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REVIEW

A Review of CAR-T Therapy in Pediatric and Young Adult B-Lineage Acute Leukemia: Clinical Perspectives in Singapore

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Abstract: Approximately 10–15% of pediatric B-cell acute lymphoblastic leukemia (B-ALL) are high risk at diagnosis or relapsed/refractory. Prior to the availability of chimeric antigen receptor T-cell (CAR-T) in Singapore and the region, the treatment options for these paediatric and young adults are conventional salvage chemotherapy or chemo-immunotherapy regimens as a bridge to allogeneic total body irradiation-based hematopoietic stem cell transplantation (allo-HSCT). This results in significant acute and long-term toxicities, with suboptimal survival outcomes. Finding a curative salvage therapy with fewer long-term toxicities would translate to improved quality-adjusted life years in these children and young adults. In this review, we focus on the burden of relapsed/refractory pediatric B-ALL, the limitations of current strategies, the emerging paradigms for the role of CAR-T in r/r B-ALL, our local perspectives on the health economics and future direction of CAR-T therapies in pediatric patients.

Keywords: cell therapy, relapsed, refractory, lymphoblastic leukemia, pediatric and young adult

Introduction

A range of mechanisms are used by the immune system to suppress cancer cells and many of these mechanisms are inactivated during the development of the cancer, allowing cancer cells to spread. Cancer immunotherapy is based on the notion that the immune response can be harnessed or reprogrammed to effectively eradicate cancer cells. As T cells play a crucial role in the adaptive immunity involved in tumor surveillance and pathogen clearance, they have been studied for their role in anti-cancer therapy.[1,2] In the 1970s, stem cell transplantation provided the first biological evidence that adoptive T cells from an MHC-compatible healthy donor could exert a powerful graft-versus-leukemia effect, leading to long-term eradication of chemo-refractory leukemias. The use of tumor-infiltrating lymphocytes by Rosenberg in 1986 to cure a subset of patients with advanced cancers[3] further supported the potential of adoptive T cell therapies. These early salvage therapies provided the foundation for the subsequent major advancements in T cell-based therapies.

Sequential seminal innovations over the last 30 years contributed to the modular development of a clinically effective CAR-T construct. The first synthesis of a chimeric immunoglobulin/T-cell receptor (TCR) molecule, now known as the chimeric antigen receptor (CAR), led to the scientific plausibility that T-cells could be engineered with antibody type-specificity for therapy against specific targets.[4] Subsequently the first generation of effector T-cells expressing a CAR was conceived around 1989–1993 by Israeli immunologists Zelig Eshhar and Gideon Gross.[5,6] Around this time, Irving and Weiss showed that following extracellular antigen-binding, signal transduction through a transmembrane CD8 and intracellular TCR CD3ζ domain present in a CAR could independently mediate T-cell activation.[7] A significant boost to this field occurred when Michel Sadelain developed retroviral vectors as a method to introduce genes into T-cells, enabling large-scale modification of their cytotoxicity and specificity for cancer cells.[8] The first-generation synthetic

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CAR that is expressed from the T cells reprograms lymphocyte function and specificity by the coupling of the intracellular T-cell signaling domains and the antigen-binding single chain Fv domain (scFv), bypassing the need for native major histocompatibility complex (MHC)-restricted T-cell activation. This worked modestly but lacked the proliferation, persistence and potency needed for effective cancer killing. This was primarily due to the lack of a second signal for T-cell activation, the co-stimulatory signal. These limitations were overcome in the second-generation construct which linked the antigen-binding activation of intracellular T-cell signaling (Signal 1) to a single co-stimulatory signal (Signal 2), either a 41BBz or CD28 module; this ingenious modification formed the basis of the first clinically effective CAR-T therapies.[9,10] More than a decade later, chimeric antigen receptor T-cell (CAR-T) therapy is now a breakthrough treatment of patients with hematologic cancers, especially with chimeric antigen receptors (CARs) targeting CD19 in B-cell malignancies. Third-generation CARs which include multiple and/or new co-stimulatory signaling modules to enhance their function are currently being studied.[11–15]

In 2011, anti-CD19 directed CAR-T cells produced complete remissions in multiply relapsed pediatric acute lymphoblastic lymphoma and adult chronic lymphocytic leukemias at around the same time, resulting in the landmark success in the clinical application of CAR-T therapies.[16,17] It is notable that the initial applications of CAR-T therapy began simultaneously in pediatric and adult patients, with the pivotal trial results leading to the breakthrough designation of tisagenlecleucel reported in pediatrics. This stood in contrast to many other small molecule therapies and drugs that were traditionally established in adult trials first before being extended to pediatric cohorts. To date, there has been just one FDA and EMA approved CAR-T for pediatric and young adult patients, tisagenlecleucel (Kymriah™, Novartis) up to 25 years of age with B-cell ALL that is refractory or in second relapse.[18,19] In this review, we focus on the burden of relapsed/refractory paediatric B-ALL, the limitations of current strategies, the emerging paradigms for the role of CAR-T in r/r B-ALL, our local perspectives on the health economics and future direction of CAR-T therapies in pediatric patients.

