Literature review

# Advance in immunotherapy for pediatric B-cell acute lymphoblastic leukemia

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## Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer among children worldwide.[1,2] With advancements in treatment, the overall survival (OS) rate of pediatric ALL in developed countries approached 90% before 2010.[1] A recent multicenter study in Thailand, Monsereenusorn, et al. demonstrated improved outcomes in Thai pediatric patients with ALL using the Thai Pediatric Oncology Group (ThaiPOG) protocols. This study reported a five-year, event-free survival (EFS) rate of 75.0% and a five-year OS rate of 81.7%.[3] However, despite these advancements, approximately 30% of patients relapse and might not respond to subsequent chemotherapy regimens.

Although multi-agent chemotherapy remains the standard of care for pediatric ALL, conventional treatments have reached therapeutic limits. Incorporating additional cytotoxic agents, such as clofarabine, into regimens has been associated with unacceptable toxicity, as reported in the Children's Oncology Group (COG) AALL1131 study.[4] Over the past decade, growing evidence has supported immunotherapy and cellular therapy as major game changers in treating pediatric ALL, especially B-cell ALL (B-ALL), in both newly diagnosed and relapsed patients. Adoptive cellular therapy (ACT) represents a dynamic biological strategy that utilizes "living drugs," wherein patient-derived immune cells are collected, expanded, and engineered in vitro before reinfusion to target and eliminate cancer cells. Among various ACT approaches, chimeric antigen receptor (CAR) T cell therapy has received marketing approval and demonstrated remarkable efficacy in treating relapsed/refractory (R/R) B-ALL in pediatric populations.[5] In addition to ACT, non-cellular therapies such as bispecific T cell engagers (BiTEs) and antibody-drug conjugates (ADCs) have been extensively evaluated in pediatric clinical trials. These strategies specifically target antigens uniquely or predominantly expressed on malignant cells to minimize off-target effects and maximize therapeutic efficacy.[6] This review focuses on the recent evidence-based immunotherapies in pediatric B-ALL and the future scope of these treatments.

## Background of immunotherapy in pediatric B-ALL

In 1863, Rudolf Ludwig Karl Virchow observed the presence of leucocytes in neoplastic tissues.[7] Subsequently, William Coley, widely regarded as the "father of cancer immunotherapy," reported improved survival among patients with sarcoma who developed erysipelas. Coley's mixed toxins likely induced therapeutic effects by provoking a broad immune response. The bacterial extract included components such as CpG DNA, lipopolysaccharide and lipoteichoic acid, which simultaneously activated multiple pattern-recognition receptors, including TLR9, TLR4 and TLR2. This activation promoted plasmacytoid dendritic cells to secrete interferon-alpha (IFN-$\alpha$), recruited neutrophils and dendritic cells to the tumor site, and triggered a self-amplifying cascade of inflammation and tissue damage signals. Consequently, robust CD4+ T-cell priming occurred, accompanied

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by elevated cytokine levels, notably interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF-α), reflecting the same immunological pathways targeted by contemporary immunotherapies.[8] Since then, knowledge of basic science, translational research and application of immunotherapy in clinical practice has continued to grow. The current definition of immunotherapy is an active therapeutic approach designed to trigger the immune system to attack tumor cells, while cellular therapy is a form of treatment that uses immune system cells to eliminate cancer.[9] Currently, several platforms of immunotherapy are employed in treating pediatric B-ALL, including CAR T cell therapy such as tisagenlecleucel, ADCs such as inotuzumab ozogamicin and BiTE such as blinatumomab.[10,11]

