Exploring CAR-T Response Variability in Pediatric vs. Adult B-ALL: A Comprehensive Review

Amaan Ali Mohammed

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B-cell acute lymphoblastic leukemia (B-ALL) is a common type of cancer affecting pediatric and adult patients. B-ALL is the most common subtype of ALL, accounting for 75% of ALL cases. Chimeric antigen receptor (CAR)-T cell therapy has emerged as a promising treatment option for B-ALL. However, growing evidence suggests that the response to CAR-T cell therapy may differ between pediatric and adult patients. This paper aims to review the available literature on the difference in response to CAR-T cell therapy in pediatric and adult patients with B-ALL. A comprehensive literature search was conducted using the PubMed database with the keywords "acute lymphoblastic leukemia," "CAR-T cells," "B-cell," "Adult," and "pediatric." The search was limited to studies published in English between 2020 and 2023. The studies were screened based on predefined inclusion and exclusion criteria, including phase II or phase II trials, age for adults above 18, and pediatrics below 18. The available literature suggests that pediatric patients with B-ALL may respond better to CAR-T cell therapy than adult patients. This difference in responses has been attributed to chemotherapy being used as a first-line treatment affecting CAR T-cell therapy efficacy and potentially from CAR T-dosage amounts, which both lead to differences in cytokine release syndrome (CRS) rates and a higher likelihood of rapid progression of B-ALL, progressive disease, severe neurotoxicities, and death rates among the adult population. Nevertheless, several possible factors still exist, including differences in B-ALL biology between pediatric and adult patients, differences in the immune system, and differences in the CAR-T cell manufacturing process, which were not discussed thoroughly in this review due to limited patient information provided in the included clinical trials. The difference in response to CAR-T cell therapy between pediatric and adult patients with B-ALL is an important area of research that requires further investigation. Understanding the factors contributing to this difference may help develop more effective CAR-T cell therapies for pediatric and adult B-ALL patients. Analyzing the overall response variability between pediatrics and adults helps suggest an average treatment effect that is a reasonable assumption for an individual patient. Furthermore, CAR T-cell therapy can be adapted to mitigate high CRS rates and enhance CAR T-cell persistence specific to each age group, improving patient outcomes and ultimately achieving better long-term survival rates.

Introduction

Acute Lymphocytic Leukemia(ALL) is a form of blood and bone marrow cancer primarily prominent in adolescents. ALL is established when immature white blood cells are created due to the white blood cell formation being disrupted and quickened. "Acute" refers to leukemia progressing rapidly throughout the body, and lymphocytic is the term used to define immature lymphocytes (white blood cells) produced [1]. Generally, lymphocytes develop from lymphoblasts (another term for immature lymphocytes), which mature over their life span and either migrate to the thymus to become T cells or remain in the bone marrow to develop into B cells. B cells produce antibodies that are proteins used to protect the human body from bacteria and viruses [2]. T cells include several different types, but their primary motive is to destroy infected cells or improve the immune system's response [3].

In the case of B-ALL, B-lymphocytes or white blood cells originating from the bone marrow have over-multiplied, causing abnormal mutations to occur. A high blood count of the mutated B-lymphocytes can lead to healthy white blood cells decreasing in number, leading to anemia, low blood count, and issues in tissues and organs around the body. B-ALL is the most prominently diagnosed subtype of Acute Lymphoblastic leukemia for pediatrics and adults. There are also two subtypes of B-cells: plasma cells and memory cells. Plasma cells provide immediate protection by releasing antibodies in response to present antigens. A mature plasma is capable of releasing up to 2,000 antibodies per second. Memory B cells will confer rapid and improved response to the same antigen that is presented in the future [4].

Formation of ALL

ALL begins in the bone marrow, where premature white blood cells mutate from changes in the cell's genetic material or DNA

sequence. Mutations brought by ALL can inactivate tumor suppressor genes or activate oncogenes to create continuous production of lymphoblasts. Oncogenes are genes that support cell growth and division. Tumor suppressor genes are genes that regulate cell growth and division by slowing down cell division or telling cells to die at the right time. Common signs and symptoms of ALL result from shortages of mature blood cells. The shortages of lymphocytes can be observed in blood tests or through bone marrow samples[5]. For blood tests, measuring blood cells' complete blood count (CBC) can help diagnose leukemia. It is still not completely understood why ALL is prevalent in children, but there are risk factors for ALL that can put some children at a higher risk of genetic damage to further develop into ALL. Several lines of evidence suspect infections behind the etiology of childhood ALL. Delayed exposure to common childhood infections or unusual responses by the child's immune system may impact B-ALL development. It is also important to mention children with congenital disorders such as Down Syndrome (DS) and Fanconi anemia are at a higher risk of developing ALL[6]. However, it is also important to note there has been no observed difference in rates of relapse or treatment-related mortality between children with DS and ALL compared with other children with ALL treated, according to the Dana-Farber Cancer Institute. Therefore, these risk factors do not align with treatment outcomes[7].