The Burden and Unmet Needs of Pediatric Acute Lymphoblastic Leukemia (ALL)

Pediatric acute lymphoblastic leukemia is the commonest childhood cancer, accounting for approximately 25% of all childhood cancers. Thirty-seven per 1,000,000 children are diagnosed with acute lymphoblastic leukemia each year in the United States.[20] In Singapore, about 30 children are diagnosed each year with paediatric leukemia, two-thirds of whom are acute lymphoblastic leukemia. Paediatric ALL is classified into B-ALL and T-ALL with B-ALL accounting for 85% of the cases and T-ALL accounting for 15% (Singapore childhood cancer registry, unpublished data, 2022).

Poor Survival of Relapsed/Refractory B-ALL

Although the 5-year overall survival (OS) rate for pediatric B-ALL has improved to approximately 85–90%,[21,22] prognosis remains poor in patients defined as high risk at diagnosis and in relapsed/refractory patients.[23]

Relapsed/refractory disease accounts for 10–15% of B-ALL in children and 18% in patients with T-ALL[23,24]. As a group, relapsed/refractory pediatric B-ALL is the fourth commonest childhood cancer.[25] Event-free survival (EFS) for high-risk pediatric B-ALL remains at about 50–67% across most protocols (Singapore childhood cancer registry 2022, National Registry of Diseases Office, personal communication, 2022).[26–28] At first relapse, 3-year survival probabilities can vary from 20–70% depending on the time to relapse and effectiveness of reinduction.[29,30] Survival after a second disease relapse after allogeneic hematopoietic stem cell transplantation (HSCT) is dismal.

Since the early 2000s, a risk-adapted, MRD-guided pediatric chemotherapy protocol (MASPORE) has been the standard treatment regimen. In the MASPORE 2003 and 2010 study cohorts,[28,31] 15% of all B-ALL patients were defined as high risk (n=126 of 823 patients) based on high-risk genetics, clinical features or poor disease response. High-risk patients had an inferior event-free survival of 51.8% ± 10% compared with 92.3% ± 4.1% in the standard-risk patients and 83.6 ± 4.9% in the intermediate-risk patients.[28]

KK Women's and Children's hospital-based registry data showed 48 out of 235 B-ALL (20%) treated on contemporary protocols from 2003 to 2021 had relapsed/refractory disease. Despite excellent overall survival across all groups of B-ALL (Figure 1A), the 5-year OS in the high-risk B-ALL group was 62.9% (Figure 1B) while relapsed B-ALL had a 5-year OS of <50% (Figure 1C).

