Advances in CAR-T therapy, Checkpoint Inhibitors and TKI for Pediatric Acute Lymphoblastic Leukemia

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Abstract

Acute lymphoblastic leukemia (ALL) is a cancer affecting the blood and bone marrow, marked by the overproduction of immature white blood cells called lymphoblasts. It is, notably, the most common form of cancer in children. Between 1998 and 2016, the number of ALL cases annually reported has increased from 110,000 to 200,000. With the growing number of cases each day, it is paramount to find improved and more advanced treatments. This study aims to explore the effectiveness of several new therapies—checkpoint inhibitors, CAR-T therapy, and TKI treatment— in comparison to more traditional treatments used to treat pediatric ALL. By evaluating the advantages and limitations of these new therapies, this study aims to offer insights into the future of pediatric ALL and improve patient survival rates. Additionally, this study could help influence clinical decision-making and inspire new and improved therapies that allow young patients to continue to live a normal life while battling this challenging disease.

Introduction

In the early 1840s and 1850s, several doctors reported cases of individuals with swollen abdomens, fevers, weight loss, and weakness, symptoms of what we now know are associated with leukemia (1). When they performed blood tests during autopsies, they noticed that these patients had an abnormally high level of white blood cells. This led them to the name “leukemia” derived from the Greek words “leukos” meaning white, and “haima” meaning blood (2). Leukemia is a hematological malignancy, another word for blood cancer, found in the blood and bone marrow. This cancer is caused by the rapid production of abnormal white blood cells. These abnormal cells do not allow the bone marrow to produce red blood cells and platelets and are unable to perform their normal function of fighting infections (3).

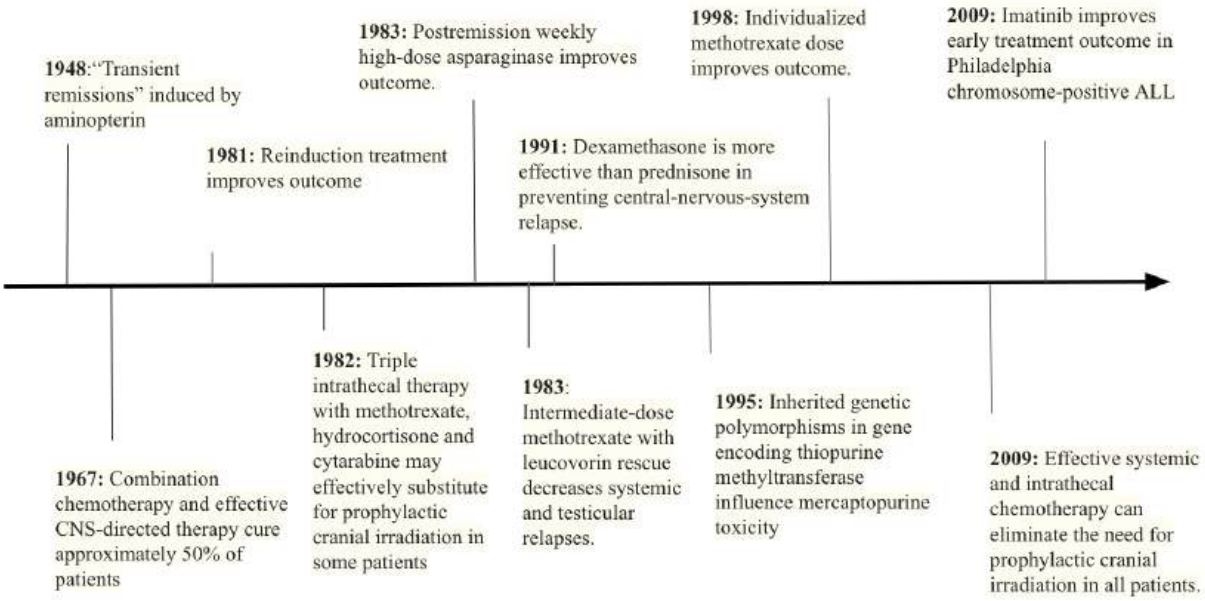

Figure I. Timeline of therapies for ALL throughout history (4)

Leukemia can be categorized into acute or chronic based on the rate of progression. Acute lymphoblastic leukemia (ALL) is a type of leukemia in which the bone marrow makes too many of a type of white blood cell called lymphocytes (2). There are about 3,000 cases of ALL in children and youth up to the age of 21 each year in the United States (5). These cases account for 30% of all pediatric cancers (6). The annual percent change of cases during the 35 years between 1975 and 2012 was estimated to be a 33% increase for ALL. It is the most common childhood malignancy (7).

