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Opinion

Potential Application of CAR-NK Cells as an *Ex Vivo* Therapy for T-cell-related Diseases

Daekee Kwon[1,2,*], Kyung-Sun Kang[3,*]

[1]Research Institute, Maru Therapeutics Co., Ltd., Seoul BioHub Global Center, Dongdaemun-gu, 02455 Seoul, Republic of Korea
[2]Department of Veterinary Medicine, College of Veterinary Medicine, Seoul National University, 08826 Seoul, Republic of Korea
[3]Adult Stem Cell Research Center, College of Veterinary Medicine, Seoul National University, 08826 Seoul, Republic of Korea
*Correspondence: dk.kwon@marurx.com (Daekee Kwon); kangpub@snu.ac.kr (Kyung-Sun Kang)

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Abstract

Anticancer therapeutics have evolved from small-molecule drugs to monoclonal antibodies and, more recently, to cell and gene therapies (CGTs). This progress has been driven by the pursuit of greater drug specificity, potency, and safety. Recent breakthroughs in chimeric antigen receptor T-cell (CAR-T) therapy for B-cell hematologic malignancies have accelerated the development of CAR-X CGTs, including CAR-T, CAR-natural killer (CAR-NK), and CAR-macrophage approaches. In this article, we compare candidate CAR-X platforms for T-cell–related diseases, such as T-cell hematologic malignancies, and propose the most suitable modality. Therefore, we analyzed the advantages and limitations of CAR-T, CAR-NK, and CAR-macrophage therapies. In T-cell-related diseases, CAR-T therapy faces multiple challenges, including fratricide, T-cell aplasia, and substantial barriers to the generation of allogeneic CAR-T products. CAR-macrophage therapies, in contrast, are constrained by relatively limited efficacy. In contrast, CAR-NK cells do not cause fratricide or T-cell aplasia and can be manufactured efficiently as allogeneic, "off-the-shelf" products. Collectively, to sustain and extend the advances in CGT initiated by CAR-T cells in B-cell malignancies, prioritizing CAR-NK research infrastructure for T-cell–related diseases represents a rational and strategic approach.

Keywords: adoptive immunotherapy; aplasia; allogeneic cell; cell therapy; chimeric antigen receptor therapy; hematologic neoplasms

1. Introduction

Anticancer therapeutics have evolved in a stepwise manner from small-molecule drugs to monoclonal antibodies and, more recently, to cell and gene therapies (CGTs) [1]. Conventional anticancer agents that inhibit cell proliferation are mostly small-molecule–based and are associated with considerable adverse effects owing to their on-target, off-tumor (OTOT) activity. Antibody-based drugs with improved specificities have been developed to reduce OTOT-related toxicity. Antibody drugs bind directly to target proteins, thereby enhancing specificity, and can also induce antibody-dependent cellular cytotoxicity in natural killer (NK) cells. However, their clinical efficacy has often fallen short of expectations.

To overcome these limitations, antibody–drug conjugates, in which a cytotoxic payload (drug) is conjugated to an antibody, as exemplified by agents such as Enhertu, are now being actively developed. Most recently, chimeric antigen receptor T-cell (CAR-T) therapies, such as tisagenlecleucel (Kymriah), in which immune cells are genetically engineered to efficiently recognize B-cell hematologic malignancies, have fundamentally shifted existing treatment paradigms [2]. Following these advances, there has been a growing interest in expanding the therapeutic scope of CAR-based approaches to T-cell–related diseases [3,4]. In this article, we systematically compare the major *ex vivo* CAR-X CGT platforms—CAR-T, CAR-NK, and CAR-macrophages—and, based on this comparative analysis, propose a CGT modality that appears most suitable for the treatment of T-cell–related diseases.

2. The Advent of CD19 CAR-T Therapy

The advent of the blockbuster CD19-directed CAR-T product tisagenlecleucel (Kymriah) represents a revolutionary milestone in the treatment of B-cell hematologic malignancies. Although various CD19-targeting antibody therapeutics have been developed, passive agents, which do not expand or persist *in vivo*, have failed to deliver transformative efficacy. A striking example of the impact of CAR-T cell therapy is the case of Emily Whitehead, a 5-year-old girl with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (ALL) who had exhausted all other treatment options and remained healthy and in long-term remission for more than a decade after receiving Kymriah. The basic principle of CAR-T cell therapy is to overexpress the CAR, which is composed of a single-chain variable fragment, hinge region, transmembrane domain, and intracellular activation domain(s), thereby enabling T cells to efficiently recognize tumor cells and undergo robust *in vivo* clonal expansion upon antigen encounter. The persistence of a subset of these cells as long-lived memory T cells after initial treatment, during which they continue to provide

immune surveillance, is another key factor underlying the strong and durable clinical efficacy of CAR-T therapy.