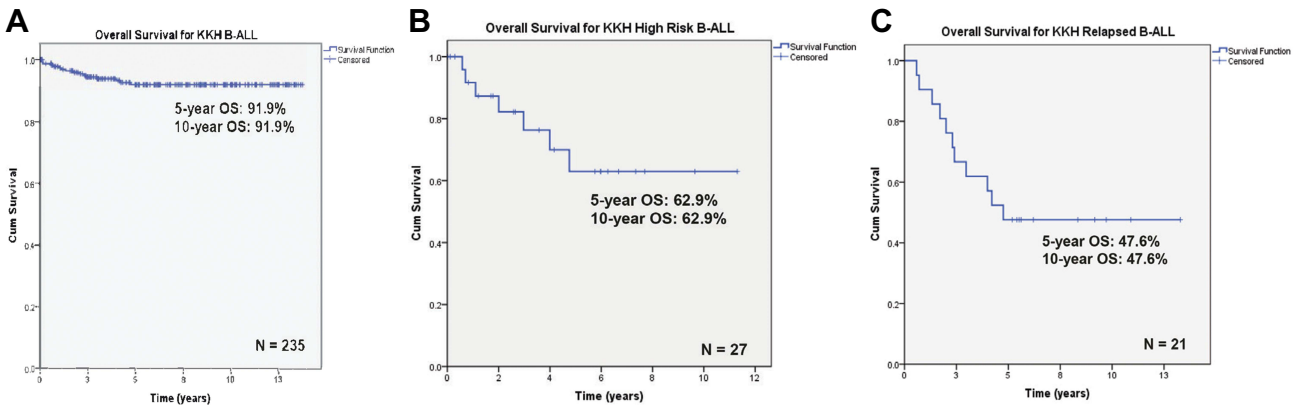

Figure 1 Five-year and 10-year Overall Survival of Pediatric and Adolescent B-ALL in (**A**) All groups. (**B**) High-risk B-ALL. (**C**) Relapsed B-ALL.
Notes: SCCR 2021 data, unpublished, with permission from KK Women's and Children's Hospital, KKH.

Late Effects of Irradiation, Transplant and Treatment Intensification for High-Risk Patients

Forty-two of 186 survivors of pediatric B-ALL, diagnosed between 1985–2012, seen in our pediatric long-term follow-up clinic had received radiotherapy as part of curative treatment including stem cell transplant; 50% had received radiation as part of relapse treatment, 44% received this within the primary treatment and 6% both during primary treatment and as part of relapse. A significant 32/42 (76%) suffered from at least one significant adverse late effect, predominantly metabolic complications, endocrinopathies and second neoplasms/cancers (LTFU registry), illustrating the cost of cure. Besides the late effects of irradiation, long-term complications of HSCT include chronic graft-versus-host disease, infertility, organ impairment, late infectious complications and cardiomyopathy.

Acute Treatment Toxicities of Pediatric-Inspired Protocols in Adolescents and Young Adults

Adolescent and young adult (AYA) B-ALL, diagnosed at age <40 years, have better outcomes when treated using pediatric-inspired chemotherapy regimens, but experience much higher toxicities compared with the children. In a retrospective review of 116 AYA B-ALL patients[32] from the registries of three tertiary hospitals (Singapore General Hospital, National University Hospital and Tan Tock Seng Hospital), 25% were treated with a pediatric-inspired MASPORE protocol[28] and 75% were treated with a HyperCVAD protocol. A higher rate of adverse events was observed for patients treated on the MASPORE arm; these events included severe pancreatitis (13.8 vs 0.0%, $p < 0.001$), avascular necrosis (13.8 vs 2.2%, $p = 0.016$), cerebral venous thrombosis (13.8 vs 1.1%, $p = 0.004$) and other thrombosis (27.6 vs 5.7%, $p = 0.0043$) deaths due to treatment-related toxicities. Although 5-year OS and progression-free survival could be improved (5-year OS 86% vs 60%) using a pediatric-inspired protocol, this comes at the cost of higher treatment-related toxicities. Furthermore, 40% of AYA patients eventually required consolidation with a hematopoietic stem cell transplant (13.8% on the MASPORE protocol and 49.4% on HyperCVAD). As current therapies in young adults and children are insufficient and lead to significant morbidities, there is an urgent need to improve quality-adjusted life years in survival.

Current Therapies, State of the Art and Limitations

Treatment options for pediatric and young adults who have r/r B-ALL include immunotherapies such as blinatumomab (BLN) and inotuzumab and salvage chemotherapy regimens (SCR) (Table 1). These treatments have sub-optimal outcomes and are used to bridge to allogeneic hematopoietic stem cell transplantation (allo-HSCT), which also has sub-optimal outcomes (Wang et al, 2022). There are at least 21 published trials on novel therapies besides CAR-T, for relapsed/ refractory pediatric leukemia (13) and lymphoma (8) since the early 2000s, excluding CAR-T.[33] We further elaborate on the success and limitations of salvage chemo-intensifications and immunotherapies as a means to allogeneic hematopoietic stem cell transplantation (HSCT) and CAR-T therapies in B-ALL.

