Applications, Efficacies, Potential Side Effects, and Expectations of CAR-T Cell Therapy in the Treatment of Acute Lymphoblastic Leukemia

Yundan Jia*

The Pennsylvania State University, Pennsylvania, United State

*Corresponding author: ykj5150@psu.edu

Abstract. CAR-T cell therapy is a highly effective and powerful treatment for acute lymphoblastic leukemia (ALL), showcasing remarkable efficacy in combating this disease. Currently, several CAR-T cell therapies are available for ALL, including Kymriah and Yescarta. CAR-T is a novel targeted therapy for tumor treatment, marking a shift in modern medicine from molecular therapy to cellular therapy. ALL is a malignant blood disorder characterized by an abnormal proliferation of immature white blood cells known as lymphoblasts. These abnormal cells may be found in bone marrow, lymph nodes, spleen, and other organs. Acute lymphoblastic leukemia (ALL) predominantly affects adolescents and children, with a higher incidence observed in males. Although immunotherapy has shown promising efficacy in hematologic malignancies, the emergence of antigen escape poses a significant obstacle, limiting its use in treating solid tumors. Extensive scientific research is underway to improve the construction and manufacturing techniques of CAR-T cells and investigate novel cell configurations. This review aims to summarize the applications, efficacy, side effects, and expected outcomes of CAR-T therapy in treating ALL. It also explores strategies to enhance CAR-T therapy and provides insights into its current status and future directions in the background of ALL.

Keywords: CAR-T therapy, cancer, acute lymphoblastic leukemia, immunotherapy, antigen.

1. Introduction

ALL is a malignancy originating from lymphoid progenitor cells of B- or T-lineage and commonly affects individuals across different age groups, including children and adults. The excessive proliferation and accumulation of leukemia cells are typically the main characteristics of ALL, leading to suppression of normal hematopoietic function[1]. Lymphocytes are a specialized type of white blood cells that coordinates immune responses and defending against infections, making them vital components of the immune system. Among the various subtypes of lymphocytic malignancies, B-cell-derived acute lymphoblastic leukemia represents the majority, accounting for approximately 75% of diagnosed ALL cases [2]. T-cell-derived ALL is less common, representing about 25% of all ALL cases [3]. According to the American Cancer Society's 2023 data report, the incidence of this disease is higher in males than females [4] and the risk of developing ALL is the highest among children under the age of five [4]. ALL is influenced by a range of factors such as prior diseases, chemical exposure, high-level radiation, among others [5]. Moreover, if either parent has leukemia, the risk of their children to develop leukemia significantly increases. Currently, standard treatment methods for ALL in most regions include chemotherapy or radiation therapy. However, these medical approaches may cause a range of side effects and have less-than-desirable treatment outcomes. CAR-T therapy is an innovative immunotherapy approach that has demonstrated promising efficacy in treating leukemia, lymphoma, and multiple myeloma. Modified CAR-T cells are meticulously crafted to selectively recognize and activate specific antigens present on the surface of tumor cells, thereby enhancing their targeting efficacy and facilitating cancer cell eradication.The targeted and durable anti-tumor effects of the therapy have significantly advanced the treatment of ALL. Nevertheless, it is of paramount importance to address safety concerns, including but not limited to cytokine release syndrome and neurotoxicity[6]. In conclusion, this review examines the treatment outcomes, potential side effects, efficacy, and future developments of CAR-T therapy ALL. Furthermore, it analyzes relevant data reports and literature to explore treatment challenges and propose potential solutions.

B-ALL is more clinically prevalent, extensively studied, and possesses distinct clinical characteristics, making it easier to provide valuable insights and inspiration for clinicians and researchers.

2. Applications

2.1. Monotherapy steps

CAR-T cell therapy represents a distinct method compared to traditional drugs, as it involves the genetic modification of T cells to improve anti-cancer properties. The therapy first collects peripheral blood from the patient through leukapheresis, followed by the isolation of mononuclear cells for further processing. In a specialized laboratory, the T cells are genetically engineered by introducing the CAR gene, enabling them to target cancer cells. After undergoing expansion and cryopreservation, the CAR-T cells are reverted to the medical facility. Once infused into the patient's body, the CAR-T cells undergo further proliferation and act as "attacker" cells. They actively scan for cancer cells that express specific antigens and kill them [7]. Following treatment, CAR-T cells persistently remain active within the patient, providing ongoing protection against cancer recurrence and achieving long-term remission [7].