**CAR T cell therapy in pediatric B-ALL**

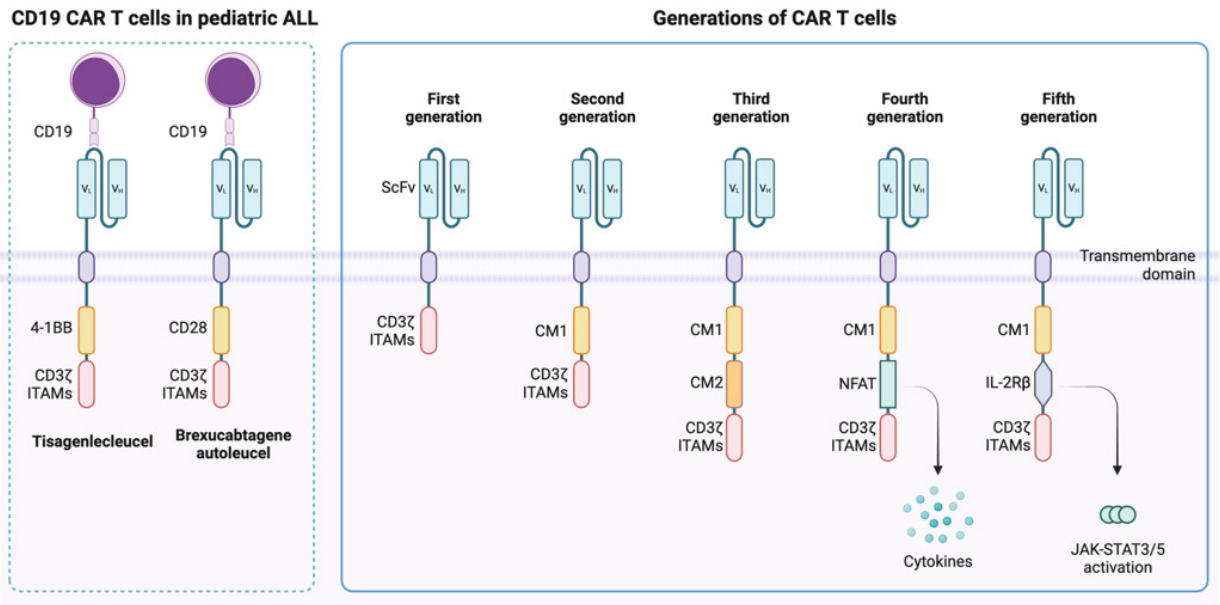
In general, cancer cells have a potential to evade the host immune system through several mechanisms, such as inducing T cell dysfunction and anergy.[12] To overcome this, adoptive T cell therapy for cancer, which involves the infusion of native or genetically modified mature T cells capable of recognizing and potentially eliminating the patient's malignant cells, has been proposed.[13] The CAR-based approach involves engineering T cells with sequences that encode antibody-based antigen recognition moieties linked to signaling domains. Common tools for the transduction of CAR T cells include viral vectors, such as lentiviruses and gammaretroviruses. Unlike T cell receptors, CARs enable T cells to recognize and eliminate tumor cells in a major histocompatibility complex (MHC)-independent manner by binding to specific surface antigens, such as CD19, which is expressed exclusively on B cells.[14,15]

Following the successful in vivo expansion and antileukemic effects of CD19 CAR T cell therapy in a pilot study of adults with chronic lymphocytic leukemia, the first phase I clinical trial of CD19 CAR T cell therapy in pediatric B-ALL was initiated at the Children's Hospital of Philadelphia, University of Pennsylvania.[16,17] Despite relapsed disease in one patient after CD19 CAR T cell infusion, another patient with refractory B-ALL achieved long term remission without subsequent management. In 2018, the landmark ELIANA phase II clinical trial in pediatric B-ALL demonstrated a groundbreaking outcome in R/R disease.[18] This result ushered in a new era of CAR T cell trials across various cancers in both children and adults. Details on the structures and generations of CAR T cells are presented in Figure 1.[10,19]

**Evidence-based CD19 CAR T cell therapy in pediatric B-ALL**

**Tisagenlecleucel (CTL019)**

Tisagenlecleucel is a second-generation CAR T cell therapy that employs autologous peripheral blood T cells, genetically engineered ex vivo to express a CD19-specific CAR with a 4-1BB costimulatory domain, enabling targeted elimination of CD19-positive B cell hematologic malignancies. As of February 2025, tisagenlecleucel is the first and only United States Food and Drug Administration (US FDA)-approved CD19 CAR T cell therapy for children and young adults up to 25 years of age with R/R B-ALL after failing two lines of treatment.[20] Tisagenlecleucel has demonstrated safety and curative potential in the ELIANA trial, with subsequent data in a three-year follow-up.[18,21] Among 79 children and young adult patients with R/R B-ALL, the median follow-up was 38.8 months. The overall remission rate (ORR) was 82%. The three-year EFS was 44% (95% confident interval (CI), 31% to 57%) and the three-year OS was 63% (95% CI, 51% to 73%). Only 17 out of 79 patients underwent subsequent allogeneic hematopoietic stem cell transplant (HSCT) following tisagenlecleucel infusion.[21] Regarding the safety profile, although the ELIANA trial initially reported grade ≥ 3 cytokine release syndrome (CRS) in up to 48.1% of patients, real-world data from the CIBMTR and the Japan CAR T Consortium reported rates ranging from 12% to 16.1%. The incidence of grade ≥ 3 immune effector cell-associated neurotoxicity syndrome (ICANS) in the real-world data was also lower than in the ELIANA trial, ranging from 7.1% to 9%.[22, 23]




ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; CM, costimulatory molecule; ITAMs, Immunoreceptor tyrosine-based activation motifs; NFAT, nuclear factor of activated T cells; ScFv, single-chain variable fragment; $V_H$, variable heavy chain; $V_L$, variable light chain

**Figure legend**

**1st generation:** Single signaling domain (basic T-cell activation); **2nd generation:** CD3ζ + 1 CM (improved T-cell activation, proliferation and persistence); **3rd generation:** CD3ζ + 2 CMs (enhanced safety, proliferation, persistence and anti-tumor effects); **4th generation:** CD3ζ, 1 CM and transgenic protein expression (improved T-cell expansion, persistence, anti-tumor activity, resistance to tumor antigen escape, and enhanced cytokine-driven immune modulation); **5th generation:** Cytokine-induced JAK/STAT signaling (superior activation, proliferation, persistence, safety profile and enhanced tumor microenvironment modulation).

