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Review

CAR-T Cell therapy in T-cell malignancies: limitations and solutions

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Abstract

CD19-targeted chimeric antigen receptor (CAR)-T cell therapy has shown high potential for treating B-cell hematological malignancies and has been approved by the US FDA. However, CAR-T cell therapy for T-cell hematologic malignancies poses feasibility challenges, including the difficulty of obtaining sufficient healthy cells from patients, CAR-T cell fratricide, and the risk of immunodeficiency. In this review, we discuss bottlenecks and possible solutions in CAR-T cell therapy for T-cell acute lymphoblastic leukemias, as well as future directions in this field.

Keywords: Immunotherapy, Chimeric antigen receptor (CAR)-T cell, T-cell malignancies

1. INTRODUCTION

T-cell acute lymphoblastic leukemia (T-ALL), a highly aggressive and invasive hematological malignancy, accounts for approximately 25% of adult and 15% of pediatric acute lymphoblastic leukemia (ALL) cases [1, 2]. T-ALL is more likely to relapse than B-cell acute lymphoblastic leukemia (B-ALL) [3]. Treatment of multiple relapsed/refractory (r/r) T-ALL is challenging, and patients have dismal prognoses [4, 5]. The estimated 5-year survival is currently 70–85% in T-ALL but 7% in relapsed T-ALL [6, 7]. Allogenic hematopoietic stem cell transplantation (SCT) is an ideal cure for T-ALL, which is recommended for patients who experience the first relapse and may induce complete remission (CR) [8, 9]. CAR-T cell therapy has been widely used for B-ALL [10-13]. To date, the US FDA has approved five CAR-T cell therapies for hematological malignancies that express the CD19 or BCMA antigen. However, CAR-T cell therapy for non-B hematologic malignancies is more challenging and remains in an early exploration stage [10-14].

Herein, we summarize clinical studies exploring CAR-T cell therapy for T-cell malignancies, and also discuss limitations and potential future research directions in this field.

2. TARGETING THE MAIN ANTIGENS

2.1 CD7

CD7 is a membrane glycoprotein expressed on T lymphocytes and NK cells [15, 16]. Studies have demonstrated that 95% of T-ALL and T-cell lymphomas are CD7 positive [17]. A case report has described autologous CD7 CAR-T cell therapy leading to CR in a high-risk patient. The patient experienced a manageable cytokine release syndrome (CRS). CAR-T cells persisted for approximately 40 days *in vivo* [18]. In autologous CD7 CAR-T cell therapy, difficulties in isolating and obtaining a sufficient number of healthy T cells without tumor cell contamination may be encountered [19]. CAR-T cell-mediated targeting of the same antigen can cause endogenous T cell depletion or CAR-T cell fratricide. The case study used CAR with inducible caspase 9 to withdraw CAR-T cells if needed. Unexpectedly, the fratricide effect was not observed in the patient [18]. In addition, Dai et al. have used autologous CD7 CAR-T cells to treat a patient with early T cell precursor lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) with the TP53 mutation. The patient achieved TP53 mutation-negativity on day 91 after receiving CD7 CAR-T cells [20]. In another ongoing clinical trial, researchers have treated nine patients: six with r/r T-ALL/LBL and three with r/r ETP-ALL/LBL with

autologous CD7 CAR-T cells. The CR rate at 3 months was 71.4% in the patients who were followed up for 3 months. Of the first six patients, two experienced grade 2 CRS, and the remainder developed grade 1 CRS [21]. In this trial, CD7 CAR-T cells with the CD7 protein expression blocker (PEBL) structure overcame fratricide [22]. In a related meeting abstract, Yang et al. have reported findings in 14 patients with r/r T-ALL who received autologous CD7 CAR-T cells, of whom 13 achieved CR or incomplete count recovery by 28 days post-infusion. Only one patient experienced grade 3 CRS, whereas others experienced grade 1 or 2 CRS. CD7 CAR-T cells persisted in the peripheral blood for a median of 52.5 days at the last evaluation [23].