Table 1 Recent Clinical Trials for R/R Pediatric B-ALL Other Than CAR-T Therapies

Consortium, Clinical Trial	Patients	Investigational Salvage Treatment	Overall Survival	Disease-Free Survival	References
TACL T2005-002	Primary refractory, any relapse 0–21 y N=313	Standard of care i.e. salvage chemotherapy and HSCT	Not reported	In CR2: 2-y 40% ± 4%; 5-y 27% ± 4% In CR3: 2-y 31% ± 7%, 5-y 15% ± 7%	[70]
COG AALL1131	Induction failure, very high risk MRD; 1–18 y N=135	Clofarabine	Closed due to unacceptable toxicities		[38]
UKALLR3	First relapse 1–18 y N=216	Idarubicin vs mitoxantrone	3-y OS 45·2% (34·5–55·3) versus 69·0% (58·5–77·3; p=0·004) respectively, favoring mitoxantrone	3-y 35.9% (95% CI 25·9–45·9) in the idarubicin group versus 64·6% (54·2–73·2) in the mitoxantrone group (p=0·0004) favoring mitoxantrone	[71]
COG AALL1331	First relapse 1–30 years (excludes post-transplant relapse) N=208	Phase III RCT blinatumomab vs chemotherapy post-induction	2-y 71.3%	2-y 54.4%	[41,42]
NCT01471782	Second or later relapse, primary refractory, any post-transplant relapse < 18 years N=70	Phase I/II blinatumomab ± HSCT	2-y 25% median OS 7.5 months (95% CI, 4.0 to 11.8	Not reported	[29]
COG AALL 1621	CD22-positive B-ALL in second or later relapse, primary refractory, any post-transplant relapse or first relapse with Down syndrome (DS) 1–21 y N=48	Phase II inotuzumab	Not reported CR/CRi rate 58%	Not reported	[40]

Total body irradiation (TBI)-based hematopoietic stem cell transplantation (HSCT) is the current standard of care for relapsed/refractory B-lineage acute lymphoblastic leukemia. The best outcomes are achieved if the patient is transplanted in deep remission, when there is no longer any measurable residual disease (MRD) in the bone marrow ("MRD negative").[30] Many genetically high-risk and relapsed/refractory patients are inherently refractory to chemotherapy.[34] Achieving MRD negativity prior to transplant requires intensification of chemotherapy traditionally, with high acute treatment-related mortality due to infectious complications. Total body irradiation-based allogeneic hematopoietic stem cell transplant (HSCT) can be curative but is associated with high incidence of acute toxicities and chronic health conditions.[35]

The last FDA approved drugs for relapsed/refractory pediatric B-ALL was clofarabine in 2004 and nelarabine for pediatric T-ALL and T-LBL in 2005,[36,37] indicating the gradual move away from salvage chemotherapies to targeted

approaches. In the very high risk (VHR) group of pediatric B-ALL, chemotherapy intensification approaches with newer drugs such as clofarabine are associated with significant toxicities.[38]

More recently, commercial antibody-based immunotherapies such as inotuzumab (an anti-CD22 antibody-drug conjugate) and blinatumomab (a bispecific CD3-CD19 T-cell engager or BiTE) have become the new standard of bridging therapy to HSCT in first relapse or in refractory disease, improving initial complete remission rates to 39% (blinatumomab) and 58% (inotuzumab) in chemo-refractory pediatric patients. Immunotherapies in general have reduced significantly the toxicities of intensive chemotherapy regimens with higher rates of leukemia response and greater likelihood of proceeding to HSCT.[29,39,40] Despite the improved CR rates, overall survival outcomes are variable, with suboptimal outcomes in second or greater relapses and high leukemia burden at the time of antibody salvage (Table 1).

In a randomized phase III study COG AALL1331, Brown et al studied if substituting blinatumomab for intensive chemotherapy in consolidation therapy would improve survival in children, adolescents, and young adults with high- and intermediate-risk first relapse of B-ALL. In first relapse, 2-year overall survival was 71.3% for the blinatumomab group vs 58.4% for the chemotherapy group (hazard ratio for mortality, 0.62 [95% CI, 0.39–0.98]; one-sided P = 0.02). However, blinatumomab did not appear to improve overall survival in second or later relapses, including post-transplant relapses.[41,42]

Inotuzumab ozogamicin (InO) is an anti-CD22 drug-antibody conjugate that has been well established in adult r/r B-ALL in the INO-VATE ALL trial[43] to produce a higher rate (80.7% vs 29.4%, P<0.001) and deeper (MRD negative 78.4% vs 28.1%, P<0.001) complete remissions than with standard therapy. The Children's Oncology Group trial AALL1621 concluded that InO was effective and well tolerated in heavily pre-treated children and adolescents with R/R CD22-positive B-ALL with a CR/CRi rate of 58.3%; 90% CI, 46.5–69.3). In both adults and children, sinusoidal obstructive syndrome (SOS) of the liver after hematopoietic stem-cell transplantation and prolonged cytopenias were notable.