**Figure 1** Generations of CAR T cells and CD19 CAR T cells therapy in pediatric ALL (adapted from Knight, et al. and Asmamaw Dejenie, et al.)[10,19]

Current studies of tisagenlecleucel in children and young adults are not limited to R/R cases. The phase II CASSIOPEIA trial (NCT03876769) is investigating tisagenlecleucel in patients with first-line, high risk B-ALL, who are minimal residual disease (MRD)-positive at the end of consolidation (EOC) therapy. This trial will help assess the feasibility of using CAR T cell therapy as an upfront treatment strategy.

**Brexubactagene autoleucel (KTE-X19)**

Brexubactagene autoleucel is another second-generation CD19 CAR T cell therapy that uses the CD28 costimulatory signaling domain. This CAR T cell product is currently approved only for adult patients with R/R mantle cell lymphoma and R/R B-ALL.[24] For the pediatric population, the ZUMA-4 phase I/II clinical trial explored the dosing and safety of brexubactagene autoleucel in pediatric R/R B-ALL.[25] Severe CRS and ICANS grade ≥ 3 were observed in 33% and 21% of cases, respectively. The overall complete remission rates were 67% among all treated patients. In this trial, 16 out of 24 cases underwent subsequent consolidate allogeneic HSCT.[25] Due to relatively frequent and serious adverse events observed in the pediatric ALL cohort, ZUMA-4 is ongoing in pediatric patients with R/R B cell non-Hodgkin lymphoma (B-NHL).[10]

**Process of CAR T cell therapy: from re-induction to long-term follow-up**

Patients with R/R B-ALL who are eligible for autologous CAR T cell therapy undergo a process involving re-induction chemotherapy, leukapheresis collection, bridging chemotherapy, CAR T cell infusion, adverse event monitoring and long-term follow-up.

**Table 1** Optimal intervals from therapy to leukapheresis[26,27]

| Time interval prior to leukapheresis | Medications/procedures |
|---|---|
| Special considerations | Alemtuzumab and ATG: washout ≥ 6 months |
| | Bendamustine and fludarabine: washout ≥ 12 weeks |
| 12 weeks | Allogeneic HSCT |
| 8 weeks | Clofarabine, T cell lytic agents |
| 4 weeks | Donor lymphocyte infusion, pegylated asparaginase |
| 2 weeks | Systemic chemotherapy, GvHD therapies (e.g., calcineurin inhibitors), imatinib, long-acting growth factors, dasatinib, ponatinib, blinatumomab |
| 1 week | Intrathecal methotrexate, therapeutic doses of corticosteroids (especially dexamethasone), lenalidomide |
| 5 days | Short-acting growth factors, nilotinib |
| 3 days | Short-acting cytotoxic/antiproliferative drugs (e.g., hydroxyurea) |

ATG, anti-thymocyte globulin; GvHD, graft versus host disease; HSCT, hematopoietic stem cell transplant

In relapsed cases requiring re-induction chemotherapy due to significant symptoms or delays in leukapheresis, the British Society of Blood and Marrow Transplantation (BSBMTCT) recommends two weeks of a three-drug regimen (dexamethasone, vincristine, asparaginase) or a four-drug regimen (dexamethasone, vincristine, daunorubicin, asparaginase). Alternative regimens may be used based on institutional experience, but the washout period of specific treatments and the timing of leukapheresis must be considered, as outlined in Table 1.[26,27]

Leukapheresis involves collecting lymphocytes from the patient for CAR T cell manufacturing. Pre-collection absolute lymphocyte counts of ≥ 0.5 $x10^9$/L and CD3 counts of ≥ 0.35 $x10^9$/L are preferred, although absolute lymphocyte counts ≥ 0.3 $x10^9$/L and CD3 counts ≥ 0.15 $x10^9$/L are acceptable. The collection of 2 to 2.5 times the total blood volume is recommended. Manufacturers specify different requirements for leukapheresis yields, ranging from specific cell counts to total volume processed. For tisagenlecleucel, the required cell counts in the leukapheresis product include ≥ 1 $x10^9$ CD3+ cells, total nucleated cells (TNCs) ≥ 2 $x10^9$ cells and CD3+ comprising ≥ 3% of TNCs.[26,27]

