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Review Article

CAR-T Cell Therapy for T-Cell Malignancies

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Abstract. Chimeric antigen receptor T-cell (CAR-T) therapy has revolutionized the treatment of B-cell lymphoid neoplasia and, in some instances, improved disease outcomes. Thus, six FDA-approved commercial CAR-T cell products that target antigens preferentially expressed on malignant B-cells or plasma cells have been introduced in the therapy of B-cell lymphomas, B-ALLs, and multiple myeloma.
These therapeutic successes have triggered the application of CAR-T cell therapy to other hematologic tumors, including T-cell malignancies. However, the success of CAR-T cell therapies in T-cell neoplasms was considerably more limited due to the existence of some limiting factors, such as: 1) the sharing of mutual antigens between normal T-cells and CAR-T cells and malignant cells, determining fratricide events and severe T-cell aplasia; 2) the contamination of CAR-T cells used for CAR transduction with malignant T-cells. Allogeneic CAR-T products can avoid tumor contamination but raise other problems related to immunological incompatibility.
In spite of these limitations, there has been significant progress in CD7- and CD5-targeted CAR-T cell therapy of T-cell malignancies in the last few years.

Keywords: Adults T cell acute lymphoblastic leukemia; CAR-T Cells; T-cell lymphoblastic lymphoma.

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Introduction. T-cell acute lymphoblastic leukemia (T-ALLs) represent about 25% of adult ALLs and 10-15% of pediatric ALLs. T-ALLs derive from the leukemic transformation of thymic progenitors during T-cell development through the accumulation of genetic abnormalities.

According to the differentiation stage and the expression of some membrane antigens, T-ALLs were classified as early/precortical, cortical, and mature. With the advent of studies of molecular analysis of genetic alterations (next-generation sequencing) and cytogenetic studies, T-ALLs have been classified according to the presence of these genetic alterations. Two types of genetic abnormalities are observed in T-ALLs: type A aberrations, characterized by ectopic activation of transcription factors dependent upon chromosomal rearrangements or deletions; type B alterations, related to additional genetic lesions that are required for full leukemia transformation.[1] According to the presence of genetic alterations, four subtypes of T-ALL have been identified, including early thymocyte progenitor (ETP)/immature ALL, TLX, TLX1/NKX2.1, and

TAL/LMO. ETP-ALLs are characterized by the expression of hematopoietic stem cell markers such as CD34, aberrant HOX4, and MEF2C gene expression, recurrent mutations in the IL7 signaling cascade, and high BCL2 protein expression. The TLX subgroup is characterized by expression of the γ/δ T-cell receptor, driver genetic events activating either TLX3 or HOXA transcription factors. The TLX1/NKX2.1 subgroup is characterized by driver genetic events involving either TLX1 or NKX2.1 transcription factors and by the occurrence of *NUP214-ABL1* fusion in TLX-rearranged cases. The TAL/LMO subgroup is characterized by the expression of mature-cell membrane markers, driver activation of the TAL1 and LMO2 transcription factors, and recurrent *PTEN* mutations.[2-3]

The treatment of ALLs, including T-ALL, has markedly progressed over the past three decades, and consistent improvements in overall survival have been obtained, particularly for children younger than 15 years.[4] However, the survival of adult T-ALL patients was clearly lower than that observed for children and young adults. Furthermore, patients with relapsed/refractory disease have a poor outcome, with survival ranging from 10-25%.[4]

T-cell lymphomas are a type of non-Hodgkin lymphoma involving the malignant transformation of T-cells; four major subtypes have been characterized, including extranodal T-cell lymphoma, cutaneous T-cell lymphomas (Sezary syndrome and mycosis fungoides), anaplastic large cell lymphoma and angioimmunoblastic T-cell lymphoma. Considerable progress has been made in understanding the molecular pathogenesis of these disorders, leading to an improvement in their therapy; however, for patients with refractory or relapsed disease, outcomes are generally poor.[5]

Chimeric antigen receptor (CAR) is a novel cell-based immunotherapy exhibiting considerable efficacy. CAR-T cells are engineered to specifically recognize an antigen expressed on a cell in a major histocompatibility complex (MHC) in an independent manner and, consequently, kill this cell. CAR-T cell production involves three steps, consisting of first obtaining healthy cells from a patient or a donor, then engineering T-cells using genomic techniques, such as lentiviral gene transduction and/or gene editing, and, finally, infusing CAR-T cells thus armed to recognize and to kill cancer cells. CAR-T cell therapy has obtained considerable success in the treatment of B-cell malignancies, such as B-cell lymphomas and B-acute lymphoblastic leukemia. These developments in the treatment of several hematological malignancies have triggered the exploration of CAR-T cell therapy in T-cell malignancies; however, the extension of CAR-T cell therapy to T-cell malignancies is particularly challenging for the co-expression of many cell membrane antigenic targets between normal and malignant cells.[6]

