The Current State of Chimeric Antigen Receptor T Cell Therapy for B Lymphoblastic Leukemia

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KEYWORDS

• Chimeric antigen receptor • CAR T cell • B lymphoblastic leukemia • B-ALL

KEY POINTS

- CAR T cell therapy for relapsed/refractory B-ALL has transformed the treatment landscape.
- CD19-directed CAR T cell therapy can induce remission in 60-90% of patients with B-ALL and can successfully promote durable remission in many patients.
- Treatment of relapse following CAR T cell therapy remains a challenge.
- Novel investigational CAR T cell therapies directed at alternative B cell targets or with improved engineering or manufacturing processes are currently in clinical trials to address this challenge.

INTRODUCTION AND BACKGROUND

Significant improvements in the treatment of pediatric and young adult B cell acute lymphoblastic leukemia (B-ALL) have yielded an overall survival rate of >90%, yet 10-20% of patients will experience relapse or refractory disease with significantly reduced survival.[1] Thus, relapsed/refractory B-ALL remains the most common cause of pediatric cancer morbidity and mortality.[1] Further, B-ALL in adults carries an overall survival of 11-65%, with age heavily impacting outcomes[2] and relapsed or refractory B-ALL remains difficult to treat with poor survival.[3] However, cellular therapies and specifically chimeric antigen receptor (CAR) T cell therapy have offered significant promise in treating both adult and pediatric B-ALL. More than 11 years ago, the first pediatric patient with B-ALL was infused with autologous CD19-directed CAR

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T cells at the Children's Hospital of Philadelphia (CHOP),[4,5] and since then thousands of children and adults have been infused with CAR T cells for refractory or relapsed B-ALL, either as part of a clinical trial or as recipients of one of the 2 current FDA-approved commercial CAR T cell products for B-ALL, tisagenlecleucel and brexucabtagene autoleucel.

CAR T cells are T cells that are genetically engineered to express a chimeric antigen receptor that targets antigens on the surface of cancer cells. This antigen specificity is generated by fusing an antibody-binding domain to signaling domains responsible for down-stream T cell activation. The use of an antibody-binding domain (scFv), rather than a T cell receptor, allows CAR T cells to recognize the antigen directly on the surface of a tumor cell in the absence of an MHC molecule, which are frequently down-regulated on cancer cells.[6,7] Most CAR T cells developed to date combine activating and co-stimulatory domains directly into the CAR construct. Most commonly, this has been a combination of CD3-ς with either 4-1BB or CD28.[6–11] The first CAR T cells developed, including the two FDA-approved products for B-ALL, are directed to the B cell antigen CD19, which is expressed widely on multiple B cell malignancies, including B-ALL.[4,12–14] However, multiple CAR T cell products targeting CD22, CD20, and other B-ALL antigens are now in clinical trials or development.[15–24] In this review, we will discuss the history of CAR T cell therapy for B-ALL, the current recommendations for its use, and its future directions.

DISCUSSION

The Road to FDA Approval of the First CAR T Cell Therapies for B-ALL

Over the past 2 decades, multiple trials have found CD19-directed CAR T cells to be highly successful at inducing an initial remission in both pediatric and adult B-ALL,[4,5,13,25–30] and this has resulted in the FDA approval of two CD19-CAR T cell products to date: tisagenlecleucel for pediatric and young adult patients with multiply relapsed or refractory B-ALL in 2017[31] and brexucabtagene autoleucel for relapsed or refractory adult B-ALL in 2021.[32]