While awaiting CAR T cell manufacturing, which typically takes approximately four to five weeks, bridging chemotherapy is essential. Unlike standard treatment goals for newly diagnosed ALL, the objectives of bridging therapy include reducing disease burden without necessarily achieving deep remission, avoiding prolonged neutropenia, minimizing mucositis and organ toxicity, maintaining quality of life through outpatient management when possible and preventing severe B cell lymphopenia before CAR T cell infusion. The BSBMTCT guidelines provide treatment protocols based on bone marrow (BM) blast percentages.[27]

For patients with BM blasts ≤ 5%, recommended regimens include:

1. Oral 6-mercaptopurine and oral methotrexate, with optional pulse vincristine and dexamethasone (similar to maintenance therapy for ALL),

2. A tyrosine kinase inhibitor combined with maintenance 6-mercaptopurine and oral methotrexate for Philadelphia chromosome-positive ALL.

For patients with BM blasts > 5%, recommended regimens include:

1. Three- or four-drug re-induction therapy for two to four weeks, considering four drugs for patients aged ≥ 10 years or with white blood cell counts ≥ 50 $x10^9$/L. Response assessment at two weeks should guide further administration of asparaginase and anthracyclines.

2. The Capizzi methotrexate protocol, starting at 100 mg/m$^2$ intravenously and escalating by 50 mg/m$^2$ every 10 days (five total doses), combined with vincristine.[28]

3. For CD22-positive B-ALL, a single dose of inotuzumab ozogamicin (InO) may be considered. Careful titration of subsequent InO doses is critical, as weekly cycles over three weeks may cause profound B cell aplasia (BCA), negatively impacting CAR T cell expansion.

4. Intermediate- to high-dose cytarabine (6-18 g/m² total, 3 g/m² intravenous infusion every 12 hours), can be repeatable every three to four weeks based on blast counts hematologic and recovery.

5. Etoposide (100 mg/m² days 1-5) and cyclophosphamide (440 mg/m² days 1-5), is based on the week 7 ALLR3 consolidation protocol.[29]

Although blinatumomab has shown benefit as a bridging therapy in several studies, large-scale prospective studies are needed to assess the risk of developing CD19-negative clones and potential reduction in CAR T cell efficacy.[30]

Disease response should be evaluated two weeks after bridging chemotherapy. Intrathecal chemotherapy is recommended every four weeks unless central nervous system (CNS) relapse necessitates more frequent intervention.[27] The washout periods for specific treatments and their intervals to CAR T-cell infusion are presented in Table 2.[18]

Prior to CAR T cell infusion, lymphodepleting (LD) chemotherapy is essential to reduce endogenous lymphocytes, create a niche for CAR T cell engraftment, reduce tumor burden, and optimize the microenvironment for CAR T cell expansion and persistence.[31] Common agents include fludarabine and cyclophosphamide due to their cytoreductive and lymphodepleting effects.

CAR T cell infusion doses vary by product. For tisagenlecleucel, the recommended doses are 0.2 to 5.0 x$10^6$ viable CAR-positive T cells/kg (patients ≤ 50 kg) or 0.1 to 2.5 x$10^8$ CAR-positive T cells/kg (patients > 50 kg).[20]

In the early phase following CAR T cell infusion, adverse events should be closely monitored. CRS is one of the most common toxicities. It is characterized by activated CAR T cells targeting cells with specific surface markers and subsequently releasing cytokines, including IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-18, IFN-γ, TNF-α, GM-CSF, MCP-1, MIP1-α and damage-associated molecular patterns.[32] This condition usually occurs within the first two weeks after infusion. The most significant risk factor for CRS among children with B-ALL is baseline bone marrow disease burden, with severe CRS risk positively correlated with marrow involvement.[33] Patients with CRS can present with a range of clinical manifestations, from fever, hypotension, and hypoxia to more severe conditions involving end-organ dysfunction. CRS severity grading and management guidelines have been established by the European society for blood and marrow transplantation (EBMT), the joint

**Table 2** Optimal intervals from therapy to CAR T infusion[18]

| Time interval prior to CAR T infusion | Medications |
|---|---|
| 8 weeks | CNS-directed radiotherapy, antiT cell antibodies (e.g., alemtuzumab) |
| 6 weeks | Donor lymphocyte infusions |
| 4 weeks | Systemic GVHD therapies, pegylated asparaginase |
| 2 weeks | Clofarabine, cytosine arabinoside > 100 mg/m², anthracyclines, cyclophosphamide, methotrexate ≥ 25 mg/m², non-CNS related radiotherapy |
| 1 week | Vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate < 25 mg/m², cytosine arabinoside < 100 mg/m²/day, asparaginase (non-pegylated), CNS prophylactic therapy |
| 3 days | Therapeutic doses of corticosteroids, TKIs, hydroxycarbamide |