CAR-T cell therapy of T-ALL based on CD7 targeting. CD7 is a membrane antigen highly expressed in T-ALL cells. CD7 is a cell membrane glycoprotein with a molecular weight of 40 KDa, pertaining to the immunoglobulin supergene family. CD7 is considered a good potential target for the treatment of T-ALLs and T-cell lymphomas.[7]

More recently, CAR-T lymphocytes engineered to express anti-CD7 have been used as therapeutic agents for T-ALL and T-cell lymphoma treatment. However, since CD7 is expressed on normal T lymphocytes and NK cells, the uninhibited CD7 expression on the cell membrane of T-lymphocytes would determine a fratricidal killing; therefore, the generation of CAR-T cells targeting CD7 requires the abrogation of blocking of CD7 on the membrane of T-lymphocytes before their engineering with a CAR encoding anti-CD7.[8]

Various methods have been used to inhibit/block CD7 expression on T cells for the development of CAR-T cells targeting CD7: gene editing, protein blockers, and natural selection.

CD7 CAR-T cells based on gene editing. Two types of gene editing were used for the generation of CD7 CAR-T cells: CRISPR/CAS9 gene editing and base editor gene editing.

CRISPR/CAS9 gene editing. The CRISPR/CAS9 gene-editing systems involve two components: the caspase 9 (CAS9) which cleaves the DNA, and a guide RNA (CRISPR, clustered regularly interspersed short palindromic repeats), directing CAS9 at the level of specific DNA sequences: thus, designing guide RNAs targeting specific DNA sequences, it is possible to use CAS9 to introduce double-strand breaks into DNA, thus generating a specific gene knockout. Preclinical studies have shown that $CD7^{KO}$ CD7 CAR-T cells are prevented from fratricide, proliferate, and exert specific antitumor activity against malignant T leukemic cells.[8]

Autologous T cells or allogeneic T cells can be used for the generation of CD7 CAR-T cells. The generation of CD7 CAR-T cells generated from autologous T-cells obtained from the patient is limited: by the difficulty of obtaining an appropriate number of healthy cells from patients for the preparation of CAR-T cells; the duration of the procedure required for the generation of CAR-T cells; the risk of a possible contamination of T cells used for CAR-T cell generation with leukemic or lymphoma T-cells; the considerable cost of autologous, individualized, CAR-T cell preparations.[6]

Allo-CAR-T cells do not have these limitations; however, these CAR-T have other problems, mainly related to the immunological compatibility: the host immune system may reject allo-CAR-T cells, recognized as not-self; the development of graft versus host disease (GvHD) of donor T cells against the host.[9]

Gene editing can be used to knock out the T-cell receptor gene to decrease the immunological incompatibility of T cells, eliminating the human leukocyte antigen (HLA) class II gene and CD52.[10] Using this approach, Xie et al. recently reported the development of "universal" CAR-T cells CD7$^{-/-}$, TRAC$^{-/-}$ CD7UCAR.[10] These cells efficiently proliferate and specifically induce the killing of primary T-ALL cells *in vitro*, with high secretion of proinflammatory cytokines; furthermore, these CAR-T cells are also able to significantly reduce tumor load and extend mice survival in T-ALL models.[10]

Hu et al. reported the first clinical trial using CD7 targeting CAR-T cells (RD13-01) with genetic modifications (knockout of *CD7/TRAC/RFX5*-related genes) to resist fratricide, GvHD, and allogeneic rejection and to potentiate antitumor activity.[11] A phase I trial using these CAR-T cells enrolled 12 patients (11 with T-ALL/T-lymphoma and 1 with CD7-expressing AML).[11] 4-wk post-infusion, 9/11 patients showed OR and 7/11 a CR; 3 patients were bridged to allo-HSCT. With a median of 10.5 months, 4 patients remained in CR.[11] (**Table 1**) Zhang et al recently reported the results of a phase I study involving the treatment of 7 T-ALL and 3 T-LBL patients with RD13-01 CAR-T cells,[12] 80% of patients achieved a CR and 7/8 responding patients had an MRD-negative status; interestingly, three patients who had failed prior autologous CD7 CAR-T cell therapy achieved a CR following treatment with CD7 allo-HSCT and 4/6 remained progression-free up to 315 days.[12] Four out of seven patients with extramedullary disease (EMD) obtained EMD CR at the median day 30. 2/6 patients relapsed without CD7 loss and subsequently died.[12] Only one patient experienced grade 3 cytokine release syndrome, and one patient experienced grade 3 neurotoxicity.[12] These observations support additional studies to define better the safety and efficacy of RD13-01 products in the treatment of patients with T-ALL and T-LBL.