CTL019, which ultimately became known as tisagenlecleucel, is an autologous CD19-directed CAR T cell product with CD3-ς and 4-1BB activating and co-stimulatory domains. The first in-human trials used CTL019 in adult patients with CLL, demonstrating feasibility[12–14] but soon after, clinical trials investigating CTL019 for children and adults with B-ALL began.[4,25,27] Of the first 30 pediatric and young adult patients treated with CTL019 in a phase I/II single-institution trial, 90% experienced a complete morphologic remission at the 1-month timepoint and 22 of these 30 achieved MRD negativity.[4] The event free survival rate (EFS) was 67% and overall survival (OS) rate was 78% at 6 months, suggesting for the first time that CAR T cells could be incredibly successful at inducing and maintaining remission.[4] ELIANA, a global phase I/II trial of the use of tisagenlecleucel in pediatric relapsed/refractory B-ALL across 25 centers, similarly reported an 81% MRD-negative remission rate within the first 3 months following infusion and 12-month relapse-free survival (RFS) of 59%.[5] Importantly, these two trials demonstrated CTL019 persistence for as long as 39 months, that durable remission could be achieved without consolidative hematopoietic stem cell transplant (HSCT), and that CTL019 could induce remissions in patients with a wide range of leukemic burden pre-infusion.[4,5] ELIANA was also the first trial to demonstrate feasibility of centralized CAR T cell manufacturing, paving the way towards a scalable CAR T cell therapy that could be accessible at sites throughout the world. The early success of CTL019 in the first single-center trial, and subsequently in ELIANA, ultimately led to the 2017 FDA approval of

tisagenlecleucel for patients up to age 25 years with B-ALL in its second or greater relapse or for chemotherapy-refractory disease in the same patient population,[31] marking the first FDA approval of both a gene therapy product and CAR T cell in the US. Tisagenlecleucel is now also approved for use in adult patients with relapsed/refractory diffuse large B cell lymphoma and follicular lymphoma.

Since its approval, additional studies have continued to assess tisagenlecleucel's efficacy, safety, and durability. Recently, the 3-year update of ELIANA demonstrated that of 79 patients enrolled, EFS at 3 years was 44%, OS was 63%, and RFS was estimated at 52%, demonstrating durable long-term remissions in nearly 50% of these pediatric and young adult patients.[33] Of these, 11 patients underwent consolidative allogeneic hematopoietic stem cell transplant (alloHSCT) while still in remission following tisagenlecleucel treatment.[33] These data further suggest that CD19-directed CAR T cell therapy can offer the potential for long-term remission and cure. Furthermore, the feasibility and efficacy of tisagenlecleucel as a commercially available CAR T cell therapy has now been assessed by multiple studies looking at real-world experiences in centers within the US.[34–36] A 2020 report from the Center for International Blood and Marrow Transplant Research (CIBMTR) detailed the experience of 255 patients with B-ALL from 73 centers and found an initial complete remission rate of 85.5%, with one year EFS 52.4% and OS 77.2%, similar to the first 2 CTL019 trials.[34] A Pediatric Real World CART Consortium report in 2022 reported that of 185 infused pediatric and young adult patients at 15 centers, tisagenlecleucel was associated with an 85% CR rate, a 12-month OS of 72% and EFS of 50%,[35] again strikingly similar to prior studies overall.

Simultaneously, clinical trials for adult B-ALL were underway.[26–28,37] KTE-X19 is a CD19-directed CAR T cell that incorporates a CD3-ζ and CD28 costimulatory domain initially developed at the National Cancer Institute.[37,38] Additionally, it involves a modified manufacturing process that specifically removes malignant cells from the leukapheresis product to improve CAR T cell production even in the setting of high peripheral blast counts.[39] In 2021, results from ZUMA-3, a multicenter phase 2 trial of KTE-X19, demonstrated a 71% overall complete remission rate (OCR) with 52% achieving complete remission at the 3-month mark and 97% of responders achieving MRD negativity.[40] Based on the findings of the ZUMA-3 trial, KTE-X19 was approved by the FDA for relapsed/refractory B-ALL under the name brexucabtagene autoleucel in 2021.[32] It had been approved for adults with relapsed/refractory mantle cell lymphoma the year prior.[32] In 2022, updated ZUMA-3 outcomes demonstrated that after 26.8-months median follow-up, median duration of remission was 14.6 months and duration of overall survival was 25.4 months.[41] Of the 71 patients, 12 patients underwent alloHSCT after KTE-X19 treatment while either in a CR, a CR with incomplete recovery, or an aplastic bone marrow without blasts and without having received any additional anti-leukemic therapy.[41]

