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Perspective

CAR T-cells therapy as a ray of hope for cancer treatment

Hitesh Chopra[1,*], Shivani Chopra[2], Sonia Arora[3], Kuldeep Dhama[4]

[1] Centre for Research Impact & Outcome, Chitkara College of Pharmacy, Chitkara University, Rajpura 140401, India
[2] Department of Biosciences, Saveetha School of Engineering, Saveetha Institute of Medical and Technical Sciences, Chennai 602105, India
[3] Chandigarh Group of Colleges Landran, Kharar 140307, India
[4] Division of Pathology, ICAR-Indian Veterinary Research Institute, Bareilly 243122, India
*** Corresponding author:** Hitesh Chopra, chopraontheride@gmail.com

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Abstract: New hope for patients with specific blood malignancies has arisen with the emergence of chimeric antigen receptor (CAR) T-cell therapy as a revolutionary approach to cancer immunotherapy. This groundbreaking therapy modifies a patient's immune system such that their own T cells can identify and destroy cancer-specific antigens by expressing CARs. Multiple myeloma, lymphomas, and leukemias are among the blood malignancies that have been treated with six CAR T-cell treatments that have been approved by the FDA since 2017. The treatment entails drawing T cells out of the patient's blood, changing their genes to produce CARs, and then reintroducing these modified cells into the patient. The CAR T-cells have the ability to identify cancer cells, proliferate, and kill them once they enter the circulation. This might lead to long-term protection from the illness. Patients with blood malignancies who have relapsed or are resistant to previous treatments have shown encouraging results in clinical studies, with some patients even managing to achieve long-term remissions. Cytokine release syndrome and neurological toxicities are two of the many potential adverse effects of CAR T-cell treatment that must be carefully managed. The complicated production method and expensive treatment cost further restrict its broad availability. Research is ongoing with the goals of improving the safety profile, increasing the effectiveness, and expanding the applicability of CAR T-cell therapy to solid tumors.

Keywords: CAR-T; cancer; solid tumors; leukaemia

Cancer immunotherapy, also known as chimeric antigen receptor (CAR) T-cell therapy, makes use of T-cells, a kind of immune cell, that have been genetically modified in a lab to better target and eliminate cancer cells. CAR T-cell therapy is showing great promise in the treatment of some blood malignancies, and although researchers are still gathering long-term data, it is already being used clinically. Several CAR T-cell therapies have been licensed by the FDA for use by patients with specific blood malignancies who have not responded to prior chemotherapy and other treatments. In addition to treating newly diagnosed cases, this therapy is also used to treat patients whose blood cancer has returned after first treatment [1].

Acute lymphoblastic leukaemia (ALL) was a primary target for the early development of CAR T-cell treatments [2]. The most common form of paediatric ALL is B-cell ALL, and more than 80% of children with this diagnosis will be cured with aggressive treatment. Patients with common lymphoma now have Tisagenlecleucelas a potential treatment. However, in 2017, Tisagenlecleucel (Kymriah) emerged as a new alternative when the FDA authorized it as the first CAR T-cell therapy for the treatment of relapsed ALL in children [3].

Long-term effects of CAR T-cell treatment in children are only now becoming

clear after years of research. Children with relapsed ALL who were treated with CAR T cells in a clinical trial, for instance, have been followed for a long time, as was recently reported by a research team lead by the National Cancer Institute (NCI) [4].