Leedom and coworkers reported the development of WU-CART-007, an allogeneic CAR-T cell therapy for T-cell malignancies manufactured using normal T-cells by deletion of CD7 and TRAC using normal T-cells by deletion of CD7 and TRAC using CRISPR/CAS9 gene editing (controlling the occurrence of possible off-target events by GUIDE-Seq), followed by CAR transduction with a lentiviral vector expressing a high-affinity and highly specific anti-CD7, cell expansion and depletion of residual TCRA/B^{+} cells.[13] WU-CART-007 cells exerted a potent antitumor activity both *in vitro* and *in vivo* through CD7 targeting.[13] Using WU-CART-007 cells, Ghobadi et al. reported the results of phase I /II study WU-CART-007-1001 involving the enrolment of 12 patients with R/R T-ALL or T-LBL, treated at four dose levels (100, 300, 600, 900 million of cells per infusion).[14] WU-CART-007 showed manageable toxicity, with treatment-related adverse events in 25% of patients; the CRR for patients treated at dosage level ≤2 was 43%. [14]

Li et al. reported the development of allo-CAR-T cells GC027 based on the lentiviral transformation with a CAR-expressing anti-CD7 of normal healthy T-lymphocytes in which TCRα and CD7 genes were silenced using CRISPR/CAS9 gene editing system.[15] The safety and the efficacy of GC027 CAR-T cells were initially explored in two patients with refractory/relapsed T-ALL, both achieving a complete response.[15] More recently, the same authors reported the results of the expanded study with GC027 CAR-T cells involving the enrolment of 12 R/R T-ALL patients: 11/12 patients displayed rapid eradication of leukemic T-lymphoblasts

Table 1. Results of fully published Trials (Phase 1,2) of relapsed/resistant T-ALL/T-LBL treated with CAR-T. CRS= Cytokine Release Syndrome.

Trial N° (Ref N°); Year	Origin CAR T-Cells	Patients number	% Response	% CR at 1-3 months	% CR at 12 months	% CR at 24Months	Allotransplants		Toxicity	Infections
							%	PFS at 2 years		
NCT04538599 (11) 2021	Allogeneic Donors (RD13-01)	12	81.8	63,6	33,3		25		No> gr 3	CMV, EBV
ChiCTR2000034762 NCT04689659 (23,25) 2021,2023	Allogeneic Matched Donors (CD7CAR-T)	20	95	85	75	38	35		CRS 3,4 10%, Cytopenia Neurotox, GVHD	Viral Activ. 25% deaths due to infections
NCT04572308 (27) 2022	Allogeneic CD7- selected (NS7CAR-T)	20 14 T-ALL 6 T-LBL	95	75; 20 extra			70		CRS. Neurotox	
NCT04004637 (22) 2022	Autologous	8	87	87					CRS; Neurotox	
NCT04572308 and NCT04916860 (28) 2023	Allogeneic CD7-selected (NS7CAR-T)	60 (T-ALL 35, T-LBL 25)	94,4	94,4	58,6	53,7	61,6	67%	CRS 3,4 11%	Infections 36% EBV, CMV 5%

and reached CR one month after CAR-T cell infusion (CR rate 91.7%). Three out of four patients with EMD showed complete remission of the lesions.[16] Infused GC027 cells expanded rapidly *in vivo* and reached a peak of expansion 5-10 days after their infusion; in most patients, GC0278 cells were not detectable 4 weeks after infusion.[16] Notably, one patient had a PFS of >3 years.[16] The toxicity profile was manageable.[16]

Base Editing. Base editing is an emerging genome technology consisting of the generation of programmable single base pair changes at the level of defined genetic loci with high specificity, precision, and efficiency. In this technique, adenine base editors (EBEs) and cytosine base editors (CBEs) combine a single-stranded DNA deaminase enzyme with a nuclease, CAS9, to install A·T to G·C or C·G to T·A point mutations at specific genomic target sites, respectively.[15] Since both ABEs and CBEs operate without causing double-strand breaks, they produce efficient on-target editing, markedly reducing the risks of editing complex genome rearrangements observed with nuclease editing.[17]

Using this technology, DiOrio et al. developed 7CAR8, a CD7-directed allogeneic CAR-T generated introducing four simultaneous base edits: CD7, TCRα, CD52, and PD1.[17] In preclinical studies, the 7CAR8-T cells were shown to be highly efficacious *in vitro* and *in vivo* T-ALL models. [17]

