CAR-modified T cell Therapy: How do we get there?

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Children’s Hospital of Philadelphia

ISCT 2014 Annual Meeting: Quality and Operations Track 12
Managing the CAR-T Before the Horse: A Cell Therapy Success Story
Disclosures

- No financial conflict of interest
- Advisory role in clinical trial development for Novartis

- CART19 licensed by Novartis
- Sponsor holds patent for technology
Redirecting the Specificity of T cells

- Gene transfer technology is used to stably express CARs on T cells, conferring novel antigen specificity\(^1,2\)

- CTL019 cells can thus be directed against any tumor cell that expresses the CD19 surface antigen

- CTL019 therapy takes advantage of the cytotoxic potential of T cells thereby killing tumor cells in an antigen-dependent manner\(^1,3\)

- Persistent CTL019 cells consist of both effector (cytotoxic) and central memory T cells\(^3\)

(Not your typical) Enrollment process

- Screening
- Leukapheresis

Manufacture

- Stabilization

Enrollment

- Infusion

CTL019
Patient Selection

– Population: Patients with multiply relapsed or highly refractory ALL
– Time from screening to treatment – weeks to months
– Need to stabilize and maintain eligibility
Case #1

9 year old female with multiply relapsed ALL

ALL History
- MUD PSCT for induction failure
- Relapsed post SCT
- Responded to reinduction

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<th>Timing</th>
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22 year old male with 1\textsuperscript{st} relapse of ALL

**ALL History**

- 1\textsuperscript{st} relapse in maintenance therapy
- Refractory to reinduction chemotherapy and clofarabine/cytarabine

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Timing of Leukapheresis

**Known eligible:**

- Multiply relapsed/refractory
  - Relapsed after allo SCT
  - Not eligible for allo SCT
  - Refractory to multiple intensive therapies

**Potentially eligible:**

- High-risk disease
  - Primary induction failure
  - Early BM relapse
  - High-risk cytogenetics
Timing of Leukapheresis

**Known eligible:**

- Multiply relapsed/refractory
  - Reserve for patients likely to need and benefit
  - May be difficult to stabilize patient
  - Intensive therapy may limit collection and T cell expansion

**Potentially eligible:**

- High-risk disease
  - Better collection
  - Better T cell growth
  - May delay therapy
  - Usually minimal
  - May not be used
  - May be difficult to stabilize patient
Screening Failures

- Inadequate ALC for collection
- Poor collection
- Poor T cell expansion
- Inability to maintain eligibility
  - Organ function
  - Infection
  - Rapidly progressive disease
- Proceed to SCT
Patient Selection

- Population: Patients with multiply relapsed or highly refractory ALL
- Time from screening to treatment – weeks to months
- Need to stabilize and maintain eligibility

- Conditions likely to preclude enrollment and/or infusion
  - Pre-existing organ dysfunction
  - Uncontrolled infection
  - Rapidly progressive disease
Patient Stabilization

Time from screening to treatment – weeks to months

• Goals:
  – Prevent rapid progression
  – Avoid organ toxicity and infectious complications
  – NOT to induce remission or reduce disease burden

• Options:
  – Maintenance chemotherapy (steroids, monthly or weekly VCR, +/- oral 6-MP and MTX)
  – Hydroxyurea
  – No chemotherapy if low white count and asymptomatic
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\textbf{ALL History}

\begin{itemize}
  \item 1\textsuperscript{st} relapse in maintenance therapy
  \item Refractory to reinduction chemotherapy and clofarabine/cytarabine
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\begin{tabular}{|l|l|}
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\textbf{Timing} & \textbf{Key notes} \\
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Month -2 & T cells collected after failed reinduction \\
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Month -1 & Started hydroxyurea \\
\hline
\end{tabular}
\end{table}
Given 1 week prior to infusion

• Purpose:
  – Induce lymphopenia to facilitate engraftment and homeostatic expansion of CTL019 T cells
  – Disease control

• Agents:
  – Cyclophosphamide 500 mg/m² IV daily Days 1-2,
    Fludarabine 30 mg/m² IV daily Days 1-4
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Case #2

22 year old male with 1\textsuperscript{st} relapse of ALL

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- 1\textsuperscript{st} relapse in maintenance therapy
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 CTL019 Infusion

• Premedication:
  – Tylenol and Benadryl

• Infusion:
  – Cell product thawed per Stem Cell Lab SOPs
  – Outpatient infusion center
  – Infused over 2 minutes by trained staff
  – Vital signs monitored every 15 minutes for 1 hour
  – Acute infusional toxicities rare
Cytokine Release Syndrome

CRS is related to T cell expansion and is likely necessary for efficacy

- Symptoms typically occur 1-14 days after CTL019 cell infusion in ALL

- Severity scales with disease burden

Fever
Myalgias
Nausea/Vomiting

Hypotension
Respiratory insufficiency
Renal insufficiency
Coagulopathy
• Symptom management
  – Antipyretics
  – Analgesics (often narcotics required)
  – Antiemetics, TPN
  – Blood products (FFP, cryo)
  – O2, CPAP, ventilation
  – Vasopressors
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Case #1 CRS Timeline