CAR T-cell therapies, like other cancer treatments, are not without their risks. These include the loss of many antibody-producing B cells and the development of infections. Cytokine release syndrome (CRS) is one of the most common and dangerous adverse effects [5]. Cytokines are chemical messengers released by T cells that play a role in stimulating and guiding the immune response. Serious adverse effects, including as dangerously high fevers and abrupt reductions in blood pressure, may occur when T cells are given due to cytokine flooding. Severe instances of CRS have been known to prove lethal. Surprisingly, CRS is seen as a "on-target" impact of CAR T-cell treatment, meaning its existence proves that T cells are active in the body. Standard supportive treatments, such as steroids, may be effective in treating mild cases of CRS in many people of all ages. More advanced methods for treating CRS have been developed as researchers have acquired expertise with CAR T-cell therapy. Tocilizumab (Actemra) is a key component of such management [6]. This medication inhibits the function of IL-6, a cytokine that is often released in high levels by T cells and macrophages and was originally used to treat inflammatory disorders including juvenile arthritis [7]. Neurologic symptoms, such as severe disorientation, seizure-like behavior, and decreased speech, are another serious risk associated with CAR T-cell therapy. Neurological symptoms (also known as immune effector cell-associated neurotoxicity syndrome; ICANS) have been seen, although their specific origin is unknown. In order to improve the safety profile and therapeutic efficacy of CAR-T cell therapy, researchers and clinicians are actively seeking strategies to mitigate On-Target, Off-Tumor effects. One approach is to refine target selection in order to identify antigens that are more selectively expressed in tumor cells. Another strategy is to incorporate safety switches into CAR-T cells in order to control their activity and prevent unintended attacks on healthy tissues [8].

Lymphoma patients may be treated with fewer side effects using a modified version of the CAR T cell therapy. Research is being done to find alternative therapies for ICANS. Anakinra (Kineret), a drug used to treat rheumatoid arthritis, has been shown in preliminary research to reduce the risk of severe ICANS in patients receiving CAR T-cell treatments. For instance, a "remodelled" CD-19-targeted CAR T cell produced at NCI resulted in much less severe neurologic adverse effects in a limited clinical study of individuals with cancer.

Researchers have also started to reevaluate the origin of immune cells used in CAR T-cell therapy, shifting focus from patients to healthy donors' T cells. The hope is to have "off-the-shelf" CAR T-cell treatments that can be used right away, rather than needing to make them for each individual patient.

The genetic material for producing the CAR is delivered into T cells by a disarmed virus in all of the FDA-approved CAR T-cell treatments. However, gene-editing technologies like TALON and CRISPR are being utilized to stimulate the donor T cells to create CARs for the off-the-shelf CAR T cells now being evaluated in modest clinical studies [9].

Natural killer (NK) cells are another kind of immune cell used by other commercially available CARs. This field of study is still in its infancy, although certain CAR NK cell treatments are moving forward into preliminary clinical studies. The location of therapy production is being rethought alongside T-cell origin and immune cell kind. Several laboratories, for instance, are developing methods based on nanotechnology and messenger RNA that facilitate the in vivo generation of CAR T-cells [10,11]. CAR T-cell therapy is often only considered after all other treatment options have been exhausted and the patient's malignancy has progressed.

CAR-T cell therapy is slowly finding its place in the world of solid tumors, after being famous for its effectiveness in treating certain blood malignancies. Despite the fact that CAR-T therapy faces formidable obstacles such the intricate tumor microenvironment, antigen heterogeneity, and obstacles to tumor penetration, it is showing encouraging results as a possible therapeutic option [12,13]. To make CAR-T cells more successful against solid tumors, researchers are looking at new ways to administer them, genetic changes, combination therapies, refined target selection, and localized delivery. Optimism for improving the effectiveness of CAR-T treatment in combating solid tumors is shown by ongoing research and clinical trials, despite the difficulties. There is hope for future transformative therapeutic interventions as our knowledge of tumor biology expands and technology improves, increasing the likelihood that CAR-T cell therapy will become a viable option for treating solid tumors [12].

