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NARRATIVE REVIEW

The challenge of applying genetically engineered T lymphocyte therapy to the treatment of solid tumors: A cross-sectional look at the clinical trial landscape (2003-2022)

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Abstract

Genetically engineered T-lymphocyte therapy is based on the induction of the expression of chimeric CAR or TCR receptors on the membrane of T-lymphocytes extracted from the patient's body. These receptors are designed for specific recognition of tumor antigens. In hematology, the FDA approved 2017 as the first therapy with T-CAR lymphocytes. In the case of solid tumors, numerous drugs have been tested in clinical trials without conclusive results. This article consists of a review of the panorama of clinical trials with T-CAR/T-TCR for the treatment of solid organ tumors to analyze where this therapy is currently in its development, its limits and challenges, and if there are theoretical aspects, practical and preclinical fundamentals aimed at overcoming them. We found 297 trials published since 2003 in NIH's ClinicalTrials.gov, developed in 15 countries, mainly China (51.9%) and the USA (39.4%). The CAR receiver was used in 84.8% and TCR in 15.2%. Only 2.7% were in phase 2 or 2/3, only 14.5% were reported as completed or finished, and only 3.4% had published results. These data support the conclusion that preclinical phase strengthening is necessary before achieving a successful approach using T-CAR/T-TCR therapy for treating solid tumors.

Keywords:
MESH: Immunotherapy, Adoptive; Receptors, Antigen, T Cell, alpha-beta; Immunotherapy; Medical Oncology; Randomized Controlled Trials as Topic.

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Introduction

Therapy with genetically engineered T lymphocytes consists of extracting CD8 T lymphocytes from the patient to transform them in vitro and direct their cytotoxic capacity, specifically against tumor cells. In the laboratory, the expression of a T-CAR chimeric receptor or T-TCR is induced in the plasma membrane of the lymphocyte. These receptors are designed for the specific recognition of a tumor antigen, so this therapy is included both within immunotherapy and directed cell therapies. While the CAR chimeric receptor recognizes membrane antigens located on the surface of the tumor cell, the TCR chimeric receptor does so through primary histocompatibility complex type 1 (MHC-I) in such a way that it recognizes cytoplasmic antigens that have been previously processed by the lysosomal-intracellular endoplasmic reticulum system [1, 2].

CAR T-lymphocyte therapy is widely known for its good results in treating hematological tumors. However, strategies have been designed to treat solid tumors that employ CAR-T lymphocytes and TCR-T lymphocytes [2].

Chimeric receptors are composed of three domains: a single-chain extracellular variable fragment (scFv) (responsible for antigen recognition), a transmembrane environment (serving functions of T-cell membrane anchoring and signal transduction), and an intracellular portion consisting mainly of a tyrosine-kinase subdomain known as ITAM (immunoreceptor tyrosine-based activation motif), responsible for the transduction of the signaling cascade. Depending on the complexity of the intracellular domain, four generations of chimeric receptors are distinguished depending on whether one or two costimulatory subdomains (second and third) are added to the ITAM subdomain (first generation) and release systems for substances such as cytokines or antibodies (fourth generation) [3].

Activated T lymphocytes induce the secretion of cytokines, start their proliferation and initiate cytotoxicity mechanisms (secretion of granzyme and perforin and induction of apoptosis through the Fas/Fas-L or TNF/TNF-R pathway) and chemotaxis. In addition, other immune system cells, such as CD4 T lymphocytes, macrophages, or natural killer cells, are activated [4].

While treating hematological tumors, the FDA has approved therapies with CAR T-lymphocytes since 2017. In solid tumors, numerous drugs have been used in the early phases of clinical trials without success to date [5]. However, new clinical trials continue to try to apply this cell therapy with enormous potential to the field of oncology. Thus, the question arises as to what point this therapy is in at the present moment regarding the treatment of solid tumors, what are its limits and challenges and if there are postulated theoretical or preclinical foundations destined to overcome them.

