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REVIEW ARTICLE

Chimeric antigen receptor T-cell therapy: A narrative review of the literature

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Abstract

Chimeric antigen receptor T cell (CAR-T) therapy is one of the most advanced forms of immunotherapy. It is based on the genetic modification of T lymphocytes through the infection by a retrovirus that serves as the vector. The genetic information is translated into the production of a chimeric membrane receptor, which is directed specifically against a tumor protein. These T lymphocytes proliferate and generate an inflammatory response targeting tumor cells, in many cases achieving a curative response. This new strategy has shown promising results in the treatment of malignancies refractory to conventional cytotoxic chemotherapies, especially in acute lymphoid leukemia and certain types of Non-Hodgkin's lymphoma. This review of the literature synthesizes the principles of the genetically engineered CAR-T cells, the anti-tumoral mechanism, clinical application, and its adverse events.

Keywords: *Chimeric antigen receptor therapy. Adoptive immunotherapy. Adoptive cell therapy. T-Lymphocytes. Hematology. Genetic engineering.*

Terapia de células T con receptores de antígenos quiméricos: revisión de la literatura

Resumen

La terapia de células T con receptores de antígeno quimérico (CAR-T, en inglés) es una de las más avanzadas formas de inmunoterapia. Se basa en la modificación genética de linfocitos T por medio de un retrovirus que funciona como vector. El material genético insertado es traducido en un receptor de membrana quimérico dirigido específicamente en contra de una proteína tumoral. Estos linfocitos proliferan y generan una respuesta inflamatoria hacia las células tumorales, alcanzado incluso, en muchos casos una, respuesta curativa. Esta nueva modalidad ha demostrado resultados prometedores en el tratamiento de malignidades refractarias a quimioterapias citotóxicas convencionales, especialmente en leucemia linfoide aguda y algunos subtipos de linfomas no Hodgkin. Actualmente existen tres formas de CAR-T aprobadas por la Food and Drug Administration. Esta revisión de la literatura sintetiza los principios de la ingeniería genética de las células CAR-T, su mecanismo de acción, aplicaciones clínicas y los efectos adversos más representativos.

Palabras clave: *Terapia de células T con receptores quiméricos. Inmunoterapia adoptiva. Terapia celular adoptiva. Linfocitos-T. Hematología. Ingeniería genética.*

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Introduction

The revolutionary chimeric antigen receptor T-cell (CAR-T) therapy is at the center of attention of modern medicine in the field of hematology-oncology. This treatment is based on directing T-cells cytotoxic effect against tumor cells by combining immunotherapy with genetic engineering[1]. CAR-T cells initial development began in the 1990s, but it was unsuccessful due to a lack of expansion within the body. It took many years and research for them to acquire relevance. Currently, this treatment modality represents a therapeutic alternative in those patients with tumors that are refractory to conventional therapies, with curative responses even been shown[1].

The target molecule at which CAR-T therapy directs its action is CD19. The CD19 biomarker (cluster of differentiation 19, a differentiation antigen) is a membrane molecule expressed by both precursor and mature B lymphocytes. B-cell tumors also express this marker, which makes CD19 an appropriate molecule for directing the immune response. Owing to this, CAR-T therapies with CD19-specificity have been among the most promising treatments within cell therapies. This is due to their high selectivity against B-cell tumors, which made for them to be approved by the Food and Drug Administration (FDA) for advanced treatment of acute lymphoid leukemia (ALL) and certain subtypes of non-Hodgkin lymphoma (NHL)[2-4].

Despite its potential benefits, CAR-T therapy has been associated with a series of adverse effects that can be severe and even fatal. The most common are cytokine release syndrome (CRS) and CAR-T-related neurotoxicity syndrome[5]. Both require constant clinical monitoring for timely detection. This literature review synthesizes the mechanism, clinical applications, adverse effects, and future implications of CAR-T therapy.

Search strategy

A comprehensive literature search was carried out in the MEDLINE and EMBASE databases. “Chimeric antigen receptor T cell therapy” “CAR-T” and “Cell therapy” were used as search terms. Articles were selected according to the relevance to the purpose of this review. In addition, the snowball principle was used to identify relevant references not detected on the initial search.