Patients whose non-Hodgkin lymphoma had reappeared after first-line chemotherapy have recently shown greater response rates to CAR T-cell therapy compared to the usual treatment [14]. Based on these results, several professionals have proposed that CAR T-cell therapy become the de facto second-line treatment for these patients. Although most CAR T-cell trial participants have been tracked for just a short period of time, data revealing early responses to treatment are rapidly appearing. The clinical trials reported as completed on website Clinicaltrials.gov had been reported in **Table 1** (accessed on dated 30 December 2023). Long-term follow-up of trial participants will allow researchers to forecast the durability of these reactions. More patients of all ages, both young and old, need to participate in clinical studies. Researchers may learn more about the effects of this technique, strategies to lessen its toxicity, and ways to better control undesirable side effects if they investigate larger samples and analyze them over longer periods of time.

Table 1. The clinical trials reported with keyword CAR-T therapy are represented (accessed on 30 December 2023).

NCT Number	Conditions	Sponsor	Phases	Study type
NCT03049449	Lymphoma, Large-Cell, Anaplastic|Enteropathy-Associated T-Cell Lymphoma|Lymphoma, Large B-Cell, Diffuse|Lymphoma, Extranodal NK-T-Cell|Lymphoma, T-Cell, Peripheral	National Cancer Institute (NCI)	Phase 1	Interventional
NCT02714426	Cognitive Aging	University of Florida	NA	Interventional

Table 1. (*Continued*).

NCT Number	Conditions	Sponsor	Phases	Study type
NCT01865617	CD19-Positive Neoplastic Cells Present|Recurrent Adult Acute Lymphoblastic Leukemia|Recurrent Chronic Lymphocytic Leukemia|Recurrent Diffuse Large B-Cell Lymphoma|Recurrent Mantle Cell Lymphoma|Recurrent Non-Hodgkin Lymphoma|Recurrent Small Lymphocytic Lymphoma|Refractory Acute Lymphoblastic Leukemia|Refractory Chronic Lymphocytic Leukemia|Refractory Diffuse Large B-Cell Lymphoma|Refractory Mantle Cell Lymphoma|Refractory Non-Hodgkin Lymphoma|Refractory Small Lymphocytic Lymphoma	Fred Hutchinson Cancer Center	Phase 1|Phase 2	Interventional
NCT03761056	B-cell Lymphoma	Kite, A Gilead Company	Phase 2	Interventional
NCT03958656	Myeloma-Multiple|Myeloma, Plasma-Cell	National Cancer Institute (NCI)	Phase 1	Interventional
NCT01354145	Knee Osteoarthritis	Bioiberica	Phase 3	Interventional
NCT03483103	Lymphoma, Non-Hodgkin|Lymphoma, Nonhodgkin|Lymphoma, B-Cell|Lymphoma, Large B-Cell, Diffuse	Juno Therapeutics, a Subsidiary of Celgene	Phase 2	Interventional
NCT00924326	Primary Mediastinal B-cell Lymphoma|Diffuse, Large B-cell Lymphoma|Diffuse Large B-Cell Lymphoma Transformed From Follicular Lymphoma|Mantle Cell	National Cancer Institute (NCI)	Phase 1|Phase 2	Interventional
NCT04456959	Precursor Cell Lymphoblastic Leukemia-Lymphoma	Pfizer	NA	Observational
NCT02761915	Relapsed or Refractory Neuroblastoma	Cancer Research UK	Phase 1	Interventional
NCT02348216	Refractory Diffuse Large B Cell Lymphoma (DLBCL)|Relapsed Diffuse Large B-Cell Lymphoma|Transformed Follicular Lymphoma (TFL)|Primary Mediastinal B-cell Lymphoma (PMBCL)|High Grade B-cell Lymphoma (HGBCL)	Kite, A Gilead Company	Phase 1|Phase 2	Interventional
NCT02659943	Lymphoma, B-Cell|Lymphoma, Non-hodgkins	National Cancer Institute (NCI)	Phase 1	Interventional
NCT02215967	Myeloma, Plasma-Cell|Myeloma-Multiple	National Cancer Institute (NCI)	Phase 1	Interventional
NCT03383783	Caries	Domenick Zero	Phase 3	Interventional
NCT01747486	Adult Patients Who Have Relapsed or Refractory CLL (3rd Line) or SLL	University of Pennsylvania	Phase 2	Interventional
NCT01658150	Schizophrenia|Schizoaffective Disorder	Icahn School of Medicine at Mount Sinai	NA	Interventional
NCT03338972	Recurrent Plasma Cell Myeloma|Refractory Plasma Cell Myeloma	Fred Hutchinson Cancer Center	Phase 1	Interventional
NCT04030195	Non-Hodgkin's Lymphoma, Relapsed|Chronic Lymphoid Leukemia in Relapse|Non-Hodgkin's Lymphoma Refractory|Chronic Lymphocytic Leukemia|Lymphoma, Non-Hodgkin|Leukemia, Lymphocytic, Chronic|B-cell Chronic Lymphocytic Leukemia|B-cell Non Hodgkin Lymphoma|Small Lymphocytic Lymphoma	Precision BioSciences, Inc.	Phase 1|Phase 2	Interventional
NCT02478632	HIV Infections	ViiV Healthcare	Phase 3	Interventional
NCT02926833	Refractory Diffuse Large B Cell Lymphoma	Kite, A Gilead Company	Phase 1|Phase 2	Interventional
NCT03289455	B Acute Lymphoblastic Leukemia|Recurrent Childhood Acute Lymphoblastic Leukemia|Refractory Childhood Acute Lymphoblastic Leukemia|B-cell Acute Lymphoblastic Leukemia	Autolus Limited	Phase 1|Phase 2	Interventional
NCT03019055	Lymphoma, Non-Hodgkin|Lymphoma, B-Cell|Chronic Lymphocytic Leukemia|Small Lymphocytic Lymphoma	Medical College of Wisconsin	Phase 1	Interventional

