Oct 13th, 12:00 AM

A Phase I Clinical Trial Combining Chimeric Antigen Receptor T-cell Therapy with Autologous Hematopoietic Stem Cells in Patients with Relapsed or Refractory Hematologic Malignancies

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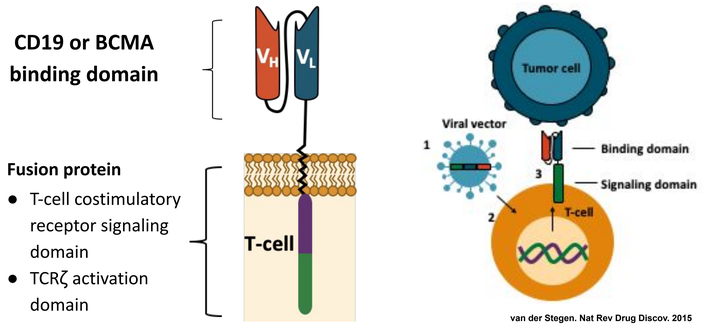
Background

Chimeric Antigen Receptor (CAR) T Cell Therapy is a type of immunotherapy in which patients' T-cells are collected and genetically modified with a retro/lentiviral vector ex-vivo to express a CAR. All current FDA approved CARs are directed against the cell surface antigens CD19 or BCMA which are expressed on B cells and plasma cells, respectively. CAR T is indicated as a second line therapy for relapsed/refractory (r/r) large B cell lymphoma (NHL), third-line therapy for acute lymphoblastic leukemia (ALL), and a fifth line therapy for multiple myeloma (MM).

Preclinical data in mice demonstrate that myeloid cells work in concert with CAR T-cells, increasing CAR T expansion in vivo and reducing tumor burden. Moreover, a retrospective study in patients receiving axi-cel for NHL show that prolonged cytopenias are associated with reduced CAR T efficacy. Addition of HSCs should help boost hematopoietic recovery and hopefully, CAR T efficacy.

We designed a phase 1 single-arm, open-label study to evaluate the safety and tolerability of autologous hematopoietic stem cells (HSCs) combined with CAR T-Cell therapy in patients with r/r NHL, ALL, or MM.

Engineered Receptor Design



Activities

Clinical Trial Documents

- Drafted the following:
  - Clinical trial protocol
  - informed consent form draft
  - Patient enrollment plan for physicians and clinical trial team
  - Guide for translating clinical trial protocols

Working with a Clinical Trial Team

- Worked with:
  - Study sponsor / PI
  - Cedars Sinai Medical Center SPIN group
  - Pharmaceutical company representatives
  - Biostatisticians
- Held regular meetings and collaboratively wrote and revised trial documents

Educating Patients and the Medical Community on Cell Therapy

- Drafted informative fliers to educate patients on cell therapy science, procedures, and clinical risks/benefits
- Created a plan to educate physicians on trial
- Presented clinical trial to Hematology & Cellular Therapy Department

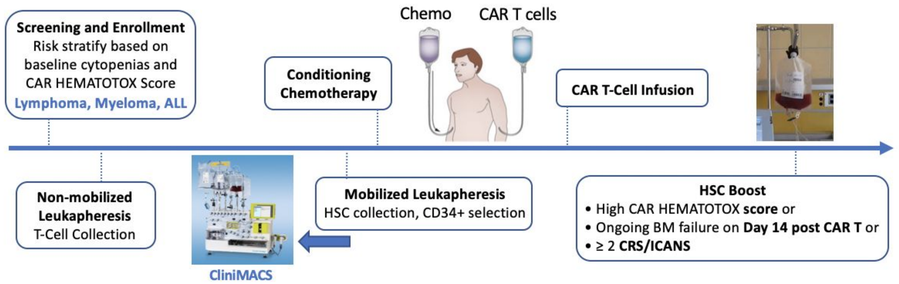
Study Objectives

- The **co-primary objective** is:
  → To evaluate the **safety and tolerability** of autologous HSC infusion shortly after CAR T

- The **secondary objective** is:
  → To evaluate the **change in CAR T efficacy** upon addition of HSCs
  → This will be evaluated through **CAR T expansion** and **hematopoietic reserve post- HSC infusion** (assessed using the CAR-HEMATOTOX criteria)

Study Schema

CAR T Phase I Trial: Autologous Stem Cell Boost



Primary Endpoint

- Assessing safety and tolerability through collection of adverse events:
  - Immune cell activation neurotoxicity syndrome (ICANS)
  - Cytokine release syndrome (CRS)
  - Macrophage activation syndrome (MAS)
  - Febrile neutropenia
  - Cytopenia
  - Infections

Secondary Endpoints

- Absolute neutrophil count (ANC) recovery by Day 28
- Red blood cell and platelet transfusion independence by Day 28
- Median progression free survival and overall survival
- Days of hospitalization

Discussions

Once this phase I, single center clinical trial at Cedars Sinai Medical Center in Los Angeles, CA is activated later this year, we plan to enroll 20 patients. In addition to our primary and secondary objectives, we will explore the impacts of adding an auto-HSC boost to the CAR T regimen on hematopoietic recovery, inflammation, T-cell polyfunctionality, stem cell exhaustion, and CAR T levels in blood. In all, we hope this trial will help improve CAR T efficacy and reduce toxicity for patients in need.

Future Steps

- Draft and submit and IRB project proposal.
- Draft and submit IND to the U.S. Food and Drug Administration
- Find, screen and enroll patients
- Conduct trial
  → Treat patients, monitor safety and collect data
- Evaluate primary and secondary study objectives

References

Acknowledgement

- A special thank you to Dr. Joshua Sasine who served as the preceptor and mentor for this project. Dr. Sasine dedicated countless hours to teaching and planning.
- Cedar Sinai Medical Center, which sponsored Bry Reinhardt as a research intern this summer.
- Dr. John Chute who helped fund this study and served as another mentor.