CHAPTER

Recent progress in CAR-T cell therapy for B-cell cancers with resistant tissues

4

Rajesh Kumar[a], Seetha Harilal[a], Mohd Aftab Siddiqui[b], Mohhammad Ramzan[c], Sumel Ashique[c]

[a]*Faculty of Pharmaceutical Sciences, Kerala University of Health Sciences, Thrissur, Kerala, India,*
[b]*Faculty of Pharmacy, Integral University, Lucknow, Uttar Pradesh, India,*
[c]*School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India*

4.1 Introduction to chimeric antigen receptor-T cell therapy

4.1.1 Overview

T lymphocytes (T cells) are the white blood cells that play an important function in the adaptive immune response. The T cells can be genetically modified and engineered to produce chimeric antigen receptor (CAR)-T cells, which can recognize cancer cells and destroy them without harming other healthy cells (Feins et al., 2019). The procedure starts with leukapheresis to extract the T cells, which are seen in the blood of the patients. The cells then undergo treatment ex vivo to make them express CARs. In this process, the gene bearing the code for the CAR is introduced into the genome of the T cell through the use of viruses such as lentiviruses/ retroviruses. The T cells that are modified and have the CAR are cultured to expand the amount as they are to be transplanted back into the patient. During this expansion, the CAR-T cells are multiplied, increasing their quantity, thus providing sufficient amounts to directly attack and destroy the cancer cells (Nair & Westin, 2020). All these processes from cell collection to reinfusion are conducted under GMP to ensure that the final CAR-T cell quality is not compromised. The CAR itself is a chimeric protein that has three domains: An extracellular antigen-binding domain, a transmembrane domain, and a cytoplasmic signaling domain. The antigen-binding domain is typically derived from a monoclonal antibody that can interact with a specific tumor-associated antigen (TAA), resulting in CAR-T cells to selectively target those cells expressing that specific antigen, minimizing the damage to normal cells. The transmembrane domain attaches the CAR to the membrane of the T cell. The intracellular signaling domain participates in the activation of T cells as well as mediates the initiation of the signaling cascade leading to the activation of T cells, further cloning, and cytotoxicity. Signaling domains such as CD28, CD137 (4-1BB), and OX40 also play a role in modulating the T cell as well as its survival rate based on the design of CAR. CAR signaling domain selection is one of the most important factors in CAR design since it can considerably influence the treatment's efficacy and safety (Xie et al., 2023). Although CAR-T cell therapy has been effective, it causes side effects, including cytokine release syndrome (CRS), neurotoxicity (CAR-T-cell-related encephalopathy syndrome), as well as B-cell aplasia, which com-

Advancements in Personalized Cellular Immunotherapy. https://doi.org/10.1016/B978-0-443-27731-3.00008-5