3. Expansion of Indications for CAR-T Therapy

CAR-T cell therapy, which begins by targeting CD19 expressed on the surface of B cells, has progressively expanded its clinical indications. To date, a total of seven CAR-T products targeting either CD19 (target diseases: ALL, Diffuse large B-cell lymphoma, Follicular lymphoma, and Mantle cell lymphoma) or B-cell maturation antigen (target disease: Multiple myeloma) have been developed, and their product names (generic names) and U.S. Food and Drug Administration approval years are as follows: Kymriah (tisagenlecleucel) 2017, Yescarta (axicabtagene ciloleucel) 2017, Tecartus (brexucabtagene autoleucel) 2020, Breyanzi (lisocabtagene maraleucel) 2021, Abecma (idecabtagene vicleucel) 2021, Carvikty (ciltacabtagene autoleucel) 2022, and Aucatzyl (obecabtagene autoleucel) 2024. To date, these indications remain restricted to B-cell–related hematologic malignancies. Additionally, clinical trials have demonstrated that CD19 CAR constructs can be repurposed to show dramatic efficacy in autoimmune diseases driven by B-cell dysregulation, such as systemic lupus erythematosus. Ongoing efforts are also aimed at extending the indications of CAR-T cell therapy to solid tumors by engineering CARs against various tumor-associated antigens. Particularly, engineered T-cell research targeting oncogenic viral antigens is being actively conducted for various solid cancers caused by viral infections [5].

4. Attempts to Extend CAR-T Therapy From B Cell-related to T Cell-related Diseases

In the field of hematological malignancies, efforts are ongoing to extend CAR-T therapy beyond B-cell cancers to T-cell malignancies [3,4]. In a study using donor-derived CAR-T cells targeting CD7, which is expressed on the surface of T cells, 20 patients with r/r T-ALL were treated and followed up for two years, achieving a high overall response rate of 95% (19/20) and a complete remission rate of 85% (17/20). However, serious late-onset adverse events, including severe infections and graft-versus-host disease (GvHD), have been observed, highlighting the major safety concerns [6]. Autologous CAR-T cells targeting CD5 have been investigated as a therapeutic strategy for r/r mature T-cell lymphoma [7].

5. Key Challenge 1: Fratricide in CAR-T Therapy

CAR-T cells that target proteins expressed on the T-cell surface can induce fratricide, which is a phenomenon where CAR-T cells attack each other through antigen sharing. In T-cell malignancies, when CAR-T cells are generated against targets, such as CD7, both normal and malignant T cells express the CD7 antigen, leading to CAR-T cell fratricide [8]. To prevent this, a complex manufacturing strategy is required in which the CD7 gene is first knocked out using CRISPR/Cas9, followed by the introduction of the CD7-specific CAR. Limited and transient fratricides have also been reported in CD5 CAR-T cells [9], and similar issues have been observed in CD3-targeted CAR-T cells [10]. Fratricide inevitably compromises therapeutic efficacy by depleting CAR-T cells, and attempts to prevent it via gene editing increase process complexity and expose cells to additional stress and potential damage during the editing procedure.

6. Key Challenge 2: Aplasia in CAR-T Therapy

An even more critical issue compared to fratricide is prolonged aplasia. B-cell aplasia refers to a state in which newly generated B-cells are continuously eliminated, resulting in sustained B-cell-free conditions. This phenomenon reflects the inherent trade-off of OTOT activity that underpins the efficacy of CD19 CAR-T cell therapy, wherein CAR recognizes CD19 on both malignant and normal B cells. B-cell aplasia is driven by the long-term persistence of a subset of CD19 CAR-T cells that differentiate into memory T cells and remain in the body for extended periods. In an early clinical study of CD19-BBζ CAR-T cells, 100% of patients who achieved complete remission developed B-cell aplasia, persisting up to 1 year in some cases [11]. Other studies have reported a median time to recovery from B-cell aplasia of approximately 35 months. A similar pattern was observed for CD7 CAR-T cells in T-cell malignancies. In a clinical trial of CD7-directed CAR-T therapy for T-cell hematologic malignancies, T-cell aplasia was detected within 15 days after infusion, and even after 2 years only about half of the patients recovered [6]. Because T cells serve as the central coordinators of adaptive immunity, prolonged T-cell aplasia can lead to severe, potentially life-threatening infections, representing a major safety concern.

7. Key Challenge 3: Allogeneic Manufacturing of CAR-T Therapy

From an industrial perspective, high-priced patient-specific (autologous) CAR-T products have intrinsic limitations in terms of cost reduction. Although there is considerable interest in developing allogeneic CAR-T therapies, their manufacturing requires extensive genome editing of multiple genes involved in immune rejection and GvHD in a cell type that is inherently difficult to modify, representing a major hurdle [12]. Moreover, even when a single batch of allogeneic CAR-T cells is successfully produced, the proliferative constraints of T cells make it challenging to generate sufficient doses for a large patient population. An alternative strategy involves the use of induced pluripotent

Table 1. Pros and cons of CAR-T, CAR-macrophage, and CAR-NK approaches for T cell-related diseases.