Currently, patients aged 18-25 years old with relapsed or refractory B-ALL may be candidates for either tisagenlecleucel or brexucabtagene autoleucel, but there are no head-to-head trials comparing the two therapies.[42] ZUMA-4, assessing the efficacy and safety of KTE-X19 for pediatric relapsed/refractory B-ALL (NCT02625480), is ongoing.

Treatment Considerations

How to incorporate CAR T cell therapy into a treatment regimen for B-ALL is an active area of study and discussion. Further, how to factor in the likelihood of toxicity, the impact of prior treatments on CAR T cell success, how to best predict long-term response, and how to approach stem cell transplant after CAR T cell therapy for

B-ALL all remain important considerations and are discussed later in discussion. For additional discussion, Myers and colleagues[42] recently reviewed current recommendations for how to approach risk factors for CAR T cell success or failure in children and young adults.

Toxicity of CAR T cells for B-ALL

Cytokine release syndrome (CRS) and Immune effector cell-associated neurotoxicity syndrome (ICANS) were recognized within the first trials of CAR T cells in humans[4,25,26,29,43] and remain the most pervasive toxicities associated with CAR T therapy. Each represents a spectrum of immunopathology associated with CAR T cell activation and expansion, and consensus definitions have now been established.[44,45] Within the clinical trials leading up to FDA approval for both tisagenlecleucel and brexucabtagene autoleucel, grade 3 or higher CRS rates ranged from 24 to 49% and grade 3 or higher ICANS ranged from 13 to 14%,[40,46] whereas lower rates have been reported in multi-center real-world scenarios following FDA approval, likely reflecting a lower disease burden in many of the patients treated off study.[34,35] How to mitigate, prevent, and treat CRS and ICANS has evolved over the last decade of CAR T cell experience and now includes a spectrum of treatment options including the IL-6 blocking antibodies tocilizumab and siltuximab, corticosteroids, and additional targeted cytokine blockade with anti-IL-1 and IFNy antibodies.[44] Please see the full discussion of CAR T cell toxicities and their management as covered in a separate article in this issue.

Pre-infusion factors impacting CAR T cell success

Disease burden at the time of CAR T cell infusion should be considered in any patient undergoing CAR T cell therapy as it may impact response, survival, and toxicities. Both ELIANA and ZUMA-3, which led to the FDA approval of CAR T cells for B-ALL, required >5% morphologic disease within the bone marrow at the time of enrollment.[40,46] However, both tisagenlecleucel and brexucabtagene autoleucel are approved for any relapsed or refractory B-ALL in their respective patient populations, regardless of disease burden. Multiple studies have now clearly established that higher disease burden is associated with an increased risk of CAR T cell treatment failure compared to low disease burden. A CHOP-based trial of tisagenlecleucel found that patients with >40% bone marrow involvement had worse EFS (34% vs 78%) and OS (60% vs 92%) compared with lower disease at the time of infusion.[47] Further, multiple studies have established that any disease burden >5% of the bone marrow is associated with decreased OS, EFS, RFS, and toxicities including CRS and ICANS.[35,48–51] Similarly, the presence of active non-CNS extra-medullary disease at the time of CAR T therapy is associated with lower EFS,[42,49,50] but prior CNS or other EMD was not associated with worse outcomes.[42,52] Thus, while patients with high disease burden can and do respond to CAR T cell therapy and may experience durable remission, they remain at higher risk of relapse or toxicity.