2.2. Combination therapy

Combination therapy refers to the use of two or more cancer treatment methods. Combination therapies involving CAR-T cells have emerged as highly promising strategies in the battle against cancer [8]. These strategies involve the integration of CAR-T cells with additional therapeutic agents, including checkpoint inhibitors, oncolytic viruses, or RNA vaccines. The development of innovative combination therapy regimens has demonstrated significant potential in enhancing treatment efficacy and improving patient outcomes. Typically, the CAR receptor targets the CD19 antigen [9]. Additionally, CAR-T therapy can work with various approaches, including RNA vaccines, hematopoietic stem cell transplantation, and checkpoint inhibitors, among others. Furthermore, in the treatment of ALL, CD22, which is another antigen found on the surface of B cells, has also been selected as a therapeutic target. In addition, scientists have designed dual-targeting CARs against CD19 and CD22, demonstrating excellent clinical outcomes in B-ALL. Currently, the primary approach for treating ALL relies on monotherapy utilizing CAR-T cells, with limited research and experimentation on combination therapies involving CAR-T cells. Therefore, this review will not address CAR-T combination therapy for ALL.

3. Side effects of CAR-T cell therapy

3.1. Cytokine release syndrome (CRS)

Despite CAR-T therapy has exhibited effectiveness, it has shown adverse reactions, including CRS and neurotoxicity. CRS occurs when immune cells interact with tumor cells, leading to a significant release of cytokines, which in turn trigger the release of more cytokines by immune cells, causing an amplified cytokine cascade. CRS clinical manifestations include excessive inflammatory response, capillary leakage, coagulation cascade activation, and in severe cases, life-threatening conditions. CRS typically presents within 14 days following CAR-T infusion [10]. The exact mechanism underlying CRS development remains incompletely understood. However, research studies have indicated that CRS is linked to the release of multiple cytokines, including IL-6, IL-10, TNF-α, among others. To address CRS, the IL-6 receptor antagonist tocilizumab has received FDA approval. A clinical case report described a pediatric patient with B-ALL who underwent CD19-targeted CAR-T therapy. The patient subsequently developed a severe fever a few days later. Cytokine testing revealed a significant elevation in various cytokine levels, including IL-6 [11]. In response to these findings, tocilizumab was administered to the patient. Remarkably, the patient's condition improved

significantly within a few hours [11]. This case highlights the potential risk of CRS associated with CAR-T therapy, demonstrating the effectiveness of tocilizumab in treating CRS.

3.2. Neurotoxicity (ICANS)

The occurrence of toxic side effects presents an important hurdle in optimizing the effectiveness of CAR-T cell therapy, as they involve neurological complications such as cognitive impairment or confusion. Neurotoxicity, also called ICANS, encompasses a range of neurological symptoms. These symptoms may include language impairments, dysgraphia, fine motor disturbances, and similar manifestations. In severe cases, patients may become obtunded or experience seizures, requiring intubation to protect the airway. Neurotoxicity is reversible and does not have significant long-term effects or require intervention [12]. However, in rare instances, patients may develop fatal malignant cerebral edema, with a reported 7.7% incidence rate of grade 3 or higher ICANS. In CD19 CAR-T cell therapy, a considerable percentage of patients reported experiencing neurotoxic reactions, ranging from 28% to 64% [13]. Among them, 13% to 50% of patients report reactions reaching ≥ 3 grades and approximately 3% of adult patients report fatal ICANS [13]. Mild ICANS are typically resolved within a few days through supportive care, whereas severe cases require multidisciplinary care in the intensive care unit to address life-threatening seizures and cerebral edema. Steroids are the main treatment for isolated ICANS, and symptomatic treatments such as mannitol or hypertonic saline and hyperventilation can be administered for patients with cerebral edema [14].

3.3. Other related safety issues

Apart from CRS and neurotoxicity, CAR-T cell therapy is associated with several other safety concerns, including off-target effects, tumor lysis syndrome (TLS), B-cell aplasia, hemophagocytic lymphohistiocytosis, and coagulation disorders [15]. These issues can lead to immune system suppression, thereby increasing the susceptibility to infections. In a study involving 53 adult patients with ALL treated using CD19 CAR-T cell therapy, bacterial infections were the primary type of infection, affecting 30% of the patients. On the other hand, late infections, which occurred between day 31 and day 180 after treatment, were predominantly viral infections.

