Future Directions and Challenges of CAR T Cell Therapy

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Disclosures

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Relapse Post CAR T Cell Therapy

CD19+
- Short persistence of CAR T cells
  - Evidenced by normal B cell recovery
- Immune mediated rejection
- Starting T cell quality. T cell exhaustion.

CD19-
- Due to antigen escape
- Is CD19 deleted/mutated/no longer expressed?
- Can happen even if CAR T cells still detected on research labs and with persistent B cell aplasia
Future Challenges: Relapsed/Refractory Pediatric ALL

- Lack of CAR T cell persistence (Early loss of CAR T cells)
- Poor T cell quality
- CD19 negative relapses
- Prevention of severe CRS
CD19 + Relapses: Lack of CAR T Cell Persistence and Poor T Cell Quality
CART19 Also Penetrates CSF in Pediatric ALL

Grupp et al. NEJM 2013
CD19 + Relapses: Lack of CAR T Cell Persistence

Normal B cells express CD19 antigen
- B cell aplasia is an on target/off tumor toxicity
- Use B cell aplasia as a marker of CAR T cell persistence

Lack of CAR T cell persistence
- Evidenced by B cell recovery
- Early B cell recovery → within 6 months of infusion
  - Concern that early loss of CAR T cells increases risk of CD19 + relapse
  - Believe that further therapy is needed for this population
CD19 + Relapses: Lack of CAR T Cell Persistence

Why does this happen?
- Immune mediated rejection
- Anti-mouse antibodies

Further therapy
- CAR T cell reinfusion
- CAR T cell reinfusion and combine with checkpoint inhibitors targeting PD-1 (Pembrolizumab)
- Help CAR T cell persistence
- Humanized CAR T cells
Humanized CAR T Cells

Humanized CAR T cells
- Address immune mediated rejection

Phase 1 Trial
- Patients with poor or transient response to murine anti CD19 CAR T cells (16 patients)
  - Early B cell recovery = 5 patients
  - CD19 + relapse = 10 patients
  - No response to prior CAR = 1 patient
  - 56% CR rate. 12 month RFS 56%.
- CAR naïve patients (22 patients)
  - 100% CR rate. 12 month RFS 82%
Humanized CAR T Cells: Phase 2 Trial Eligibility

1st cohort
- Predicted to have poor outcome with conventional chemotherapy
  - Induction failure
- High risk 1st relapse
  - Relapse < 36 months from diagnosis
- 2nd or greater relapse
- Refractory disease
- Ineligible for SCT

2nd cohort
- Partial or no response to prior CAR T cell therapy
- CD19 + relapse after prior CAR T cell therapy
- Early B cell recovery (≤ 6 months from infusion) post CAR T cell therapy
CD19 + Relapses: 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)

BARRETT ET AL, CANCER DISCOVERY, APRIL 2019
Factors to consider
- Circulating blasts
- Heavy pretreatment leads to impaired T cell function and therefore manufacturing issues
- Severe lymphopenia

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

Some patients unable to receive CAR T cell therapy due to failure of in vitro expansion

Universal CAR T cell therapy

- Off the shelf product
- Available for immediate use
- Allogeneic donors
- GVHD risk
- More cost effective
- Unlikely to produce long term efficacy due to CAR cells would eventually be rejected by the host
CD19 Negative Relapses
CD19 Negative Relapses

Why does this happen?

- Loss of antigen expression/antigen escape
- Acquired mutations
- Prior history of blinatumomab (anti CD19 monoclonal antibody)
CD19 Negative Relapses

**Treatment** after CD19 negative relapse (antigen escape)
- **CD22 CAR**
  - Target is the CD22 antigen

**Prevention**

Use multi-agent chemotherapy for initial treatment of ALL to avoid relapse

Same may be true for immunotherapy
- Use of single agents may lead to escape mechanisms
- Combined approaches may reduce events
Dual Targeting

**Prevention** of CD19 negative relapse (antigen escape)
- Combat antigen escape by targeting more than 1 antigen receptor

- **Dual targeting**
  - 2 antigen recognition domains
    - Expressing multiple CARs in 1 T cell
    - Infuse multiple T cell products
  - Combination CD19 CD22 CAR
Dual Targeting

A Coadministration

B Bicistronic

C Cotransduction

D Tandem

SHAH ET AL, FRONTIERS IN ONCOLOGY, 2019
CD19 and CD22 expression

Stem cells do not express CD19 or CD22
Prevention of Severe CRS
Prevention of Severe CRS

**Early Tocilizumab study**
- Randomized to early Tocilizumab administration based on amount of leukemia in marrow prior to T cell infusion
  - ≥40% blasts in marrow = high tumor burden
  - Attempt to prevent severe CRS

**Earlier referrals**
- Patients coming with lower disease burden
  - With lower disease burden there is decrease risk of severe CRS
Future Options For Relapsed/Refractory Pediatric ALL
COG AALL1721 (Phase 2 Single Arm Trial for HR Pediatric ALL)