Second, how prior therapy may impact CAR T cell success may also be considered. Blinatumomab is a bispecific T cell engager (BiTE) which targets CD19 on leukemia cells and engages with CD3 on endogenous T cells to increase T cell activation and cytotoxicity. As its use for B-ALL has expanded in both adults and children, there has been concern that its prior use could impact the efficacy of CD19-directed CAR T cells by downregulating CD19 or impacting the ability of CD19-specific CAR T cells to target CD19,[3,42] and case studies described CD19 CAR T cell failure in patients who had previously received blinatumomab.[53] Indeed, several studies did suggest that prior blinatumomab use was associated with worse outcomes, including

decreased rate of CR[40,54]; however, in ZUMA-3 it did not affect relapse-free survival or OS.[40] Furthermore, in a multicenter study of 420 children and young adults who received CD19-directed CAR T cell therapy, prior blinatumomab failure was directly associated with lower CR rates (65% vs 93%), and shorter EFS, RFS, and OS, whereas blinatumomab exposure alone was not,[49] suggesting that the association of prior blinatumomab treatment to lower CR may be more directly due to either sensitivity to CD19-directed therapy in general or due to the prolonged antigen exposure and immunologic pressure caused by incomplete CD19 clearance. In fact, Myers and colleagues[42] recommend that blinatumomab exposure or non-response should not be a contraindication to CAR T cell therapy as most patients will achieve CR with CAR T cell therapy despite this history.

Inotuzumab ozogamicin is an antibody-drug conjugate which targets CD22 and has demonstrated success in both pediatric and adult ALL, with further studies ongoing.[15,16,55] While Inotuzumab would not be expected to directly alter CD19 expression on leukemic blasts, it can induce widespread B cell aplasia (BCA) due to the expression of CD22 on endogenous, healthy B cells. This BCA decreases the overall $CD19^+$ antigen load within the body, which may be important for CD19-directed CAR T cell expansion and persistence.[42,56] Furthermore, inotuzumab significantly increases the risk of sinusoidal obstructive syndrome following stem cell transplant, and this may be a significant consideration for patients proceeding to HSCT following CAR T cell infusion.[55] Thus, the timing of inotuzumab prior to CAR T cell therapy should be carefully considered.

How CAR T cell response after infusion can inform the likelihood of future relapse

Thus far, following infusion of CAR T cells for B-ALL there are two primary post-infusion factors that can inform the likelihood of future relapse: (1) duration of B cell aplasia and (2) next-generation sequencing (NGS)-MRD status at 1- and 3-months following infusion. B cell aplasia is a well-accepted proxy for CAR T cell persistence given that CD19 is expressed by healthy B cells as well as B cell leukemia.[30,42,57] In general, early B cell recovery is associated with a high risk of $CD19^+$ relapse,[30,42,56,57] in contrast to $CD19^-$ relapse thought to be associated with leukemic factors that drive immune evasion. In adults, loss of B cell aplasia with loss of CAR T cell persistence was highly associated with $CD19^+$ leukemic relapse.[30] Furthermore, in pediatric and young adult patients, loss of B cell aplasia within 1 year of tisagenlecleucel infusion significantly increased the risk of relapse, with highest risk associated with loss within 6 months.[57] In a trial of a humanized CD19 CAR T cell therapy for pediatric and young adult B-ALL, recovery of B cells within 6 months shortened EFS and RFS.[48] However, whether B cell aplasia beyond the first year after infusion is associated with higher rates of relapse remains unclear. Secondly, NGS-MRD positivity is highly associated with relapse following tisagenlecleucel in pediatric and young adult patients, both at day 28 and 3 months following infusion.[57] Better understanding of the predictive value of both CAR T cell persistence and NGS-MRD positivity for future relapse and how that may inform post-CAR T cell therapy treatment decisions remains an important focus of current CAR T cell investigation.

