Chimeric Antigen Receptor-engineered T cells for B acute lymphoblastic 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.
• Explain 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
CAR therapy is a type of gene therapy in which T cells are modified to express CARs that recognize cancer cells. The CARs consist of three main parts: the extracellular domain, the transmembrane domain, and the intracellular domain.

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 transposition-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, RO1.

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.

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.

Gene transfer approach
Lentivirus Rétrovirus

Persistence of CAR-T cells
Up to 2 years with continued follow-up No CARs detected after day 60

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)

Conclusion
• 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 TAsAs 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).

Clinical trial results with CD19-specific CAR+ T

Bibliography
- Altadill Ferrando, Cinta – Universitat Autònoma de Barcelona