Patients with undiagnosed ALL usually have symptoms including fatigue, frequent infections, bruising, bone or joint pain, and swollen lymph nodes. ALL is detected when a blood test is done, and doctors find abnormal blood counts or leukemic cells. Bone marrow biopsy, flow cytometry, and cytogenetics can also determine the best treatment course and type of leukemia. Flow cytometry evaluates surface markers on the cells, often Tdt and CD10 positive, which are B-cell markers or proteins that help identify and analyze B-cells (8). In addition, cytogenetic features are usually evaluated because chromosome abnormalities can affect treatment responses and prognosis. For example, Philadelphia chromosome-positive ALL (Ph+ ALL) is a subtype of ALL that can be identified with the presence of the Philadelphia chromosome (9). As demonstrated in Figure 1, Ph+ ALL occurs when parts of chromosomes 9 and chromosome 22 break off and swap places. The new chromosome 22 formed after the swap is known as the Philadelphia chromosome (Figure 1). The BCR-ABL1 fusion gene on the Philadelphia chromosome is formed when the BCR gene on chromosome 22 and ABL1 gene on

chromosome 9 bond together. The fusion gene codes for a protein that overactivates the bone marrow, making it produce several abnormal white blood cells (10). The Philadelphia chromosome can also develop new mutations that make leukemia resistant to treatment and make Ph+ALL more difficult to treat.

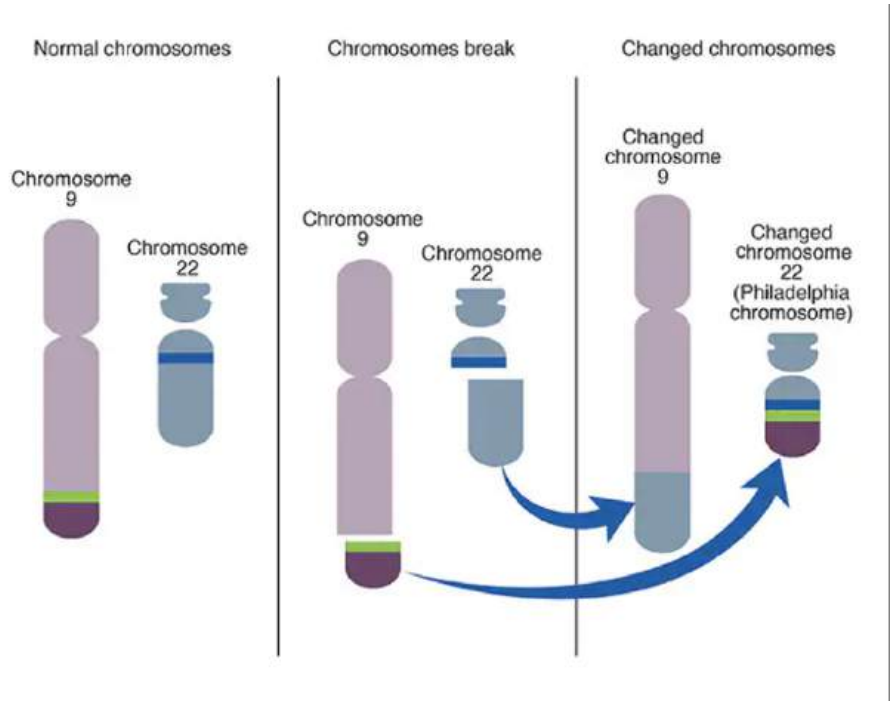

Figure II. Philadelphia translocation in ALL (3)