In conclusion, while there are gains made in effective and less toxic regimens other than chemotherapy for relapsed/refractory B-ALL, the major limitations of antibody therapies are the short half-life and the inability to cross the blood–brain barrier to treat or prevent central nervous system (CNS) leukemia. Complete remission after these antibody therapies is not durable in the absence of a stem cell transplant. Therefore, total body irradiation-based stem cell transplant still cannot be avoided for long-term cure in younger patients.

CAR-T Therapy for Relapsed/Refractory Pediatric B-ALL

Finding a curative salvage therapy with fewer long-term toxicities would translate to improved quality-adjusted life years in these children and young adults. Chimeric antigen receptor (CAR)-T cell therapy is one such promising therapy. Briefly, the patient undergoes a leukapheresis for lymphocytes prior to chemotherapy intensification, the lymphocytes are sent to a cell and gene therapy facility (either local or overseas) where CAR-T is produced by ex vivo lentiviral vector transduction of T cells to express the chimeric antigen receptor (CAR) that will provide a T-cell activation signal and a 4–1BB domain to provide a costimulatory signal (Maude et al, 2018b). These patients receive lymphodepletion, typically fludarabine 120 mg/m^2 given over 4 days and cyclophosphamide 1000 mg/m^2 over 2 days, followed by a single infusion of CAR-T.

In 2016, autologous anti-CD19 CAR-T cell therapy resulted in unprecedented 12-month overall survival (OS) rates of 77.2% in chemo-refractory B-ALL patients,[44] leading to an FDA breakthrough therapy designation as tisagenlecleucel (Tisa-cel). Notably, only 9% in the pivotal study[44] and 16.1% in a subsequent real-world analysis[45] underwent a consolidative HSCT while in remission, strengthening the value of "living" cell therapy as an alternative to a HSCT.

Clinical Trials in CAR-T Therapies in Paediatric r/r B-ALL

The success of anti-CD19 CAR-T therapies including the pivotal ELIANA trial has been amply summarized in literature. Here, we describe the current clinical evidence that is relevant specifically to pediatric B-ALL and the clinical considerations for CAR-T in the treatment of r/r pediatric B-ALL.

Tisagenlecleucel (Other Names: CTL019, Tisa-Cel, CART-19, Trade Name: Kymriah)®

The first pediatric application of Tisa-cel, previously known as CTL019, was reported in a case report of two children with relapsed/refractory B-ALL. CTL019 resulted in the remarkable induction of remission of relapsed and refractory leukemia in the first two patients treated on this protocol. Remission has been sustained in one patient and was accompanied by relapse due to the emergence of CD19-blasts in the other patient.[16] CTL019 contains a lentiviral transduced anti-CD19 CAR, with the scFv derived from the recombinant monoclonal murine antibody clone FMC63, a CD8-alpha hinge, a 4–1BB costimulatory domain and CD3z intracellular signaling domain. Table 2 summarizes the clinical trials for tisagenlecleucel in pediatric and young adult R/R B-ALL patients leading to marketing approval.

The first phase I/II trial investigating CTL019 in pediatric CD19+ R/R B-ALL was a single-arm, phase II, open-label study (B2101J, NCT01626495) conducted at the Children's Hospital of Philadelphia (CHOP). A total of 30 r/r ALL patients were enrolled and treated with CTL019, including 25 patients between the ages of 5 and 22 years and 5 other patients between the ages of 26 and 60 years. After 1 month of infusion 27 patients were in complete remission. The event-free survival and overall survival rates at 6 months were 67% and 78%, respectively. The probability that CTL019 would persist at 6 months was 68% and sustained remissions were observed up to 2 years.[46] A longer follow-up of the same study included 59 patients with r/r B-ALL pediatric and young adults of whom 93% (55/59) achieved CR/CRi 1 month post infusion, with 52/55 in MRD negative remission. Five patients (8% of all responders) proceeded to HSCT consolidation, and 17 patients (31%) received reinfusions due to loss of B cell aplasia or MRD recurrence. CTL019 was subsequently studied across 13 US study sites (ENSIGN, NCT02228096) in a multicenter, single-arm, phase II trial for r/r B-ALL pediatric and young adult patients aged 3–21 years. The number of enrolled patients was 73 and 58 of those patients were infused. The overall remission rate was 69% with 64% being in CR and 5% in CRi. Relapse-free survival rate was 71% and 61% for 6 and 12 months. In responding patients CTL019 could be detected for up to 764 days.[47] ELIANA was the global pivotal registration trial for tisagenlecleucel (NCT024358491) which included a total of 92 patients, of whom 75 received CTL019. The overall remission rate after 3 months of follow-up was 81%. From the 75 patients who received CTL019 infusion, they had an overall rate of survival of 90% after 6 months and 76% at 12 months after infusion.[47] In a managed access Phase IIIb trial (B2001X, NCT03123939), tisagenlecleucel was studied in a multicenter global study to provide access to patients with r/r ALL including prior anti-CD19 therapy after enrolment ended in the pivotal ELIANA (NCT02435849) study with a focus in post-blinatumomab and post-inotuzumab outcomes. The efficacy and safety of tisagenlecleucel in the B2001X study remain consistent with outcomes in ELIANA. In patients

