Novel Immunotherapies for the Treatment of Acute Lymphoblastic Leukemia

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ABSTRACT

CAR T-cell therapy and immune checkpoint inhibitors are groundbreaking immunotherapies with great promise for cancer treatment. CAR T-cell therapy uses engineered T-cells from the patient to help the immune system better identify and eliminate cancer cells. Immune checkpoint inhibitors for PD-1 and PD-L1 use monoclonal antibodies to block the PD-1/PD-L1 interaction that would otherwise allow cancer cells to go unnoticed by the immune system, continuing the growth of the cancer. For acute lymphoblastic leukemia (ALL), CAR T-cell therapy has led to favorable responses, with the potential to induce complete remission. Conversely, the PD-1 and PD-L1 immune checkpoint inhibitors have not shown a significant effect on the disease. Though CAR T-cell therapy is an effective treatment for ALL, its accessibility is impacted by cost and lack of availability. With the initiation of further clinical trials, commercialized CAR T-cell therapy could become more widely available, thus lowering the cost of treatment, and increasing accessibility.

Introduction

Acute Lymphoblastic Leukemia

Acute Lymphoblastic Leukemia (ALL) is a hematological malignancy stemming from bone marrow (*National Cancer Institute* [*NCI*], 2023). It occurs when the bone marrow produces abnormal immature lymphoblasts (*NCI*, 2023). These cells are dysfunctional and overcrowd the bone marrow, which can prevent the creation of healthy blood cells (*NCI*, 2023). ALL has two subtypes, B-ALL and T-ALL, each characterized by its respective B or T-lymphoblasts (*Leukemia and Lymphoma Society* [*LLS*], n.d.a). B-ALL is the more prevalent subtype, representing 75% of ALL cases (*LLS,* n.d.a). ALL is the most common cancer in children, most commonly occurring in those aged three to seven (*Acute Lymphoblastic Leukemia (ALL) - UF Health*, n.d.). Children generally experience better outcomes with ALL than adults, with survival rates of 89% and 40%, respectively (Miller et al., 2022).

Symptoms of ALL include bone and joint pain, easy bruising and bleeding, weakness, fatigue, fever, loss of appetite, weight loss, pallor, enlarged liver or spleen, swollen lymph nodes, pinpoint red spots, and night sweats (*NCI*, 2023). While there is no direct cause of ALL, various factors may increase one's risk of developing it, such as chromosomal mutations, radiation exposure, previous chemotherapy use, receiving a bone marrow transplant, and toxin exposure (*NCI*, 2023). Furthermore, those with Down syndrome or a family history of leukemia are at greater risk for developing ALL (*NCI*, 2023). The current treatment for ALL, radiation and chemotherapy, works to normalize the patient's healthy blood cell count (*NCI*, 2023). A healthy adult's lymphocyte count is between 1,000-4,000 lymphocytes per μL of blood, and a patient with ALL would be diagnosed after having >5,000 B cells/uL for a minimum of 3 months (*LLS,* n.d.b; *LLS,* n.d.c). Remission is defined as having normal blood counts and bone marrow that appears healthy when observed beneath a microscope (*NCI*, 2023). The most common form of treatment is chemotherapy (*NCI*, 2023). Post-remission, more treatment is

used to ensure the cancer's elimination, such as brain radiation, stem cell transplants, bone marrow transplants, or further chemotherapy (*NCI*, 2023). The post-remission treatment is chosen based on the age and health of the patient, the number of chemotherapy courses needed for remission, and the availability of stem cell and bone marrow donors (*NCI*, 2023). For patients with relapsed or refractory (R/R) ALL, novel treatments utilizing the immune system are being explored, such as CAR-T cell therapy and immune checkpoint inhibitors (Haslauer et al., 2021; Miller et al., 2022).

CAR T-Cell Therapy

Introduction to CAR T-Cell Therapy

CAR T-cell therapy genetically modifies a patient's T-cells to more effectively identify and attack malignant cells (Haslauer et al., 2021). T-cells and T-lymphocytes are members of the immune system that work to identify and eliminate tumor cells, preventing cancer (Haslauer et al., 2021). Tumor cells can learn to recognize the T-cells' immune response and avoid or silence it by restricting antigen recognition (Kim & Cho, 2022). The 'CAR' of CAR T-cell therapy stands for chimeric antigen receptor; CARs are the receptors that are introduced to the T-cells during the modification process, either through viral or micelle transduction (Haslauer et al., 2021). As technology improves and the CAR evolves, newer generations of CARs are introduced, with the most recent being the fourth generation (Meng, et al., 2020). Each succeeding generation has focused on enhancing a different aspect of the CAR: activation, proliferation, and persistence (Meng et al., 2020). Different CARs target different antigens commonly found on certain malignant cells (Haslauer et al., 2021). The most common target is CD19, as it is often expressed on B-lymphoblasts associated with B-ALL (Haslauer et al., 2021).

