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Editorial

CAR-T Cell Immunotherapy: Hopes and Challenges for Cancer Treatment

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Chimeric antigen receptor T (CAR-T) cell is a novel class of immunotherapy that involves genetically manipulating immune cells derived from the patient to better recognize tumor antigen. This cell-based gene therapy has become the standard of care in some hematological malignancies including pediatric acute lymphoblastic leukemia and for certain types of Non-Hodgkin lymphomas. Three kinds of CAR-T cell therapies, Kymriah, Yescarta were approved for clinical application in 2017, and Tecartus was approved in 2020, while several others are still under the clinical trial phase. These approved therapies target CD19, a surface antigen, found on B cells. CAR-T cells have existed since the late 1980s but over the years the design has become more complex and more effective as our knowledge of how the immune system functions have expanded. There have been four generations of CAR-T cells. The first-generation CAR construct consisted of a single-chain variable fragment (ScFv) antigen-recognition domain, a transmembrane domain, and an intracellular T cell activation domain derived from the CD3 zeta chain but there was no costimulatory domain included, so these cells had limited capabilities as far as expansion and cytotoxicity were concerned. The second generation of CAR constructs addressed this limitation and added the intracellular costimulatory domain (either CD28 or 4-1BB) and are being commercially used as current CAR-T cell therapy. The third generation of CARs combined multiple costimulatory domains (e.g., CD3 ζ-CD28-41BB, CD3 ζ-CD28-OX40) to augment T cell activity. The fourth generation of CAR constructs consists of a similar co-stimulatory domain to the previous generation but adds factors such as IL12, and other costimulatory ligands which augments T-cell activation and activates innate immune cells to eliminate antigen-negative cancer cells in the targeted lesion. This generation of a CAR construct is still being investigated in preclinical studies, with the hope that they will result in better effector functionality and have improved persistence in the patient. While these constructs are improving potential efficacy for CAR-T cell therapy, there are still technical challenges involved with getting them produced and infused into patients on time. Fortunately, there has been technological developmental design to speed up the process of creating CAR-T cells and getting them to patients quickly.

The creation of CAR-T constructs starts with the isolation of T cells via apheresis and is then engineered to express tumor-specific receptors usually using a retroviral and lentiviral vector. The newly modified cells are expanded ex vivo then injected back into the patient who is monitored over time to determine the persistence and efficacy. For clinical applications, the purified T cells generally come from the patient or an allogenic donor. In these cases, after the blood is taken and separated, magnetic beads containing antibodies to T cell surface markers are mixed with PBMCs. The antibody beads conjugate binds with T cells which are then isolated and ready for activation and expansion. T cell activation generally requires a cell medium containing IL-2 and antibodies to CD3. Once cells are expanded, they are ready to be transduced with an appropriate vector using retroviral vectors, and the production and testing of which can take some time. Recently there have been CAR constructs created using the CRISPR-CAS9 system instead of retroviral vector. While this is an active and exciting area of research, it is still too early to tell how successful this method will be in the long term. Once the cells have been transduced and tested, they are ready to be re-infused into the patient. The protocol for this therapy varies across the clinical centers and even from patient to patient but generally requires a patient to undergo lymphodepletion chemotherapy before being reinfused with CAR-T cells. This is to decrease the competition between CAR-T cells and normal cells such as interleukins and other factors in the body. Once CAR-T cells have been reinfused, the patient is then closely monitored for the impact of therapy having on cancer, CAR-T cells persistency, and ad-

verse side effects. The monitoring of the patient is critical as CAR-T cells therapy can have several potentially dangerous side effects including cytokine release syndrome and neurotoxicity, cytopenias, hypogammaglobulinemia, and allergic reactions.

Although CAR-T cell therapy represents an exciting advance in cell-based gene therapy, this is still facing many challenges. Some of the biological challenges are tumor antigen escape, on-target off-tumor effect, accessing solid tumors, overcoming immunosuppressive tumor microenvironment, and CAR-T cell-associated toxicities. Some of the technical challenges are identifying appropriate targets and the time required to create personalized medicines. Identifying new more specific targets is an active area of study. So, while the technical challenges of CAR-T cell therapy are being worked out and biological challenges are being studied, the future of this unique approach to fight cancer looks promising.