Table 2 Clinical Trials for Tisagenlecleucel in Pediatric and Young Adult R/R B-ALL Patients

Clinical Trial	B2101J (Infused Patients N=30)		ENSIGN (Infused Patients N=58)		ELIANA (Infused Patients N=75)		B2001X (Infused Patients N=67)	
ORR	90%		69%		81%		85%	
	CR	CRi	CR	CRi	CR	CRi	CR/CRi	
							Prior vs No Inotuzumab	Prior vs No Blinatumomab
	N/A	N/A	64%	5%	60%	21%	67% vs 88%	67% vs 90%
OS	6m	12m	6m	12m	6m	12m	12m	12m
	78%	N/A	79%	63%	90%	76%	71 vs 85%	53 vs 91%
RFS	6m	12m	6m	12m	6m	12m	–	–
	N/A	N/A	71%	61%	80%	59%	–	–
EFS	6m	12m	6m	12m	6m	12m	–	–
	67%	N/A	N/A	N/A	73%	50%	–	–

Abbreviations: ORR, overall remission rate; OS, overall survival rate; RFS, relapse-free survival rate; EFS, event-free survival rate; CR, complete remission; CRi, complete remission with incomplete hematologic recovery.

with prior BLINA or INO as bridging therapy, a trend toward suboptimal outcomes was observed. Since the post-marketing approval of Tisa-cel as a salvage treatment, real-world experience has been reported with the largest cohort from the prospective multi-center observational CIBMTR study conducted across North America. Overall response rate was comparable with ELIANA at 86% with 16% proceeding to pre-emptive consolidative HSCT. The minority of patients who had received blinatumomab (15%) and inotuzumab (11%) prior to CAR-T infusion had a complete remission rate of 78% and 65%, respectively, although a not insignificant proportion of patients eventually experienced treatment failure, relapse or died from ALL during a median of 10.9 months.[45]

The published Tisa-cel evidence to date indicates that in pediatric r/r B-ALL, there is a subset of patients cured by a single infusion of CAR-T despite multiple lines of previous salvage and without any post-infusion interventions. Secondly, the median marrow blasts at infusion was about 2% in the real-world study and much higher in the original ELIANA cohort. With this in mind, the goal of bridging to CAR-T should not be to render the patient with no disease prior to CAR-T infusion, but to maintain disease control until infusion. The use of blinatumomab and inotuzumab bridging, while discouraged if disease can be controlled with a light-handed chemotherapy approach, may still be the only means to safely infuse a patient with high disease burden, and should not preclude a patient from using CAR-T to achieve long-term remission. The question of which patient and when to consolidate with a HSCT continues to be studied. In the real-world analysis, about 10–15% of patients who responded to CAR-T later received pre-emptive consolidative HSCT while in remission due to a lack of CAR-T persistence of early loss of B cell aplasia. A smaller subset of patients received repeated infusions of Tisa-cel. In a separate analysis of anti-CD19 CAR-T infusion across three different clinical trials of anti-CD19 CAR-T, an overall response rate in 7/18 (38.9%) to the second infusion was reported, hampered by poor CAR-T expansion and antigen modulation, which could potentially be overcome by intensification of lymphodepletion.[48]

Other Anti-CD19 CAR-T Therapies for Pediatric B-Lineage Leukemias

Other variations of anti-CD19 CAR-T products with a 4–1BB costimulatory domain and with a CD28 co-stimulatory domain have been developed by other groups since, all reporting similar success in the r/r pediatric B-ALL. The main difference between the second-generation CAR designs is the costimulatory domain. The 4–1BB domain has been shown to improve CAR-T persistence through amelioration of T-cell exhaustion.[49]