The therapeutic process of CAR T-cell therapy is the following: the patient's T-cells are extracted, modified in a lab, grown in large quantities, and administered intravenously back to the patient (Figure 1) (Haslauer et al., 2021). CAR T-cell therapy has proven to be most effective in treating hematological malignancies (cancers of the blood, bone marrow, and lymph nodes) (Haslauer et al., 2021). Tumor heterogeneity hinders CAR T-cell therapy's ability to treat solid cancers (Yang et al., 2022). Tumor heterogeneity refers to the differences between tumor cells of the same tumor, as well as differences between primary and secondary tumors (*NCI*, n.d.). It complicates the process of choosing a target antigen that will induce a significant impact on the tumor's elimination, since the tumor cells may express different antigens (Yang et al., 2022). Thus, the FDA has only approved CAR T-cell therapy for the treatment of hematological malignancies (Haslauer et al., 2021).
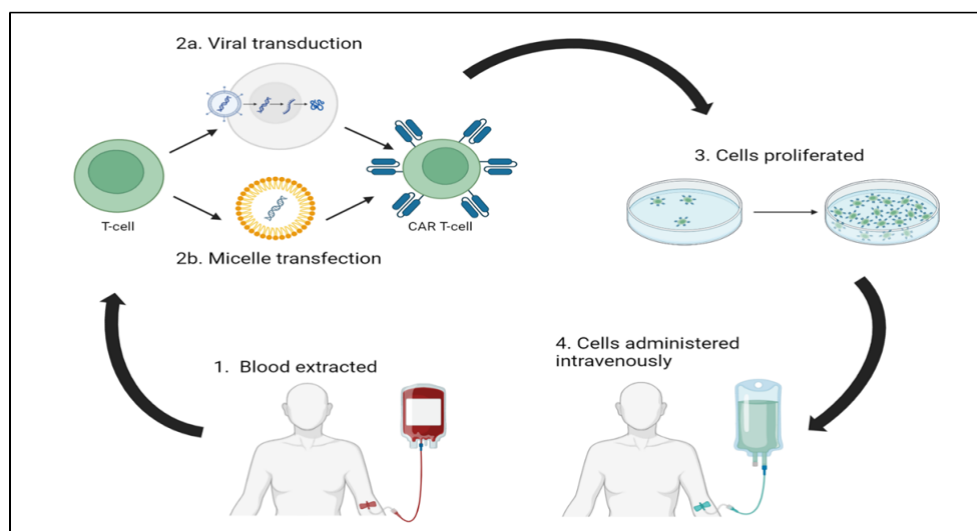
Figure 1. CAR T-Cell Therapy Process. The CAR T-cell therapy process begins with blood extraction from the patient. Once T-cells are isolated from the blood, they are transfected with micelles or viruses containing CARs to generate CAR T-cells. The cells are then proliferated and administered to the patient intravenously. (Created with BioRender.com)