Mechanism of action

In 1990, gene transfer techniques were developed for directing T cells specificity with the use of CAR. CARs are designed receptors that generate a defined specificity to an effector cell, which increases its function and immune response[6]. Antitumor activity consists of both innate and adaptive immune response complementary action. Innate immunity, comprised of natural-killer (NK) cells and myeloid cells, recognizes and kills tumor cells without major histocompatibility complex restriction. On the other hand, adaptive immunity is mediated by B and T lymphocytes through antigenic specificity controlled by antigen-presenting cells, such as dendritic cells and macrophages[1].

The chimeric receptor is made up of an extracellular, a transmembrane and an intracellular domain. The extracellular domain is made up of heavy and light chains of an immunoglobulin with the ability to specifically bind to a target molecule expressed on tumor cells surface[2]. It contains antigen recognition regions in the form of single-chain variable fragment (scFv); however, other molecules, such as cell surface receptor ligands can also be used[2]. The intracellular domain corresponding to CD3 complex Z chain (CD3ζ) provides the activation signal towards the T cell once the extracellular domain has contact with its target (Fig. 1)[1].

First-generation CARs were engineered only with CD3ζ, to mimic T cell receptors (TCRs) natural signaling. Although they were shown to destroy target cells with no problem, these CARs in turn were inefficacious in subsequent clinical studies due to their poor proliferation and limited signaling capacity[7-9].

CARs second and third generation obtained better results, and became current CAR-T therapy. They included more than one intracellular signaling domain in order to co-stimulate T cell activation through TCR and CD3ζ integration, which are responsible for the first signal, followed by one or more costimulatory receptor domains, such as CD28, 4-1BB (CD137) or OX40 (CD134), responsible for the second signal[2]. The co-stimulatory signal has been able to increase the production of cytokines, thus promoting the proliferation and survival of said T cells in order to direct their expansion in repeated exposure to antigens and avoid relapses[2]. For example, 4-1BB domain co-stimulation induces mitochondrial biogenesis and promotes memory T cells differentiation[10]. This improves CAR-T cells efficacy and generates a surveillance system that, in theory, can prevent tumor cells recurrence[2].