Often patients MRD + at end of consolidation (EOC) proceed to allogeneic stem cell transplant
  - Poor outcomes for High Risk patients

Patients on trial will proceed to CAR T cell therapy

**Eligibility**

- EOC MRD + (≥0.01%)
- Cannot have an M3 marrow at end of induction
- Cannot have an M2 or M3 marrow or persistent extra-medullary disease at the completion of 1st line consolidation therapy
- CNS + eligible if no active CNS involvement at enrollment

Loss of CAR T cell persistence within 6 months
  - Patients with early B cell recovery or who become MRD + again may receive a re-infusion
Future Concepts

Manufacture CAR T cells modified to secrete immune stimulatory cytokines
- IL12 is a pro-inflammatory cytokine
- Promote T cell expansion
- Goal is to result in increased antitumor efficacy
- Modulates the tumor microenvironment, making CAR T cells resistant to suppression from regulatory T cells

Combine CAR T cell therapy with Inotuzumab
- Inotuzumab: Anti CD22 monoclonal antibody
- Attempt to prevent CD19 negative relapse
Relapsed AML, T Cell ALL, and Solid Tumors
Relapsed AML

- Often have chemo resistant/refractory disease at relapse
- Limited therapeutic options
- SCT providing the only curative potential

AML CARs

- CD33: expressed on AML and myeloid progenitor cells
- CD123: expressed on AML cells, myeloid progenitor cells and AML leukemic stem cells--involved in resistance to chemotherapy and relapse after initial therapy
- Potential for irreversible myelotoxicity
- Should have BMT donor available

PICTURE: HOFMANN ET AL, JOURNAL OF CLINICAL MEDICINE, 2019
CAR T Cells for T Cell ALL

**T Cell ALL:** 15-25% of cases of ALL

**Shared target antigens**

- T cell leukemia
  - T cell leukemia destruction

- Normal T cell (on target/off tumor toxicity)
  - Leads to immunodeficiency

- CAR T cell (on target/off tumor toxicity)
  - Potential killing of CAR T cells → CAR T cell fratricide
Solid Tumors: Barriers

- Tumor Associated Antigen
- Tumor Microenvironment
- Inefficient Trafficking
- Heterogeneous Expression
CAR T Cells for Solid Tumors: Lack of Unique Tumor Associated Antigen

Difficult to find specific tumor antigen uniformly expressed on solid tumors.

Many solid tumor antigens are not unique to the tumor and are expressed on indispensable tissues causing excessive toxicity.

- **Renal cell cancer**: hepatotoxicity due to expression on bile duct epithelium
- **Metastatic colon cancer**: pulmonary toxicity due to expression on lung epithelium
CAR T Cells for Solid Tumors: Heterogeneous Expression

Heterogeneous antigen expression

- Solid tumors show variability in antigen expression to avoid recognition by the immune system
- Look at targeting multiple antigens to avoid immune escape

Tumor heterogeneity. Each patient behaves differently.

- **Inter-patient heterogeneity**: each tumor is genetically different due to factors like germ line mutations and immune surveillance
- **Intra-tumor heterogeneity**: within a tumor there are distinct clonal subpopulations with different genetic phenotypes. A clone that escapes the primary site may develop heterogeneity in the metastatic site.
CAR T Cells for Solid Tumors: Inefficient Trafficking

Trafficking: CAR T cells must travel to tumor site

- Irregular tumor blood flow impairs trafficking of CAR T cells (outgrow blood supply, new vessels are irregular, hypoxia to tumor cells)
- CAR T cells lack ability to degrade extracellular matrix. Results in poor tumor penetration.

Local delivery of CAR T cells

- Decreased systemic toxicity
- Only controls local site
CAR T Cells for Solid Tumors: Immunosuppressive Tumor Microenvironment

- Create a hostile tumor microenvironment making it inhospitable to T cells (both CAR and tumor specific T cells)
  - Impedes engagement of CAR T cells with antigen
  - **Hostile tumor environment induced by immunosuppressive cytokines and expression of inhibitory molecules like PD ligand 1 (PD-L1)**
    - Induce T cell exhaustion and/or dysfunction
    - Decrease T cell mediated tumor immunity → tumor proliferation
  - Enhance tumor escape
  - **Metabolic barriers**
    - Inhibit T cell proliferation
      - Hypoxia
      - Nutritional starvation

Solid tumors flourish in restrictive locations. Have evolved mechanisms to actively suppress the immune system.
Access
Access

Geographical barriers
- Wider access at more local centers now that FDA approved, but still access can be difficult

Financial barriers
- Cost and insurance

Infrastructure
- Need facilities and expertise
- Meet the needs of the target population
- Need successful manufacture and infusion in a timely manner
- Central manufacturing: supports greater standardization, quality oversight, minimizes variability between products, increased product turnover
Long Term Follow Up

**CAR T Cell Long Term Follow Up Study**
- Secondary cancer
- Autoimmune disorder
- Infections
- Contraception
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