Use of donor-derived CAR-T cells rather than autologous CAR-T cells can circumvent the challenges of obtaining adequate healthy T cells from patients and tumor cell contamination. Donor-derived CAR-T cells are not affected by patient disease status, but may cause graft-versus-host disease (GVHD) and rejection [24]. In our center, we have treated 20 patients with r/r T-ALL with CD7 CAR-T cells derived either from new donors or from prior transplantation donors [25]. When patients received new donor-derived CAR-T cell therapy, they underwent SCT derived from the same donors to alleviate long-term hematologic toxicity [25]. However, this strategy is limited to patients who have received prior SCT or those who are eligible for transplantation and have matched donors. A total of 90% of patients achieved CR, whereas only 10% of patients developed grade 3 or higher CRS. CD7 CAR-T cells proliferated effectively and persisted *in vivo* for more than 3 months [25].

The CAR construct also incorporated a PEBL sequence causing retrograde transport of CD7 protein to the endoplasmic reticulum (ER). Consequently, the antigen was entrapped in the ER/Golgi, thus blocking its normal expression and minimizing fratricide [25, 26]. Previously, other researchers advocated for a similar technique for decreasing CD7 expression and preventing fratricide [27]. CD7 CAR-T cells can still target endogenous CD7-positive T and NK cells, thus increasing infection risk. A total of 25% of patients developed viral activation, and one patient with a fungal infection died of fungal pneumonia. *In vitro* analysis showed that the CD7-negative T cells reacted to fungi and viruses, thus indicating that they might have had some immunoprotective activities [25]. A total of 60% of patients had grade 1 or grade 2 GVHD, but all adverse effects were managed with ruxolitinib and/or methylprednisolone [25]. The above evidence indicates that donor-derived CD7 CAR-T cell therapy is highly efficient, but care should be taken to manage the related adverse effects, including infections and GVHD.

Universal CAR-T (UCAR-T), as an "off-the-shelf" product, is under intensive investigation. Gene-editing systems such as TALEN and CRISPR/Cas9 have been used to delete endogenous TCR and MHC genes to prevent GVHD and rejection [28, 29]. UCAR-T cells may offer the benefit of preventing tumor cell contamination in T-cell malignancies. UCAR-T cells are not affected by patient disease status, thus allowing patients to receive standard and timely treatment. In 2018, Cooper et al. used CRISPR-Cas9 to eliminate TCR alpha chain and CD7 expression on CD7 CAR-T cells. Consequently, the CD7 CAR-T cells not only demonstrated efficient tumoricidal activity against T-ALL primary cell lines without GVHD but also increased proliferation efficiency *in vitro* [30]. However, to date, UCAR-T cell amplification and persistence *in vivo* and the possible safety issues associated with gene-editing remain limitations of UCAR-T cell therapy. In 2020, Li et al. used CD7 UCAR-T cells to treat two patients with T-ALL, both of whom achieved CR. One patient had been in remission for more than 1 year after infusion of CAR-T cells [31]. Because T and NK cells express CD7, CD7 CAR-T cells target patients' alloreactive T and NK cells, thereby preventing rejection [32]. However, UCAR-T cells may have less ability to persist *in vivo* than autologous and donor-derived CAR-T cells [25, 31].

From the above-mentioned CAR-T cell targeting of CD7, the persistence of autologous and donor-derived CAR-T cells appears to be much higher than that of UCAR-T cells. The efficacy of autologous CAR-T cells has been confirmed, although tumor cell contamination remains a challenge. Donor-derived CAR-T cell therapy has achieved convincingly high efficacy, but it involves donors, thus posing obstacles under some conditions (such as a lack of suitable donors) [33]. The efficacy of UCAR T cell therapy, despite its ability to avoid tumor cell contamination, fratricide, and GVHD, requires confirmation through more clinical trials. Nonetheless, endogenous T-cell depletion is a common problem awaiting resolution.