Table 1. (*Continued*).

NCT Number	Conditions	Sponsor	Phases	Study type
NCT02614066	Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia	Kite, A Gilead Company	Phase 1|Phase 2	Interventional
NCT02030847	Patients With B Cell ALL, Relapsed or Refractory, With no Available Curative Treatment Options	University of Pennsylvania	Phase 2	Interventional
NCT01626495	B Cell Leukemia|B Cell Lymphoma	University of Pennsylvania	Phase 1|Phase 2	Interventional
NCT03028870	Osteo Arthritis Knee	Purdue Pharma LP	Phase 2	Interventional
NCT02650999	CD19+ Diffuse Large B-cell Lymphomas|Follicular Lymphomas|Mantle Cell Lymphomas	Abramson Cancer Center at Penn Medicine	Phase 1|Phase 2	Interventional
NCT03744676	Lymphoma, Non-Hodgkin|Lymphoma|Lymphoma, B-Cell|Lymphoma, Large B-Cell, Diffuse|Neoplasms|Neoplasms by Histologic Type|Lymphoproliferative Disorders|Lymphatic Diseases|Immunoproliferative Disorders|Immune System Disorder	Juno Therapeutics, a Subsidiary of Celgene	Phase 2	Interventional
NCT01709799	Aged	University of Florida	NA	Interventional
NCT02601313	Relapsed/Refractory Mantle Cell Lymphoma	Kite, A Gilead Company	Phase 2	Interventional
NCT01593696	ALL|B Cell Lymphoma|Leukemia|Large Cell Lymphoma|Non-Hodgkin Lymphoma	National Cancer Institute (NCI)	Phase 1	Interventional
NCT03301623	Chronic Pain	Cedars-Sinai Medical Center	NA	Interventional
NCT01460901	Neuroblastoma	Children's Mercy Hospital Kansas City	Phase 1	Interventional
NCT02030834	Non-Hodgkins Lymphoma (NHL) Patients, With CD19+B Cell Lymphomas	University of Pennsylvania	Phase 2	Interventional
NCT01454596	Malignant Glioma|Glioblastoma|Brain Cancer|Gliosarcoma	National Cancer Institute (NCI)	Phase 1|Phase 2	Interventional

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