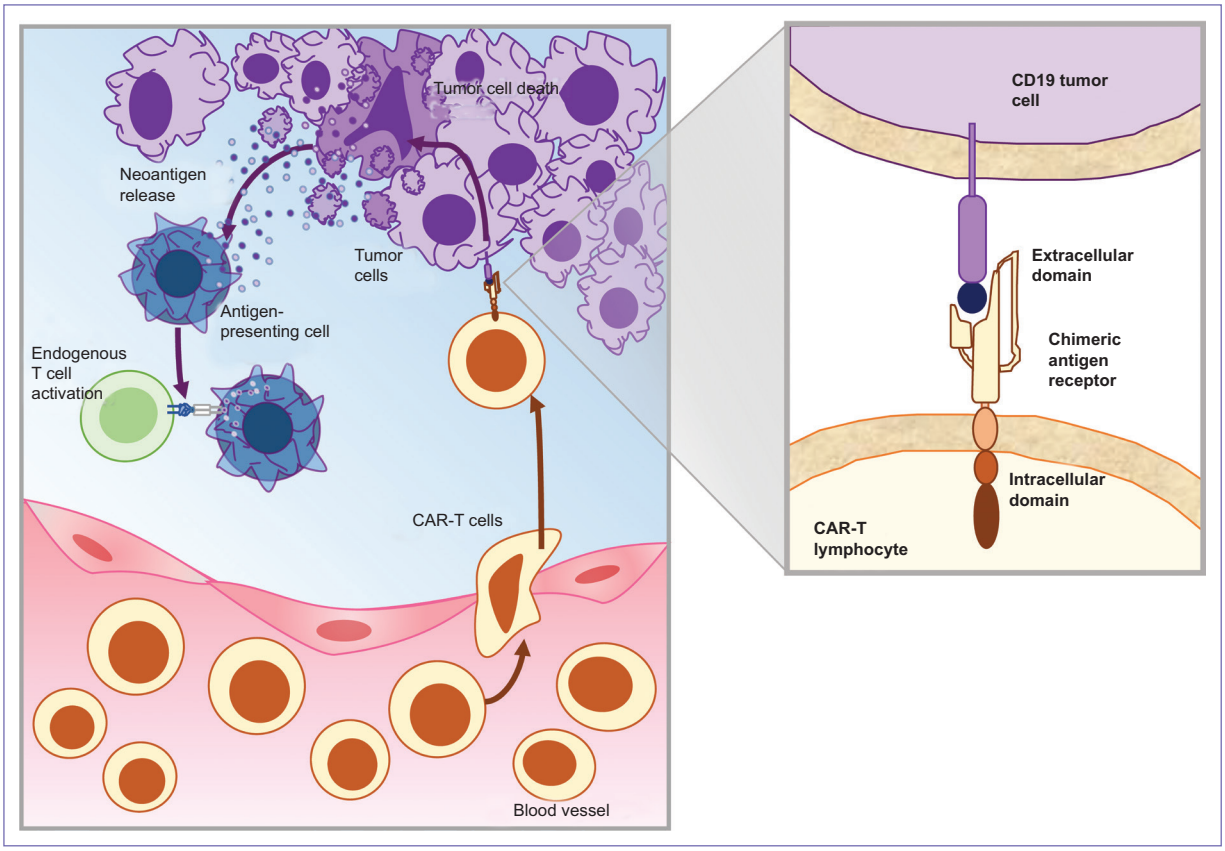


Figure 1. Chimeric antigen receptor (CAR). T cells with chimeric antigen receptor (CAR-T) leave the circulation and travel to the tumor, where they identify and lyse malignant cells. This leads to CAR-T cells proliferation and to the release of tumor antigens, which activates the immune system to recruit non-CAR-T cells, with antitumor response thus being amplified. CAR structure: CAR is made up of extracellular, transmembrane, and intracellular domains. The extracellular domain is in contact with the antigen presented by the tumor cell, and the intracellular domain drives to CAR-T cells signal activation and amplification.

The real challenge this therapy is faced with is to find the right molecule to direct the chimeric receptor recognition fraction, since these are antigens that often are also expressed in normal tissues. Several molecules have been experimented with, but the one that has had the highest effectiveness is CAR-T therapy against CD19 for treating B-cell tumors. On August 30, 2017, CAR-T cell therapy was approved by the FDA for the treatment of children with ALL and for adults with certain types of NHL, specifically diffuse large B-cell lymphoma, follicular lymphoma, transformed follicular lymphoma, primary mediastinal lymphoma and mantle cell lymphoma[1,2].

FDA-approved CAR-T therapies

Three CAR-T therapy designs are currently approved (Table 1):

- Tisagenlecleucel (trade name Kymriah®). It is an anti-CD19 CAR-T agent that uses 4-1BB/CD3ζ as co-stimulatory domain. It was developed by the Novartis company and the University of Pennsylvania. It is used for the treatment of young patients with refractory B-precursor ALL and in adults with diffuse large B-cell non-Hodgkin lymphoma (DLBCL) refractory to two or more lines of treatment[13].
- Axicabtagene ciloleucel (trade name Yescarta®). It is a second-generation anti-CD19 CAR-T agent that uses CD28 as costimulatory domain. It was developed by the Kite/Gilead pharmaceutical company. It has been evaluated in adult patients with refractory DLBCL, with primary mediastinal B-cell lymphoma or transformed follicular lymphoma[13].
- Brexucabtagene autoleucel (trade name Tecartus®). It is a cell therapy targeted against CD19. As axicabtagene ciloleucel, Tecartus® was developed by

Table 1. Comparison of approved CAR-T products

	Tisagenlecleucel CTL019	Axicabtagene ciloleucel KTE-C19	Brexucabtagene autoleucel KTE-X19
Trade name	Kymriah	Yescarta®	Tecartus®
Manufacturer	Novartis	Kite/Gilead	Kite/Gilead
Date of approval	August 2017	October 2017	July 2020
Target molecule	CD19	CD19	CD19
Costimulatory domain	4-1BB/CD3ζ	CD28/CD3ζ	CD28/CD3ζ
Approved therapeutic indications	– Acute lymphoid leukemia – Diffuse large B-cell lymphoma	– Diffuse large B-cell lymphoma – Primary mediastinal B-cell lymphoma – Transformed follicular lymphoma	– Mantle cell lymphoma
Dose, chimeric antigen receptor T-cells/kg	– Acute lymphoid leukemia: Patients ≤ 50 kg → 0.2-5 x 10^6 cells/kg Patients > 50 kg → 0.1-2.5 x 10^8 cells/kg – Diffuse large B-cell lymphoma: 0.6-6 x 10^8 cells/kg	2 x 10^6 cells/kg, maximum dose 2 x 10^8 cells/kg	2 x 10^6 cells/kg, maximum dose 2 x 10^8 cells/kg
Clinical response	– Acute lymphoid leukemia: 81% complete remission at 3 months[11] – Diffuse large B-cell lymphoma: 52% objective response rate, 42% complete response rate[3]	82% objective response rate 54% complete response rate[4]	93% objective response rate 67% complete remission rate[12]

Kite/Gilead. It was recently approved by the FDA for the treatment of refractory mantle cell lymphoma[12].