Materials and methods

Clinical trials regarding the use of T-CAR/T-TCR for treating solid tumors registered in NIH's ClinicalTrials.gov (CTgov, Bethesda, MD, USA) were selected. The first trial identified for this indication dates back to 2003. Data were collected up to April 2022. Information was collected regarding the country where the test was developed, the recipient used the antigenic target, the organ involved, the trial phase, and the status and clinical trial results. Descriptive analysis was carried out using the IBM-SPSS version 25.0 program.

Results

A total of 297 trials distributed in 15 countries were identified (Figure 1). Of these, the most significant percentages were in China (154 clinical trials, 51.9%) and the United States (117; 39.4%). Three clinical trials (1%) with participation from multiple countries were found. The first registered clinical trial with the application of T-CAR/T-TCR to a solid organ dates from 2003. However, most clinical trials (92.3%) were written between 2015 and 2022. The year with the highest number of studies enrolled was 2020 (52; 17.5%). A total of 92.6% (275) were performed in the adult population, 18 (6.1%) in pediatrics, and 1.3% (4) in both populations (Figure 2).

Of the total of 297 clinical trials, 252 (84.8%) used the CAR receptor, while 45 (15.2%) used the TCR receptor (Figure 1). A total of 69 different antigenic targets were identified, the most frequent being mesothelin (10.8%), GPC3 (7.4%), EGFR (6.4%), GD2 (6.4%), HER2 (5.7%), various targets (5.1%), B7H3 (3.7%) and CEA (3.4%) (Table 1, Figure 2). A total of 34.7% of the clinical trials (103) were designed to include multiple organs with the same antigenic target. The other clinical trials were organ specific, highlighting in order of frequency: CNS (49, 16.5%), liver (30, 10.1%), lung (17, 5.7%), pancreas 12 (4%), and colorectal 12 (4%) (Table 2, Figure 2).

Figure 1. Country distribution map of clinical trials with T-CAR/T-TCR for solid organs.