In 2022, the CD7 CAR-T basic editing clinical trial (ISRCTN 15323014) started. In this trial, healthy donor T cells were base-edited at the level of *TCRβC1* and *TCRβC2*, *CD7*, and *CD52* and then transduced with a lentivirus vector encoding a CAR that recognizes CD7; using this procedure, were generated base-edited CAR7 (BE-CAR7) T-cell banks.[18] Phase I of this study will involve the enrolment of 10 children with refractory/relapsed T-ALL or other T-cell malignancies; these patients received first lymphodepletion, followed by infusion of $0.2x10^6$ to $2x10^6$ CE-CAR7 T cells per Kg; patients in molecular remission at 28 days underwent allo-HSCT, with consequent depletion of any persisting BER-CAR7 cells by conditioning regimen used before HSCT.[18] The results on the first 3 treated patients were recently reported: the first patient, a 13-year-old girl with relapsing T-ALL after allo-HSCT, had molecular remission after BE-CAR7 infusion and was then transplanted with cells from her original donor, with successful immunological reconstitution and ongoing leukemic remission; patient 2 developed fatal fungal complications; patient 3 achieved a molecular remission following BE-CAR7 cell infusion and then underwent allo-HSCT while in remission. Serious adverse events were observed in these patients, including CRS, multilineage cytopenia, and opportunistic infections.[18]

CD7 protein blockers. A different method to block CD7 expression in T-lymphocytes consists of the use of protein blockers that consist of single-chain variable fragment and an intracellular retention domain, anchoring the targeted antigen in the endoplasmic reticulum and Golgi apparatus before its proteolytic degradation. This technique can be used to downregulate CD7 expression in T-cells without CD7 gene editing.[19] This technique can be used to generate functional and proliferating CAR-T cells that do not express CD7 on their cell membrane.[20] Wong et al., using this technique, have recently reported the development of anti-CD7 CAR-T cells depleted of both CD7 and CD3 expression (PCART7), exhibiting potent cytotoxicity against T-ALL and T-lymphoma cells.[21]

Zhang et al. have developed a CD7 blockade strategy based on the use of tandem CD7 nanobody VHH6 coupled with an endoplasmic reticulum/Golgi-retention motif to intracellularly block CD7 molecules, thus favoring their degradation.[22] Preclinical studies have supported the efficacy of CD7 blockade in preventing fratricide and the capacity of CAR-T cells developed with this CD7 blocking strategy to exert a potent cytotoxicity against CD7-positive leukemic cells.[20] A phase I clinical trial with these CAR-T cells showed that 7/8 R/R T-ALL and T-lymphoma patients achieved a CR after 3 months of CAR-T cell infusion; 1 patient achieved an MRD-negative status, and one patient with T-lymphoma achieved a CR for more than 12 months.[20] The majority of patients had only grade 1 or 2 CRS.[22]

Pan et al. evaluated donor-derived CD7 CAR-T cells in the treatment of R/R T-ALL. To minimize CD7 CAR-T cell-mediated fratricide, the authors have generated a retroviral vector containing an anti-CD7, 4-1BB costimulatory domain, and CD3 ζ signaling domain and a CD7-binding domain fused with an endoplasmic reticulum retention signal sequence enabling intracellular retention of CD7 molecules.[23] In a phase I clinical trial, CD7 CAR-T cells manufactured from either previous HSCT donors or new donors were administered to 20 R/R T-ALL patients. 90% of patients achieved a CR, with seven patients proceeding to HSCT at a median follow-up of 6.3 months, 15 patients remained in remission. Grade 3-4 CRS occurred in 2 patients (10%) and grade I neurotoxicity in three patients (15%); both side effects were not correlated to T-cell donor type or dose level.[23] More recently, an interim report from phase II of this trial was presented, involving the enrolment of 20 R/R T-ALL patients, with a median follow-up of 11.0 months.[24] 90% of patients achieved a CR; 3 patients remained in remission, 7 relapsed, 2 died of infection, and 8 patients proceeded to HSCT.[22] The 1-year PFS and OS rates were 62% and 60%, respectively.[24] Patients without mediastinal mass had longer OS compared to those with mediastinal mass.[24] Of 18 responders, seven had a relapse (three CD7+, 3 CD7-

and one unknown.[24]

Recently, Tan and coworkers reported the results of long-term (24-27 months) follow-up of T-ALL patients included in the phase I study with CD7 CAR-T cells.[23] After a median follow-up of 27 months, the ORR and CRR were 95% and 85%, respectively, with 35% of patients proceeding to HSCT; 6/20 patients had relapsed, and 4 of these 6 patients lost CD7 expression on tumor cells.[25] After 24 months of follow-up, PFS and OS were 37% and 42%, with a median PFS and OS of 11 and 18.3 months, respectively.[25] (**Table 1**) Severe adverse events observed at >30 days after treatment included 5 infections and 1 grade 4 intestinal GvHD.[25] Cytopenia occurred in all 20 patients within 30 days, while three patients had late-onset grade 3 cytopenia at 8, 12.5, and 13 months after infusion.