Treatment with CAR-T CD19 against B-cell tumors

The CD19, CD20 and CD22 molecules usually are expressed specifically in B-cell tumors and not in other tissues, and are an ideal target for CAR-T cells. Anti-CD19 CAR-T cells have been shown to be highly effective in the treatment of severe B-cell malignancies that are refractory to chemotherapy treatment. The response rate varies from 50 to 90%, depending on the type of malignancy[14-22]. Prolonged remission has been highly relevant in ALL, NHL, and chronic lymphoid leukemia (CLL), which suggests that this therapeutic strategy may even be curative.

Acute lymphoid leukemia

Although ALL in children usually responds favorably to chemotherapy, children with relapses and young adults of up to 25 years of age with ALL have a somber prognosis. Several studies, including the ELIANA trial[3], have shown a response rate of around 70-93% with the use of tisagenlecleucel in those patients with multiple relapses to ALL treatment[3,14-16,22,23]. Prior to CAR-T cells administration, the preconditioning regimen that was used was cyclophosphamide monotherapy or in combination with fludarabine[24,25]. Combination therapy vs. monotherapy showed superiority in remission response and CAR-T cells duration[22,23]. Tumor grade did not appear to decrease the possibility for complete remission to be achieved. However, patients with a high number of leukoblasts were found to have a higher degree of toxicity[22].

Non-Hodgkin lymphoma

In patients with chemotherapy-refractory NHL, immunotherapy with CAR-T demonstrated a favorable response. CAR-T 4-1BB/CD3ζ or CD28/CD3ζ therapy antitumor activity against follicular lymphoma, transformed follicular lymphoma, diffuse large B-cell lymphoma and primary mediastinal lymphoma was initially described in single-center trials and case reports[17-19,26,27]. However, it was ZUMA-1 trial phase 2 analysis that consolidated CAR-T clinical benefit for the treatment of refractory diffuse large B-cell lymphoma with the axicabtagene ciloleucel formulation[4]. This multicenter study of 111 patients showed an objective response of 82% and complete response of 54%.

Response rates were higher than those found in the international retrospective study SCHOLAR-1, which evaluated the outcomes in a similar population, with an objective response of 26% and a complete response of 7% being found[28]. That is, CAR-T therapy was more effective in comparison with alternative salvage regimens, even in patients in whom lymphomas were refractory to autologous hematopoietic stem cell transplantation[4]. Subsequently, the JULIET multicenter trial, which used tisagenlecleucel for diffuse large B-cell lymphoma, achieved an objective response rate of 50%[11].

Chronic lymphoid leukemia

In contrast to CAR-T advances in ALL and NHL, its use in CLL has been slow. This is due to the positive results obtained by ibrutinib, idelalisib and venetoclax in chemotherapy-refractory CLL[2]. However, one clinical trial reported complete remission with CAR-T 4-1BB/CD3ζ in two of three patients with chemotherapy-refractory CLL[29]. On the other hand, a phase I/II clinical trial evaluated 24 patients with CLL treated with CAR-T 4-1BB/CD3ζ, including 22 patients actively on treatment with ibrutinib or who were intolerant to it. In said study, a high degree of CLL elimination was observed both in the bone marrow and lymph nodes[20]. These findings demonstrate that CAR-Ts could be effective and perhaps have great curative potential in patients with CLL refractory even to ibrutinib and venetoclax treatment[20]. In addition, the combination of ibrutinib, venetoclax and idelalisib with CAR-T cells sequential infusion targeting multiple antigens such as CD19, CD23, and FcμR (immunoglobulin G Fc receptor) may be CAR-T therapy trend for CLL in the future[30].

Mantle cell lymphoma

Outcomes for patients with refractory mantle cell lymphoma are poor. However, the ZUMA-2 trial evaluated the effectiveness of the brexucabtagene autoleucel product (KTE-19) and obtained promising results[12]. This multicenter phase 2 clinical trial included 74 patients with recurrent or refractory mantle cell lymphoma. The objective response rate was 93%, while complete remission rate was 67%. These results were consistent across all subgroups, including the high-risk group. At a median of 12.3 months, 57% of patients who achieved an objective response maintained a sustained response. This led for the FDA to grant its approval in July 2020. The reported toxicity profile was similar to that of the other CAR-T products[12].