The role for consolidative hematopoietic stem cell transplant following CAR T cell therapy for B-ALL

CAR T cell therapy for B-ALL has demonstrated remarkable results with most patients experiencing a complete remission following treatment, more than half remaining disease-free one year after infusion,[40,46] and nearly half of the patients that responded to tisagenlecleucel remaining relapse-free without further therapy at the 3-year

mark.[33] However, treatment options for relapsed leukemia after CAR T cell therapy are incredibly limited, and in pediatric patients, relapse after tisagenlecleucel is associated with poor prognosis.[36] Thus, there is considerable debate in the field regarding which patients would benefit from consolidative allogeneic hematopoietic stem cell transplant (alloHSCT) following CAR T cell infusion in an attempt to decrease the risk of disease recurrence. Importantly, there have been no prospective clinical trials designed to directly evaluate the role of alloHSCT after CAR T cell therapy for adults or children.[3] Yet, several trials have provided some important information that may help guide decisions. In ZUMA-3 and ELIANA, only 17% and 14%, respectively, of the patients enrolled underwent post-infusion consolidative alloHSCT while in remission,[5,33,40,41] suggesting that many patients can sustain a durable remission without a consolidative transplant. Furthermore, neither trial demonstrated an obvious survival benefit to alloHSCT following CAR T cell therapy,[5,33,40,41] but neither trial was designed or large enough to directly ask this question. In general, CD28-based CAR T cells have decreased cell persistence compared to 4-1BB constructs, including tisagenlecleucel, and recent recommendations have supported alloHSCT following CD28-directed CAR T cell therapy in pediatric and young adult patients.[42,58] However, for older adults or patients with significant co-morbidities, the risk/benefit of alloHSCT is less clear given the increased risk of non-relapse death following transplants in these patient populations.[59] Thus, there remains no explicit guidance for who should and should not go to transplant following CAR T cell therapy for B-ALL, rather the decision should be made based on the CAR T cell construct received, age and co-morbidities of the patient, and disease assessments and bone marrow recovery post-infusion.[3,42]

Ongoing Clinical Trials and Future Directions

While CAR T cell therapy has drastically improved treatment options for patients with multiply relapsed or refractory B-ALL, up to 50% of patients who receive CAR T cells will ultimately relapse. Thus, optimization in manufacturing or engineering to improve persistence and efficacy as well as investigations into additional CAR T cell targets remain critical to further advance the field and improve patient outcomes.

Humanized CD19 CAR T cells for B-ALL

$CD19^+$ relapses are associated with early B cell recovery, poor CAR T cell persistence, and account for the majority of post-CAR T cell relapses in B-ALL.[28,56,60] Thus, efforts are underway to address factors that may contribute to early CAR T cell clearance. Tisagenlecleucel, brexucabtagene autoleucel, and most CD19-directed CAR T cells, contain an scFv domain derived from mouse monoclonal antibodies, which may cause unwanted immunogenicity that promotes CAR T cell loss.[61] To mitigate this, several groups have developed humanized or fully human constructs. The University of Pennsylvania developed a CAR T cell containing a humanized anti-CD19 scFv domain with the 4-1BB costimulatory domain (huCART19).[48] In the phase I huCART19 trial at CHOP, 74 patients were infused, with day 28 CR rates of 98% and 64% for patients without and with prior CAR T cell exposure, respectively. Patients who had received no prior CD19-directed CAR T cell therapy had an 84% RFS at 12 months and 74% at 24 months, whereas patients who had received prior CAR T cell therapy had a 74% RFS at 12 months and 58% at 24 months, demonstrating that while outcomes were better for CAR T cell naïve patients, patients who had received prior CAR T cell therapy also could experience a durable remission after huCART19 treatment.[48] Furthermore, while B cell recovery at 6 months was higher in patients who had received prior CAR T cell therapy compared to those who had not

(58% vs 15%),[48] these initial results also demonstrate that huCART19 can induce BCA and can persist in patients with prior CAR T cell therapy. Further trials assessing huCART19 are underway.