Mutations caused by ALL

B-ALL forms from mutations in the KRAS (Kirsten rat sarcoma viral oncogene homolog), NRAS (neuroblastoma rat sarcoma viral oncogene homolog), or FLT3 (FMS-like tyrosine kinase 3) genes in B-lymphocytes. These mutant genes are responsible for the Ras Pathways, Notch pathways, epigenetic modification, and cell-cycle regulation[8]. The RAS (rat sarcoma) gene family includes KRAS and NRAS, which encode a protein that plays a key role in cell signaling. When RAS genes mutate, cells can grow uncontrollably and evade signals from tumor suppressor genes. However, the progression of these gene mutations will not play an important factor in the treatment outcomes of patients in this study as these factors are not included in prevalent clinical trials. As previously mentioned, ALL affects both the pediatric population ($<$18 years old) and the adult population ($>$18 years old), but there are key genetic alterations in each group that differentiate their prognosis. The long-term prognosis for adults is currently poor, and ALL continues to be a challenge to treat in both pediatric patients and adult patients. Advancements in the genomic profile of patients across the age spectrum have shown biological differences in disease between children and adults, which provide further insight into possible therapeutic targets. B-ALL can be characterized by multiple genetic subtypes, including chromosomal alteration, which is essential for risk stratification (a technique for systematically categorizing patients based on their health status and other factors), including aneuploidy (gains and losses of whole chromosomes). Secondary genetic factors contributing to leukemogenesis include copy number alteration (commonly involving lymphoid transcription factors) and sequence mutations. For children (age younger than 15) diagnosed with ALL, the cure rates are typically exceeding 85%. However, the prognosis for ALL decreases with an increase in age, with historic cure rates of 30-40% in adults (older than the age of 40); however, relapsed ALL remains a major cause of cancer-related death for all ages[9].

Treatment Plans for ALL

Common treatment plans for ALL include chemotherapy for a majority of patients; however, there is still a chance of relapse occurring. After relapsing from 6 months or more of initial treatment, patients go through more intensive chemotherapy, with the 5-year overall survival rate for children with ALL at 50% and adults at 10%[10].

An immunotherapy procedure known as CAR T-cell therapy is a recently developed treatment plan primarily used for ALL chemo-relapsed patients[11]. Chimeric Antigen Receptor (CAR) T-cell therapy is a revolutionary, effective method that has been approved for clinical use by the US FDA since 2017. CAR T cells are engineered synthetic receptors that attach to natural killer(NK) cells to direct them towards targeting antigens expressed on tumor cells present in cancer patients. CAR T-cells have become adaptable to target these tumor cells no matter the complexity of the patient's MHC (major histocompatibility complex) haplotype or particular combination of MHC alleles found on a single chromosome. CAR T Cells consist of four domains: the ectodomain, a hinge domain, a transmembrane domain, and a costimulatory domain[12].

CAR T-cell Domains

The ectodomain is the region where the CAR T-cell specifies the target antigen and comprises both a heavy chain and light chain of monoclonal antibodies by connecting a flexible linker, forming a single-chain variable fragment (scFv). Heavy chains work to recruit cells to the tumor cell the antibody will bind to, and light chains ensure the expression and secretion of the functional CAR T-cell to the antigen binding. The heavy chains attract cells to the tumor cell targeted by the antibody, while the light chains guarantee the expression and release of the functional CAR T-cell for binding to the antigen. The hinge domain of the CAR T-cell provides flexibility to the antibody, enabling it to adjust its shape to the binding antigen. The hinge region contains two heavy chains and links two Fab arms to the FC (fragment crystallizable) portion. The transmembrane domain

regulates the amount of CAR signaling by controlling the CAR expression level. It also acts as a fulcrum for transmitting ligand recognition signals to the intracellular cytoplasmic domain, allowing CAR T-cells to identify target tumor cells regardless of the patient's MHC haplotype [13]. The costimulatory domain has four different generations, with the fourth having the ability for universal cytokine killing. This generation produces cytokines, including IL-12 (Interleukin 12) [14].

Autologous vs. Allogeneic

Furthermore, CAR T-cell therapy can either be autologous or allogeneic. Autologous T cells are extracted from the patient's peripheral blood, given improved specificity and killing efficacy against the patient's cancer cells, and then reinjected into the host, where they will help remove the tumor. This is accomplished by genetically altering the T cells to express the CAR, a receptor designed to identify a specific antigen present in the patient's cancer cells and trigger the growth and cytotoxic capacity of CAR T cells upon recognition [15]. Allogenic CAR T-cell therapy involves T-cells from a single volunteer that provide a high amount of peripheral blood mononuclear cells, which are healthy as donors compared to cancer patients, with no chemo drugs present in the blood. Despite many desirable traits, CAR T-cells also come with challenges. In 2021, Darel Martinez Bedoya provided an overview of clinical trials that involved allogeneic and autologous approaches. His findings showed allogeneic T cells might cause severe graft-vs.-host disease (GVHD) and the host immune system might, in turn, induce allorejection, which will impede anti-tumor activity [16]. However, due to recent findings of allogeneic CAR T-cell therapy showing higher remission rates among patients, all of the clinical trials included in this review include allogeneic T-cell transplants (allo-SCT).