Adverse effects

Despite its great benefits, this therapy is associated with toxicities (Fig. 2). The most common are cytokine-release syndrome (CRS) and CAR-T-related neurotoxicity syndrome[5]. However, there are other less frequent toxicities such as B-cell aplasia and hemato-phagocytic lymphohistiocytosis[5].

Cytokine-release syndrome

CRS is the most common adverse event and typically occurs within the first few days after T cell infusion. This reaction is due to a massive release of pro-inflammatory cytokines such as interferon gamma, interleukin (IL) 6, and IL-2 due to CAR-T lymphocytes activation and proliferation. In addition to cytokine increase, C-reactive protein and ferritin are usually elevated[14-16,20-23,31].

CRS is characterized for causing a wide spectrum of manifestations that include febrile syndrome, hypotension, tachycardia, coagulopathies, hypoxia, and even multiple organ dysfunction[14,32]. It is usually mild, but can be life-threatening for the patient. The main risk factors for developing CRS include a high degree of tumor burden (patients with a higher predisposition to tumor lysis), a high number of CD19+ cells in the bone marrow, thrombocytopenia prior to treatment, and high doses of CAR-T[31]. Nevertheless, although it is not entirely clear, those patients who do not develop CRS are suspected to tend to have a poor clinical response to CAR-T therapy. The treatment indicated for the management of CRS consists of the use of monoclonal antibodies against IL-6 receptor such as tocilizumab, chimeric monoclonal antibodies against IL-6 such as siltuximab and glucocorticoids such as dexamethasone[14,32]. Rarely, patients may develop fulminant hemophagocytic lymphohistiocytosis[5,33].

CRP: C-reactive protein.

CAR-T-associated neurotoxicity syndrome

CAR-T-related neurotoxicity syndrome manifests itself with neurological symptoms such as headaches, delirium, disorientation, aphasia, focal neurologic deficit and, in its most severe form, with seizures and loss of consciousness. In most cases, these symptoms are reversible; however, certain patients rarely may develop cerebral hemorrhage or edema[5,34]. It usually occurs