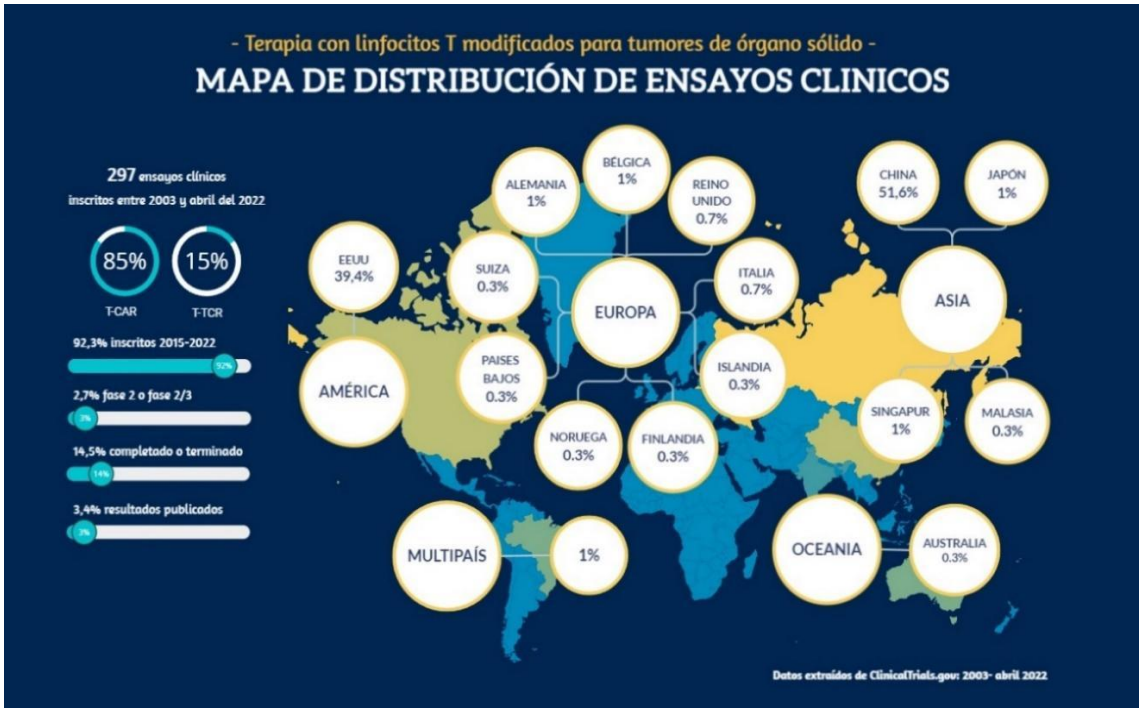


Figure 2. Population, organs, and molecular targets of clinical trials

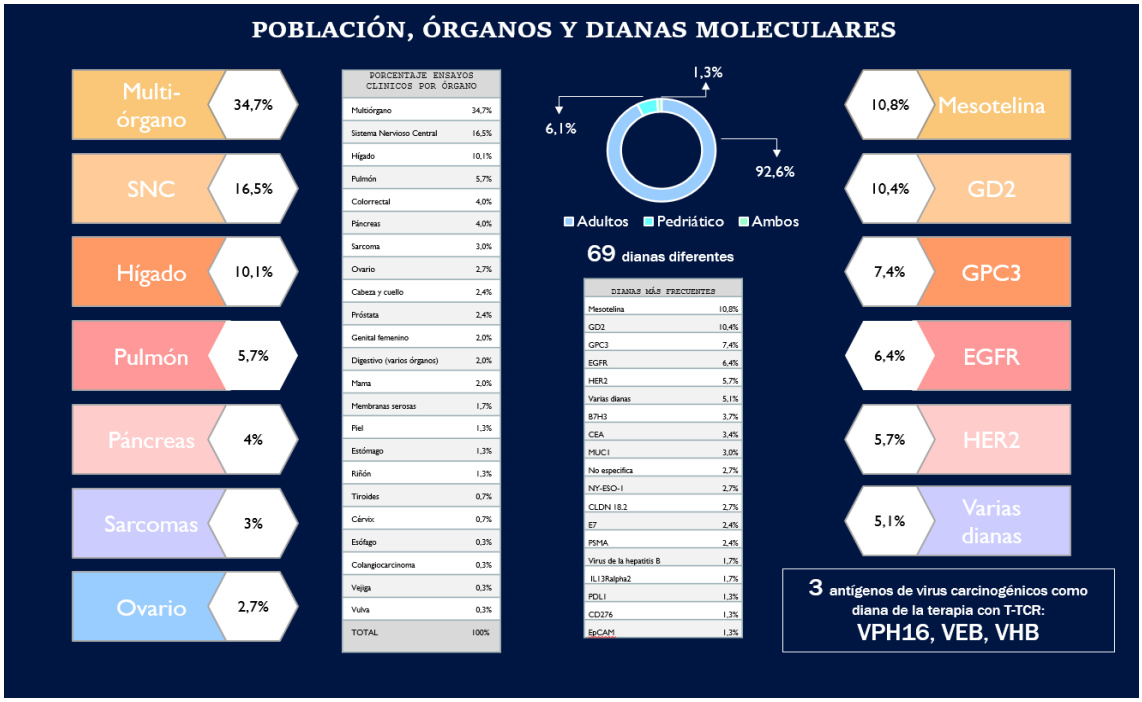


Table 2. Target Organs in Adoptive Cellular Immunotherapy Trials

Organ	Frequency	%	Organ	Frequency	%
multiorgan	103	34.7%	female genitalia	6	2.0%
Central Nervous System	49	16.5%	mesothelioma	5	1.7%
Liver	30	10.1%	Kidney	4	1.3%
Lung	17	5.7%	Stomach	4	1.3%
Pancreas	12	4.0%	Fur	4	1.3%
colorectal	12	4.0%	Thyroid	2	0.7%
Sarcoma	9	3.0%	cervix	2	0.7%
Ovary	8	2.7%	Vulva	1	0.3%
Prostate	7	2.4%	cholangiocarcinoma	1	0.3%
Head and neck	7	2.4%	Esophagus	1	0.3%
Mother	6	2.0%	Bladder	1	0.3%
Digestive (several organs)	6	2.0%			

Total 297, 100%

Regarding the phase of the clinical trial, 31 (10.4%) were early phase 1, 176 (59.3%) phase 1, 68 (22.9%) phase 1-2, 7 (2.4%) phase 2 and 1 (0.3%) phase 3. In 13 studies (4.4%), this classification was not applicable; most were studies aimed at finding new antigenic targets (Figure 1).