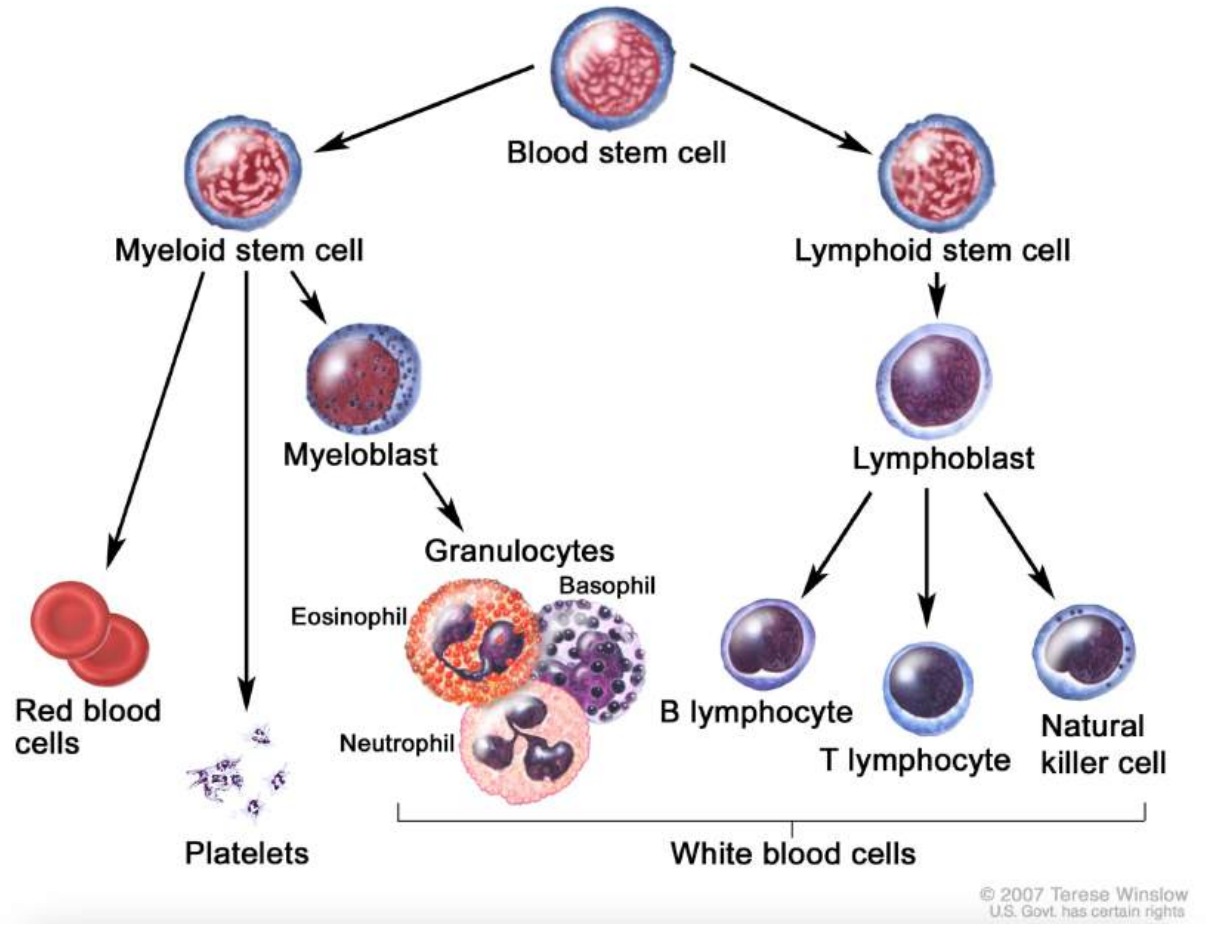

Figure III. Differentiation of Hematopoietic stem cells (11)

Conventional Treatment

The standard treatment for children with ALL is chemotherapy given in 3 different steps; induction, consolidation, and maintenance (Figure 3)(12). Induction chemotherapy starts with chemotherapy drugs such as L-asparaginase, Vincristine, and a steroid drug (12). L-asparaginase is an enzyme that breaks down L-asparagine, a vital amino acid that plays a vital role in the development of cancer cells (11). Without enough asparagine, the cancer cells cannot perform protein synthesis effectively and are unable to grow and proliferate, eventually leading to cell death (13). Vincristine is a vinca alkaloid antineoplastic agent that inhibits mitosis in cancer cells by interfering with hollow, tube-like structures inside the cell called microtubules. Microtubules are absolutely vital for mitosis because they form a mitotic spindle that separates chromosomes in order for the cell to split (14). Pediatric ALL patients are also prescribed a drug called methotrexate that is put into the cerebrospinal fluid to kill any leukemia cells that might have spread to the brain and spinal cord (15). Methotrexate is an antineoplastic agent that inhibits enzymes needed for nucleotide synthesis, such as dihydrofolate reductase (13).