4. Evaluation of efficacy

4.1. Complete Remission (CR)

ALL poses a significant threat regardless of factors such as age, comorbidities, or social environment. In adults, the relapse rates for this condition are alarmingly high, with approximately 60%-70% of patients eventually progressing to relapsed/refractory B-cell ALL (r/r B-ALL). Conventional chemotherapy typically yields an overall remission rate of around 25% and a complete remission rate of approximately 16% among this type of patients.The median survival typically ranges from 2 to 6 months. However, in a clinical trial specifically assessing CAR-T therapy using Kymriah, encouraging outcomes were observed. The trial reported a complete remission rate of 66% among patients, with a confidence interval of 95% (56-75) [16]. In addition, the overall response rate was 86% with a confidence interval of 95% (78-92). Other relevant clinical trials have also shown improved complete remission rates in patients undergoing this therapy. "Brexucabtagene autoleucel" developed by Kite Pharma (now Gilead Sciences) is a CAR-T cell therapy that has shown a complete remission in 65% of patients, although some patients did not have their white blood cell counts fully recovered [17]. It was reported that more than half of those who achieved complete remission did not show signs of cancer for at least one year.

4.2. Survival analysis

Following induction chemotherapy for adult ALL, around 25% to 40% achieved long-term remission [18]. Prognosis is even worse for those assessed as high-risk at diagnosis. However, for

adult patients undergoing this therapy, the 12-month overall survival (OS) rate may reach 76% [19]. Currently, several institutions are utilizing CAR-T immunotherapy to enhance survival rates in patients. The JULIET trial stands as a noteworthy clinical investigation that assessed the effectiveness of Kymriah in adult individuals diagnosed with recurrent or resistant diffuse large B-cell lymphoma. This research also included clinical trials of CAR-T therapy for r/r B-ALL. In the JULIET trial, B-ALL patients who had previously undergone multiple ineffective treatments or experienced relapse were enrolled. The trial utilized JCAR015, a CD19 CAR-T therapy regimen. According to the trial results, a subset of patients (n = 48) demonstrated a 65% probability of remaining free from relapse at the 12-month mark following the initial response. The associated 95% confidence interval ranged from 49% to 78% [20]. Among all patients who underwent CAR-T therapy, the overall survival rate at 12 months was 49%. The average overall survival was 11.7 months, with a 95% confidence interval ranging from 6.6 to NE (not estimable). The median duration from the infusion to the data cutoff was 14 months, and the longest recorded duration was 23 months.

5. Expectations

5.1. Bispecific CAR-T cells

Despite CAR-T cell therapy has shown remarkable advancements in treating ALL, there remain certain limitations, including the issue of antigen escape. To address this challenge, scientists are investigating the potential of dual-specificity CAR-T cells. In a clinical trial focused on B-ALL, researchers conducted tests using a dual-specific CAR that targeted CD19 and/or CD22. Results showed a 100% response rate with 88% of patients achieving minimal residual disease-negative CR [21]. This indicates the tremendous potential of dual-specific CAR-T cells in therapy. Furthermore, the study demonstrated that antigen escape is a main reason of CAR-T cell resistance [21]. In the future, scientists will aim to produce CAR-T cells with enhanced specificity and anti-tumor effects by improving CAR design, further improving the treatment outcomes for B-ALL patients.

5.2. Prevention and reduction of CAR-T therapy-related toxicities

Researchers have implemented several measures to prevent and mitigate toxicities associated with CAR-T therapy. One approach involves administering pre-treatment chemotherapy to reduce the tumor burden. This helps create a more favorable environment for the therapy and potentially enhances treatment efficacy [22], closely monitoring patients' vital signs and relevant indicators, promptly assessing and managing toxic reactions, reducing the severity of adverse events and increasing treatment safety. For common adverse reactions such as neurotoxicity, measures involve enhancement of monitoring and managing, including regular neurologic assessments and early intervention. Developing more accurate neurotoxicity biomarkers and predictive models helps identify and manage early neurotoxicity reactions [23]. Providing supportive care is also an important measure. For inflammatory reactions like CRS, control measures such as anti-inflammatory drugs and immunosuppressants may be implemented. Regular neurologic assessments, including cognitive, neurological, and behavioral evaluations, aid in the early detection of neurotoxic reactions. To prevent and mitigate the adverse effects linked to CAR-T therapy, measures such as pre-treatment strategies, close monitoring, supportive care, and enhanced management of treatment-related side effects are implemented. The goal is to strengthen treatment safety and sustainability. By employing these strategies, better clinical outcomes will be achieved in the application of CAR-T cell therapy for ALL, which will lead to improved treatment efficacy and quality of life for patients, as they receive more effective and well-managed therapy.

5.3. Future combination therapies

Currently, extensive research is being conducted globally to explore combination therapies, involving CAR-T cells. Regarding ALL, these therapies are still in the investigational phase. One practical approach that has gained increased consideration is the integration of CAR-T cells with OVs.