Limitations Addressed

CAR T-cell therapy for B-ALL has been approved for treating children and adolescents with fairly advanced B-cell acute lymphoblastic leukemia. Still, it is limited and not applicable to all leukemias or pediatric cancers. However, it is essential to note that CAR T-cell therapy is only used for advanced B-ALL after ineffective chemotherapy has been used.

As of 2017, six CAR T-cell therapies have been approved by the Food and Drug Administration (FDA) for treating relapsed or refractory diffuse large B-cell lymphoma. However, CAR T-cell therapy has apparent side effects, including cytokine release syndrome (CRS). There is also continued development for using CAR-natural killer (CAR-NK) and CAR macrophages (CAR-Ms) alongside challenges with CAR-T therapy in facing solid tumors. It is also important to note the criticism behind CAR-T therapy in the case of expenses, with the procedure costing upwards of $450,000 due to it being customized for each patient's T cells [17]. Current constraints and prospective methods for CAR T-cell treatment include severe life-threatening toxicities, low antitumor effectiveness, antigen evasion, restricted trafficking, and limited tumor invasion. To add on, the host and tumor microenvironment interaction with CAR T-cells critically alters CAR T-cell function, and a complex workforce is required to develop and implement these treatments [14].

Comparing Pediatric and Adult ALL

Adolescents with ALL have been reported to have higher success rates in long-term survival than Adults. ALL can affect individuals of all ages, beginning from birth to late stages in life, making it an extremely heterogeneous disorder. There has been an improvement in survival rates for ALL over the past decades. This improvement has mainly occurred in children and adolescents with currency 5-year event-free survival (EFS) rates varying from 76% to 86% [18]. The diminished frequency of genetic subtypes linked to positive outcomes and the concurrent rise in subtypes linked to negative outcomes are important factors that impact prognosis in the adolescent and young adult (AYA) and adult populations. Significant increases in the EFS rates, primarily in children and adolescents, are due to efforts made in chemotherapy protocols in the last decade tailored specifically for this population. Additionally, the adult population has had unfavorable outcomes with intensive chemotherapy due to comorbidities and organ dysfunctions. Chemotherapy can increase the synthesis of chemokines at the tumor site and the penetration of these CAR T-cells into cancerous cells; chemotherapy also makes the tumor cells more sensitive to granzyme B, allowing it to infiltrate the layer of tumor cells more readily, thus increasing the efficacy of CAR T-cell therapy [19]. Current developments in genomic profiling throughout the age range contribute significantly to our understanding of the biological differences between childhood and adult diseases and offer new avenues for developing therapeutic targets [20].

Methods

In this review, the effectiveness of CAR T-cell therapy was assessed through the observation of Phase II and Phase III clinical trials, specifically on B-ALL in a specific sample size of patients, often lasting from several months to a couple of years. The goal of a Phase II trial is to answer if the CAR T-cell therapy improves their treatment for B-ALL. A majority of trials will consist of patients who have relapsed or refractory B-ALL, as CAR T-cell Therapy is often prescribed to patients who have undergone chemotherapy and faced chemorelapse [21]. A Phase III trial compares the safety and effectiveness of CAR T-cell therapy against current chemotherapy treatment.

CAR T-cell therapy has shown durable responses and manageable safety profiles in children, adolescents, and young adults less than 26 years old with B-ALL, including patients who have relapsed after allogeneic stem cell transplant[22]. To examine differences between CAR T-cell therapy in pediatrics with B-ALL and adult patients with B-ALL, this review has observed clinical studies performed on both age groups of patients with B-ALL and compared the treatment outcomes. The studies are based on three FD-approved CAR-T-cell therapies, tisagenlecleucel, axicabtagene ciloleucel (axi-cel), and lisocabtagene maraleucel (liso-cel) for ALL. These therapies have culminated in several phase I and II clinical studies. Outputs, including the complete response rate and the probability of cytokine release syndrome in each trial, have been recorded in a table format. Additionally, the age range of the pediatrics observed in the study has been below the age of 18 to effectively compare the response between developing children and fully developed adults. The clinical trials must also follow the International Ethical Guidelines for Biomedical Research Involving Human Subjects or the International Conference on Harmonization Good Clinical Practice guidelines.

Additionally, the effects of CAR-T-cell therapy are examined based on the age, blood count, and genetics of B-ALL patients. Suitable candidates for CAR-T-cell therapy include those who are under 25 years of age for particular B-cell-targeted CAR-T therapies[23].

Due to this paper covering a systematic review, a PRISMA diagram has been constructed below to view the criteria and number of reviews found in the PubMed database that cover clinical trials involving studying the effects of CAR T-cell therapy on pediatric and adult patients with B-cell Acute Lymphoblastic leukemia.