Non-relapse mortality occurred in five out of 20 patients (25%), mainly due to infections; in one case, it occurred for engraftment syndrome in patients who received SCT consolidation. In all patients, non-CAR CD7+ T and NK cells were cleared in 15 days after CD7 CAR-T cell infusion, remaining undetectable until the last follow-up in all but one patient. In 2 patients, the long-term monitoring of T-cell phenotype showed that the central memory T-cell compartment gradually increased and that in one patient, low levels of naïve and stem-cell-memory T-cell subpopulations were measurable.

CAR-T cells are generated with naturally CD7-negative T-cells or with CD7-negative CAR-T cells obtained by natural selection. The generation of CAR-T cells from T-lymphocytes that do not express CD7 antigen represents a potential alternative to CD7 gene elimination or blocking. In this context, Freiwan and coworkers provided evidence that naturally occurring $CD7^-$ T cells exist in healthy subjects and represent functional effector T lymphocytes that can be used for CAR-T cell generation.[26] These $CD7^-$ T cells represent 0.7-19% of T-lymphocytes and have mainly a $CD4^+$ memory phenotype.[26] CAR-T cells generated starting from these $CD7^-$ exhibited predominantly a $CD4^+$ memory phenotype and had significant antitumor activity upon antigen exposure *in vitro* and *in vivo* in mouse xenograft models; importantly, these CAR-T cells bypass fratricide.[26]

Lu et al. described a different approach to obtaining $CD7^-$ CAR-T cells through a process of *in vitro* natural selection.[27] Particularly, these authors have compared three different approaches to generate CD7-targeted CAR-T cells and have evaluated their properties in preclinical studies: NS7CAR T-cells generated first transducing T-cells with a CD7-targeting vector and then subjected to a process of natural selection during two weeks of cell culture; Neg7CAR T-cells obtained transducing $CD3^+CD7^-$ T lymphocytes with a CD7 targeting vector; KO7CAR T-cells generated using T cells in which CD7 expression was silenced by CRISPR/CAS9 gene editing.[27] Compared with sorted $CD7^-$ CAR-T cells and CD7 knocked-out CAR-T cells, NS7CAR T-cells displayed similar or superior therapeutic properties, including a higher proportion of $CD8^+$ memory T cells and a higher proportion of CAR^+ cells.[27] Using these NS7CAR T-cells, a phase I clinical study was carried out in 14 patients with R/R T-ALL and 6 with T-LBL; 19 of these patients achieved an MRD^- CR in the bone marrow and 5/9 achieved extramedullary CR.[27] 14 patients proceeded to allo-HSCT (10 consolidative, 4 salvage) following NS7CAR-T cell therapy, with no relapses; of the 6 patients not receiving allo-HSCT, 4 remained in CR at a median time of 54 days.[27] Only one patient experienced a grade 3 CRS.[27]

Zhang and coworkers reported the results observed in 60 R/R T-ALL (35) and T-LBL (25) treated with CD7 CAR-T cells NS7CAR at three different dose levels: $5x10^5$/Kg, $1\text{-}1.5x10^6$/Kg and $2x10^6$/Kg.[28] After 28 days of treatment, 94% of patients achieved a CR in bone marrow; in 32 patients with EMD, 78% displayed an objective response, with 56% in CR and 22% in PR; the 2-yr OS and PFS were 63.5% and 53.7%, respectively.[28] Importantly, PFS was significantly better in 37 CR patients proceeding to consolidation HSCT compared to 10 patients who did not proceed to transplantation (67% vs 15%, respectively); of the 10 patients without a transplant, 8 relapsed. No differences were observed in OS and PFS in patients with or without EMD, while patients with a previous history of transplantation showed a trend toward a lower 1yr-OS rate (49.4% vs 77.6%).[28] Patients with complex cytogenetics alterations demonstrated a significantly reduced OS and PFS as compared to those patients without these alterations (30% vs. 79% and 25% vs. 64.2%, respectively); in the same way, patients carrying TP53 gene mutations showed a significant lower OS (25% vs. 77.9%). The safety profile was acceptable, with grade 1-2 CRS in 80% and grade 3-4 in 11% of patients. Two patients (3.3%) experienced grade I ICANS, and 1 (1.7%) experienced grade 4. CRS and ICANS occurrence was not correlated with the proliferation of NS7CAR. Thirty-seven patients (61.7%) demonstrated the occurrence of grade 3 or higher cytopenia not recovered on or after day 30 post-infusion.[28]

Comparison of the efficacy of autologous and allogeneic CD7 CAR-T cells. Zhang et al. have made a comparative analysis of autologous and allogeneic CD7 CAR-T cells for the treatment of T-cell malignancies. The study involved 10 patients with R/RT-ALL and T-LBL, 5 treated with autologous CD7 CAR-T cells, and 5 with allogeneic CD7 CAR-T cells; the CAR-T cells were Intrablock anti-CD7 CAR-T cells described by Pan et al.[23] Although the very limited number of patients, some

comparisons between patients treated with auto and allo CD7 CAR-T cells have been attempted: the CRR was higher for allo than for auto (80% vs 40%, respectively); the relapse rate was higher in allo than in auto patients (100% vs 25%, respectively); CAR-T cell survival *in vivo* was higher in allo than in auto patients.[29]

