Experience at Center for Cell and Gene Therapy
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CAGT
CENTER FOR CELL AND GENE THERAPY

Baylor College of Medicine · Texas Children's Hospital · Houston Methodist

HOUSTON Methodist TEXAS MEDICAL CENTER

Baylor College of Medicine

Texas Children's Hospital

Disclosure

- Licensing agreement with Cell Medica for LMP CTLs in NHL and nasopharyngeal cancer
- Collaborative Research Agreement with Celgene for genetically modified T cells
- Founder Viracyte

Summary of all cases of Grade 3/4 (life threatening) and 5 (fatal) Cytokine Release Syndrome (CRS) and Macrophage Activation Syndrome (MAS)

Disease	CART/TCR Construct	Dose	Treated (N)	Grade 3/4 (N/%)	Grade 5 (N/%)	Risk Factors
ALL/NHL post SCT	CD19 CD28	2-20 x10E7 /m2	16			
CLL/NHL/ALL	CD19 CD28	1.5-20 x10E7 /m2	14	2	1 (? related)	Disease burden
Neuroblastoma	GD2 CD28/ OX40	1-20 x10E7 /m2	6	1		Disease burden

Patient

- 17-year-old female with a history of multiply relapsed and then refractory Pre-B ALL.
- Co-morbidities
  - Morbid obesity with BMI >50
  - Insulin dependent diabetes mellitus – poorly controlled
  - Chronic adrenal insufficiency.

First Dose CAR CD19 Cells

- Received 2×10^8 CD19-CAR-CD28-zeta T cells/m^2 (based on idealized BSA of $2m^2$).
- No immediate adverse events related to the infusion
- No subsequent signs of cytokine release syndrome
- Progressive disease at 8 weeks.