Regarding the clinical trial status, 49.5% (147) were listed as "recruiting." Twenty (6.7%) were active but not recruiting, 19 (6.4%) still needed to recruit, and 1 (0.3%) enrolled by invitation. Of 50 (16.8%), the current status still required to be discovered. Four (1.3%) were listed as "suspended," and 13 (4.4%) as "withdrawn." Only 24 (8.1%) appeared as completed, and 19 (6.4%) as finished. Of them, only 10 (3.4%) had published their results (Figure 1).

Discussion

Genetically engineered T lymphocytes constitute an advanced technology with great potential that, however, has not yet found the key to be postulated as a therapy to be considered in daily clinical practice for the treatment of solid tumors. The results of the search carried out in NIH's ClinicalTrials.gov (297 trials worldwide, 69 targets, major toxicities, low completion rates, and low publication of results) suggest that strengthening of the preclinical phase continues to be necessary to provide a successful response to the challenges outlined in this article. However, we are aware that beyond the trials registered on this platform, other trials are underway worldwide, each time with better molecular design, the results of which the entire scientific community awaits with expectation.

Table 3. FDA-approved drugs for the treatment of hematologic tumors.

Year	Receiver Type	Name	Pathology
2017	T-CAR CD19	Tisagenlecleucel (Kymriah®)	Refractory acute lymphocytic leukemia > 25 years, refractory diffuse large B-cell lymphoma, follicular lymphoma after at least 2 lines of treatment.
2017	T-CAR CD19	axicabtagene ciloleucel (Yescarta®)	Diffuse large B-cell lymphoma (DLBCL) Primary mediastinal B-cell lymphoma High-grade B-cell lymphoma DCLB resulting from follicular lymphoma Follicular lymphoma after at least 2 lines of treatment
2020	T-CAR CD19	brexucabtagene autoleucel (Tecartus®)	Mantle cell lymphoma after at least 2 lines of treatment
2020	T-CAR CD19	isocabtagene maraleucel (Breyanzi®)	Large B-cell lymphoma in adults, after at least 2 lines of treatment
2020	T-CAR BCMA	idecabtagene vicleucel (Abecma®)	Multiple myeloma, after at least 4 lines of treatment
2022	T-CAR BCMA	ciltacabtagene autoleucel (CarvyktiTM)	Multiple myeloma, after at least 4 lines of treatment

Table 4. Summary of the characteristics of the clinical trials whose results have been published in NIH's ClinicalTrials.gov.

NCT Record	Year	Country	Phase	Receptor and Antigenic Target	Pathology
2280811	2014	USES	1-2	T-TCR anti-E6	HPV-related tumors
2588612	2015	USES	1	T-TCR anti-NY-ESO-1	Lung cancer
3937791	2019	USES	2	T-TCR anti-E7	HPV-related female genital tumors
4015336	2019	USES	2	T-TCR anti-E7	HPV-related head and neck tumors
924287	2009	USES	1-2	anti-HER2 T-CAR	Multiorgan, HER2+ tumors
1460901	2011	USES	1	T-CAR antiGD2	CNS tumors in the pediatric population
2761915	2016	United Kingdom	1	T-CAR antiGD2	CNS tumors
1454596	2011	USES	1-2	anti-EGFRvIII CAR-T	CNS tumors
2664363	2016	USES	1	anti-EGFRvIII CAR-T	CNS tumors
3330834	2017	China	1	T-CAR anti PDL1	lung tumors

As early as 2017, Lim W. et al. established the theoretical basis for why applying genetically engineered T lymphocytes to treat solid tumors is challenging. These authors point out five trouble spots in the in vivo action process of T-CAR/T-TCR therapy that must be considered in the preclinical phase of drug design if adequate treatment is to be achieved [6].