CAR-T cells developed with CD7 knockout associated with specific CAR-T cell integration. Recently, Jiang and coworkers have evaluated in preclinical models the efficacy of Elongation Factor 1α (EF1α)-driven CAR in which the CAR vector was selectively inserted at the level of the disrupted CD7 locus or of the TCR-alpha constant locus or at random integration sites using a CAR retroviral vector.[30] EF1α-driven CAR expressed at the CD7 locus enhances tumor rejection in a xenograft model of T-ALL, suggesting possible clinical applications for this CAR-T cell strategy.[30]

Alternative methods to avoid fratricide killing of CD7 CAR-T cells. Recently, two alternative approaches have been proposed to avoid the fratricide killing of CD7 CAR-T cells without implying genomic manipulations. One approach proposed by Ye et al. was based on the blocking of the CD7 antigen on the membrane of T-cells with a free anti-CD7 monoclonal antibody containing the same binding domain as the CAR during the preparation of CAR-T cells.[30] CAR-T cells cultured with the anti-CD7 antibody displayed inhibition of fratricide killing, improved cell viability, and were active in mediating effective cytotoxicity against CD7-positive leukemic cells.[31]

The other approach was based on the addition to CD7 CAR-T cells of ibrutinib or dasatinib, pharmacologic inhibitors of key CAR/CD3ζ signaling kinases, during *in vitro* expansion of these cells: the addition of these inhibitors rescued *ex vivo* expansion of unedited CD7 CAR-T cells regaining full CAR-T cell *in vivo* mediated cytotoxicity upon withdrawal of the inhibitors.[31] The CAR-T cells prepared using this methodology were shown to be suitable for cancer therapy purposes.[32]

CAR-T cell therapy of T-ALL based on CD5 targeting. In addition to CD7, other membrane antigens expressed on normal, as well as on leukemic T-lymphoid cells, are suitable targets of CAR-T cells.

One of these antigens is CD5; CD5 expression on normal cells is restricted to T-lymphocytes and B1 cells.

As observed for CD7, CD5 expression on CAR-T cells leads to fratricide of CD5 CAR-T cells.

Since CD5 targeting with CAR-T cell therapy could be an attractive strategy for the treatment of T-cell malignancies, several experimental studies have characterized the properties of CAR-T cells engineered to target CD5 antigen. Thus, Dai et al. reported the development of CD5 targeting bi-epitopic CARs with fully human heavy-chain-only antigen recognition domains; CAR-T cells generated in T-lymphocytes with CD5 knockout by CRISPR/CAS9 gene editing were transduced with a lentiviral vector encoding anti-CD5.[32] In preclinical models these CAR-T cells exert potent cytotoxicity against leukemic lymphoid T-cells.[33]

Ho et al. have provided evidence that the affinity of CAR and cognate antigen expression of CAR-T cells influence the intensity of CAR-T fratricide.[33] Thus, it was shown that the expression of a single chain fragment variable (scFv) with a low-intensity of fratricide is induced in T-lymphocytes in which CD5 expression is downregulated, resulting in the generation of CAR-T cells with maximized anti-CD25 effector activity.[34]

Another recent study reported the development and the characterization of CAR-T cells engineered to express anti-CD5 and anti-CD7 with fully human heavy-chain-only domains and to mitigate fratricide by CD5 and CD7 gene knockout using CRISPR/CAS9 gene editing.[34] These CD5/CD7 bispecific CAR-T cells displayed potent antitumor activity against T-cell malignancies.[35]

Few clinical studies have explored the safety and efficacy of CD5 CAR-T cells in T-cell malignancies.

In 2019, Hill et al. reported the results of a phase I dose-escalation study (MAGENTA study) investigating autologous CD5-directed CAR-T cells engineered to produce minimal and transient fratricide when expressed in T-cells.[36] This treatment was considered as a bridge to allogeneic HSCT. Nine patients were included in this study, and 4 of these patients showed an objective response, with 3 CRs in an angioimmunoblastic T-cell lymphoma, a peripheral T-cell lymphoma, and a T-ALL patient.[36] After infusion, there was a decrease in PB CD3+ cell numbers, but there was no complete T-cell aplasia.

In 2021, the same authors reported the results observed in an additional 9 patients with R/R T-cell lymphomas treated with autologous CD5 CAR-T cells.[37] Three of these four responding patients proceeded to HSCT, and two of them remained alive and in CR for 29 and 24 months, respectively.[37] Clinical response did not correlate with cell dose infused or degree of T-cell expansion.