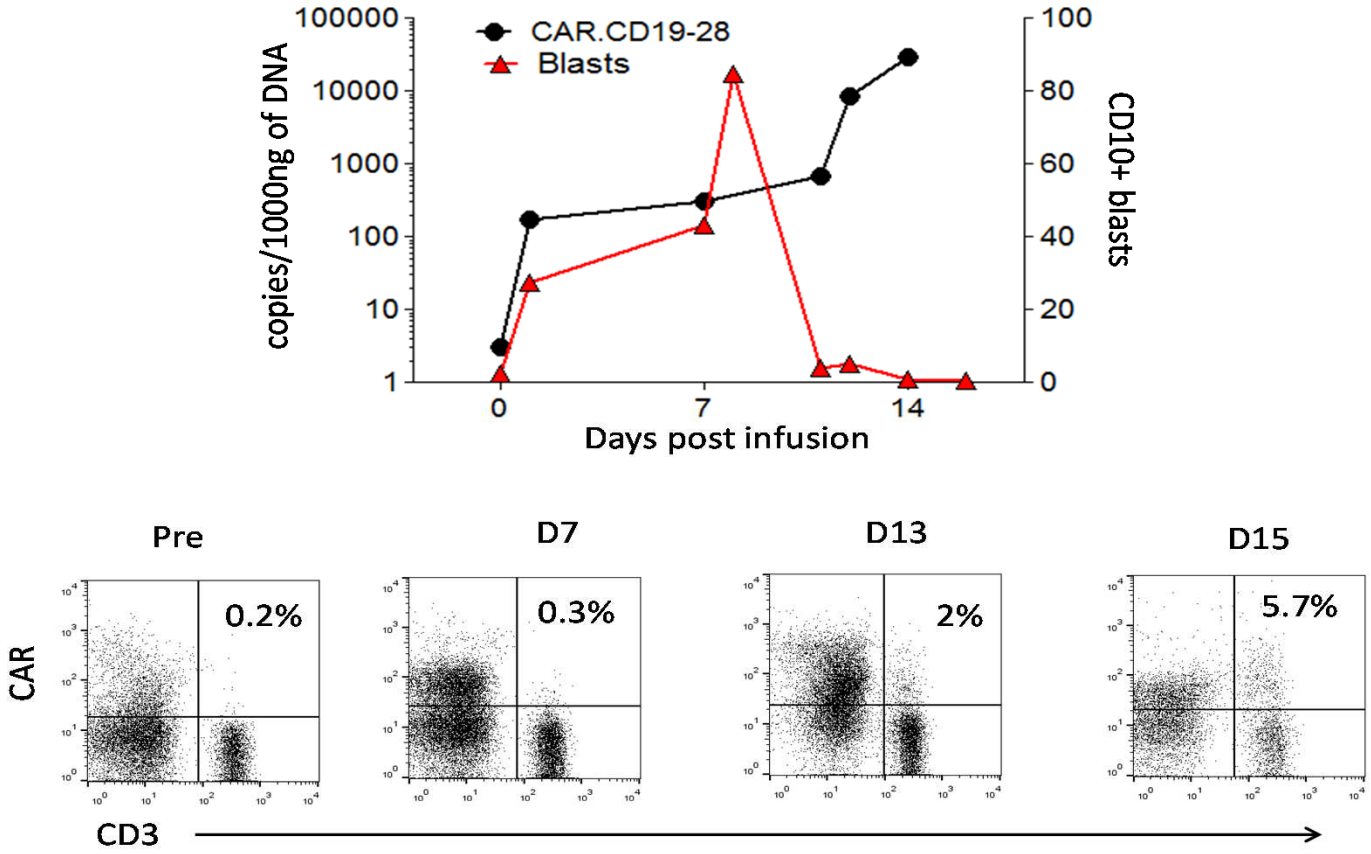
Second Dose CD19CD28 CATR T cells

- Pancytopenic after chemo at infusion
- 2×10^8 CD19.CAR-CD28-zeta T cells/m^2 (based on ideal BSA of 2.0).
- Day +11 fevers up to 103°F.
  - Peripheral blast percentage 60%.
  - Flow CAR T cells <1%
  - Started on empiric broad-spectrum antibiotics.