The first generation of CAR includes a single-chain variable fragment (scFv), a transmembrane domain, and a signaling domain, CD3z (Subklewe et al., 2019). The second generation includes the addition of a costimulatory domain, either CD28 or 4-1BB (Subklewe et al., 2019). The third generation includes two costimulatory domains, either a pairing of CD28 and 4-1BB or CD28 and OX40 (Guercio et al., 2020; Subklewe et al., 2019). The fourth generation is modeled after the second, having a singular costimulatory domain (either CD28 or 4-1BB), as well as a chemokine (often IL-12) inducer to aid in a greater immune response (Subklewe et al., 2019). The CAR interacts with the immune system by binding to the tumor ligand (commonly CD19), which induces phosphorylation in the CD3z signaling domain (Meng et al., 2020). This activates kinases PI3K and AKT, cascading into the release of transcription factors AP-1, NFAT, and NKB1 to activate the production of cytokines (Meng et al., 2020). Cytokines are then released causing an increase in immune response, and thus, tumor cell elimination (Figure 2) (Meng et al., 2020).
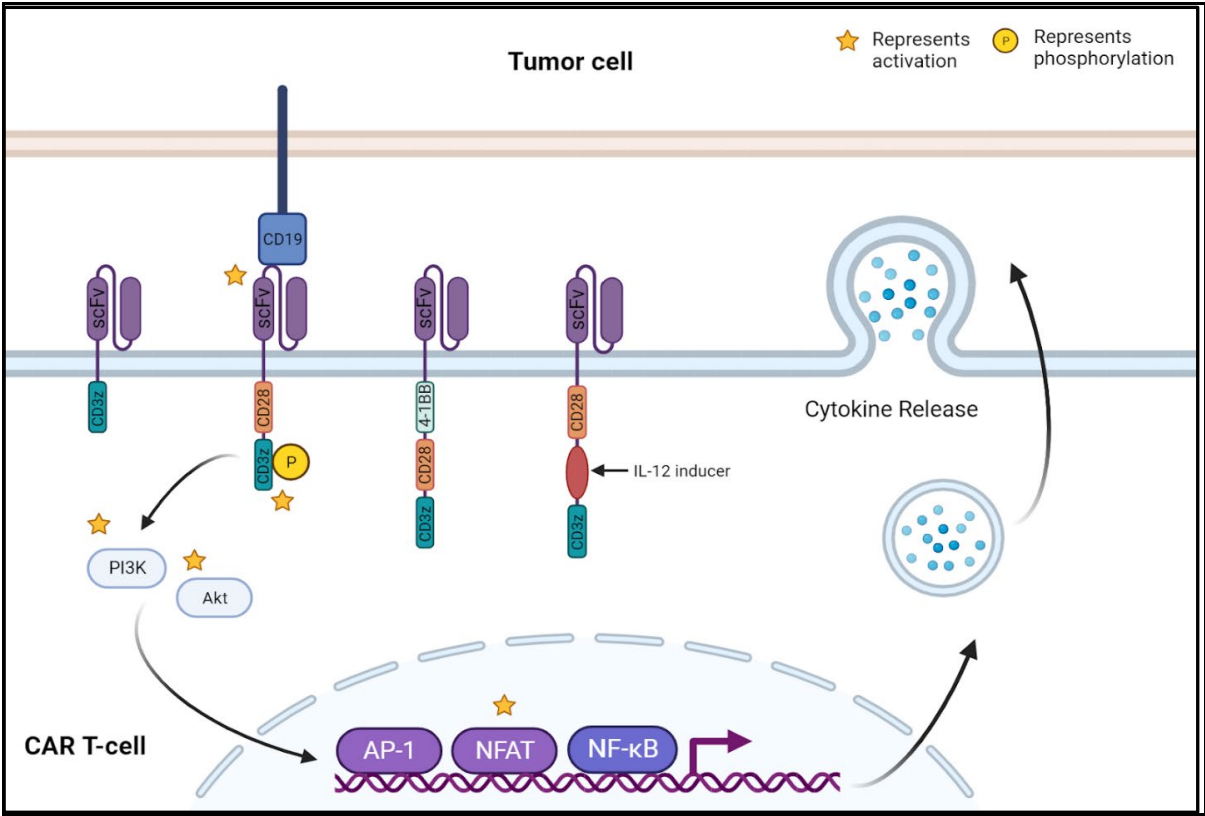

Figure 2. CAR T-Cell/Tumor Cell Interaction and Immune Cascade. The CAR generations are shown in increasing order from left to right, beginning with the first generation. As a note, all FDA-approved treatments use second generation CARs along with (most) clinical trials, as generations beyond the second have not yet entered expansive clinical trials (Tomasik et al., 2022). (Created with BioRender)

Efficacy of Approved CAR T-Cell Therapeutics

As of February 28, 2022, six CAR T-cell therapies have been approved by the FDA for treatment of hematologic malignancies, with varying degrees of effectiveness (Haslauer et al., 2021; *U.S. Food and Drug Administration* [*FDA*], 2022). The overall response rate was somewhat consistent across drugs, with a maximum of 25% deviation (Table 1) (Abramson et al., 2020; Ali et al., 2019; Haslauer et al., 2021; Munshi et al., 2021). Complete remission rate deviated greatly, from 33% to 83% (Abramson et al., 2020; Ali et al., 2019; Haslauer et al., 2021; Munshi et al., 2021). This inconsistency deems the treatment's outcome very variable; it is vital that this range decreases.

Table 1. Efficacy of Current CAR T-Cell Therapies.