Baseline characteristics of the patients in the respective clinical trials include patients with relapsed or refractory B-cell acute lymphoblastic leukemia (R/R B-ALL). The specific dosage of CAR T-cells will vary, with some ranging from 2×10^6 CAR T cells per kilogram of body weight to 100×10^6 CAR T cells, along with either autologous or allogeneic T-cell treatment. Moreover, the toxicity of CAR T-cell therapy in children and adult patients with B-ALL was examined through clinical trials. It is noted that with CAR T-cell therapy, there have been associated toxics by CRS and an immune effector cell-associated neurotoxicity syndrome (ICANS). Cytokine Release Syndrome (CRS) is an acute systemic inflammatory syndrome that occurs when the immune system responds more aggressively to immunotherapy drugs than it should. ICANS can lead to confusion, tremors, or difficulty with communication and occurs when cytokines disrupt the blood-brain barrier. The overall response rate (ORR), complete response (CR), duration of response (DOR), median overall survival (OS) rate, and outcome of CRS will be determined and compared for each of the pediatric and adult clinical trials.

The objective response rate shows the percentage of patients whose B-ALL has decreased in growth or disappeared after treatment. The complete response in clinical trials is defined as the lack of detectable evidence of mutated B lymphocytes present in the patient or the complete remission of B-ALL. The duration of response (DOR) refers to the period of time from the beginning of a response to its progression or, if it happens sooner, its demise for any reason. Usually, DOR is evaluated in the absence of study treatment termination or any type of treatment adjustment. The median overall survival (OS) rate is a percentage that describes the average length of time individuals live or recover from a condition following a particular treatment. This is the estimated time, in months or years, at which 50% of the patients should still be alive. That indicates a 50% probability of surviving past that point.

Results

ELIANA

In the ELIANA trial, 92% of patients had relapsed B-ALL with 22% undergoing allogeneic stem cell transplant. A grade 3 or higher CRS rate was 13.3%, and ICANS was 8.6%. Additionally, 35.2% of patients experienced clinically significant bacterial infections within the first three months of treatment. From a median of a 4.8-year follow-up of CD19-CAR T-cell Therapy in Children and Young Adults with B-ALL, a high response rate was observed, 81%, in children and young adults with B-ALL but high relapse rates. Furthermore, no new or unanticipated long-term adverse effects were noted. Improvements in quality of life have also been observed by patients up to 36 months following delivery. These results guarantee long-term safety and propose tisagenlecleucel as a curative therapeutic option for pediatric and adult patients with R/R B-ALL who have had extensive pretreatment[25].

ZUMA-1

ZUMA-1 examined the safety and effectiveness of axicabtagene ciloleucel, also known as axi-cel, a CAR T-cell treatment in individuals with large B-cell lymphoma (LBCL) that was resistant. Patients with diffuse large B-cell lymphoma (DLBCL) were the main focus of the experiment. Patients received lymphodepleting chemotherapy followed by axi-cel (2×10^6 cells per kg). With a sizable percentage of patients obtaining a meaningful response, Axi-cel showed a high objective response rate. The majority of patients had a decrease in tumor burden, according to the trial's 82% ORR. The study demonstrated a strong complete response rate, with 58% of patients attaining a complete response. A deep and long-lasting response to axi-cel is indicated by a full response, which denotes the total eradication of detectable malignancy. Individuals who received a full response