2.2 CD5

CD5 is a glycoprotein with an extracellular domain that spans the cell membrane. CD5 is expressed on thymocytes, T lymphocytes, and B-1a cells [34, 35]. In 2015, Mamonkin et al. revealed that CD5 CAR-T cells exhibit partial and temporary fratricide, and mediate antitumor activity *in vitro* [36]. Unlike CD7 CAR-T cells, CD5 CAR-T cells can proliferate without knockdown of CD5 gene expression. In 2018, Mamonkin et al. found that CD5 CAR-T cells with the 4-1BB co-stimulatory domain, instead of CD28, can enhance antitumor activity but may enhance CAR-T cell fratricide [37]. However, stringent CD5 knockdown may favor CAR-T cell proliferation [38].

Hill et al. have performed a clinical trial in which four patients with T-ALL and five patients with T-cell non-Hodgkin lymphoma received autologous CD5 CAR-T cell therapy. Three of nine patients achieved CR, one of whom had T-ALL. Three of nine patients experienced grade 1 or 2 CRS [39]. Interestingly, fratricide was not a major problem, because CAR-T cells expanded in the patients from 0.7 to 6 months, according to polymerase chain reaction (PCR) detection, and normal CD3-positive T cells were not completely depleted. This result might have been because CD28-costimulation and CD5 down-regulation

on T cell surfaces cause CAR-T cells to experience only transient fratricide. In 2021, the same team updated their data and reported that four of nine patients with T-cell lymphoma achieved responses. CR was observed in two patients (22.2%): one with angioimmunoblastic TCL and one with peripheral T-cell lymphoma. Grade 1 CRS and grade 2 CRS were observed in three patients and one patient, respectively. No other neurotoxicity events were observed in this clinical trial [40]. Despite these encouraging findings, more trials are needed to verify the safety and efficacy of CD5 CAR-T cell therapy.

In 2020, Feng et al. treated a patient with T-LBL with donor-derived CD5 CAR-T cells [41]. The researchers produced CD5 CAR-T cells that secreted IL-15 protein to potentiate CD5 CAR-T cell function [42]. Blasts in the cerebrospinal fluid decreased from approximately 80% to approximately 2% 1 week after CD5 CAR-T cell infusion and were undetectable by the fourth week. GVHD was not observed in this patient. The patient subsequently underwent SCT [41].

Table 1 summarizes the above-mentioned preliminary results from several clinical trials of CD5 or CD7 CAR-T cell therapy.

3. TARGETING OTHER ANTIGENS

CD3 is a pan-T cell antigen, and cytoplasmic CD3 is considered an indicator of T-cell lineage [43]. CD3 is not an ideal antigen target for CAR-T cell therapy, because of fratricide. Researchers have used TALEN to knock out the endogenous TCR$\alpha\beta$/CD3 before modifying CD3 CARs. CD3 CAR-T cells have been found to kill primary T cells with high specificity and potency [44]. CD1a is expressed on cortical T-ALL cells, but not on normal T cells or CD34-positive progenitor hematopoietic cells [45-48]. These characteristics makes this antigen suitable for cortical T-ALL. CD1a CAR-T cells have shown robust anti-tumor activity in preclinical investigations, but more clinical trials are needed [48].

T-cell-derived hematologic malignancies may come from $CD4^+$ T cells [49]. CAR-T cells targeting CD4 may spare endogenous CD8 T cells, thus avoiding complete T cell immunodeficiency after infusion in patients. Preclinical assays have demonstrated that CD4 CAR-T cells can efficiently eliminate CD4-positive leukemic cells in co-culture assays [50]. However, we did not see any evidence of CD4 CAR-T cell therapy in clinical trials.

Most T cells express the TCR chain, which is encoded by the T cell receptor beta constant 1 (TRBC1) or TRBC2 gene [51]. TCR is expressed in more than 95% of peripheral T cell lymphoma (PTCL) and 30% of T-ALL cases [52, 53]. TRBC1 CAR-T cell therapy may decrease fratricide to some extent by sparing TRBC2 T cells [54]. CAR-T cell therapy is currently being developed for PTCL. In clinical trials, CD30 CAR-T cell therapy for Hodgkin lymphoma has been demonstrated to be effective. CD30 is also present on a subset of PTCL, including anaplastic large cell lymphoma, and may serve as a promising target [55, 56]. In one clinical trial, two patients with anaplastic large cell lymphoma received CD30 CAR-T cell therapy, but the efficacy was limited [57].