Brand Name	Drug	Target Antigen	Target Cancer	Overall Responders[1] (%)	Complete Responders (Remission) (%)
Kymriah	Tisagenlecleucel	CD19	B-ALL	81%	60%
Yescarta	Axicabtagene cioleucel	CD19	Refractory Large B-cell Lymphomas	83%	58%
Breyanzi	Lisocabtagene maraleucel	CD19	Refractory Large B-cell Lymphomas	73%	53%
Tecartus	Brexucabtagene autoleucel	CD19	Mantle Cell Lymphoma	90%	82%
Abecma	Idecabtagene vicleucel	BCMA[2]	R/R Multiple Myeloma	73%	33%
Carvykti	Ciltacabtagene autoleucel	BCMA	R/R Multiple Myeloma	98%	83%

Each FDA-approved CAR T-cell therapy drug is listed along with the efficacy of each.
[1]'Overall Responders' includes responders who did not achieve remission as well as those that did
[2]B-cell Maturation Antigen (BCMA)
(Abramson et al., 2020; Ali et al., 2019; Haslauer et al., 2021; Munshi et al., 2021)

CAR T-Cell Therapy and ALL

CAR T-cell therapy has favorable outcomes in treating ALL (Haslauer et al., 2021). Across five clinical trials, Kymriah has had a remission rate ranging from 70%-89% (Martino et al., 2021). Though, many patients still do not reach any remission using Kymriah, as they experience T-cell exhaustion and/or antigen loss of the tumor cells; thus, without antigens to identify, CAR T-cell therapy is rendered ineffective (Haslauer et al., 2021). In response, various trials have emerged focusing on testing new targets, as well as combined targets to combat

this issue (Haslauer et al., 2021). Some new targets and combinations include CD20, CD19 + B-cell maturation antigen (BCMA), and CD19 + CD22 (Haslauer et al., 2021). The AMELIA trial, which used the combination CD19 + CD22 as its targets, achieved a 75% remission rate, which demonstrates the possibilities of target combinations beyond CD19 (Haslauer et al., 2021).

Adverse Effects of CAR T-Cell Therapy

Despite encouraging results from using CAR T-cell therapy to treat ALL, many side effects are experienced by patients as well. One of the most common effects is cytokine release storm (CRS), where an excessive number of cytokines are released due to the CAR T-cell treatment process. CRS is often accompanied by fever, tachycardia, and neurotoxicity, and, in rare cases, has been fatal. If CRS occurs in the cerebrum specifically, then aphasia, delirium, seizures, and syncope may occur. Immunosuppressants and corticosteroids are the principal forms of treatment for CRS and its symptoms. Another unfortunate effect of CAR T-cell therapy is tumor lysis syndrome (TLS), the sudden and overwhelming release of malignant cell parts into the body resulting in hepatotoxicity and nephrotoxicity. If CRS and TLS are present comorbidly, cardiac arrhythmia may occur. Beyond adverse physical symptoms, the efficacy of CAR T-cell therapy may also be hindered by possible dysfunction through an on-target off-tumor effect due to cross reactivity; targeted antigen[s] are also present in non-malignant cells and are in turn attacked instead of (or along with) the malignant cells. Thus, the therapy has the potential to damage healthy cells. (Haslauer et al., 2021)

Availability and Commercialization of CAR T-Cell Therapy

Regardless of the efficacy of CAR T-cell therapy, its cost, complexity, and conditions required for treatment make the therapy difficult to access (Abou-El-Enein & Gauthier, 2022). The average cost of therapy, which includes a single infusion, is between $373,000 and $475,000 (Abou-El-Enein & Gauthier, 2022). Medicare covers the cost, Medicaid's coverage varies by state, and coverage by private health plans varies (*Blood & Marrow Transplant Information Network* [*BMT Infonet*], n.d.). For any plan, though, it may not include the additional costs incurred by the treatment process, such as deductibles, co-pays, prescription drugs, food, lodging, and travel (to treatment center) (*BMT Infonet*, n.d.). Furthermore, there is limited equipment for generating CARs, increasing costs (Abou-El-Enein & Gauthier, 2022). Due to the near-inevitable adverse effects of the therapy, specialized facilities and medical personnel are required to monitor patients and ensure their safety during and post-treatment (Abou-El-Enein & Gauthier, 2022). Due to the regulations required to develop a clinic and the existence of few certified centers, the therapy primarily exists in trials, further decreasing availability (Abou-El-Enein & Gauthier, 2022). This lack of public availability leads to great delays in treatment (Abou-El-Enein & Gauthier, 2022). Additionally, the individualized process of treating a single patient with CAR T-cell therapy hinders the therapy's commercialization greatly, as each patient's treatment must be personalized (Abou-El-Enein & Gauthier, 2022).