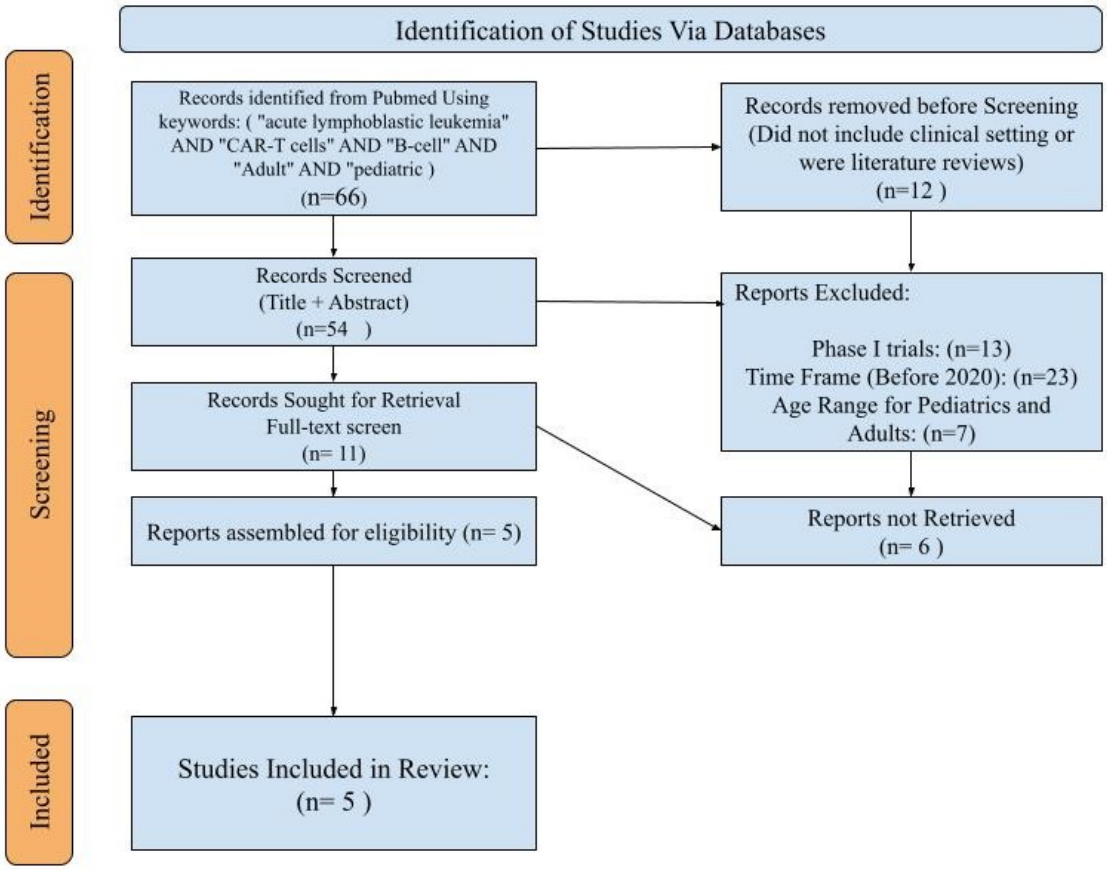

Fig. 1 PRISMA Diagram. In the Identification process, a total of 66 studies have been found using the search phrases "acute lymphoblastic leukemia, CAR T-cells, B-cell, Adults, and pediatric." Records were removed if they did not include a clinical setting that was sought or did not follow regulations as a part of the International Clinical Trials Registry Platform (ICTRP). From the records taken for screening, reports were excluded if they included phase I trials (which only focus on small sets of people for a short period of time), were not within a recent time frame of 2020-2023, or did not fit the age ranges to be effectively used in comparing pediatric outcomes from adult outcomes. After the screening, a total of five trials were identified as implicit for this systematic review. The following trials include ELIANA, ZUMA-1, ChiCTR 2000032211, InO single-agent ITCC-059, and TRANSFORM.

showed a durable response to axi-cel therapy. The reported median response length of 11.1 months highlighted the potential for long-lasting efficacy. Crucially, long-term follow-up data from the trial confirmed the potential for long-term benefit with axi-cel and showed how durable the response was. According to the material supplied, the 5-year examination of ZUMA-1 demonstrated long-term survival and persistent responses in patients with refractory LBCL. It is important to note all patients observed in this study reported an astounding 93% CRS rate. Most patients (84%) had lactate dehydrogenase levels above the upper limit of normal, and the median tumor burden by the sum of product diameters was 3723 mm^2. Among 42 patients with pretreatment tumor samples, 33 (79%) had poor prognostic markers, including 6 with high-grade B-cell lymphoma and 27 with double-expressor lymphoma [24].

ChiCTR 2000032211

Patients were treated at the RP2D (recommended phase II dose) of 1.8 mg/m^2. The results presented indicate a highly favorable response to CAR T-cell therapy in 194 patients with refractory leukemia or hematologic relapse. It is noted that no specific CAR T-cell was mentioned in this trial. Complete remission was achieved in an impressive 99.0% of these patients, all of whom were negative for minimal residual disease. The 12-month EFS for the entire cohort was 73.5%, showcasing the durability of the treatment response. Despite the overall positive outcomes, relapse occurred in 43 patients, with 24 experiencing $CD19^+/CD22^+$ relapse, 16 $CD19^-/CD22^+$ relapse, one $CD19^-/CD22^-$ relapse, and two cases with unknown characteristics. Consolidative transplantation and persistent B-cell aplasia at six months were identified as factors associated with favor-

Age Range	N	Median Follow-Up Time (Years and Months)	ORR(overall response rate) CR n, %(Complete Response) EFS: Event Free Survival OS (Overall Survival) DOR (Duration of Remission)	Toxicity Cytokine Release Syndrome (n, %) Grade:	Trial Name	Reference
(3-24) Mix (Mostly (Pediatric)	79	> 3 Years 38.8 months	ORR: 82% (3 months) CR: 66/75 = 88% EFS: 44% (24 months, median) OS: 63% DOR:	CRS: (- , 29%) Grade: 3-4	ELIANA	21
≥18 (Adult) 23-76 years	101	5 Years 63.1 months	ORR: 82% CR: 58% EFS: - OS: 25.8 months (median) OS (5-year): 42.6% DOR: 11.1 months	CRS: (n = 94, 93%) Grade: - Neurologic events (n=65, 64%)	ZUMA-1	24
≤ 22 (Pediatric)	225	2 Years 24 months	ORR: - CR: (194, 99.0%) EFS: 73.5% (1 year) OS: - DOR: -	CRS: (n = 198, 88%) Neurologic events: (n = 47, 20.9%))	ChiCTR 2000032211	23
≤ 18 (Pediatric) (1-18)	32	1.33 16 months	ORR: (22, 81.5%) CR: - EFS: 36.7% (6 months) OS: 56.3% (12 months) DOR: 7.74 months	CRS: (n=20, 71.4%) Grade: 3–4	InO single-agent ITCC-059	25
18-74 (Adult)	184	1.45 Years 17.5 months	ORR: 80, (87%) CR: 74% EFS: - OS: 73% (18 months) DOR: -	CRS: (-, 1%) Grade: 3-4	TRANSFORM - Phase III Trial	