CD22-directed CAR T cell therapy for B-ALL

CD19 antigen loss on relapsed leukemia following upfront therapy or after prior CD19 CAR T cell therapy is a challenging mechanism of resistance to CD19-targeted immunotherapy. However, several trials are investigating alternative B-ALL targets. CD22 is expressed on most B-ALL cases, even after CD19 loss[62–64] and its expression is restricted to the B cell lineage. Furthermore, the success of the antibody-drug conjugate inotuzumab ozogamicin, which targets CD22,[15,16] suggests that CD22 may be a potent target for CAR T cell therapies in B-ALL. In a phase I trial investigating a fully human CD22-directed CAR T cell, 73% of 15 patients experienced a CR,[62] and in an updated report of 58 patients from the same trial, 70% experienced a CR, but median RFS was short at 6 months.[17] Rates of HLH-like CRS were high (32%).[17] Yet, these studies demonstrate that CAR T cells targeting CD22 may induce remission and may be a useful tool in addressing CD19 antigen loss. Further trials developing anti-CD22 CAR T cells are underway at multiple institutions.

Another attractive method of targeting CD22 with CAR T cell therapy is to combine an anti-CD22 CAR with a CD19 CAR in order to prevent antigen escape from either CD19 or CD22 alone. Multiple trials have now reported variable success with combinatory CAR T therapy using the co-administration of CD19-and CD22-directed CAR T cells[18,19] or bispecific CD19/CD22 CAR T cells,[20–22] with poor persistence emerging as a limitation, and trials are ongoing at multiple institutions. Constructs targeting three targets, including CD19, CD22, and CD20, are all in pre-clinical development.[23,24]

Allogeneic CAR T cell therapy for B-ALL

The two FDA-approved CAR T cell constructs and most other CAR T cell products in development for B-ALL have all been autologous therapies; that is, the CAR T cells are manufactured from T cells leukapheresed directly from the recipient patient. This poses several challenges. First, not all patients are able to produce an adequate T cell collection due to prior treatment, ongoing cytopenias, high peripheral blast burden, or poor medical suitability for apheresis. Secondly, autologous CAR T cell manufacturing is time-consuming. Thus, there is significant interest in the development of an allogeneic CAR T cell product for B-ALL.[3] Multiple trials in children and adults have now reported preliminary findings suggesting that allogeneic donor-derived CAR T cell therapy may be possible[65,66]; however, limitations have been encountered, including rejection causing poor expansion or persistence. Further trials are ongoing to assess safety, efficacy, and scalability of a universal CAR T cell product.

SUMMARY

Over the past decade, CAR T cell therapy has transformed the treatment paradigm for relapsed or refractory B-ALL in both adults and children. With the FDA approval of two CD19-directed CAR T cells for B-ALL and with many other constructs in clinical trials, the landscape of available cell therapies for B-ALL has never been wider. Indeed, CAR T cell therapy has the power to induce remission in a large majority of B-ALL patients and can provide long-term durable remissions for many. However, significant challenges remain for patients who experience CAR T cell non-response or post-infusion relapse. How to mitigate these challenges is a highly important focus of CAR T cell research.

CLINICS CARE POINTS

- CAR T cell therapy induces durable, MRD-negative remissions for many patients with relapsed or refractory B-ALL.
- Tisagenlecleucel is currently approved for patients up to 25 years old with multiply relapsed or refractory B-ALL.
- Brexucabtagene autoleucel is currently approved for patients 18 years or older with relapsed or refractory B-ALL.
- Factors such as patient age, co-morbidities, post-infusion NGS-MRD, presence of BCA, and bone marrow recovery should all inform the decision on consolidative alloHSCT following CAR T cell therapy for B-ALL.
- Many patients remain eligible for a number of clinical trials investigating current or new CAR T cell strategies for B-ALL and these should be discussed on an individual basis.

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