pre UCART: CNS 1; MRD 80%

7/2019 UCART infusion

- Seizure prophylaxis with levetiracetam d/t history of seizures
- Day 4 Fever (39.1)
  - Desaturations. O2 NC
  - Tachycardia. Fluid bolus.
- Persistent fevers (40s)
- Day 8 Respiratory distress. PICU
- Tocilizumab (IL-6 receptor antagonist; Blocks IL-6 mediated inflammatory effects)
- BIPAP
- Max CRP 22 (day 7); max ferritin 202,000 (day 13)
- Day 15 Off BIPAP; transfer out of PICU

Day 28: CNS 1; MRD negative

Returned to home institution

8/2019 MSD BMT (brother)

Remains in remission

Universal CAR-T Cell Trial

Side Effects (21 patients)

- CRS 91%
  - 14% grade 3-4
  - Tocilizimab 42%, 16% steroids, 37% ICU, 16% vasopressor support
- Neurotoxicity 38% (median duration 3 days)
- GVHD Gr 1 10% (skin)
- Prolonged cytopenia 32%
- Infections 62%
  - 24% gr 3 or greater (CMV, adenvirus, human metapneumovirus, BK virus)
- 2 treatment related deaths
  - Neutropenic sepsis during CRS
  - Pulmonary hemorrhage (with persistent cytopenias)

UCAR-T cells showed rapid expansion after infusion

67% had a complete response at day 28

71% proceeded to SCT

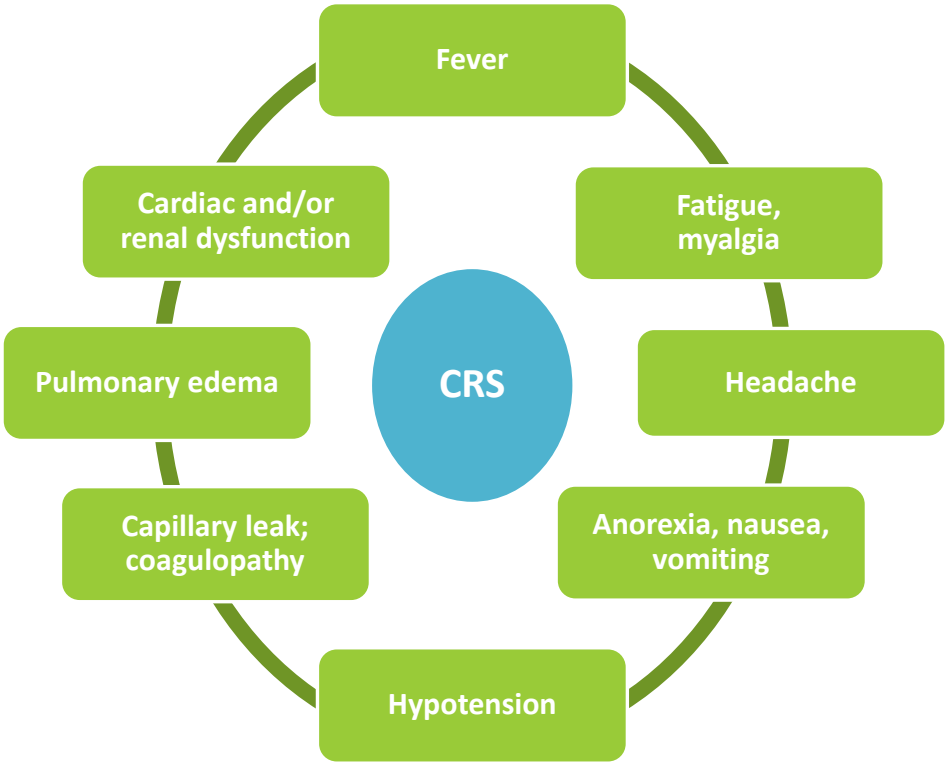
27% PFS at 6 months

55% OS

Cytokine Release Syndrome

Cytokine Release Syndrome	Severity related to disease burden. Correlates with T cell proliferation.
	Elevation in inflammatory markers. Massive elevation in IL-6.
	Reversible
	Constellation of inflammatory symptoms related to T-cell engagement and expansion