Table 1 Comparing all Clinical Trials. It provides the age range, number of patients, median follow-up time, ORR, CR, EFS, OS, and DOR, and the number and percentage of those who had CRS in each trial.

able outcomes. The 12-month EFS was notably higher at 85.0% for patients treated with transplantation compared to 69.2% for those who did not undergo transplantation. Remarkably, all 25 patients with persistent B-cell aplasia at six months remained in remission at 12 months, emphasizing the potential predictive value of this marker.

Additionally, the 12-month EFS for patients with isolated testicular relapse was 95.0%, while for those with isolated CNS relapse, it was 68.6%. However, the treatment was not without its challenges. CRS developed in a substantial proportion of patients (88.0%), and CAR T-cell neurotoxicity was observed in 20.9% of cases, leading to two deaths. These adverse events highlight the importance of carefully managing and monitoring patients undergoing CAR T-cell therapy [26].

InO single-agent ITCC-059

Patients aged 1–18 years, with R/R $CD22^+$ BCP-ALL (B-cell precursor acute lymphoblastic leukemia), were treated at the RP2D (recommended phase II dose) of $1.8\,mg/m^2$. Promising outcomes were observed in pediatric patients with relapsed or refractory leukemia who participated in the inotuzumab ozogamicin (InO) clinical trial. Subjects initiated InO at the RP2D of $1.8\,mg/m^2$/cycle fractionated in three weekly administrations or $1.5\,mg/m^2$/cycle once remission was achieved. An astounding ORR of 81.5% was achieved among the 28 patients who underwent treatment, with the majority exhibiting complete responses. MRD negativity was observed in a substantial percentage of those who responded. The median DOR was reported to be 7.74 months. One crucial factor contributing to the positive results was the smooth transition to consolidation therapy, including CAR T-cell therapy and hematopoietic stem cell transplantation (HSCT). Three patients received blinatumomab as bridging therapy before HSCT; one patient received chemotherapy, and the others did not receive additional treatment between the last InO administration and transplant. Despite observing adverse events such as neurotoxicity and CRS, the trial's safety profiles were manageable. The EFS rate, the cumulative incidence of relapse and non-relapse death at six and twelve months, and OS probabilities provided valuable insights into the treatment's efficacy and safety in this patient population [27].

TRANSFORM

Adults eligible for autologous stem cell transplantation (ASCT; $N = 184$) were randomly assigned in a 1:1 ratio to liso-cel (100×10^6 chimeric antigen receptor–positive T cells) or SOC (3 cycles of platinum-based immunochemotherapy followed by high-dose chemotherapy and ASCT in responders). Patients were randomly assigned to the Lisocabtagene maraleucel (liso-cel) arm and received lymphodepleting chemotherapy (fludarabine, $30\,mg/m^2$ and cyclophosphamide, $300\,mg/m^2$ daily for 3 days), followed by a liso-cel infusion at a dose of 100×10^6 CAR^+ T cells. Liso-cel, also known as Breyanzi, is a second-line CAR T-cell treatment option. It's used to treat large B-cell lymphoma (LBCL) that has relapsed or is refractory, including in older patients with comorbidities. Liso-cel can improve survival outcomes and has a manageable safety profile. The TRANSFORM study showed that liso-cel was better than standard-of-care (SOC) for patients with relapsed or refractory large B-cell

lymphoma (LBCL), with a median follow-up of 17.5 months. Comparing Liso-cel treatment to SOC, there were notable gains in progression-free survival (PFS), CR rate, and EFS. Neurotoxicities and CRS of any grade occurred across 49% of all patients, with 1% experiencing grade 3 or 4. Severe infections were reported in 14 (15%) patients in the liso-cel arm. Fifty-eight (63%) patients in the liso-cel arm received bridging therapy. The most common reasons for receiving bridging therapy, as per investigator assessment, were high tumor burden (28 of 58 [48%]) and rapid progression (23 of 58 [40%]). For patients with primary refractory or early recurrent LBCL, liso-cel demonstrated sustained disease control, with longer EFS and greater response rates than SOC. Patients in the SOC arm were allowed to cross over and receive liso-cel upon independent review committee (IRC) confirmation of a failed response after 3 cycles of SOC. These findings support the medication's use as a preferred second-line treatment. Although the difference was not statistically significant, overall survival favoring liso-cel numerically may have been caused by patients who switched from the SOC arm to liso-cel. The outcomes affirmed the significance of earlier treatment with CAR T-cell therapy in this patient population [28].

