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BRAZIL IN THE USE OF CRISPR/CAS9 TECHNOLOGY IN THE CAR-T CELL. IMMUNOTHERAPY PRESENTS POSITIVE AND SAFE CLINICAL RESULTS IN THE TREATMENT OF CANCER.

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INTRODUCTION

The year 2022 marked the tenth anniversary of the development of CRISPR, and over the past decade, immunotherapies and cellular therapies have gained attention as promising alternative treatments for cancer, aiming to stimulate the patient's immune system. The latest immunotherapy relies on modified specialized immune T cells, which have the T cell receptor (TCR) on their surface to recognize foreign antigens bound to the MHC. Although the immune system can continuously eliminate malignant cells, tumor cells can evade the patient's immune system through negative regulation or mutation of the MHC in T cells, preventing activation of the body's additional defense mechanism.For this reason, through the CRISPR technique, patients' T cells are genetically modified to express multivalent chimeric antigen receptors (CARs), capable of recognizing tumor-associated antigens (TAAs) on tumor cells. These modified cells are then infused back into the patient's bloodstream. Recent clinical trials in Brazil have focused on four types of T cell editing to cure cancer, including general T cells, tumor-infiltrating lymphocytes (TIL), T cells carrying T cell receptors (TCR), and T cells carrying chimeric antigen receptors (CAR-T cells). During CAR- T cell treatment, the patient's T lymphocytes were collected, modified in vitro, and reinfused into the patient to provide increased efficiency and potency in targeting tumor cells. CAR-T immunotherapy has shown remarkable results and has become a promising therapy for the treatment of refractory or relapsed solid cancers. However, various obstacles such as T cell exhaustion, antigen escape, toxicity, CAR-T cell trafficking, cytokine release syndrome from the immunosuppressive icroenvironment, insertional oncogenesis, and so on have been associated with CAR-T cells. However, it is important to report that we are currently in the phase of punctual clinical trials in the use of CRISPR gene therapy, and only if they are successful, we can move forward to broader tests. Brazil has ample intellectual and technological capacity to participate in this story and advance research with CRISPR, having in its favor an extremely relevant population genetic diversity. By combining gene editing with the genomic database of Brazilians, we open up horizons for diagnostic tests and unimaginable treatments that can bring advancements to research worldwide. In this work, we will show everything that currently exists in Brazil regarding the application of CRISPR/Cas9 technology in CAR-T cells and its positive and safe clinical outcomes for cancer treatment.

CRISPR/CAS9 TECHNOLOGY IN THE CAR-T CELL

CAR-T cells are self-replicating cells that have made significant strides in the treatment of malignancies. The advancement of CAR T cell treatment is an example of translating fundamental research into clinical practice. In recent years, new generations of CAR-T cells have generated a great lot of excitement in the field of cancer treatment. Despite recent success in many clinical studies, CAR-T cell treatment has resulted in substantial morbidity and death from related toxicities. The cytokine release syndrome and neurotoxicity are the primary reasons for the clinic's limited usage of CAR-T cell treatment. With a greater knowledge of the mechanism of toxicity, substantial advances in CAR-T cell therapy toxicity control may be made. While CAR treatment has shown significant effectiveness in hematological malignancies, its main goal is to investigate its potential in non-hematological tumors. It seems as if novel immunotherapy methods will be required to overcome the many obstacles that CAR-T cell treatment faces in solid tumors. However, this type of immunotherapy is still very new, so there is still much to learn about how well it works. Current development in gene editing tool has critically enhanced the development of gene editing from bench to clinical practice, especially CRISPR/Cas9 that has become an encouraging tool for creating gene knockouts. Unlike other gene-editing tools that require engineering of unique proteins for each target sequence, CRISPR/Cas9 offers support to T-cell based immunotherapies and development of next-generation and universal CAR-T cells due to its ease of handling and flexibility as only varying guide RNA is required in all cases and the same nuclease protein Cas9. Moreover, CRISPR/Cas9 capacity for multiple gene-editing and competency in editing primary T-cells makes it more scalable compared to other gene-editing tools. In sum, we guess that more CRISPR/Cas9 based studies to improve CAR-T cell safety efficacy, and accessibility should be conducted to reach the desired therapeutic outcomes in the clinic. Also From the detailed observation of above two clinical studies, we can say that ex vivo CRISPR/Cas9 engineered CAR-T therapy may be a promising line of treatment as they appear clinically safe with tolerable side effects and has been proven to hold immense potential to treat several cancers. The inclination towards off-the-shelf treatments is particularly interesting, given the possibility for quicker and broader access. Recently, researchers are working on developing natural killer cells and stem cell-derived cells to target cancers in addition to allogenic products.

CONCLUSIONS

The first therapies that use a CAR-T Cell had their use approved in Brazil by the National Health Surveillance Agency (Anvisa) this year. The first, authorized in February, may be indicated for cases of acute lymphocytic leukemia (ALL) and diffuse large B-cell lymphoma. The second, approved in March, is recommended for patients with multiple myeloma. In addition, several studies are evaluating the application of the technique to other types of hematological cancers and scientists are optimistic that, soon, new treatments will be available. The first gene therapy approved in the country was Kymriah® (tisagenlecleucel), from the company Novartis Bioscience, whose use was already authorized in several other countries. In Brazil, treatment may be indicated for ALL patients aged up to 25 years and adult patients with Diffuse Large B-Cell Lymphoma. The second, Carvykti® (ciltacabtageno autoleucel), from the company Janssen-Cilag Farmacêutica, is recommended for multiple myeloma patients who have already undergone at least three previous therapies. Six CAR-T immunotherapy drugs have already been approved by the U.S. Food and Drug Administration (FDA) and the European Commission (EC) between 2017 and starting of 2022

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