CAR, chimeric antigen receptor; CNS, central nervous system; TKIs, tyrosine kinase inhibitors

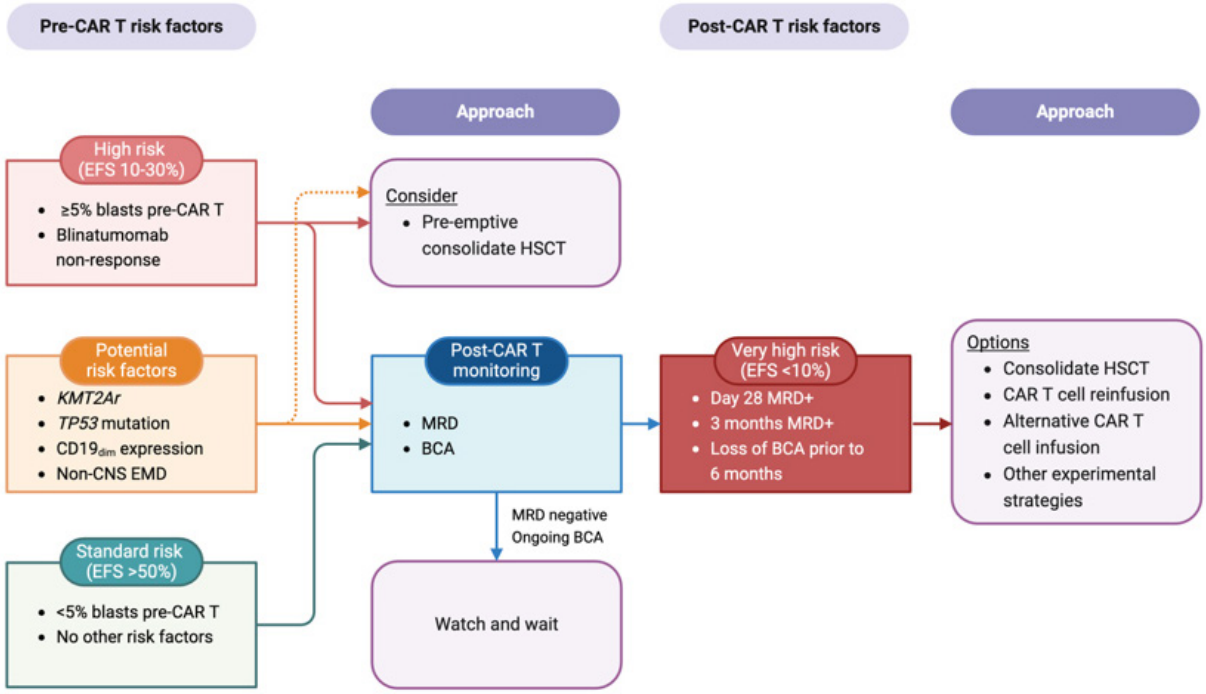
accreditation committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA).[34] The first-line treatment for CRS includes supportive care and tocilizumab, a humanized anti-IL-6 receptor antibody. Corticosteroids, which may negatively impact CAR T cell efficacy, should be reserved for more severe cases. ICANS is another potentially serious adverse event that typically arises within the first several weeks, generally later than CRS.[32] Risk factors for ICANS include prior CRS, elevated C-reactive protein (CRP) and high serum ferritin levels.[35] Clinical manifestations of ICANS include aphasia, seizures, headaches, and encephalopathy. The mainstay of ICANS treatment is supportive care. Anticonvulsant prophylaxis can be considered in high-risk patients, such as those with CNS disease. Corticosteroids are recommended for higher-grade ICANS, whereas tocilizumab is not typically indicated for isolated ICANS without CRS, due to its limited penetration across the blood-brain barrier.[36] Zandaki, et al., used the EASIX score (LDH x creatinine/platelet count) and the modified EASIX score (LDH x CRP/platelet count) to predict the development of CRS and ICANS among children, adolescents and young adults (AYA) undergoing CD19 CAR T cell therapy.[37] Another rare complication is immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), for which treatment with anakinra, an interleukin-1 receptor antagonist, with or without corticosteroids, may be beneficial.[38]

A common long-term complication following CD19 CAR T cell infusion is hypogammaglobulinemia. Among children and AYA, the ASTCT guidelines recommend routine immunoglobulin supplementation whenever IgG levels are ≤ 400 mg/dL, with supplementation at doses of 250-500 mg/kg IVIG every four weeks.[39] Conversely, early loss of BCA is associated with an increased risk of relapse.[40] A recent report from the DESCAR-T registry indicated that one patient among 2,536 treated for lymphoma developed T cell malignancy following CAR T cell therapy.[41] Although this complication is exceedingly rare, it should be included in discussions with patients before initiating treatment.