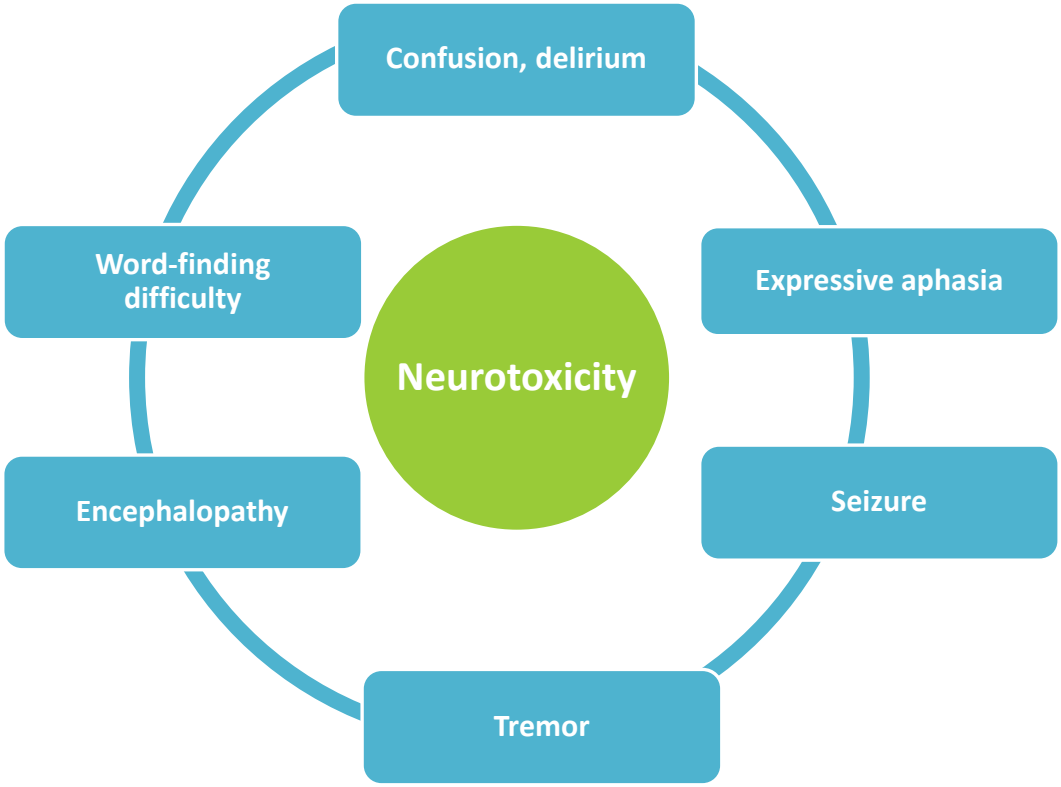
Cytokine Release Syndrome



Treatment

- Want to prevent multi-system organ failure but do not want to stop the T cells from working
- Supportive care
- Tocilizumab: monoclonal antibody to IL-6 receptor. Blocks the IL-6 mediated inflammatory effects.

Neurotoxicity



GVHD

Occurs when the “graft” (the UCAR-T cells) see the “host” (the patient) as foreign, and begin to attack certain target organs

- Skin
- Gut
- Liver

Future UCAR-T Cell Trials

Industry sponsored

UCART 123: relapsed/refractory AML

UCART 22: relapsed/refractory ALL adults

UCART CS1: relapsed/refractory multiple myeloma

ALLO-501: relapsed/refractory NHL

ALLO-715: relapsed/refractory multiple myeloma

Nursing Role

Anticipatory guidance

Patient/family education

- Begins with first contact with institution
- Consent meeting
- Chemotherapy
- Post infusion side effects

Clinical management of side effects

Continuity for patient and family

Acknowledgements

Diane Baniewicz MSN, CRNP

Stephan Grupp MD

Shannon Maude MD

Sue Rheingold MD

Amanda Dinofia MD

Lisa Wray MD

Laura Smith MSN, CRNP

Kim Venella MSN, CRNP

Stephanie Fooks-Parker MS, MSW

Alissa Feirson MS, MSW

Claire White RN, MSN

Brooke Leibfried RN, BSN

Mark Duckworth

Lauren Vernau

Beth McBride

Nick Kawchak

Denise Gallagher

Raabia Khan

BMT Team

CHOP inpatient and outpatient nursing staff

CGTL staff

Apheresis Staff

Interventional Radiology

Child Life Staff