![Graph showing temperature changes over days post-infusion with annotations for CTL019 Infusion, D/C home, Narcotics (days 3-6), Myalgias (days 2-7), and Antibiotics (days 1-7).]
Severe CRS management

• Lympholytics
  – Steroids tried with some effect but potential to reduce efficacy

• Cytokine-directed therapy
  – IL-6 noted to be very elevated
  – Anti-IL-6 therapy highly effective with no apparent effect on efficacy

Grupp et al. NEJM 2103
Systemic inflammatory response with vascular leak, hypotension, respiratory and renal insufficiency

Extraordinarily high ferritin levels suggest MAS/HLH
  – 16,000 to 415,000 ng/ml

Coagulopathy
  – Elevated D-dimer and low fibrinogen

HSM, Transaminitis

Genetic w/u – patients 100 and 125, both gr 4 CRS, have a potentially predisposing perforin mutation

Entirely reversible with cytokine blockade
  – IL-6R blocking agent tocilizumab

Abbreviations: MAS/HLH, macrophage activating syndrome/hemophagocytic lymphohistiocytosis (HLH)
Tocilizumab

- IL-6 receptor antagonist
- Blocks IL-6 mediated effects
- Indicated in:
  - juvenile idiopathic arthritis (JIA)
  - Rheumatoid arthritis (RA)
  - In Japan, indication for Castleman’s Disease
- Typically given monthly
- Rare side effects of transaminitis and neutropenia
- Not required long-term, but a few patients have required 2 doses
Case #2

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Case #2 CRS Timeline

**CTL019 infusion**
Day 0: 10% of dose
Day 1: 30% of dose

**Tocilizumab**
(days 5 and 8)

<table>
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<tr>
<th>Days (post-infusion)</th>
<th>Temperature, °C</th>
<th>LDH, IU/Liter</th>
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<tbody>
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<td>42</td>
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**Presentation Title**

**Presenter Name**

**Date**

**Subject**

**Business Use Only**

**Confusion**
(day 2-11)

**Rasburicase**
(Day 9)

**High dose steroids**
(days 7-11)

**Respiratory support**
(days 3-10)

**High-dose vasopressors**
(days 2-9)

**Transfusion support**
(days 2-15)

**Cryoprecipitate**
(days 10-15)

**FFP**
(days 2 and 8)
Case #2 - Coagulopathy

CTL019 infusion
Day 0: 10% of dose
Day 1: 30% of dose

FFP (days 2 and 8)

Fibrinogen, mg/dL

PT, PTT, seconds

Days (post-infusion)

FFP, Platelets (days 2-15)

Cryoprecipitate (days 10-15)
Neurotoxicity issues

- Seen in several CD19 trials:
  - NCI
  - CHOP/UPenn
  - MSKCC
  - Blinatumomab
- In CHOP/UPenn experience with CTL019:
  - Self-limited, generally untreated, fully resolves
  - ??? Related to CRS
  - Not prevented by tocilizumab
Over 80 patients have been treated with CTL019 (CLL, ALL, and B-cell Lymphomas)

- **Pediatric ALL cohort (N=25):**
  - 22/25 CRs (88%)
  - 6 relapses, including 2 CD19(-) relapses

- **All ALL (N=30)** (pediatric plus adult):
  - 27/30 CRs (90%)
  - 7 relapses
  - Short followup (median 6 months, range 2-21 months)
Event-free and Overall Survival

Event-free Survival

- 6-month EFS: 66% (95% CI: 49,87)

Overall Survival

- 6-month OS: 78% (95% CI: 64,95)
Patient population

- ≥ 2\textsuperscript{nd} relapse
- Majority refractory to multiple prior therapies

Abbreviations: BM, bone marrow; CR, complete response, MRD, minimal residual disease; NR, no response
Most patients treated POST allo

- 18 patients post-allo SCT
- T cells collected from patient
  - No evidence of GVHD
  - 6 months post-SCT
- Median donor chimerism 100%
- No GVHD to date

Abbreviations: GVHD, graft-versus-host, disease; SCT, stem cell transplant
Long-term Management

• B cell aplasia:
  – Monthly IVIG

• Follow-up:
  1st year
  – Close follow-up for CTL019 persistence and relapse
  – Discuss SCT (particularly for patients in CR2)
  Long-term
  – 15-year follow-up for gene therapy
It really does take a village

ACC TRP
Carl June
Anne Chew
Michael Milone
Yangbing Zhao
John Scholler
Elizabeth Veloso
Dana Hammill

Grupp Lab
David Barrett
David Teachey
Alix Seif
Shannon Maude
Sarah Tasian
Junior Hall
Jessica Hulitt
Terry Ryan
Yueh Chang
Yong Li
Jessica Lee

CVPF
Bruce Levine
Julio Cotte
Zoe Zheng
Alexey Bersenev

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Colleen Callahan

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Frazana Nazimuddin
Vanessa Gonzalez

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CTO/IND Office
CHOP Stem Cell Lab
Giuliana Pierson
Yongping Wang

CHOP Vector Core
Frasier Wright

Adaptive TcR

Patients and Families

St. Baldrick’s Foundation
Conquer Childhood Cancers

The Leukemia & Lymphoma Society
Fighting Blood Cancers