**CAR T cell therapy: risks of relapse and when to consider bridging to HSCT**

Currently, no standardized recommendation exists regarding bridging to HSCT following CD19 CAR T cell therapy in children. However, several publications have proposed management guidelines based on identified risk factors associated with inferior outcomes both before and after CAR T cell infusion. The risk factor-based approach proposed by Buechner, et al. and Myers, et al., has been adapted and is reviewed in Figure 2.[30,42]

Several pre-infusion risk factors are recognized, including leukemic cytogenetics, prior treatments such as blinatumomab, bone marrow disease burden, extramedullary disease (EMD), CD19 antigen load and LD chemotherapy. Three cytogenetic abnormalities warrant particular attention: *KMT2A* rearrangement (*KMT2Ar*), *TP53* mutations and hypodiploidy.[30,42,43] Although patients with *KMT2Ar* ALL show similar relapse risks to other groups, an increased incidence of myeloid lineage switch has been observed, leading to poor survival outcomes after lineage switch and thus, worse OS.[44] *TP53*-mutated ALL has been associated with substantially lower leukemia-free survival (LFS) and OS.[45] Similarly, hypodiploid ALL has consistently demonstrated poor outcomes.[44,46] Regarding blinatumomab exposure before CAR T cell therapy, Pillai, et al., from the Children's Hospital of Philadelphia reported higher composite outcomes of non-response and CD19-negative MRD/relapse among blinatumomab-exposed patients.[47] Myers, et al., further demonstrated significantly lower complete response (CR) rates and six-month EFS in blinatumomab non-responders (CR 64.5%, EFS 27.3%) compared to blinatumomab responders (CR 92.9%, EFS 66.9%) or blinatumomab-naïve patients (CR 93.5%, EFS 72.6%).[48] High bone marrow disease burden prior to CAR T cell infusion (generally defined as ≥ 5% BM blasts) is consistently associated with an increased risk of relapse compared to low disease burden.[48] Myers, et al., reported that active non-CNS EMD at the time of infusion independently predicted




BCA, B cell aplasia; CAR, chimeric antigen receptor; CNS, central nervous system; EFS, event free survival; EMD, extramedullary disease; HSCT, hematopoietic stem cell transplant; *KMT2Ar*, *KMT2A* rearrangement; MRD, minimal residual disease; MRD+, MRD positive

**Figure 2** CAR T cell risk stratification and approach (adapted from Buechner, et al. and Myers, et al.)[30,42]

worse EFS (hazard ratio (HR) 1.94, $p = 0.01$).[48] Gardner, et al., in the PLAT-02 trial, revealed that a low CD19 antigen load (< 15% normal B cells and blasts) prior to lymphodepletion was independently associated with an increased risk of early loss of BCA (HR 2.99, $p = 0.005$).[49] Additionally, optimal LD chemotherapy is crucial. Fabrizio, et al., demonstrated that achieving optimal fludarabine exposure (AUC ≥ 13.8 mg x h/L) significantly reduces the risk of relapse, while suboptimal exposure increases relapse risk by 2.5-fold and the risk of relapse or loss of BCA by twofold.[50]

Post-infusion risk factors include early loss of BCA and MRD positivity. Myers, et al. identified B cell recovery as significantly associated with worse relapse-free survival.[51] MRD positivity, assessed primarily using next-generation sequencing (NGS), is a strong predictor of relapse. Pulsipher, et al. reported that positive NGS MRD at day 28 and three-months post-infusion significantly increased relapse risk, with HR of 4.87 and 12, respectively.[40]

**Managing relapse after CD19 CAR T cell therapy**

Three primary relapse phenotypes are observed following CD19 CAR T cell therapy: CD19-positive relapse, CD19-negative relapse and lineage switch.[52] The incidence of CD19-positive relapse is approximately 22%, with higher cumulative treatment burdens posing greater risk.[46] Relapse mechanisms include insufficient CAR T cell persistence, CAR T cell exhaustion and immune rejection. Therapeutic options for CD19-positive relapse include CD19 CAR T cell reinfusion, blinatumomab, CD22 CAR T cell therapy, inotuzumab ozogamicin and alternative molecular-targeted therapies or chemotherapy.[52] CD19-negative relapse occurs in roughly 15% of cases. Risk factors include younger patient age, the specific CAR T cell product used, high disease burden and previous failure of blinatumomab therapy.[46] Mechanisms underlying this relapse phenotype involve disease heterogeneity, splice variants and antigen modulation. Treatment options include CD22 CAR T cell therapy, inotuzumab ozogamicin and other targeted therapies

or chemotherapy.[52] Importantly, CD19-directed immunotherapies are ineffective due to the absence of CD19 expression. Lineage switch is the least common relapse phenotype and predominantly occurs in *KMT2Ar* leukemia.[46] Salvage treatments typically involve acute myeloid leukemia-based regimens, including gemtuzumab ozogamicin, conventional chemotherapy, and menin inhibitors such as revumenib, specifically in *KMT2Ar* leukemia cases.[52,53]

