Chimeric Antigen Receptor-engineered T cells for B acute lymphocytic leukemia

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Introduction: B Acute Lymphoblastic Leukemia

B acute lymphoblastic leukemia (ALL) is a cancer that affects the early white blood-forming cells in bone marrow. Chemotherapy treatment only achieves 33% survival rate in adult ALL , far from the 90% seen in children.

Immunotherapy has a great potential for the treatment of lymphomas and leukemias by redirecting T cells specificity to a tumor-associated antigen (TAA).The constructions that allow TAA recognition by T cells are called single chain antigen receptors (CARs).

Objectives

- Understand the basic molecular mechanisms of CAR therapy.
- Analyze the different variables present in clinical trials.
- Analyze the efficacy of CAR-engineered T cells in the ALL treatment.
- Explain the possible toxicities and the future challenges to improve CAR therapy.

Methodology

- Scientific literature search on PubMed based on specific words such as: CAR T Therapy, immunotherapy, lymphodepleting.
- Scientific literature search on specialized books.
- Interview done to Dr. Sonia Guedan, specialist in CAR therapy.

Principle of CAR therapy

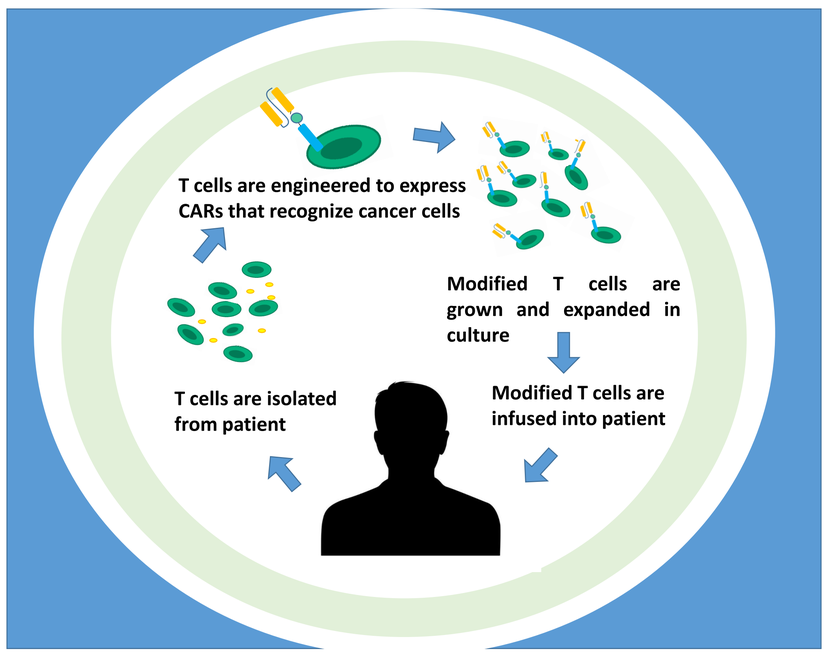


Figure 1. CAR therapy overview. Modified from "Living Therapies: Developed at MSK Provide New Approach for Cancer Treatment by Julie Grisham"

CAR structure

- Exodomain: it consists in the single-chain fragment variable (scFV) and it provides specificity to CAR. Derived from a murine monoclonal Ab that links to a TAA independent of the MHC.
- Transmembrane domain: such as CD8.
- Endodomain: which activates T cells. It includes cytoplasmatic domains that transmit activation signals such as CD3, CD28 or 4-1BB. The CARs can include more than one activation domain and it results in first-, Second- and third-generation CARs.