CAR-X	Pros	Cons
CAR-T	Clonal expansion	Fratricide
	Long *in vivo* persistence	Aplasia
	Strong efficacy	Difficult in allogenic manufacturing
	Many approved drugs	Strong toxicity
CAR-macrophage	Fratricide-free	Low efficacy
	Aplasia-free	Short *in vivo* persistence
	Safety	No approved drug
CAR-NK	Fratricide-free	Short *in vivo* persistence
	Aplasia-free	Post-thaw potency
	Ease of allogeneic manufacturing	No approved drug
	High efficacy[a]	
	Safety	

[a] Efficacy rating for T-cell-related diseases is based on preclinical evidence (*in vitro* and animal models); no clinical trial data for CAR-NK in T-cell malignancies are available to date.
CAR-T, chimeric antigen receptor T-cell; CAR-NK, CAR-natural killer.

stem cells (iPSCs), which offer an essentially unlimited cell source for allogeneic CAR-T cell manufacturing. However, this approach faces substantial challenges, particularly in achieving efficient T-cell differentiation and expansion, and remains technically more demanding than methods based on peripheral blood–derived T cells.

8. CAR-macrophage

Unlike T and NK cells, which are lymphoid-lineage cells, macrophages are myeloid-lineage cells. In contrast to T and NK cells, which circulate and mediate direct cytotoxicity, macrophages are typically tissue-resident cells whose primary functions include the clearance of damaged cells and foreign materials within tissues. In solid tumor models (e.g., glioblastoma), CAR macrophages have demonstrated lower direct cytotoxicity than CAR-T or CAR-NK cells [13]. This suggests that their primary mechanism of action, tumor microenvironment remodeling, may be less suitable for T-cell hematologic diseases, which require potent direct cytolytic activity. Clinically, HER2-targeted CAR-macrophages exert their main therapeutic effects through tumor infiltration, remodeling of the solid tumor microenvironment, and enhancement of $CD8^+$ T-cell recruitment, thereby converting "cold" tumors into "hot" tumors [14]. Because T-cell–related diseases are hematologic disorders, they require therapies with potent cytotoxicity and acceptable toxicity profiles, rather than primarily tissue-infiltrative functions. Therefore, CAR macrophages are likely to realize their full potential in solid tumors, particularly in combination with CAR-T or CAR-NK therapies rather than as standalone agents for T-cell–related hematologic diseases.

9. CAR-NK Cells

Like T cells, NK cells arise from lymphoid lineages. Both NK and T cells have been widely used as lymphoid effector cells for anticancer immunotherapy. When a CAR targeting a T-cell antigen is expressed in NK cells, the resulting CAR-NK cells remain intrinsically fratricide-free because NK cells do not express T-cell–restricted targets. Additionally, unlike T cells, NK cells exhibit relatively short *in vivo* persistence, which effectively reduces the risk of prolonged T-cell aplasia but also limits durable efficacy (Table 1). This limitation can be mitigated through repeated NK cell administration. Moreover, NK cells do not express the T-cell receptor responsible for GvHD in allogeneic T-cell products, making allogeneic use of NK cells feasible. This enables large-scale off-the-shelf manufacturing and the potential for substantial cost reduction. Although shorter persistence may be viewed as a drawback, it also contributes to the favorable safety profile of CAR-NK-based therapies. Clinical studies on B-cell hematologic malignancies have shown that CAR-NK cells can achieve efficacy comparable to that of CAR-T cells, while offering superior safety [15]. The efficacy of CAR-NK cells has also been confirmed in an acute T-cell lymphoblastic leukemia model [16]. NK cells from various sources (e.g., peripheral blood, umbilical cord blood, iPSC-derived NK cells, and NK-92 cell lines) have been studied in translational research [17,18]. However, no CAR-NK product has yet been approved as a marketed therapy. Large-scale off-the-shelf manufacturing, preservation of post-thaw potency, and solid tumor infiltration are challenges to be solved.

10. Discussion and Conclusion

T-cell-related diseases are being actively explored as the next major therapeutic target for CAR-based immunotherapies following the success of CAR-T cells in B-cell hematologic malignancies. Although CAR-T cells of-

fer advantages such as robust clonal expansion, potent antitumor efficacy, and long *in vivo* persistence, their application to T-cell–related diseases is hindered by fratricide, prolonged aplasia, challenges in establishing allogeneic products, and serious treatment-limiting adverse events. In contrast, CAR–macrophage approaches are primarily constrained by their low cytotoxic efficacy in this setting. However, CAR-NK cells represent a promising alternative, owing to their intrinsic resistance to fratricide and T-cell aplasia, suitability for allogeneic, off-the-shelf manufacturing, and favorable safety profile. Collectively, considering efficacy, safety, and manufacturability, CAR-NK cells appear to be a more suitable platform than CAR-T or CAR-macrophage therapies for T-cell–related diseases. Accordingly, future efforts should prioritize (1) optimizing CAR-NK designs for T-cell antigen targets and (2) establishing robust, cost-effective, and scalable manufacturing processes for allogeneic CAR-NK products.

Author Contributions

DK: Conceptualization, Writing and editing, Supervision. KSK: Conceptualization, Editing, Supervision. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. Both authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest. Although Daekee Kwon was an employee of Maru Therapeutics Co., Ltd., the judgments in data interpretation and writing were not influenced by this relationship.

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