OVs (oncolytic viruses) are viruses that can occur naturally or be genetically modified. They have the ability to replicate within tumor tissues, leading to the destruction of cancer cells[24]. Combining OVs with CAR-T cells offers advantages over CAR-T cell monotherapy and may generate synergistic effects. There are various mechanisms through which viral infection positively impact anti-tumor CAR-T cell therapy. Firstly, viral infection triggers the release of danger signals, which reverse tumor immune suppression and facilitate the trafficking, proliferation, and sustained expression of CAR-T cells within the tumor microenvironment [25]. Secondly, viral infection induces tumor lysis and releases tumor-associated antigens (TAAs), thereby stimulating adaptive anti-tumor responses and potentially reducing tumor escape caused by antigen loss [25]. In addition, viral vectors are utilized to deliver therapeutic transgenes, further augmenting the effector functions of T cells [25]. Certain strategies combining OV) with CAR-T cells have o FDA approval. An example of an innovative approach in cancer treatment is the combination of T-VEC (Talimogene Laherparepvec) and CAR-T cells, which has received approval in treating advanced melanoma. T-VEC is a genetically modified type I herpes simplex virus that exhibits selective replication within tumor cells, leading to their direct destruction through a process known as oncolysis. Furthermore, T-VEC activates the immune system by releasing tumor antigens [26]. Although specific CAR-T cell combination therapies for ALL have not yet been developed, scientists remain optimistic about achieving results in the near future. With persistent efforts and ongoing innovation, it is anticipated that researchers will achieve the development of effective combination therapies utilizing CAR-T cells that specifically target ALL. This advancement will offer improved treatment options and enhanced survival alternatives for patients diagnosed with ALL.

6. Conclusion

CAR-T cell therapy has emerged as an extremely powerful and promising therapeutic choice for acute lymphoblastic leukemia (ALL). It has demonstrated significant response rates and the potential to induce long-lasting remissions, particularly in patients who have shown resistance to conventional therapies. Nevertheless, it is crucial to acknowledge that the therapy may cause side effects. CRS and neurotoxicity are the two most frequently reported adverse events associated with CAR-T cell therapy. CRS encompasses a spectrum of inflammatory responses that can vary in severity, necessitating prompt and effective management strategies. Efforts are underway to better understand and address CAR-T cell therapy-related neurotoxicity. Researchers are working on predictive biomarkers and treatment algorithms to reduce these adverse events. Future advancements include optimizing CAR design to improve efficacy, durability, and safety. Future research should involve the exploration of novel target antigens and the development of new generation CAR-T cells, including dual-specificity CAR-T cells, to enhance tumor specificity and overcome antigen escape. Moreover, combination therapies, such as the integration of CAR-T cell therapy with targeted drugs or immune checkpoint inhibitors, are under investigation to enhance treatment outcomes and address relapse in patients with ALL.

References

[1] Puckett Y, Chan O. Acute Lymphocytic Leukemia. In: StatPearls. Treasure Island (FL): StatPearls Publishing; June 27, 2022.

[2] S. Srakocic. B-Cell Acute Lymphoblastic Leukemia: Symptoms, Treatment, and Outlook. Healthline. Published February 10, 2021. Accessed June 15, 2023. https://www.healthline.com/health/leukemia/b-cell-acute-lymphoblastic-leukemia

[3] Vadillo E, Dorantes-Acosta E, Pelayo R, Schnoor M. T cell acute lymphoblastic leukemia (T-ALL): New insights into the cellular origins and infiltration mechanisms common and unique among hematologic malignancies. Blood Reviews, 2018, 32(1): 36-51.

[4] Key Statistics for Acute Lymphocytic Leukemia (ALL). www.cancer.org. Published January 12, 2023. Accessed June 15, 2023. https://www.cancer.org/cancer/types/acute-lymphocytic-leukemia/about/key-statistics.html

[5] Mayo Clinic. Acute lymphocytic leukemia - Symptoms and causes. Mayo Clinic. Published 2018. Accessed June 15, 2023. https://www.mayoclinic.org/diseases-conditions/acute-lymphocytic-leukemia/symptoms-causes/syc-20369077

[6] Morris EC, Neelapu SS, Giavridis T, Sadelain M. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nature Reviews Immunology, 2021, 22: 85–96.

[7] How CAR T-cell Therapy Works. www.uchicagomedicine.org. Accessed June 16, 2023. https://www.uchicagomedicine.org/cancer/types-treatments/car-t-cell-therapy/how-car-t-cell-therapy-works

[8] Burik A. Combination Therapies: Opportunities for Improved CAR-T Cell Therapy? Labiotech.eu. Published March 10, 2022. Accessed June 18, 2023. https://www.labiotech.eu/partner/combination-therapy-improved-car-t-cell-therapy/#:~:text=Combination%20therapies%20with%20CAR-T%20therapy%20are%20one%20of

[9] Park JH, Rivière I, Gonen M, et al. Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. New England Journal of Medicine, 2018, 378(5):449-459.