Consolidation therapy, also known as intensification therapy, is a vital phase of treatment after the induction phase. During consolidation therapy, doctors usually perform a bone marrow or stem cell transplant after myeloablative conditioning. Myeloablative conditioning is a high-dose of chemotherapy that destroys most cancer cells and inevitably bone marrow and stem cells in the bone marrow. The last phase, maintenance, aims to eliminate the few remaining leukemia cells giving lower doses of drugs like methotrexate over a long, several year period (16).

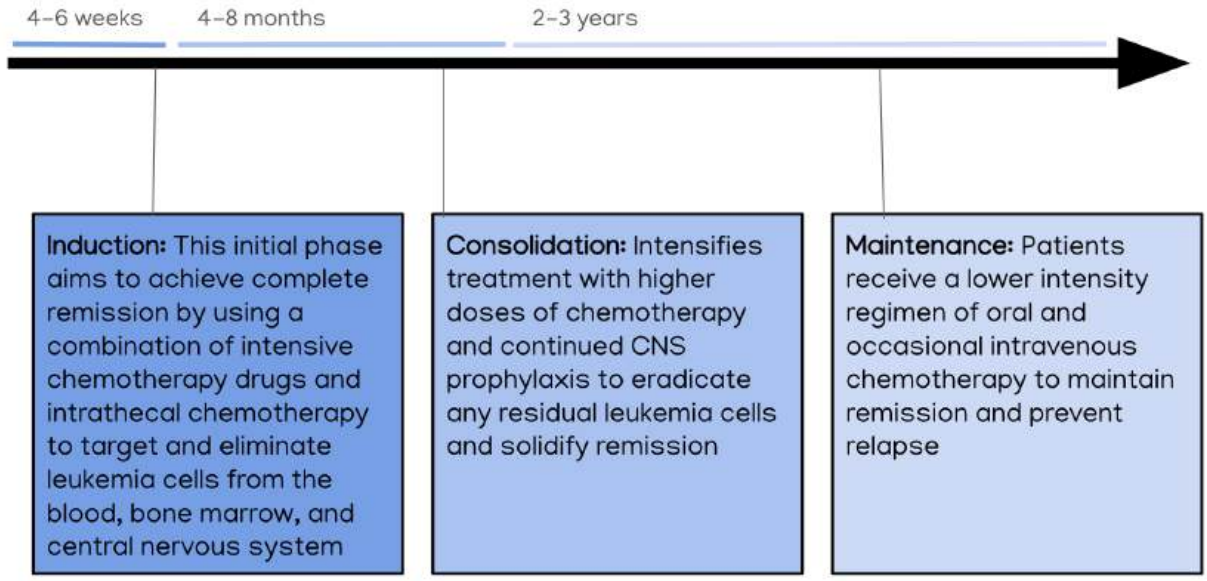

Figure IV. Chemotherapy Treatment (11)

Challenges

Standard Acute lymphoblastic leukemia (ALL) treatment remains a challenge for all ages to battle. Therapies usually result in 5-year overall survival rates of about 70% for adults and 90% for children (4). Relapse remains the primary cause of treatment failure despite the numerous advances in ALL research. About 80%–90% of patients with ALL achieve complete remission (where no more leukemia cells are detectable in the bone marrow), but about half of these patients eventually relapse (2). Only 40%–50% achieve complete remission without subsequent relapse (2).

Relapse in ALL usually occurs due to the leukemia cells developing resistance to chemotherapy. This can be due to factors like genetic mutations. For example, mutations in the NT5C2 gene increase the enzyme's activity which acts as resistance against thiopurine drugs (17). Mutations in the TP53 gene can prevent apoptosis, allowing leukemia cells to survive (18). Leukemia cells can also evade treatment by hiding in "sanctuary sites" in the body, such as the central nervous system (19). It is difficult for standard chemotherapy to reach these places

because of barriers like the blood-brain barrier that protects the brain from harmful substances (20).