PD-1/PD-L1 Therapy

Introduction to PD-1/PD-L1 Immune Checkpoint Therapy

Programmed death cell protein 1 (PD-1) and programmed death ligand 1 (PD-L1) therapy is a form of immunotherapy that inhibits immune checkpoints by using monoclonal antibodies to reactivate T-cells deactivated by malignant cells (Patel et al., 2023). PD-1 and PD-L1 are partner proteins normally present on T-cells and

cancer cells, respectively (though, PD-L1 is also expressed on some healthy cells) (*NCI*, 2022; *American Cancer Society* [*ACS*], n.d.a; Yang et al., 2019). The purpose of the PD-1/PD-L1 interaction, as with other immune checkpoints, is to prevent the destruction of healthy cells by deactivating T-cells (*NCI*, 2022). This function is manipulated by cancer cells that over-express PD-L1; the PD-1/PD-L1 binding deactivates T-cells, thus protecting cancer cells and furthering the progression of disease (Patel et al., 2023). PD-1 and PD-L1 inhibitors are monoclonal antibodies that inhibit the PD-1/PD-L1 binding interaction (*ACS*, n.d.a). This allows for the immune response against cancer to be restored (*ACS*, n.d.a). (Figure 3a/b)
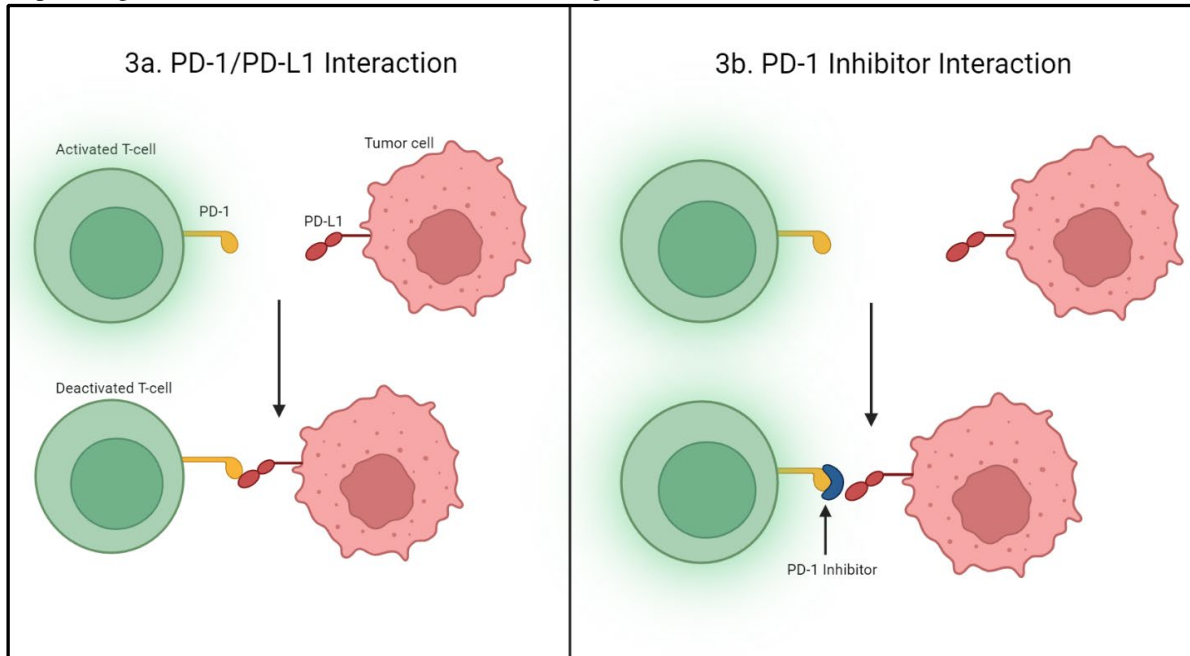

Figure 3. PD-1/PD-L1 Interaction with and without Inhibitor. On the left, the uninhibited PD-1/PD-L1 interaction is displayed. On the right, the PD-1 inhibitor is shown to block the interaction and sustain the T-cell's activation. (*ACS*, n.d.a; Patel et al., 2023). (Created with Biorender.com)