Discussion

The response to CAR T-cell therapy in pediatric and adult patients with relapsed or refractory B-cell malignancies, specifically B-ALL and aggressive B-cell lymphomas, reveals interesting distinctions. Tisagenlecleucel, the approved CAR T-cell therapy for pediatric and young adult patients with relapsed or refractory B-ALL, exhibits durable efficacy with a 36-month RFS of 52%, EFS of 44%, and OS of 63%. Notably, the majority of responding patients did not undergo consolidative alloSCT. Long-term safety-related factors, including hypogammaglobulinemia and infections, do not compromise the improvements in quality of life up to 36 months after infusion. B-cell recovery within the first six months after infusion predicts the risk of relapse, but this does not always precede relapse. High disease burden before infusion correlates with an increased risk of nonresponse and early relapse. However, the study acknowledges limitations in exploring disease burden hypotheses due to incomplete data.

In contrast, the 5-year analysis of the ZUMA-1 study, focusing on axicabtagene ciloleucel (axi-cel) for refractory DLBCL, indicates continued durability of response over the course of 5 years, with deaths by year decreasing from 58% to 1% and with a 5-year disease-specific survival rate of 51%. However, the OS rate was lower compared to other trials, potentially due to the dosage patients received. The dosage for ZUMA-1 patients was axi-cel (2×10^6 cells per kg), compared to the dose of 100×10^6 CAR^+ T cells in TRANSFORM patients. Among 42 patients with pretreatment tumor samples, 33 (79%) had poor prognostic markers, including 6 with high-grade B-cell lymphoma and 27 with double-expressor lymphoma. 84% of the patients in ZUMA- had lactate dehydrogenase levels above the upper limit of normal, indicating the plausibility of tissue damage from significant cell death and leading to a low OS rate of 42.6%. Additionally, a majority of ZUMA-1 patients who died seemed to be suffering from progressive disease, which is caused by worsening, growth, or spread of the B-ALL [24]. Since ZUMA-1 consisted of adult patients, this would provide evidence that the adult population is prone to fatal treatment outcomes more than pediatrics, including higher than normal lactate dehydrogenase levels leading to lower OS rates compared to pediatrics in the InO trials where no cases of toxic death, or study-treatment related death, were observed.

The Chir trial also included the pediatric population and had one of the highest complete remissions of 99% of the patients, with only two deaths due to neurotoxicity and CRS. This also suggests pediatric patients may have a more robust immune system, enhancing CAR-T cell therapy's efficacy, which can be due to the administration of chemotherapy to patients prior to the beginning of all clinical trials observed. As previously mentioned, due to efforts made in chemotherapy protocols tailored specifically for this population in the last decade, pediatrics have better treatment responses for chemotherapy. Additionally, the adult population has had unfavorable outcomes with intensive chemotherapy due to comorbidities and organ dysfunctions [15]. Chemotherapy can increase the synthesis of chemokines at the tumor site and the penetration of these CAR T-cells into cancerous cells; chemotherapy also makes the tumor cells more sensitive to granzyme B, allowing it to infiltrate the layer of tumor cells more readily, thus increasing the efficacy of CAR T-cell therapy.

Zuma -1 focuses on the adult population and has the highest CRS rate of 93% among patients. Factors that contribute to a higher CRS rate include a higher inflammatory response or due to a more advanced or developed progression of B-ALL. It is known that the inflammatory response varies from patient to patient. In the ChiCTR 2000032211 trial, the patient outcomes also reported a CRS rate of 88%, which consists of the pediatric population.

Therefore, there is no observed difference in the CRS rates between pediatric and adult populations, and it primarily depends on the safety measures and inflammatory response of the patient population in each trial. Furthermore, CRS rates are also dependent on advancements made in clinical trials, such as the TRANSFORM trial (phase III trial), where a 1% CRS (grade 3-4) rate is observed within the adult population. The TRANSFORM trial also focuses on the adult population and reported 49% of patients with CRS of any grade also, the SOC included immunochemotherapy, which did not show strong efficacy compared to liso-cel. Fifty-eight (63%) patients in the liso-cel arm received bridging therapy, with the most common reason being high tumor burden (28 of 58 [48%]) and rapid

progression (23 of 58 [40%]). Due to bridging therapy primarily being used to reduce the risk of CAR T-associated toxicities by debulking the disease, this can suggest the patient population did not respond well to CAR-T cell infusion, leading to lower CAR T-cell efficacy rates. The Ino trial also incorporated bridging therapy but for three pediatric patients (9.4%) of the trial's population, suggesting avid immune response following CAR T infusion for pediatrics.

Current methods to help control CRS rates in clinical trials, including tocilizumab and/or corticosteroids, have been reserved for treating severe CRS and/or ICANS. In 2023, authors Michael D. Jain, Melody Smith, and Nirali N. Shah suggested strategies including pre-emptive tocilizumab and/or steroids with lower-grade toxicity to prevent the onset of more severe manifestations or even prophylactic treatment before any toxicity is observed. These strategies appear to be more effective at reducing CRS severity than ICANS, and caution remains because of the concern that these interventions could affect longer-term CAR T-cell efficacy[29].