Treatment protocols for pediatric ALL are long and often span two to three years (12). It also involves multiple phases, and the extended treatment period can have significant physical, emotional, and psychosocial consequences on pediatric patients, especially (21). Children may experience long-term side effects, such as growth delays, cognitive impairments, and an increased risk of secondary cancers but much of these effects have yet to be studied due to the relatively recent research (19). The demanding nature of treatment also leads to psychosocial issues, including anxiety, depression, and social isolation (19). These issues can also intensify as children face disruptions to their normal activities and schooling during treatment, further affecting their mental and emotional development (19). To address these issues, we must turn towards new therapies to minimize side effects and be more effective overall.

New therapies

New therapies, such as checkpoint inhibitors, CAR-T therapy, and tyrosine kinase inhibitors (TKIs), are promising because they utilize innovative mechanisms to target cancer more precisely in individual patients.

Checkpoint inhibitors

Checkpoint inhibitors are cancer immunotherapy that helps the body's immune system recognize and attack cancer cells. They work by targeting specific proteins like PDL1 and CD

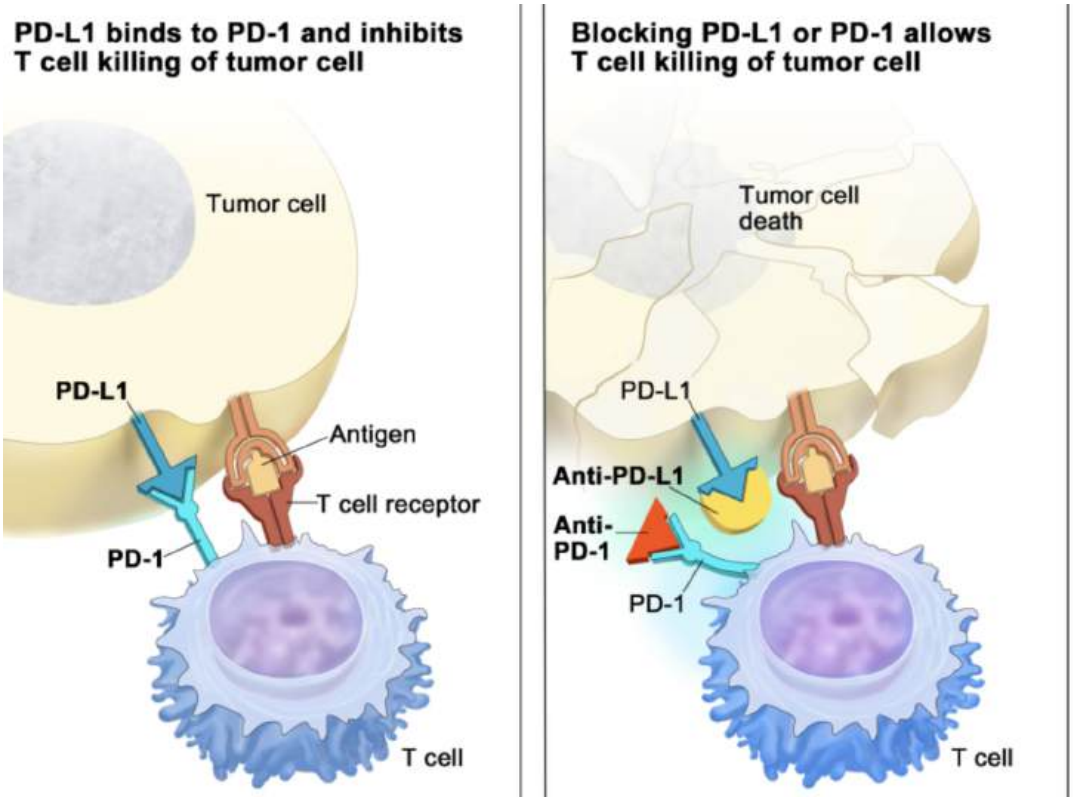

Figure V: Checkpoint Inhibitors binding to specific proteins on tumor cell (22)