## Future potential strategies in CAR T cell therapy for pediatric B-ALL

### CD22 CAR T cell therapy

CD22 is a promising alternative antigen highly expressed on B-ALL cells, with lower expression on normal B cells. Schultz, et al., in a phase Ib study, reported adverse events including IEC-HS in 16.7%, severe CRS in 5.6% and severe ICANS in 5.6% of cases. The CR rate was 75%, with 56% achieving MRD-negative remission. However, responses were generally transient, indicating that CD22 CAR T cell therapy may be most effective as a bridge to HSCT in heavily pretreated patients.[54]

### Combined antigen-targeting CAR T cell therapy

Four main strategies have been developed for combined antigen-targeting CAR T cell therapy: bivalent CAR T cells, bicistronic CAR T cells, co-transduction and sequential or co-infusion.[52] The phase I AMELIA trial evaluated bicistronic CD19/CD22 CAR T cells in children and AYA with R/R B-ALL, demonstrating a favorable safety profile with no dose-limiting toxicities or severe CRS/ICANS reported. At one-year, OS was 60%, and EFS was 32%, with relapses attributed to limited long-term CAR T cell persistence.[55] The CARPALL phase I trial assessed dual-targeted CAR T cells co-transduced with CD19 and CD22 CARs in 12 pediatric patients with R/R B-ALL, achieving a one-year EFS of 60%. Severe CRS was not observed, but grade 4 ICANS occurred in 8.3% of cases. At a median follow-up of 8.7 months, no antigen-negative relapses were reported.[56] Pan, et al., explored sequential CD19 and CD22 CAR T cell therapy in a phase II study involving pediatric patients with R/R B-ALL in China. With a median follow-up of 17.7 months, the 18-month EFS and disease-free survival (DFS) rates (with transplantation censoring) were 79 and 80%, respectively.[57]

### Allogeneic CAR T cell therapy

Allogeneic CAR T cell therapy offers potential advantages due to the enhanced fitness of T cells derived from healthy donors who have not been exposed to chemotherapy or immunosuppressive drugs. These cells can be readily obtained from any suitable donor, avoiding delays caused by lymphopenia and eliminating the risk of contamination from leukemic blasts or other cells during autologous CAR T cell manufacturing. However, graft-versus-host disease (GvHD) remains a critical risk in the allogeneic setting. Various approaches to mitigate this risk are currently being explored in ongoing clinical trials.[58]

## Current status of CAR T cell therapy for pediatric B-ALL in Thailand

In the Asia-Pacific region, developed countries such as Japan, South Korea and Australia exhibit a strong state of readiness for CAR T cell therapy. These nations have established robust regulatory pathways for CAR T cell registration, supported by mature infrastructure for CAR T cell administration and dedicated centers of excellence. Within Southeast Asia, Singapore is currently the sole advanced archetype country where tisagenlecleucel (KYMRIAH®) has received approval. Conversely, countries including Thailand are categorized as initializing archetypes, facing notable gaps in regulatory frameworks, delivery capabilities and healthcare funding essential for CAR T cell therapy implementation.[59]

Despite these limitations, Thailand has shown progress in CAR T cell research and clinical applications under compassionate use settings. Several academic institutions have contributed significantly, reporting promising results from preclinical studies and early clinical trials targeting CD19-positive B cell hematologic

malignancies.[60-64] For instance, Yuti, et al. demonstrated in vitro efficacy of fourth-generation CD19 CAR T-cells engineered to secrete anti-PD-L1, a single-chain variable fragment (scFv).[60] An in vivo study by Khopanlert, et al. using third-generation CD19 CAR T cells with CD28/CD40 signaling domains, achieved tumor clearance in murine B-ALL models.[61] Additionally, Prasongtanakij, et al., reported a durable remission in an 11-year-old boy with R/R B-ALL using haploidentical second-generation CD19 CAR T cells post-haploidentical HSCT.[62] Furthermore, in a pilot study by Luanpitpong, et al., involving adults with B cell hematologic malignancies treated with point-of-care manufactured second-generation CD19 CAR T cells, five out of nine patients maintained complete remission at the six-month follow-up.[63] These encouraging local research initiatives indicate significant potential for expanded and more accessible CAR T-cell therapy for the Thai patient population in the foreseeable future.