Furthermore, Knochelmann HM et al. (2018) agree that these five points are transported to the tumor bed and migration through the parenchyma, survival in the tumor microenvironment, specificity in recognition, persistence, and proliferation, and control of tumor activity. T lymphocytes [7].

While transport is not a problem for treating hematologic malignancies, in the case of solid tumors, the modified T-cell must be able to extravasate through the neovascular tumor endothelium and the fibrous parenchyma. However, some tumors develop cytokine signal suppression mechanisms contributing to lymphocyte chemotaxis [8].

To improve transport, the induction of the expression of adhesion molecules in T lymphocytes specific for the recognition of selective proteins of the tumor vascular endothelium has been studied in the preclinical phase. Examples of this are the induction of the CD6 adhesion molecule whose ligand is ALCAM, a protein that is expressed in the tumor vascular endothelium originated by glioblastomas, or induction of CCR2 expression, which has been shown to increase anti-GD2 (glioblastoma treatment) and anti-mesothelin (mesothelioma treatment) CAR T-CAR T-lymphocyte migration [9, 10].

The adverse cytokine environment and regulation through the checkpoint can trigger lymphocyte anergy and apoptosis. In addition, the tumor competes with the T lymphocyte for metabolic supplies. Therefore, achieving the survival of T lymphocytes in the tumor

microenvironment is another significant challenge. In the literature, it is postulated to equip modified T lymphocytes with the ability to remodel the microenvironment through the synNotch system (these cells equipped with the ability to produce cytokines are known as "TRUCKs": T cells Redirected for Universal Cytokine Killing) fusing receptors for suppressive signals with stimulatory intracellular domains in the modified lymphocyte or combining T-CAR/T-TCR therapy with checkpoint inhibitors [8].

Regarding proliferation, the effective proliferative response is the best predictor of clinical efficacy. Without the addition of costimulatory domains in the intracellular portion of the receptor, no T-cell proliferation, persistence, or clinical efficacy is observed, either in vitro or in vivo. In addition, genes can be transferred to elongate telomeres, introduce modulating mechanisms of T-cell exhaustion (such as knockdown of PD1 expression), or boost lymphocyte metabolism [8].

Identifying effective tumor antigens that simultaneously have sufficient discriminatory power between self-tissue and tumor tissue is one of the significant design challenges of T-lymphocyte therapy. To date, toxicities have been reported in several clinical trials. Serious effects derive from the expression in host tissues of antigens similar to those expressed in the tumor, such that a cross-reaction identical to graft-versus-host disease occurs. Furthermore, many particular tumor tissue antigens are heterogeneously expressed only in a subpopulation of tumor cells. This would be the case for the EGFR-viii antigen found in glioblastoma [4].

Of the clinical trials analyzed in this study, trial NCT03330834 (2017, China, T-CAR anti-PDL1 for lung cancer treatment) had to be terminated due to severe toxicity after recruiting the first and only patient. The toxicity was a cytokine release syndrome that triggered grade 4 interstitial pneumonitis and required ICU admission. The NCT02664363 trial (2016, USA, anti-EGFRvIII HRCT for CNS tumors) recruited three patients before being terminated due to lack of funding; two developed grade 3 psychosis and grade 3 muscle toxicity. However, this toxicity was not registered in the clinical trial NCT01454596 for the same target, where the only profound adverse effect related to the treatment reported was a case of hypoxia.

The results of the NCT02761915 trial (2016, United Kingdom, T-CAR anti-GD2 for treating neuroblastoma in the pediatric population) were published by Straathof, K. et al. (2020), They concluded that the trial had passed without cross-toxicity phenomena. Nevertheless, the desired clinical response results still need to be obtained [11]. However, three deaths were documented in the clinical trial NCT01460901 (2011, USA) for the same molecule, and the cause is not specified.