Pan et al. reported the initial results of a phase I study involving the treatment of five patients who had CD7-negative T-ALL relapsed after CD7 CAR-T cell therapy and received prior HSCT donor-derived CD5 CAR-T cells; all these 5 patients achieved a CR at day 30 and remained MRD-negative at a median follow-up of 27 months.[38] Although these results are promising, a longer follow-up is required to assess the duration of response and the reconstitution of a functional immune system.[38]

Patel and coworkers developed a new preparation of CD5 CAR-T cells, Senza 5™, an autologous CD5 CRSPR-CAS9 knockout anti-CD5 CAR-T product with

high specificity for CD5 targets; their strategy, with >90% of CD5 KO and with >30% of CAR transduction, allowed the generation of two main cell populations: one of CD5 KO CAR-T cells and the other of CD5KO normal untransduced cells.[39] CD5 KO CAR-T5 cells are expected to target CD5-positive T-leukemia/lymphoma cells but lead to toxicity to normal T cells, which will be mitigated by the CD5 KO normal T cells exhibiting a survival advantage after infusion.[38] Autologous Senza 5^{TM} CART5 cells will be evaluated in CD5-positive T-cell lymphoma patients in a phase I clinical study.[39]

Chun et al. initially reported the development of an anti-CD5 CAR-T cell population in which CD5 expression was eliminated by CRISPR-CAS9 gene editing: CRISPR-CASp KO of CD5 consistently enhances the antitumor activity of CAR-T cells by increasing CAR-mediated activation and proliferation.[40]

CD37 targeting with CAR-T cells for treatment of T-cell malignancies. CD37 is a transmembrane protein of the tetraspanin superfamily. A part of T-cell lymphomas express CD37 on their cell membrane. Scarfs et al. reported the development of CD37-targeting CAR-T cells (CAR37) with 4-1BB as a costimulatory domain. CAR-T cells demonstrated antigen-specific activation, cytokine production, and cytotoxic activity in models of peripheral T-cell lymphomas.[41] No significant fratricide-related events were observed in CAR-37 cells.[40]

To date, the only ongoing trial involving CD37-directed CAR-T cells (NCT 04136275) involved the enrolment of CD37-positive hematological malignancies, including leukemia, B-cell and T-cell lymphomas.[42] In a preliminary phase I report, 4 patients were treated with CD37 CAR-T cells, including 1 patient with CTCL who achieved a CR on the 28th day post-infusion.[42]

CD70 targeting by CAR-T cells in T-cell lymphomas. CD70 is a type 2 transmembrane glycoprotein that is a member of the Tnf ligand family. CD70 interacts with its ligand CD27. CD70 exhibits some properties that make it a suitable therapeutic target in some hematological malignancies: CD70 is only transiently expressed on activated T- and B-cells, NK cells, and dendritic cells; CD70 is widely expressed in some hematological malignancies, including some B-cell lymphomas and systemic T-cell lymphomas; CD70 interaction with its ligand CD27 induces a costimulatory signal in T and B lymphocyte activation.

Targeting CD70 in CTCL using an antibody-drug conjugate in patient-derived xenograft models resulted in marked antitumor activity.[43]

The phase I COBAL-LYM dose-escalation study evaluated allogeneic anti-CD70 CAR-T cells (CTX 130) in R/R patients with PTCL or CTCL.[44] CTX 130 cells are allogeneic T-lymphocytes modified with CRISPR/CAS9 gene editing to abrogate expression of TCRα, MHC-I by β2-microglobulin disruption and of CD70 and then transduced with a lentiviral vector encoding anti-CD70.[44] 15 patients with T-cell lymphomas were treated with CTX 130; responses were observed both in PTCL (ORR 75%) and in CTCL (ORR 67%) patients; 29% of patients achieved a CR.[44]

T-cell receptor targeting by CAR-T cells as a therapeutic strategy in T-lymphomas. Another targeting strategy for T-cell malignancies is based on the eventual exclusive expression of T-cell receptor-beta chain constant domains 1 and 2 (TRBC1 and TRBC2). Normal T-lymphocytes contain both TRBC1$^+$ and TRBC2$^+$ cell compartments, while T-cell malignancies are restricted to only one.[45] CAR-T cells targeting TRBC1 can recognize and kill normal and malignant TRBC1$^+$ cells, sparing TRBC2$^+$ T-cells.[45]

Recently, the results of a phase I/II clinical study (AUTO4) involving the treatment of 10 patients with R/R T-cell lymphomas with a TRBC1-directed autologous CAR-T cell therapy, using four flat dose levels.[46] 40% of patients achieved a CR. The most common treatment-related adverse events were cytopenias (anemia and neutropenia); however, 30% of patients had grade 3 or higher adverse events, and PCR observed no CAR-T cell expansion.[46] With a longer follow-up, 50% of patients treated with the highest dose ($450x10^6$) maintained a complete metabolic response at 6 and 9 months, respectively.