Efficacy of PD-1/PD-L1 Immune Checkpoint Therapeutics Approved

Various PD-1 and PD-L1 inhibitors have been approved by the FDA (*ACS*, n.d.a). For PD-1, the inhibitors Keytruda (pembrolizumab), Opdivo (nivolumab), Libtayo (cemiplimab), Jemperli (dostarlimab), and Zynyz (retifanlimab) have been approved (*ACS*, n.d.a; *NCI*, 2022). For PD-L1, Tecentriq (atezolizumab), Bavencio (avelumab), and Imfinzi (durvalumab) have been approved (*ACS*, n.d.a; *NCI*, 2022). PD-1 therapies have had overall positive outcomes in the treatment of some hematological malignancies (specifically myeloid, lymphoid, and virus-related) (Patel et al., 2023). PD-1 inhibitors have shown particular efficacy in treating Hodgkin's Lymphoma (Ok & Young, 2017). Though, in treating ALL, there has not been such success (Patel et al., 2023). In a phase 2 trial with T-ALL using the drug nivolumab, the drug was found to not slow the progression T-ALL, and the trial was terminated (Patel et al., 2023).

Adverse Effects of PD-1/PD-L1 Immune Checkpoint Therapeutics

PD-1 and PD-L1 inhibitors, like CAR T-cell therapy, can inadvertently target the patient's native cells, causing adverse effects (*ACS*, n.d.a). The more common effects are mild, including diarrhea, fatigue, cough, nausea, skin rashes, poor appetite, constipation, and muscle and joint pain (*ACS*, n.d.a). More serious, but rarer, effects

include autoimmune reactions, which may damage the lungs, intestines, liver, endocrine glands, and kidneys (*ACS*, n.d.a). As with CRS in CAR T-cell therapy, these reactions are treated with corticosteroids (*ACS*, n.d.a). Patients may also experience chest pain, diabetes, numbness, and kidney dysfunction (*NCI*, 2022). Reactions during the infusion, including fever, chills, flushing, rash, pruritus, dizziness, wheezing, and difficulty breathing, are common as well (*ACS*, n.d.a).

Cost of Immune Checkpoint Therapeutics

Immune checkpoint inhibitors are significantly more affordable than CAR T-cell therapy, the cost of which continues to decrease as more therapies become available (Abou-El-Enein & Gauthier, 2022; Gunturu et al., 2022). As of 2022, the average total cost of treatment for immune checkpoint inhibitors is $26,741, and the average out of pocket cost to patients is $387 (Gunturu et al., 2022). Compared to the average $60,000 a patient would pay in 2015, this is an immense improvement in terms of affordability (Andrews, 2015). The affordability of immune checkpoint inhibitors is an advantage to the therapy, but its lack of effectiveness in treating ALL renders it irrelevant to the cancer's treatment.

Conclusions

ALL is the most common cancer in children and has a high survival rate (89%) (Miller et al., 2022). It has a much lower survival rate of 40% for adults (Miller et al., 2022). If chemotherapy, the primary treatment for ALL, is not effective, further trials of chemotherapy are not guaranteed to improve prognosis (*ACS*, n.d.b). CAR T-cell therapy has proven to be effective in taking the place of chemotherapy in R/R ALL (Haslauer et al., 2021). CAR T-cell therapy has achieved tremendous success in only six years since it has been commercialized (Office of the Commissioner, 2017). While CAR T-cell therapy may be an effective treatment option for many with R/R ALL, it is still accompanied by various adverse effects, such as CRS and TLS, as well as the possibility of treatment dysfunction (Haslauer et al., 2021). Additionally, depending on one's health plan and financial circumstances, the therapy may not be an affordable option (Abou-El-Enein & Gauthier, 2022). With time and further clinical trials, widespread commercialization could increase availability (Abou-El-Enein & Gauthier, 2022). The improvement of the therapy itself depends on the management of adverse effects, the prevention of treatment dysfunction, and experimentation with additional CAR generations and target antigens. For PD-1 and PD-L1 immune checkpoint inhibitors, more research is needed to identify why the inhibitors are effective treatments for many hematological malignancies but not ALL. In addition to these studies, testing other immune checkpoint inhibitors with ALL would be helpful in identifying another possible treatment option for the cancer. The recent advancements of immunotherapy in the treatment of ALL have been groundbreaking, but further research and experimentation are needed to utilize its full potential.

Acknowledgments

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