[10] Stewart AG, Henden AS. Infectious complications of CAR T-cell therapy: a clinical update. Therapeutic Advances in Infectious Disease, 2021, 8: 204993612110367.

[11] Si S, Teachey DT. Spotlight on Tocilizumab in the Treatment of CAR-T-Cell-Induced Cytokine Release Syndrome: Clinical Evidence to Date. Therapeutics and Clinical Risk Management, 2020, 16: 705-714.

[12] https://www.lls.org/treatment/types-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy. www.lls.org. Accessed June 23, 2023. https://www.lls.org/treatment/types-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy#:~:text=Another%20known%20side%20effect%20of%20CAR%20T-cell%20therapy

[13] Bhojwani D, Bansal R, Wayne AS. Managing therapy-associated neurotoxicity in children with ALL. Hematology, 2021, 2021(1): 376-383.

[14] Cook AM, Morgan Jones G, Hawryluk GWJ, et al. Guidelines for the Acute Treatment of Cerebral Edema in Neurocritical Care Patients. Neurocritical Care, 2020, 32(3): 647-666.

[15] Miao L, Zhang Z, Ren Z, Li Y. Reactions Related to CAR-T Cell Therapy. Frontiers in Immunology, 2021, 12: 663201.

[16] Novartis Kymriah® pivotal trial demonstrates strong response rates and a remarkable safety profile in relapsed or refractory follicular lymphoma. Novartis. Published June 2, 2021. Accessed June 25, 2023. https://www.novartis.com/news/media-releases/novartis-kymriah-pivotal-trial-demonstrates-strong-response-rates-and-remarkable-safety-profile-relapsed-or-refractory-follicular-lymphoma#:~:text=Kymriah%20led%20to%20responses%20for%20the%20majority%20of

[17] Justin Benavidez. Tecartus Approved for Some Adults with B-Cell ALL - NCI. www.cancer.gov. Published November 10, 2021. Accessed June 25, 2023. https://www.cancer.gov/news-events/cancer-currents-blog/2021/fda-tecartus-adults-b-cell-all#:~:text=On%20October%201%2C%20the%20Food%20and%20Drug%20Administration

[18] Acute Lymphoblastic Leukemia Treatment. ucsfhealth.org. Accessed June 28, 2023. https://www.ucsfhealth.org/conditions/acute-lymphoblastic-leukemia/treatment#:~:text=The%20first%20two%20phases%20use%20intensive%20chemotherapy%20medications

[19] Elsallab M, Ellithi M, Hempel S, Abdel-Azim H, Abou-el-Enein M. Long-term response to autologous anti-CD19 chimeric antigen receptor T cells in relapsed or refractory B cell acute lymphoblastic leukemia: a systematic review and meta-analysis. Cancer Gene Therapy, 2023, 30: 845–854.

[20] Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. New England Journal of Medicine, 2019, 380(1): 45-56.

[21] Spiegel JY, Patel S, Muffly L, et al. CAR T cells with dual targeting of CD19 and CD22 in adult patients with recurrent or refractory B cell malignancies: a phase 1 trial. Nature Medicine, 2021, 27(8): 1419-1431.

[22] CAR T-cell Therapy and Its Side Effects. www.cancer.org. Published March 1, 2022. Accessed June 29, 2023. https://www.cancer.org/cancer/managing-cancer/treatment-types/immunotherapy/car-t-cell1.html

[23] Castaneda-Puglianini O, Chavez JC. Assessing and Management of Neurotoxicity After CAR-T Therapy in Diffuse Large B-Cell Lymphoma. Journal of Blood Medicine, 2021, 12: 775-783.

[24] Tian Y, Xie D, Yang L. Engineering strategies to enhance oncolytic viruses in cancer immunotherapy. Signal Transduction and Targeted Therapy, 2022, 7(1): 117.

[25] Guedan S, Alemany R. CAR-T Cells and Oncolytic Viruses: Joining Forces to Overcome the Solid Tumor Challenge. Frontiers in Immunology, 2018, 9: 02460.

[26] Melanoma Skin Cancer Immunotherapy | Skin Cancer Immunotherapy. www.cancer.org. Published March 22, 2022. Accessed July 1, 2023. https://www.cancer.org/cancer/types/melanoma-skin-cancer/treating/immunotherapy.html#:~:text=Along%20with%20killing%20the%20cells%20directly%2C%20the%20viruses