4. LIMITATIONS OF CAR-T THERAPY FOR T-ALL/T-LBL

4.1 Difficulty in obtaining autologous healthy T cells

Normal and malignant T cells usually have some overlap in phenotypes. Therefore, obtaining healthy T cells without tumor cell contamination from patients who have tumor cells in the peripheral blood or considerable lymphopenia after intensive therapy may be difficult [19]. The incorporation of tumor cells may cause the emergence of treatment-resistant cells, through a mechanism of antigen masking, as previously reported in CD19 CAR-T cell therapy [19]. As described earlier, generating allogeneic CAR-T cells from transplantation donors or healthy third-party donors may be a viable option. Furthermore, UCAR-T cells also serve as good sources.

4.2 CAR-T fratricide

The developed targeted antigens in CAR-T cell therapy to treat T-ALL, such as CD7 and CD5, are expressed on healthy T cells and CAR-T cells [58, 59]. CAR-T cell fratricide results, thus decreasing CAR-T cell amplification [30, 32]. As described earlier, researchers have used the PEBL system, composed of a target-targeting scFv associated with a retention domain, which entraps antigen in the ER/Golgi and hinders expression [27]. In addition, UCAR-T cells are resistant to fratricide after deletion of the antigen via a gene-editing system [30].

4.3 Immunodeficiency

T-cell aplasia and severe immunodeficiency occur when CAR-T cells deplete endogenous normal T cells. Exogenous immunoglobulin replacement therapy can be used to treat B-cell aplasia caused by CAR-T cell persistence in patients with B-ALL [60, 61]. In contrast, T-cell aplasia may be more serious or even life-threatening and have no effective treatment [62]. T-cell aplasia may be prevented through several suggested methods. Targeting an antigen that is absent on normal T cells or is expressed on only a small percentage of normal T cells may leave at least some of the normal T cells intact [63]. Using CAR-T cells with a regulated lifespan or activity whose anti-tumor effects are limited can be advantageous for preventing the onset of T-cell aplasia [64]. In addition, bridging to SCT after CAR-T cell therapy may be an additional choice that can be made to decrease the risk of CAR-T-associated T-cell aplasia [65, 66]. The ultimate strategy to circumvent this problem may involve deletion of the target antigen gene from hematopoietic stem cells to differentiate T cells lacking target antigen expression. In a preclinical study by Kim et al., stem cells with CD7 deletion have been transplanted into recipient mice before CD7 UCAR-T cell therapy. Stem cells can successfully differentiate into CD7-negative T cells and CD7-negative NK cells *in vivo* without dysfunction, and these

Table 1 | Outcomes and characteristics of clinical trials of CAR-T cell therapy for T-ALL.

