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Perspective

The Changes that Occur in Cell Functions after CAR T Cell Treatment in Patients with Resistant Myeloma

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DESCRIPTION

For patients with recurrent or refractory illness, Chimeric Antigen Receptor (CAR) T cell therapy has completely changed the treatment landscape for hematological malignancies. CD19-CAR T cells have the potential to be curative for a subgroup of patients, particularly those with lower baseline tumor sizes and deep early responses, according to long-term follow-up studies. Crucially, research has demonstrated that CD19-CAR T cells can endure for years, indicating their potential role in long-lasting remissions and even healing. Furthermore, the ZUMA-1 experiment has reported favorable effects on the activation of non-CAR immune cells. Due to encouraging early results and high response rates, Idecabtagene vicleucel (Ide-cel) and Ciltacabtagene autoleucel (Cilta-cel) have been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of triple-class exposed relapsed/refractory Multiple Myeloma (MM). It is yet unclear how long-lasting these reactions are, how long BCMA-CAR T cells remain persistent, and whether they have any impact on bystander T cells. It is also necessary to investigate the effect on side effects such as extended cytopenia and Cytokine Release Syndrome (CRS).

The FDA and EMA's approval of Ide-cel completely changed the Relapsed/Refractory Multiple Myeloma (RRMM) treatment market. However, this study addressed these factors in the current work because the dynamics of BCMA-CAR T cells, as well as the impacts on bystander cells and side effects, are still not fully characterized. Pre-infusional traits that were linked to unfavorable results, such as increased sBCMA levels and insufficient Low Density Protein (LDP) has been discovered, and demonstrated that CAR T cell growth is connected with both superior response and the development of CRS. Prolonged cytopenia accompanied the latter. Although the *in vitro* activity of isolated CAR T cells did not differ significantly between responders and non-responders, there were notable impacts on bystander T cells.

It has been demonstrated that the kinetics of CD19-directed CAR T cells follow three distinct phases: expansion, contraction, and persistence. In individuals with B-cell neoplasia, response and outcome are associated with CD19-directed CAR T cell growth. Furthermore, the disease progressed quickly and there was no response to the lack of expansion.

In this study most of the patient's CD19-targeting CAR T cells were undetectable in peripheral blood 100 days after infusion, even in those who had sustained response. This is in contrast to CD19-targeting CAR T cells in Acute Lymphoblastic Leukaemia (ALL) and Diffuse Large B-Cell Lymphoma (DLBCL), which require long-term persistence for durable remissions.

This is also different from the KarMMa experiment, where CAR T cell levels lasted up to a year. Using different analysis techniques could account for these discrepancies. Flow cytometry finds CAR-expressing T cells directly, but Quantitative Polymerase Chain Reaction (qPCR) quantifies CAR transgene levels more sensitively, allowing for longer-term tracking of CAR T cells.

Following infusion, the data showed that the compartment was dominated by CD8+ CAR T cells, which is consistent with a study using non-commercial BCMA-CAR T cells. It has been shown that several CD19-targeting infusion products already had this shift in responder's favor of CD8+ CAR T cells.

Additionally, study found that the significantly lower cell counts and lower cytotoxic activity upon infusion explained the limited significance of CD4+ CAR T cells. The findings demonstrate that, as with patients receiving Tisa-cel treatment, following CAR T cell infusion, naïve CD8+ T cells (CD45RA+CD45RO-CCR7+) are essentially nonexistent, and the majority of CD8+ T cells are characterized by an effector memory phenotype (CD45RA-CD45RO+CCR7-), which subsequently transitions to an effector subtype (CD45RA+CD45RO-CCR7-).

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