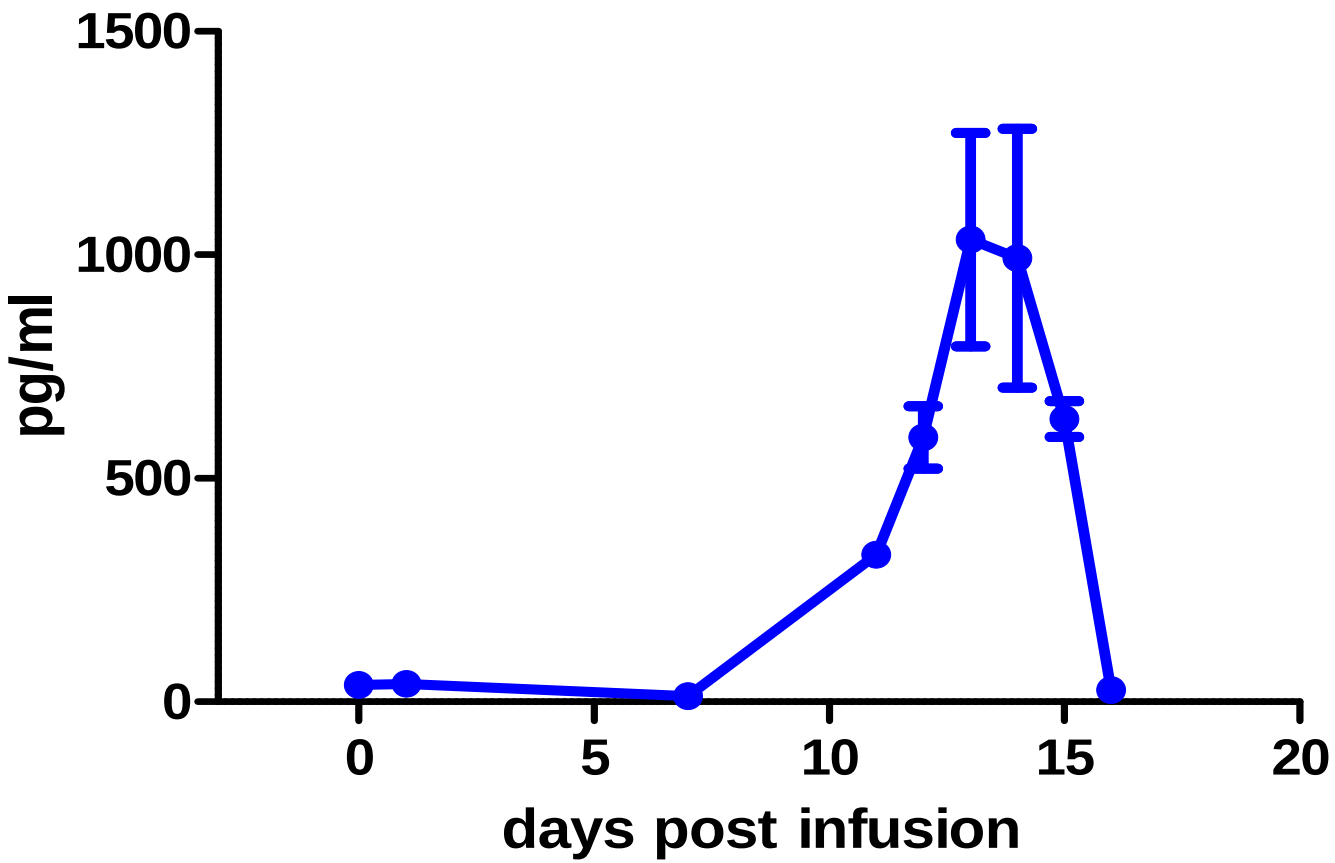
Cytokine Storm

- Day +13 developed a mild oxygen requirement (2 L via NC).
  - Peripheral blasts down 9%, and CAR-T cells rose to 3% by flow
  - Elevated ferritin at 66,000, serum IL-6 levels (1034.2 at day +13)

Detection of Blasts and CAR-T cells



IL6 Levels



Inflammatory Markers

- Ferritin rose from 2450 on 7/17 to >100,000 on 7/22/14 (Day 14)
- D-dimers increased from 2 on 7/19/14 to >20 on 7/22 and 7/23 (Day 14 and 15)
- INR 1.2 to 1.3
- PTT 36-50

Cytokine Storm

- Transferred to the PICU and was placed on high flow nasal cannula at 20 L/min, FiO_2 calculated at ~ 40%.
- Dopamine for inotropic support (initially at 10 µg/kg/min, quickly weaned to 7.5 then 5 then 2.5 µg/kg/min).
- Remained alert and cooperative.
- Did not meet algorithm criteria for intervention

SAE

- Day + 16, afebrile for more than 24 hours and weaned off O2
- Got out of bed to use the bedside toilet and had sudden onset respiratory distress
- FiO_2 increased to ~100%, without improvement
- Intubated due to concern for acute pulmonary embolism
- HR dropped, BP became undetectable
- CPR for 30 minutes
  - initially in ventricular tachycardia progressing to pulseless electrical activity.

SAE Attribution

Both the intensive care team and the primary treating team considered the likely cause of death to be acute pulmonary embolism with the main differential being a bleed

SAE Attribution

- Event during recovery from a cytokine storm.
- Preexisting risk factors
  - diagnosis of refractory ALL
  - morbid obesity
  - prolonged hospital admission of 3 months
- PI and IND sponsors possibly related to the investigational agent
  - inflammatory response during the cytokine storm
  - bed rest with activity restriction
- IRB and DRC not related

Questions

- Should ferritin be included in treatment algorithm?
- Poor prognosis when ferritin >100,000 in patients with HLH

Dosing

- Per Kg or per m2
  - Does m2 better reflect volume of distribution
- Adjustment for ideal body weight
  - Actual, ideal or adjusted
- Dose on transduced cells or total cells

Dosing

- Is their any influence of dose on toxicity and activity
  - Likely threshold
  - Range with activity
  - Dose with high risk toxicity
- Other factors influencing risk
  - Disease status

Lymphodepletion

- Most series use lymphodepletion
  - Specific regimen
  - Dealer's choice
  - Does regimen or degree lymphodepletion matter?
- Do you always need lymphodepletion?

Post Transplant

- 8 year old with ALL received CD19.28 CAR trivirus specific CTLs
- Early expansion and long term persistence
- No B cells at 9 months