In the PLAT-02 Phase I trials (NCT02028455), the Seattle group infused lentiviral transduced CD19 (GCM63) CAR-T in a defined 1:1 CD4+: CD8+ ratio. The rate of MRD-negative CR at 1 month was 93%, with a median duration of B cell aplasia of 3 months. The 12-month EFS was 50% and OS 66%. Factors favoring persistence of B-cell aplasia (BCA), defined in this trial as peripheral B cells <1% of lymphocytes, were pre-infusion CD19+ antigen load of >15% and the use of lymphodepletion. Point-of-care CAR-T treatments using an anti-CD19 41BB lentiviral vector are currently in clinical trials across various countries, including Barcelona, Russia, Germany, including the authors' institutions in Singapore.[50,51]

The Memorial Sloan Kettering Cancer Centre (USA), National Cancer Institute (USA) and Sheba Medical Centre (Israel) have developed CD28z second generation anti-CD19 CAR-T cells generated with gamma-retrovirus. In a phase I study of KTE-C19, which contains a CD28 domain and based on the NCI CAR-T, involving 21 children and young adults, CAR-T cells were not detected beyond 68 days;[47,52,53] therefore, KTE-C19 and similarly, other CD28 CAR-T serve as a bridge to allogeneic transplantation for most patients who receive it. The CD28z CAR-T patients in all three centres were consolidated with HSCT in remission due to the recognized shorter persistence of the CD28z CAR-T. Results from all centres were comparable with this approach with CR rates at 28 days ranging from 70–90% and long-term EFS between 53–73%.[54–56]

Lambel et al extensively characterized pre-infusion risk factors associated with the development of each relapse pattern via a multicenter, retrospective review of children and young adults with r/r B-ALL treated with a murine-based CD19-CAR construct. Of 420 CAR-treated patients, 166 (39.5%) relapsed, including 83 (50%) CD19 positive, 68 (41%) CD19 negative and 12 (7.2%) lineage switch (LS) relapses. A greater cumulative number of prior complete remissions was associated with CD19 positive relapses, whereas high pre-infusion disease burden (defined as >5% marrow blasts), prior blinatumomab non-response, older age, and 4–1BB CAR construct were associated with CD19

negative relapses. The presence of a KMT2A rearrangement was the only pre-infusion risk factor associated with lineage switch.[57]

CAR-T Toxicities

Toxicities such as cytokine release syndrome (CRS) and neurotoxicity are common complications that occur after CAR-T-cell infusion.[58] Scoring and management algorithms are well summarized in guidelines and beyond the scope of this review.[59,60] With increasing experience with the early use of tocilizumab and steroids, the management of these potentially fatal toxicities is now anticipatory.

Cost-Effectiveness

Thielen et al (2020) found that Tisa-cel is cost-effective with a willingness-to-pay (WTP) threshold of 80,000 EUR per QALY gained for the treatment of children and young adults with r/r ALL in the Netherlands. This favorable result is because of the survival gains from Tisa-cel treatment compared with other treatments with a total of 14.01 life years.[61] Cost-effectiveness analysis conducted by Wang et al (2022) reveals that at a unit price of S$500k for commercial CAR-T treatment for children and young adults with r/r ALL, it is a cost-effective treatment when compared with salvage chemotherapy and blinatumomab from Singapore's healthcare system perspective. The studies suggest that CAR-T is cost-effective because of the avoidance of higher drug administration, hospitalization cost, and the following allo-HSCT cost. Cost effectiveness of CAR-T cells is also seen with treatment of other hematological malignancies such as lymphoma (Wang XJ et al, J Med Econ 2021. DOI: 10.1080/13696998.2021.1922066). With the establishment of point-of-care CAR-T, we anticipate an even larger cost-effective margin, with the reduction of centralized manufacturing costs, cryopreservation and long-distance courier and economy of scale due to relative affordability. The initial cost incurred would include several years of capital-intensive infrastructure building, technology transfer and talent development, as well as maintenance of the good manufacturing practice (GMP) licensure of the cell therapy facilities. Patient-related outcomes are significant, in terms of gains in quality-adjusted life years (QALYs) and reduction of acute and long-term toxicities from high-dose chemotherapy and total body irradiation. A cost-effective analysis is not yet available in the Singapore healthcare setting.