Study	Autologous CD7 CAR-T	Autologous CD7 CAR-T	Autologous CD7 CAR-T	Autologous CD7 CAR-T	Donor-derived CD7 CAR-T	CD7 UCAR-T	Autologous CD5 CAR-T	Donor-derived CD5 CAR-T
Reference	18	20	21	23	25	31	40	41
No. of patients	1	1	9	14	20	2	9	1
Dose	2×10^6/kg	5×10^6/kg	$1–2\times10^6$/kg	0.5×10^5/kg to 2×10^6/kg	$0.5–1\times10^6$/kg	6.44×10^6/kg, 1.1×10^7/kg	1×10^7/m^2 to 1×10^8/m^2	2×10^6/kg
Disease phenotype	T-ALL	ETP-ALL/LBL	6 T-ALL/LBL and 3 ETP-ALL/LBL	T-ALL	T-ALL	T-ALL	2 AITL, 6 TCL, and 1 T-ALL	T-LBL
Efficacy	CR	CR	CR: 88.9% NR: 11.1%	CR: 92.9% NR: 7.1%	CR: 90% PR: 5% NR: 5%	CR: 100%	CR: 22.2%	CR
CAR-T fratricide	No	Decreased fratricide with ER retention of CD7	Decreased fratricide with ER retention of CD7	NA	Decreased fratricide with ER retention of CD7	Decreased fratricide with knockout of CD7	Minimal and transient*	NA
CAR-T persistence in PB (by FCM)	Approximately 1.3 mo	Approximately 1.2 mo	NA	Approximately 1.7 mo	3 mo, >6 mo (by PCR)	<1 mo	3 wk to 9 mo (by PCR)	NA
CRS grade ≥1; ≥3	100%; 0	0; 100%	100%; 0 (in case 1–6)	100%; 7.1%	100%; 10%	100%; 100%	NA; 0	100%; 0
ICANS grade ≥1; ≥3	NA; NA	NA; NA	NA;NA	7.1%; 0	15%; 0	NA; NA	NA; NA	NA; NA
Incidence of GVHD	No	No	No	No	High (60%)	No	No	No
Risk of T cell deficiency	NA	Depletion of CD7$^+$ T cells (CD7$^-$ T cells expanded)	Severe and transient T cell deficiency	NA	Depletion of CD7$^+$ T cells (CD7$^-$ T cells expanded)	Depletion of CD7$^+$ cells	Decreased, but not complete depletion of CD3$^+$ T cells	Mild and transient T cell deficiency

*Probably because of CD5 down-regulation in CAR-T cells.

Abbreviations: AITL, angioimmunoblastic TCL; CAR, chimeric antigen receptor; CR, complete remission; CNS, central nervous system; CRS, cytokine release symptom; ETP-ALL, early T cell precursor lymphoblastic leukemia/lymphoma; FCM, flow cytometry; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; ICANS, immune effector cell–associated neurotoxicity syndrome; mo, months; NA, not available; NR, not remission; PB, peripheral blood; PCR, polymerase chain reaction; PR, partial remission; T-ALL, T-cell acute lymphoblastic leukemia; TCL, T-cell lymphoma; T-LBL, T-cell lymphoblastic lymphoma; wk, weeks.

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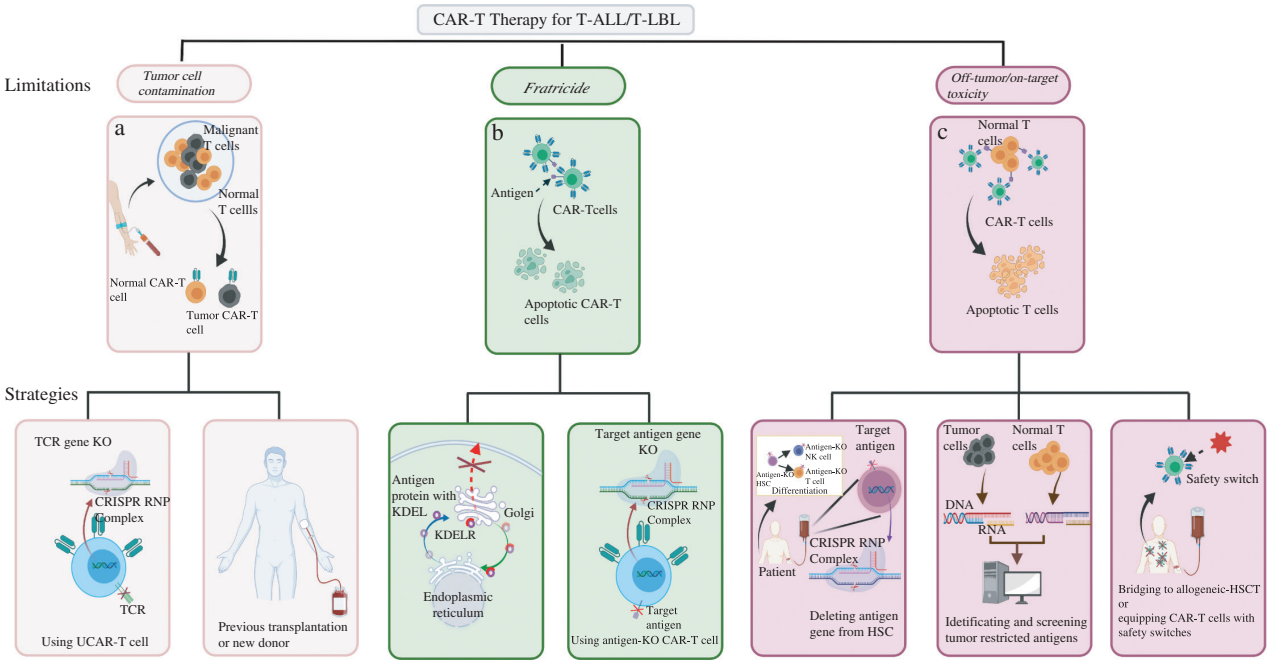