The NCT00924287 trial (2009, USA, T-CAR anti-HER2, multiorgan) had to be terminated due to the death of the first recruited patient due to multiorgan failure in the context of a cytokine release syndrome. In the NCT02588612 trial (2015, USA, T-TCR NY-ESO-1, lung) 4, the five enrolled patients had severe adverse effects, including cytokine release syndrome and pneumonitis encephalopathy, intracranial hemorrhage, and respiratory distress. Last, in the NCT02280811 trial (2014, USA, T-TCR anti-E6 for treating HPV-related tumors), alveolar hemorrhages, febrile neutropenia, and infections were recorded among grade 3 or higher adverse effects.

Other clinical trials are not listed on the NIH's ClinicalTrials.gov search engine but have also reported severe toxicities in the literature. An example is the anti-CAIX (carbonic

anhydrase IX) T-CAR assay for renal carcinoma, which caused liver toxicity in 4/8 enrolled patients due to basal expression of CAIX in the bile duct epithelium [12].

Likewise, cases of severe toxicity related to T-CAR therapy have been published; for example, in treatment with T-CAR anti-CEACAM5, a patient suffered pneumonitis secondary to a cross-reaction with a similar protein expressed in the lung epithelium [13]. Additionally, due to cross-reaction against the lung epithelium, anti-HER2 CAR T-therapy applied in treating a patient with colorectal cancer caused acute pneumonitis which ended in death [14].

Among the strategies to improve the specific recognition of the tumor antigen are the "and-gate" circuits (a particular combination of two or more antigens to activate the lymphocyte), "not-gate" (variety in the same lymphocyte of an activating CAR to one antigen ("killing antigen") with an inhibitory CAR (iCAR) for a second antigen ("dominant antigen"), "or-gate" (two independent antigen recognition domains), and density/affinity strategies (i.e., that the lymphocyte is only activated when faced with tissues with a high density of the target antigen) [1, 2, 6].

Finally, the fifth and last challenge consists of the control of the T lymphocyte once administered. There are numerous reported cases of serious adverse effects secondary to CAR-T/TCR-T therapy, some of which are fatal, indicating the enormous action potential of T-lymphocytes once activated [3]. In addition, the adverse tumor microenvironment means that to achieve a clinical response in the treatment of solid tumors, it is necessary to design potent T lymphocytes, which increases the risk of toxicity [6]. The problem is that once the modified T lymphocyte is infused into the patient, it functions autonomously, which is why it is essential to provide the lymphocyte in the design phase of control systems [3]. An example of this is apoptosis switches (such as iCasp9) or the expression of extracellular domains of monoclonal antibody targets so that infusing the antibody into the patient could achieve lymphocyte apoptosis (for example, EGFR and cetuximab). [6]. There are also theoretical underpinnings for feedback control strategies; for example, it is theoretically possible to design feedback loops that respond autonomously to excess production of other molecules, for example, cytokines such as IL-6 [6]. This interleukin forms part of the pathophysiological foundation of the typical adverse reactions of CAR-T therapy, which are cytokine release syndrome and CAR-T-related encephalopathy [3]. Thus, an excess of IL-6 could cause the T lymphocyte endowed with the regulatory system to enter apoptosis so that severe toxicities could be avoided [6].

Conclusions

Genetically engineered T lymphocytes constitute an advanced technology with great potential that, however, has not yet found the key to be postulated as an efficient therapy in the treatment of solid tumors, both due to the multiple adverse effects reported in the literature and the lack of clinically relevant response to date. The results of the search conducted on NIH's ClinicalTrials.gov (297 trials worldwide, 69 targets, low completion rates, and low publication of results) suggest that the preclinical phase may need to be strengthened before the treatment of solid tumors with this therapy.

Nota del Editor
La Revista Oncología (Ecuador) permanece neutral con respecto a los reclamos jurisdiccionales en mapas publicados y afiliaciones institucionales.

Abbreviations

CAR: chimeric antigen receptor.

Administrative information

Additional Files

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Author contributions

Irene Solana López: conceptualization, validation, visualization, methodology, project administration, writing: revision and editing.

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Statements

Ethics committee approval

It does not apply to review studies.

Consent for publication

It does not apply to studies that do not publish explicit images such as CT scans, MRIs, or physical exam images.

Conflicts of interest

The author declares that they have no conflicts of competence or interest.

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