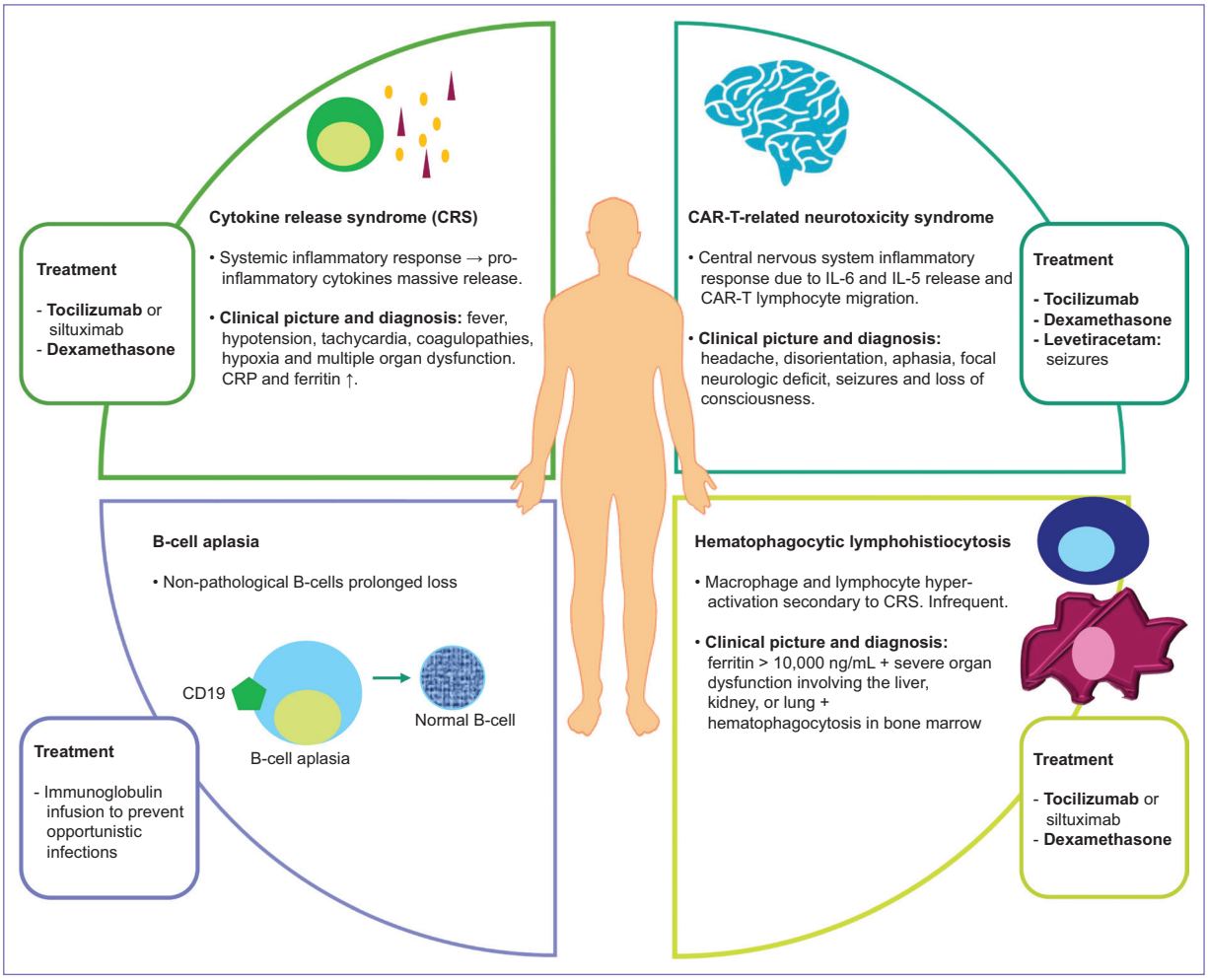


Figure 2. Chimeric antigen receptor T cell (CAR-T) therapy adverse effects. Description of potential adverse effects after CAR-T treatment. Cytokine release syndrome (CRS): is a systemic inflammatory response; it is characterized by fever, tachycardia, hypotension, hypoxia, and multiple organ failure. CAR-T-related neurotoxicity syndrome: it is a central nervous system inflammatory response; it causes disorientation, aphasia and even decreased consciousness. B-cell aplasia: Non-pathogenic B cells prolonged loss. Hematophagocytic lymphohistiocytosis: macrophage and lymphocyte hyper-activation secondary to CRS. Treatment is based on the use of monoclonal antibodies against interleukin (IL) 6 receptors, such as tocilizumab and siltuximab. Glucocorticoids such as dexamethasone are also used. CRP: C-reactive protein.

concomitantly with CRS or on many occasions after it[2]. Risk factors that contribute to the development of neurotoxicity include having a high tumor burden or CAR-T dose, CRS and preexisting neurological symptoms[34]. Although no consensus has yet been reached, there are several theories that explain the development of neurotoxicity. One of them is the spread of inflammatory cytokines to the brain due to high serum levels of IL-6 and IL-15 and CAR-T lymphocytes migration to the central nervous system, indicated by the detection of CAR-T cells in cerebrospinal fluid[5,16]. In addition, protein level in cerebrospinal fluid is usually elevated, suggesting a disruption of the blood-brain barrier. Hepatic or renal dysfunction, as well as hypoxemia and infections, are predisposing factors that may contribute to the development of CAR-T encephalopathy. Management is similar to CRS, with levetiracetam being added in case of seizures[5].

B cell aplasia

Another adverse effect that often arises after anti-CD19+ CAR-T treatment is healthy B-cell aplasia and hypogammaglobulinemia. Prolonged or transient loss of non-pathological B cells is usually well tolerated, with their levels being normalized in most patients as CAR-T

cells decrease throughout treatment[35]. However, aplasia and its consequent immunoglobulin decrease predispose patients to the development of opportunistic infections[36]. Therefore, management is carried out with immunoglobulin monthly infusions[36].

Hematophagocytic lymphohistiocytosis

Hematophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) encompasses a group of severe immune disorders characterized by macrophage and lymphocyte hyper-activation, pro-inflammatory cytokines production, lymphohistiocytic tissue infiltration, and multiple organ failure[37]. Patients with CRS have clinical features and laboratory findings similar to HLH/MAS. HLH/MAS diagnosis is established if ferritin levels increase above 10,000 ng/mL during the CRS phase, typically within the first five days after cell infusion, plus severe organ dysfunction involving the liver, kidney, or lung. The presence of hematophagocytosis in bone marrow biopsy can also guide the diagnosis[5]. Treatment focuses on the use of anti-IL-6 therapy and steroids[5]. Prognosis of this complication is poor and is usually associated with the persistence of cytopenia caused by lymphodepleting chemotherapy, especially increasing the risk of infectious or hemorrhagic complications.