L4 on the surface of T-cells and cancer cells that act as “checkpoints”(23). Checkpoint inhibitors are a promising type of cancer treatment with several advantages. One of their primary advantages is that they help boost the immune system's ability to recognize and destroy malignant cells (24). Checkpoint inhibitors can also prevent ALL cells from manipulating their microenvironment and avoiding immune system attacks. These unique characteristics can significantly improve survival rates and be used to achieve higher remission rates. Checkpoint inhibitors are available to purchase, however, their high cost limits availability for many patients (25). Compared to traditional chemotherapy, checkpoint inhibitors generally have fewer side effects, making treatment more tolerable for many pediatric patients because they are more sensitive to harsher traditional therapies compared to adults (11). Common side effects of checkpoint inhibitors include fatigue, nausea, vomiting, diarrhea, and skin rashes (26). Checkpoint inhibitors can also lead to more severe complications, such as cardiotoxicity or inflammation of the intestines or lungs (11). Another negative aspect of checkpoint inhibitors is that the frequency, timing, and long-term side effects are not fully understood and studied because this treatment type is relatively new. There are also no FDA-approved checkpoint inhibitors to treat pediatric ALL (27). Despite these limitations, ongoing research suggests that checkpoint inhibitors can be effectively combined with another relatively new therapy called CAR-T cell therapy to enhance outcomes in children with relapsed ALL.

Car-T

Chimeric Antigen Receptor T-cell therapy, or CAR-T, is a type of cancer immunotherapy that uses a patient's T-cells to identify and kill cancer cells. The process involves collecting T-cells from a patient's blood, modifying the T-cells by adding a chimeric antigen receptor, and infusing it back into the patient (28). The chimeric antigen receptor makes the T-cells specifically target and bind to specific antigens on cancer cells. Unlike traditional chemotherapy, the treatment targets specific markers on cancerous cells like CD19, which allows it to differentiate between normal healthy cells. CAR T has been proven on multiple accounts to significantly increase remission rates and be used to target leukemia cells that have become resistant to conventional treatment (29). Moreover, the treatment stays in the body for a significant amount of time after treatment ends so the T-cells can fight off any remaining or returning leukemia cells (17). However, CAR-T cells can become exhausted over time, reducing their long-term effectiveness. Additionally, CAR-T doesn't rely on the patient's major histocompatibility complex molecules (MHC), meaning they can recognize cancer cells regardless of genetic differences between patients (15). Despite the many advantages of CAR-T, the treatment does come with some drawbacks. These drawbacks include cytokine release syndrome, neurotoxicity, and B-cell aplasia (30). Cytokine release syndrome (CRS) is a life-threatening complication that occurs when therapies, such as CAR-T, trigger an immune inflammatory response due to the release of cytokines such as IL6 (31). Cytokines are small proteins that control the growth and activity of the immune system and blood cells (32). The occurrence and severity of CRS depend on several factors, including CAR-T cell dosage, proliferation of CAR-T, and the number of blasts in the bone marrow. Blasts are immature white blood cells produced in the bone marrow that eventually become fully functioning white blood cells (33). Neurotoxicity occurs when the nervous system is damaged by exposure to toxic substances called neurotoxicants (22). B-cell aplasia (BCA) is a condition that occurs when there are very low B-cell levels in the body. It occurs when anti-CD19 CAR T-cells attack and destroy B-lymphocytes that express CD19 (35). Though there are many advantages to using CAR-T therapy for ALL, there remain limitations for the therapy in cases involving specific genetic abnormalities like the Philadelphia chromosome. Tyrosine kinase inhibitors can be used as an alternative treatment to treat this mutation.

TKIs

With only 20-30% of children with Ph(+) ALL cured with traditional chemotherapy, it is paramount to find more effective treatment methods (9). ALL cells with the Philadelphia chromosome express an abnormal gene called the BCR-ABL gene formed as a result of translocation (4). This gene creates the BCR-ABL1 protein that signals cells to grow, divide, and prevent apoptosis (10). Tyrosine kinase inhibitors (TKIs) specifically attack and target the BCR-ABL1 protein, slowing the proliferation of ALL cells. Researchers looked at six studies involving 536 children with Ph+ALL (23). They compared two treatments, one with TKIs and one without traditional chemotherapy and HCT. The risk of death in the TKI group was reduced by

32% compared to the conventional treatment group. Additionally, they observed a 37% lower risk of experiencing relapse in the group treated with TKIs (36). This study highlights the promising benefits that TKIs could bring to the future of pediatric ALL. However, common side effects of this drug include diarrhea, nausea, muscle pain, fatigue, and skin rashes. One of the most concerning side effects is that certain TKIs have even been associated with growth retardation in pediatric patients (37). These TKIs interfere with growth hormone and insulin-like growth factor-1 (IGF1), leading to reduced bone growth and potential height deficits. Nevertheless, their ability to significantly reduce relapse risk and improve survival rates often outweighs these risks. In addition, TKIs should be used in all phases of treatment, including consolidation, induction, and maintenance to maximize their potential (38).