Figure 1 | Bottlenecks and proposed solutions of CAR-T cell therapy for T-ALL/T-LBL.
a) Proper separation and purification T cells without tumor cell contamination is challenging. Strategies using donor-derived CAR-T or UCAR-T cells should be considered. b) The shared expression of antigen leads to CAR-T cell fratricide. Proposed solutions include the use of a CAR construct with KDEL to retain antigen protein in the endoplasmic reticulum and the use of a gene-editing system to delete antigen genes in CAR-T cells. c) The shared expression of target antigens by endogenous healthy T cells results in off-tumor/on-target toxicity. Proposed solutions include rebuilding the T-cell compartment from HSCs lacking expression of target antigens (such as CD7) or screening for truly specific tumor-restricted antigens. Abbreviations: CAR, chimeric antigen receptor; CRISPR, clustered regularly interspaced short palindromic repeats; KDEL, endoplasmic reticulum retention signal; KDELR, endoplasmic reticulum retention signal receptor; scFv, single-chain fragment variable; T-ALL/T-LBL, T-cell acute lymphoblastic leukemia/T-cell lymphoblastic lymphoma; HSC, hematopoietic stem cell; KO, knockout; RNP, ribonucleoprotein; TCR, T cell receptor; UCAR, universal chimeric antigen receptor.

CD7-negative cells can tolerated well to CD7 UCAR-T cells [67]. Transplantation of gene-edited stem cells may be applied to other targets, such as CD5. However, gene-editing of stem cells is in the immature stage poses safety concerns and may require further optimization before widespread use in clinics.

These bottlenecks and strategies in CAR-T cell therapy for T-ALL/T-LBL are illustrated in **Figure 1**.

5. CONCLUSION

Currently, chemotherapy and SCT are recommended for ALL therapy but are limited by the problem of relapse [3]. CAR-T cell therapy has been found to improve outcomes in patients with r/r B-ALL, but the difficulties in obtaining sufficient healthy T cells from patients, CAR-T cell fratricide, and the risk of immunodeficiency limit its clinical applications in T-ALL.

Preliminary outcomes have been obtained for CD7, the most common target of CAR-T cell therapy for T-ALL. However, the same antigens shared by malignant T cells, CAR-T cells, and healthy T cells can cause tumor cell contamination, fratricide, and immunodeficiency. As previously described, allogeneic CAR-T cell therapy has demonstrated several advantages over autologous CAR-T cell therapy in overcoming the problem of tumor cell contamination in manufacturing CAR-T cells [25, 31]. The problem of fratricide can be solved by decreasing the expression of the target antigen on CAR-T cells with PEBL or a gene-editing system [27, 30]. Furthermore, major efforts should be focused on finding solutions to prevent immunodeficiency. Screening for novel and specific antigens restricted to malignant cells, equipping CAR-T cells with safety switches, and post-CAR SCT may be beneficial in controlling immunodeficiency [63-66]. In addition, transplanting stem cells with deletion of target antigen genes before CAR-T cell infusion may be a promising strategy to prevent immunodeficiency [67]. All these strategies will require in-depth evaluations to validate their safety and efficacy in preclinical and clinical trials.

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DISCLOSURE OF INTEREST

We declare no competing interests in relation to this work.

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