Tumor mechanism to escape CAR-T cells treatment

One of the greatest advantages CAR-T therapy has in comparison with conventional cytotoxic therapies is its continuous antitumor activity over time. Once T cells are stimulated, they are able to remain active for decades[3,16,23,38-40]. However, their persistence is not universal in all patients. Patients who experience CAR-T cells early loss, typically demonstrated by the return of CD19+ B cells, are at high risk of post-treatment relapse[3,23,38,41]. Anti-CD19 T cells intrinsic deficiency or an immune response to scFv CARs are among the main mechanisms that can generate failure of said therapy[22]. In certain cases, despite CAR-T cells preservation, relapse can occur due to surface molecule CD19 decreased or absent expression, or even by the presence of CD19 splicing variants that lack scFv-specific epitopes[41,42].

On other occasions, some tumors often express programmed death ligand 1 (PD-L1) or have cells in the tumor microenvironment that can inhibit CAR-T cells proliferation and effector function[43,44]. The use of combined therapies targeting these pathways might improve the outcomes in this type of patients. Alternative strategies for improving efficacy include an effective selection of T cells during the production and engineering of CAR-T cells, which grants additional co-stimulation pathways, as well as 4-1BBL or secretion of cytokines such as IL-12, which alters tumor microenvironment[45,46].

Perspective toward the future

In oncology

The use of genetically modified T cells faces major challenges on its way to transforming the landscape of cancer treatment[1]. The most representative challenges include:

- First, to provide constant training to all health personnel in institutions seeking to implement the use of CAR-T cells[1].
- Second, to test long-term effectiveness for generating complete remission in the treatment of acute lymphoblastic leukemia and B-cell lymphomas[2].
- Third, to demonstrate effectiveness in the treatment of solid tumors[1,2].
- Fourth, to establish alternative methods to CAR-T, as it is the case of NK cell therapy, which could be considered safer than treatment with CAR-T cells, since they secrete IL-3 and macrophage-granulocyte colony-stimulating factor, which are cytokines that are different to those responsible for CRS[47,48].

In other branches of medicine

This new type of gene-transfer-based therapy has opened up a wide array of possibilities for the future of modern medicine. Currently, the application of the CAR-T principle in different fields is on investigation phase. Among the possible applications, infectious diseases stand out, such as that acquired by human immunodeficiency virus (HIV), where promising results have been found in in vitro studies, which require to be reproduced in in vivo models of HIV latency induced by antiretroviral therapy[49]; fibrotic processes through fibroblast ablation by directing CAR-T cells against fibroblast-activation protein[50], in cases such as cardiac fibrosis[51]; organ transplants and autoimmunity, where it has been shown that they could be used as antigen-specific regulatory T cells to help establishing transplant tolerance and restore it in autoimmune diseases[1,52].

Allogeneic CAR-T

The revolutionary development of these therapies has generated the need for faster access to treatments, but there is the limitation of having to perform an apheresis on the patient and wait for the processing time, as previously mentioned. In addition, the product is extracted from patients whose immune systems are more exhausted. For this reason, active research is being carried out for the development of allogeneic products. The challenge lies in manufacturing an equally or more efficacious product, but without producing graft-versus-host disease manifestations. One of the main strategies consists of modifying the T lymphocyte receptor[53].

Conclusions

Therapy with T cells with chimeric receptors constitutes a great advance in the area of oncology-hematology. It is the first form of gene transfer therapy designed to obtain commercial approval by the FDA. Despite the high level of complexity for its manufacturing, the use of CAR-T is transforming cancer treatment, especially in refractory cases of B-cell lymphoma and acute lymphoblastic leukemia. Its characteristic adverse effects, CRS and neurotoxicity syndrome, require for doctors and hospital personnel to be properly trained and qualified for early detection and timely management. The immunological principle employed by CAR-T therapy is being investigated to design cell therapies aimed at conditions such as autoimmune diseases, HIV infection and fibrosis secondary to heart failure. We hope that, in a not too distant future, these therapies can also be implemented in specialized centers throughout Latin America.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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