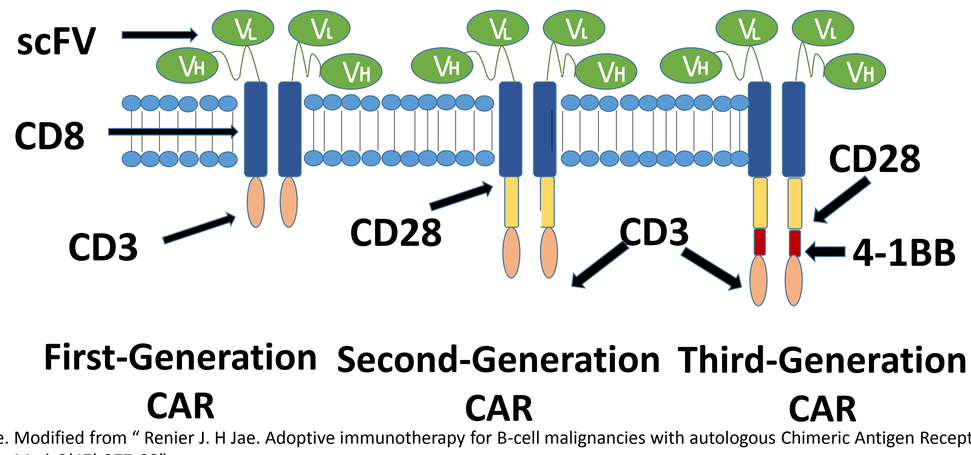
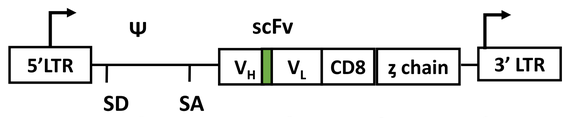


Figure 2. CAR structure. Modified from " Renier J. H Jae. Adoptive immunotherapy for B-cell malignancies with autologous Chimeric Antigen Receptor Modified Tumor Targeted T cells. *Discov. Med.* 9(47):277-88".

Gene modification of T cells

- Virus Vector-based approaches: using gammaretrovirus or lentivirus.

CAR retroviral vector:



- Non virus-based approaches: random Integration with electroporation or transposon-based Integration.

Tumor-associated antigen

- CD19: highly expressed on B cells, both malignant and normal. It's the most TAA used in CAR therapy.
- CD22: also expressed on B cells. It could be useful in case of immune escape with CD19-blasts.
- Others: CD20, ROR1.

Prior Conditioning chemotherapy

Most of the clinical trials use prior Conditioning chemotherapy, which include y-irradiation or cyclophosphamide. It is used before CAR T cell infusion for two reasons.

Lymphodepleting eliminate endogenous T cells that compete with transferred CAR cells for cytokines.

Lymphodepleting reduces tumor mass prior to CAR-modified T cell infusion

Although it's clearly demonstrated in pre-clinical and clinical trials that prior conditioning chemotherapy provides better results it is still being studied which one of this two factors is more relevant and which kind of conditioning chemotherapy is more effective.

PROBLEM → Patients with relapsed-ALL could present resistance to conditioning chemotherapy as they were treated before with chemotherapy

Clinical trial results with CD19-specific CAR+ T

Institution	UPenn	NCI
Patient population	-Relapsed/refractory ALL -N=30 -Age 5-60 years old -Detectable disease before CAR infusion N=24 .MRD-(minimal residual disease) N=5 -Morphologic remission, MRD not assessed, N=1	-Relapsed/refractory ALL -N=21 -Age 1-30 years old -Detectable disease before CAR infusion, N=21
Patients who had failed prior alloHCT	N=18 of 30	N=8 of 21
Lymphodepletion before CAR	Variable	Fludarabine/cyclophosphamide
CAR-signaling endodomain	CD137+CD3	CD28+CD3
Gene transfer approach	Lentivirus	Retrovirus
Persistence of CAR-T cells	Up to 2 years with continued follow-up	No CARs detected after day 68
Response	CR/CRi(N=27)=90% MRD-ve(N=22)=73% (Median follow-up; 7 months)	CR/CRi(N=14)=70% (B ALL) MRD-ve (N=12)=60%(BALL) (Median follow-up 10 months)

Conclusions

- Clinical Trials using CAR therapy are in phase I and II and the most used TAA is CD19. There is a high interest in other TAAs as CD22.
- Conditioning therapy has a great importance in CAR therapy results.
- The main limitations of this technique are:
  - The short-follow up post T cell infusion when it has to be done an allogenic stem cell transplantation.
  - The relatively small among of patients treated until now.
- The main toxicities detected are B-cell aplasia (ameliorated by infusing immunoglobulin), liver toxicity (difficult to correct) and cytokine storm (ameliorated by introducing antibodies blocking TNF and IL-6).

Bibliography

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