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Chimeric Antigen Receptor T Cell (CAR T Cell) Therapy- An Overview

Introduction

- CAR T Cell therapy is a form of immunotherapy where a patient's own T Cells are genetically engineered to express chimeric antigen receptors (CARs) that specifically recognize cancer cell antigens.
- Enables targeted killing of cancer cells in a Major Histocompatibility Complex -unrestricted manner, overcoming tumor evasion of immune detection.
- India's first indigenous CAR T Cell Therapy – NexCAR19 (Actalycabtagene autolucel), developed by ImmunoACT, was approved in 2023 and has been employed to treat various B Cell lymphomas such as diffuse Large B Cell lymphoma, primary Mediastinal B Cell lymphoma, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, high grade B Cell lymphoma and also B Cell Acute Lymphoblastic Leukemia.

Steps involved in CAR T Cell therapy

- **Patient evaluation:** Assess disease status, prior treatments, and eligibility.
- **Leukapheresis:** Collection of patient's own T cells for engineering.
- **T Cell Engineering:** Genetic modification using viral vectors to insert CAR genes and cultivation of CAR T cells in the lab.
- **Lymphodepletion:** Cytotoxic chemotherapy (e.g., Fludarabine, Cyclophosphamide) to prepare host for CAR T Cells.
- **CAR T Cell infusion:** Intravenous administration of engineered cell therapy products.
- **Monitoring :** Intensive observation for cytokine release syndrome (CRS) and supportive care to optimize therapy outcomes

Pharmacology

- CAR T cells are "living drugs" with integrated CAR genes that confer sustained activity and potential long-term persistence.
- **Pharmacodynamics:** The CARs on engineered T cells are synthetic receptors composed of an extracellular antigen-binding domain usually Single-chain variable fragment, hinge, transmembrane, and intracellular signaling domains e.g., Cluster of differentiation 3ζ (CD3ζ,), costimulatory domains like CD28 or CD137. When the CAR engages its specific antigen on tumor cells, it triggers receptor activation, leading to T cell activation. Activated CAR T cells release an array of cytokines such as Interleukin -2, Interferon -γ, and Tumor necrosis factor-α, which mediate immune cell recruitment and tumor cell apoptosis. They also secrete cytolytic granules containing perforin and granzyme B, directly inducing apoptosis of targeted cancer cells.
- **Pharmacokinetics:** The duration of CAR T cell activity varies widely among patients, typically lasting from several months to years, depending on factors like the persistence of CAR T cells, immune environment, and tumor burden.
- **Do CAR T cells get destroyed like our natural T Cells?**

  Yes, CAR T Cells can be eliminated over time by mechanisms such as activation-induced cell death, immune clearance, or exhaustion, like natural T Cells. However, many CAR T Cells can persist for extended periods, sometimes for years, providing durable remission.

- **In summary,** receptor activation on CAR T cells leads to cytokine secretion and cytolytic activity, with the duration of persistence being variable but often prolonged, and their eventual destruction like natural T Cells, contributing to long-term immune surveillance.

Pharmacotherapy & clinical management

- **Pre-medications:** Acetaminophen and Antihistamines to prevent infusion reactions.
- **Lymphodepleting chemotherapy:** Customized chemotherapy regimens tailored for each patient.
- **Supportive therapies:** Anti-infectives, Antiemetics, seizure prophylaxis if necessary.
- **Toxicity Management:** Tocilizumab reserved to treat severe CRS and other immunological adverse events.
- **Closely monitoring :** Any delayed adverse drug reactions or toxicity.

Conclusion

CAR T cell therapy necessitates intricate collaboration among oncologists, pharmacists, nurses, and laboratory staff. Careful safety oversight and prompt identification of side effects are essential for ensuring positive patient results. Ongoing research is improving outpatient administration protocols and expanding indications.