CCR4 targeting in T-cell malignancies using CAR-T cell therapy. The chemokine receptor CCR4 (also known as CD194) is a seven trans-membrane G protein-coupled cell membrane molecule with selective expression on cells of the hematopoietic system: particularly, CD4$^+$CD25$^+$Foxp3$^+$ regulatory cells, TH_2 and TH_7 T cells predominantly express CCR4. CCR4 is highly expressed in many T-cell malignancies, including ATL, CTCL, MF, and SS, and represents a biochemical therapeutic target for these diseases. Thus, mogamulizumab, a defucosylated humanized antibody engineered to exert enhanced antibody-dependent cytotoxicity that targets CCR4, was approved for the treatment of R/R CTCL, MF, SS, and ATLL.[47-48]

These observations have represented a strong rationale for the development and evaluation of CAR-T cells targeting CCR4. Thus, Perera et al. generated a lentiviral vector for the genetic engineering of T cells to express a CAR that targets CCR4 using humanized variable heavy and kappa light chain derived from an anti-human CCR4 antibody different from mogamulizumab.[49] CCR4-targeting CAR-T cells efficiently lysed patients-derived CTCL cell lines and exerted potent antitumor activity *in vivo* in a murine xenograft model of ATL.[49]

Watanabe et al. have recently explored the

development of CAR-T cells targeting CCR4: during the *in vitro* expansion of these cells, fratricide events specifically depleted Th2 and Tregs while sparing $CD8^+$ and Th1 cells.[49] At the end of the expansion process, a population of CAR-T cells with potent antitumor efficacy against CCR4-expressing T-cell malignancies is generated.[50]

CCR9 targeting in T-ALL. A recent study showed that CCR9 is expressed in >70% of cases of T-ALL, including >85% positivity in R/R patients, compared to a scarce positivity (<5%) at the level of normal T-cells.[51] CAR-T cells targeting CCR9 are resistant to fratricide and have potent antileukemic activity both *in vitro* and *in vivo*, even at low antigenic density.[51] These observations suggest that anti-CCR9 CAR-T cells could represent a potentially promising treatment strategy for R/R T-ALLs.[51]

CD2 targeting CAR-T cell therapy. Xiang et al. reported the development of an allogeneic "universal" CD2-targeting CAR-T cells (UCART2), in which the CD2 antigen is deleted to prevent fratricide, and the T-cell receptor is removed to prevent GvHD; UCART2 cells exhibited marked efficacy against T-ALL and prolonged the survival of T-ALL-engrafted immunodeficient mice.[52] Treatment with rhIL-7-hyFc, a long-acting recombinant human IL-7, prolonged UCART2 persistence and increased survival in primary patient T-ALL model in vivo.[52] According to these observations, it was suggested that allogeneic fratricide-resistant UCART2, in combination with rhIL7-hyFc, could represent a suitable approach for the treatment of T-ALL.

CD38 targeting CAR-T cell therapy. A recent study reported the preclinical activity of CAR-T cells targeting the CD38 antigen.[53] CD38 antigen is a validated tumor antigen in multiple myeloma and in T-ALL. CD38 expression on activated T cells did not impair CD38-CAR-T cell expansion and *in vitro* function. In mice xenotransplanted with primary T-ALL cells, CD38-CAR-T cells mediated prolonged survival.[53]

Conclusions. CAR-T cell therapy for T-cell malignancies is still in its infancy, and additional studies are required before its introduction in the standard treatment strategy for these diseases.

Several factors have hampered the successful development of CAR-T cell technology in the therapy of T-cell malignancies: (i) tumor contamination, related to the admixture of manufactured CAR-T cell products with leukemic/lymphoma T-cells; (ii) T cell aplasia as a consequence of the unwanted targeting extended also to normal T cells; (iii) fratricide, a phenomenon related to the cytotoxicity exerted by CAR-T cells not only targeting malignant T cells but also other CAR-T cells expressing the target antigen.

Some strategies have been developed to eliminate or mitigate some of these limitations; thus, allogeneic CAR-T cells bypass the problem of CAR-T cell contamination with tumor cells. On the other hand, various strategies have been developed to mitigate fratricide, from gene editing using either CRISPR-CAS9 technology or base editing to intracell blocking or natural selection. However, some of these strategies solve a problem, but at the same time raise other problems.

In spite of these limitations, only some studies based on enough patients with T-cell malignancies, with a follow-up of at least two years, have provided initial encouraging results that need to be confirmed in larger prospective studies.

Future studies have to clarify: (i) the "optimal" membrane antigen to be targeted by CAR-T cells on the surface of malignant T-cells; (ii) the comparative evaluation of auto- and allo-CAR-T cells in terms of safety and efficacy; (iii) the role of CAR-T cell therapy alone or as a bridge to allo-HSCT.

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