Future Directions of CAR-T

R/R Pediatric B-ALL

Tisa-cel, as of September 2022, is the only CAR-T approved for r/r pediatric B-ALL in the primary refractory state, in post-transplant relapse or in second or later relapses. In the latter cases, the opportunity to minimize long-term toxicities and improve quality-adjusted life years from prolonged hospitalization and treatment complications has already been missed. Many centers, including ours, are actively investigating the role of a long-acting CAR-T in high-risk or very high-risk patients, extending the definitions of "refractory" to the context of high MRD after first induction or consolidation with the aim to replace treatment intensification approaches including hematopoietic stem cell transplant in these children (NCT03876769, NCT05429905, NCT05038696). Antigen escape-mediated relapse is one of the major limitations of single-targeting CAR-T therapies, particularly with the 41BBz-CAR-T which exerts a sustained immune pressure on a single antigen. To reduce this relapse, targeting multiple antigens such as CD20 and CD22 by using dual CAR constructs is an important approach to investigate[62,63] and beyond the scope of this review. Improving manufacturing capacities by shortening the manufacturing time is an important future direction which will shorten the waiting time for a patient to receive CAR-T, reducing the risk of disease progression which would compromise eligibility and safety.

Other Relapsed/Refractory Pediatric Diseases

CAR-T therapy has shown a tremendous success in the treatment of hematological malignancies. Novel CAR-T therapies to r/r T-cell ALL and AML are currently in phase I/II clinical trials. Unlike B-cell aplasia which can be supported with immunoglobulin infusions, profound T-cell aplasia and marrow aplasia results in opportunistic, fatal infections, as such, T-ALL and AML-directed CAR-T treatment will need to be followed by a stem cell transplant in chemo-refractory patients unless CARs to leukemia specific antigens are developed.

Future translational efforts will be focused on developing a successful CAR-T for relapsed/refractory pediatric solid tumors with the primary barriers in homing, persistence in a hostile microenvironment, antigen heterogeneity and on-tumor, off-target toxicities.[64,65] Preclinical and early phase I trials of CAR-T targeting GD2, Glypican 3, B7-H3, HER2 and CD47 are some of the therapeutic candidate targets and will include biomarkers for success.[66]

Conclusion

Relapsed/refractory acute lymphoblastic leukemia has a dismal prognosis and standard-of-care salvage therapies involve intensive alkylator-based chemotherapy and irradiation-based allogeneic stem cell transplant. The challenge of acute toxicities, cumulative long-term morbidities and late mortality are particularly important in pediatric and young adult survivors, taking into account the person-years of follow-up and the non-plateauing trajectory of mortality due to adverse late effects.[67] In Singapore, where healthcare is advanced and salvage treatments pursued intently, CAR-T therapy has demonstrated improved survival with a low risk of long-term side effects with significant improvements in quality-adjusted life years. CAR-T as salvage for multiply-relapsed, incurable pediatric B-ALL was a pivotal moment in 2016.[44] The full potential of CAR-T, in our opinion, would be to realize the curative, toxicity-sparing potential of engineered T-cells earlier on in treatment, allowing one to depart from treatment intensification approaches and the need for irradiation-based hematopoietic stem cell transplants in a pre-defined group of patients. Newer clinical paradigms and innovations need to be investigated: Moving CAR-T therapies front-line for high-risk patients; loosening the definitions of "refractory" to include poor MRD-response and those with high-risk genetics; incorporating strategies for persistence and overcoming antigen escape-mediated relapse with dual-targeting approaches.

Several studies have shown CAR-T cell therapy to be a cost-effective treatment option with limited budget implications in the treatment of r/r ALL patients who have failed at least two lines of prior therapies. Studies in adult patients with diffuse large B-cell lymphoma also show similar cost-effectiveness.[68] Equitable and sustainable access to CAR-T therapy in this part of the world, regardless of socioeconomic status, remains an area of clinicians' and patients' advocacy.

Clinical trials, point-of-care CAR-T manufacturing capabilities, and industry-academic collaborations are important avenues for generation of new paradigms, improving access and advancing innovations in CAR-T therapies. Anti-CD19 CAR-T has provided a valuable and evolving framework for this. While CAR-T cell therapy has expanded to include multiple myeloma in adults and T-cell leukemias in both adults and children, clinical applications appear to be limited to hematological malignancies at present due to the ability to target cell surface determinants on blood cells (which can be transiently or permanently eradicated without major consequence) without significant deleterious effects on major organs. Future translational efforts are focused on developing a successful CAR-T for relapsed/refractory pediatric solid tumors, where a large unmet need resides and where there are even greater barriers to overcome such as persistence in a hostile microenvironment, antigen heterogeneity, and on-tumor, off-target toxicities.[64,65] Advances in T-cell receptor therapy could expand the role of cellular immunotherapy in patients with solid tumor.[69]

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