Notably, liso-cel, another CAR T-cell therapy, demonstrates superiority over standard-of-care in the TRANSFORM study, with significant improvements in EFS, CR rate, and PFS. The prolonged efficacy of liso-cel, particularly in patients achieving CR, emphasizes its potential as a preferred second-line treatment compared to standard-of-care for primary refractory or early relapsed LBCL. Comparisons with other CAR T-cell therapies, such as axi-cel and tisagenlecleucel, suggest unique efficacy and safety profiles, underlining the importance of tailoring treatment strategies based on disease characteristics and patient populations. One possible explanation for the difference in response is the biology of B-ALL. Pediatric patients with B-ALL may have a higher proportion of B-ALL cells expressing the CD19 antigen, which is the target of CAR-T cell therapy. This shows the likelihood of a better response to CAR-T cell therapy in pediatric patients.

Regarding B-ALL biology, Large B-cell lymphoma is a heterogeneous disease with various molecular subtypes and genetic alterations. The biology of LBCL, including tumor cell characteristics, such as antigen expression and microenvironment interactions, can influence the response to CAR T-cell therapy. Also, variations in patients' immune systems, such as the prior treatment of chemotherapy to all patients, immunosuppression, and comorbidities, can impact the efficacy and safety of CAR T-cell therapy. Differences in T-cell function, cytokine profiles, and immune cell composition may affect CAR T cells' activation, expansion, and persistence following infusion. Patients with compromised immune function or pre-existing immune dysregulation may experience altered responses to CAR T-cell therapy compared to those with healthier immune systems.

However, it is also important to note the limitations and challenges each clinical trial has shown. To begin with, the information on the patient history provided was insufficient in the ChiCTR 2000032211, ELIANA, ZUMA-1, and InO single-agent ITCC-059, and TRANSFORM trial and failed to include patient characteristics (ethnicities, medical history, etc.) or discuss possible confounding variables that may lead to differences in treatment responses. The follow-up time for the ELIANA trial was a median of 38.8 months, which is relatively short, given that long-term data is essential to understanding the sustained effectiveness of the treatment. The ZUMA-1 trial also included a heterogeneous group of patients with refractory DLBCL, encompassing different subtypes and prior treatment histories. This heterogeneity may impact the generalizability of the results to specific patient subgroups or other lymphoma types. Also, many trials do not include the variability of disease biology in account for potential factors that may influence treatment responses and affect the results' generalizability. Ultimately, most of the trial reports do not include a randomized control group, except for TRANSFORM, which limited the ability to compare the outcomes directly with standard treatments, making it challenging to determine the exclusive contribution of specific therapies, including axi-cel.

Conclusion

In conclusion, the available literature confirms that there is a difference in response to CAR-T cell therapy between pediatric and adult patients with B-ALL. This difference may be attributed to various factors, including differences in B-ALL biology between pediatric and adult patients, differences in the immune system, and differences in the dosage patients received in the observed clinical trials. However, it is noted that chemotherapy being used as a first-line treatment for each of all subjects in each trial can show favorability to pediatric patients due to clear advancements in chemotherapy protocols tailored specifically for this population in the last decade, which led to tumor cells being more sensitive to granzyme B, allowing it to infiltrate the layer of tumor cells more readily, thus increasing the efficacy of CAR T-cell therapy. Furthermore, adults are shown to be prone to progressive disease and mortality observed in the ZUMA-1 trial. The Ino trial also supports how pediatric patients may have a more robust immune system, enhancing CAR-T cell therapy's efficacy due to the observed ORR of 71.4% and 82% in ELIANA. In contrast, adult patients may have a compromised immune system due to prior treatments or comorbidities, which may result in a lower response to CAR-T cell therapy. The difference in response to CAR-T cell therapy between pediatric and adult patients with B-ALL is an important area of research that requires further investigation. Understanding the factors contributing to this difference may help develop more effective CAR-T cell therapies for pediatric and adult B-ALL patients. Future studies should aim to address the knowledge gap by investigating the underlying mechanisms of the difference in response and developing strategies to improve the efficacy of

CAR-T cell therapy in both pediatric and adult patients with B-ALL. Future implications and optimizations for CAR T-cell therapy in B-ALL patients include enhancing CAR persistence and avoiding antigen downregulation, including developing a multi-specific CAR platform and clarifying optimal approach toward equipotent multi-specificity and engineering maneuvers to decrease CAR activation threshold[30]. Overall, CAR-T cell therapy has emerged as a promising treatment option for B-ALL, and further research is needed to optimize its use in both pediatric and adult patients by first mitigating high CRS rates in both age groups and addressing the effectiveness of the first-line of treatment, chemotherapy, leading to increased efficacy of CAR T-cell therapy in pediatrics. Addressing the knowledge gap and developing more effective CAR-T cell therapies will improve outcomes for patients with B-ALL and ultimately achieve better long-term survival rates.

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