## Non-CAR T cell immunotherapy in pediatric B-ALL

### Bispecific T cell engagers (BiTE)

Bispecific antibodies are engineered to simultaneously bind two distinct antigens. Blinatumomab, a notable bispecific antibody, targets CD19 on B-ALL cells and CD3 on T cells, facilitating a cytotoxic response that eradicates CD19-positive lymphoblasts. In an early phase I/II study of blinatumomab in pediatric patients with R/R B-ALL, the recommended dosage was established at 5 μg/m²/day intravenously for the first seven days, followed by 15 μg/m²/daythereafter.[65] Subsequently, the Children's Oncology Group has investigated the efficacy of blinatumomab in pediatric patients with B-ALL, both in newly diagnosed cases and in relapsed settings.[66,67] Given its short half-life, blinatumomab is generally administered via continuous intravenous infusion at a dose of 15 μg/m²/day for 28 days per cycle. Although subcutaneous administration of blinatumomab has shown efficacy in adults, its effectiveness in pediatric populations requires further investigation.[68] Adverse events observed with blinatumomab therapy include CRS and ICANS, similar to those seen with CAR T cell therapies.[68]

The COG AALL1331 phase III trial evaluated blinatumomab versus conventional chemotherapy in patients aged 1 to 30 years experiencing low-risk, first relapse of B-ALL. The results for patients with BM ± EMD relapse demonstrated significantly improved four-year DFS and OS rates with blinatumomab (DFS 72.7±5.8%, OS 97.1±2.1%) compared to chemotherapy alone (DFS 53.7±6.7%, OS 84.8±4.8%) (DFS $p = 0.015$, OS $p = 0.020$). These findings demonstrate blinatumomab's significant benefit in improving DFS and OS for approximately two-thirds of patients experiencing BM ± EMD relapse.[66] While the US FDA has approved blinatumomab (BLINCYTO®) for both pediatric and adult patients with CD19-positive B-ALL in newly diagnosed and R/R settings, the Thai FDA has approved it exclusively for R/R cases.

The subsequent COG AALL1731 phase III trial included children with newly diagnosed standard-risk B-ALL who exhibited average or higher relapse risk. Participants were randomized to receive either chemotherapy alone or chemotherapy combined with two non-sequential cycles of blinatumomab. The estimated three-year DFS rate was substantially higher in the combined treatment group (96.0±1.2%) compared to chemotherapy alone (87.9±2.1%) ($p < 0.001$).[67]

Furthermore, blinatumomab has been used as consolidation therapy before HSCT in pediatric and AYA patients with R/R B-ALL, achieving two-year DFS and OS rates of 72.2% and 89.2%, respectively.[69] Additionally, studies assessing blinatumomab as maintenance therapy post-HSCT in adults have indicated potential benefits, warranting further investigation to confirm its effectiveness in pediatric populations.[70]

### Inotuzumab Ozogamicin (InO)

InO is an antibody-drug conjugate composed of a CD22 monoclonal antibody linked to calicheamicin (ozogamicin), a potent cytotoxic agent that damages double-stranded DNA and induces apoptosis. The COG AALL1621 phase II trial assessed InO in pediatric and adolescent patients with R/R B-ALL. Participants received InO intravenously at 0.8 mg/m² on day 1 and 0.5 mg/m² on days 8 and 15 of a 28-day cycle, with response

evaluation on day 28. Of the 48 participants, the rate of CR or CR with incomplete count recovery (CRi) was 58.3%. Among the 21 patients who proceeded to HSCT following InO treatment, 28.6% of cases developed grade 3 sinusoidal obstruction syndrome (SOS).[71]

The ongoing COG AALL1732 phase III trial is evaluating the safety and efficacy of integrating InO into post-induction therapy for patients aged 1 to 24 years with high-risk B-ALL features. Following initial safety evaluations, the InO dosage was reduced to 1.2 mg/m$^2$ per cycle, and additional anti-infective supportive care measures were implemented. A subsequent safety analysis identified persistent concerns regarding infection risk and SOS. Consequently, the trial protocol has been amended to further reduce the InO dosage to 0.9 mg/m$^2$ per cycle for the second InO course, replacing a particularly toxic chemotherapy block with InO Block 2. These modifications aim to minimize toxicity while maintaining therapeutic efficacy.[72] Although the US FDA has approved InO (BESPONSA®) for pediatric and adult patients with R/R CD22-positive B-ALL, it has not yet received approval in Thailand.

## Conclusion

Advancements in immunotherapy for pediatric B-ALL have yielded promising results toward achieving curative outcomes for children with relapsed or refractory disease. Furthermore, multiple, ongoing clinical trials have incorporated these innovative treatments into upfront therapy protocols to explore their efficacy in the newly diagnosed B-ALL setting.

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