Discussion

The advancements in checkpoint inhibitors, CAR-T therapy, and TKIs present transformative possibilities for not only pediatric ALL but other forms of leukemia and other types of cancer. Checkpoint inhibitors enhance the immune system's ability to recognize and attack leukemia cells; CAR-T therapy modifies a patient's T-cells to target and destroy ALL cells; and TKIs inhibit the BCR-ABL1 protein in Philadelphia chromosome-positive ALL. Together these therapies represent significant milestones in pediatric ALL research. Each therapy presents its individual strengths and weaknesses, leading many researchers to explore strategies to combine them in order to maximize their strengths and minimize side effects

A potential strategy for Ph+ ALL involves combining CD19-targeted CAR-T therapy with TKIs sequentially to mitigate some of the negative side effects of using either therapy individually. In this approach, TKIs are administered first to inhibit signaling pathways such as BCR-ABL1. Then, CAR-T is infused to get rid of residual leukemic cells. The initial infusion of TKIs reduces tumor burden, reducing the amount of cytokines released at once and therefore reducing the risk of CRS. This approach could reduce overall treatment toxicity and shorten therapy duration for pediatric patients. While both of these therapies have been used individually, their combined application in children has not been systematically tested, making it a novel proposal (39). CAR-T cells can adopt different phenotypes: Th1 and Th2. The Th1 phenotype is cytotoxic meaning the cell actively attacks and destroys cancer cells while the Th2 phenotype is suppressive and can reduce CAR-T cell killing activity. When CAR-T and certain TKIs like ibrutinib work in conjunction, ibrutinib promotes a Th1 phenotype by irreversibly binding to and inhibiting IL-2-inducible T cell kinase, which reduces Th2 cytokines (IL-4, IL-10) and enhances production of Th1 cytokines such as IFN-γ, TNF-α, and IL-2. Other TKIs like dasatinib can suppress CAR-T activation and cytokine release, reducing CRS but not inherently pushing Th1 polarization. Therefore, choosing the correct TKIs to use with CAR-T is critical in enhancing CAR-T cell antitumor activity.

Another combination approach is CAR-T therapy in combination with checkpoint inhibitors. CAR-T cells are highly effective at eliminating leukemic cells, but they become exhausted over time, compromising their long-term abilities. Checkpoint inhibitors, such as anti-PD-1 or anti-CTLA-4 antibodies, can block these inhibitory pathways to sustain and restore CAR-T cell function. By preserving CAR-T activity, checkpoint inhibitors could maintain remission without the need for reinfusions or increased doses of CAR-T, reducing treatment-related toxicity. Although this strategy has already shown encouraging early results, it is also not well studied in pediatric ALL and thus represents a direction for future research (40).

In addition to combination therapies, artificial intelligence (AI) is transforming the way cancer therapies are developed and optimized. With the emergence of advanced artificial intelligence, science and research are now undergoing significant changes. AI's revolutionary capabilities allow new treatments to be created and tested at an unprecedented rate. For example, AI can speed up research by analyzing vast datasets to identify patterns, predict patient responses, and optimize therapy combinations. Additionally, AI-driven simulations can show different treatment outcomes under various scenarios instead of trying each treatment on actual patients in clinical trials. For instance, a study performed by Chareontong utilized machine learning to analyze large data sets of tumor samples in order to look for patterns in the immune system's response to the tumor, demonstrating how AI is already accelerating discoveries (41).

As AI develops, however, it also starts to pose ethical concerns such as maintaining patient confidentiality or ensuring equitable access to innovation. Overcoming these barriers requires the collaboration between clinics, scientists, and AI engineers so that innovation doesn’t come at the cost of patient trust (42). In conclusion, these novel treatments and technologies have the ability to fundamentally reshape the treatment of pediatric ALL into safer, more effective, and more personalized care.

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