Relapsed ALL: CAR T vs transplant vs novel therapies

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Chimeric antigen receptor T-cell therapy targeting CD19 (CART19) has expanded the treatment options for patients with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (ALL). The approval of tisagenlecleucel for pediatric and young adult patients with r/r ALL has allowed broader access for some patients, but the treatment of older adults is available (at the time of this writing) only within a clinical trial. High remission rates have been consistently observed with varied CART19 products and treatment platforms, but durability of remissions and thus the potential role of a consolidative allogeneic stem cell transplant (SCT) is more uncertain and likely to vary by product and population treated. The immunologic characteristics of CARTs that confer high response rates also account for the life-threatening toxicities of cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome, the severity of which also varies by patient and disease characteristics and product. Further considerations informing a decision to treat include feasibility of leukapheresis and timeline of manufacture, alternative treatment options available, and the appropriateness of a potential consolidative allogeneic SCT. Advances in the field are under way to improve rate and duration of responses and to mitigate toxicity.

LEARNING OBJECTIVES

- Understand the efficacy and toxicity outcomes of CART19 in r/r ALL and how they vary by product, patient, and disease-related factors
- Understand factors that inform a decision to consolidate a recipient of CART19 in CR with allogeneic SCT

Efficacy outcomes of CART19 in relapsed and refractory ALL

Response

Autologous T cells engineered to express a chimeric antigen receptor T-cell therapy targeted to CD19 (CART19) have consistently shown high complete remission (CR) rates (62%-95%) in adult and pediatric patients with relapsed or refractory (r/r) acute lymphoblastic leukemia (ALL).[1–12] The chimeric antigen receptor (CAR) T cells used in the studies summarized in Table 1 are made from a patient's T cells collected through leukapheresis that are then transduced with a CAR targeting CD19 using a replication-incompetent retrovirus or lentivirus. The CARs include a costimulatory molecule, which is either CD28 or 41BB depending on product. Patients typically receive lymphodepleting chemotherapy (commonly cyclophosphamide and fludarabine) prior to CART19 infusion. Importantly, despite differences in patient populations, clinical trial procedures, CAR molecules, and manufacturing differences, high initial response rates are maintained. Across studies, remissions are achieved quickly (by 1-month postinfusion), are often minimal residual disease (MRD) negative, and are not discriminated by mutational status or number and type of prior therapies. The trial populations represent heavily pretreated patients, with over a third of patients in some studies having relapsed after prior allogeneic stem cell transplant (SCT).[1–3,6,8,9] Importantly, several studies have shown CART19 cells tracking into the central nervous system (CNS) with responses seen in patients with CNS disease.[2,5,10,11] Although the outcomes discussed here are focused on recipients of CART19, CARTs to other targets (specifically CD22) have been shown to be effective.[13–16] In a large series of pediatric and adolescent young adult (AYA) patients (N=58), many of whom had relapsed after CART19 therapy (N=51), anti-CD22 CAR therapy induced a CR in 70% of patients.[14]

Survival and durability of response

Median overall survival (OS) in most studies using CART19 is beyond 1 year and importantly is noted within some reports to vary by dose level or other changes to study

Table 1. Outcomes of CART19 in patients with relapsed and refractory acute lymphoblastic leukemia

Reference	CART domain	No. treated	Median age, y	Prior blinatumomab, %	Prior SCT, %	CR, %	CRS	ICANS
Adult patients								
Frey et al[1]	41BB	35	34 (21–70)	31	37	69	94% total 9% grades 4–5	40% total 6% grade 3
Hay et al[3]	41BB	53	39 (20–76)	20	43	85	75% total 19% grades 3–4	23% total
Park et al[9]	CD28	53	44 (23–64)	25	36	83	85% total 26% severe 1 grade 5	42% grades 3–4
Shah et al[12]	CD28	55	40 (28–52)	45	42	71	89% total 25% grade 3 or higher	60% total 23% grades 3–4 1 grade 5
Combined pediatric and adult patients								
Jiang et al[4]	41BB	58	28 (10–65)	NA	5	88	38% grades 3–5	16% grades 2–3
Ortíz-Maldonado et al[8]	41BB	38	24 (3–67)	26	87	85	13.2% grades 3–5	2.6% grade3 or higher
Wang et al[16]	41BB	23	42 (10–67)	NA	0	83	100% total 18% grade 3	13% total
Maude et al[5]	41BB	30	14 (5–60)	10	60	90	100% total 27% severe	43% total
Pediatric and AYA patients								
Gardner et al[2]	41BB	45	12.2 (1.3–25.3)	14	62	93	93% total 21% severe	49% total 21% severe
Maude et al[6]	41BB	75	11 (3–23)	0	61	81	77% total 25% grade 4	13% grade 3
Shah et al[11]	CD28	50	13.5 (4.3–30.4)	10	40	62	70% total 22% grades 3–4	20% total 8% severe

NA, not available.

design throughout the clinical trial. Multicenter studies using consistent products reflect more generalizable outcomes. In the pivotal ELIANA trial leading to approval of tisagenlecleucel for pediatric and young adult patients, 75 patients were treated, with a CR rate of 81%. Median OS was not reached, with event-free survival (EFS) and OS at 12 months of 50% and 76%, respectively. For responders, the median duration of remission was not reached.[6] In the multicenter ZUMA-3 study treating 55 adults with r/r ALL with KTE-X19, CR rate was 71% and median OS was 18.2 months. The median duration of remission for responders was 12.8 months.[12] Another multicenter study treated 38 adult and pediatric patients with CART19 with a CR rate of 71%, with OS and progression-free survival of 67% and 47%, respectively, at 1 year. The median duration of response was 14.8 months.[8]

Impact of prior blinatumomab on efficacy

Blinatumomab is a bispecific T cell engaging a single-chain antibody construct linking CD3+ T cells with CD19+ B cells. There is a logical concern that due to its similar mechanism of action and target, prior treatment with blinatumomab could adversely affect outcomes from CART19. For this reason, early CART19 studies, such as the ELIANA study, prohibited prior treatment with blinatumomab or other CD19-targeted therapies.[6] Since these initial studies, the use of blinatumomab has increased significantly, especially in adults, which is reflected in a progressively higher proportion of patients (20%-45%) on CART19 studies having received blinatumomab (see Table 1).[1,3,9,12] In the recently published ZUMA-3 multicenter trial, 45% of the 55 adult patients treated with KTE-X19 had received blinatumomab. Although prior exposure to CD19-targeted agents may affect risk of subsequent CD19− relapse, initial response rates do not seem greatly affected. The Children's Hospital of Philadelphia reported outcomes from 166 patients treated with CART19 at their institution. The CR rate was 93%, and 67 patients ultimately relapsed, 39 with CD19− disease due to antigen escaper. Prior therapy with blinatumomab was associated with a higher risk for CD19− relapse.[17]

Importance of persistence for durable remissions

Several ALL trials using CART19 products containing a 4-1BB costimulatory domain have shown a strong correlation between CART19 persistence (often represented by B-cell aplasia, a biological surrogate for functional persistence) and CD19+ relapses.[1-3,6,7,18] In an analysis of outcomes with tisagenlecleucel in patients with ALL on the ELIANA trial, the patients with CD19+ relapses had a more rapid loss of CART persistence compared with those with durable remissions. Of interest, patients who developed a CD19− relapse had persistence similar to those who had sustained responses with mechanism of relapse due to antigen escape.[18] In another pediatric study using a different 4-1BBCART19 product at Seattle Children's, a longer

duration of B-cell aplasia correlated significantly with the durability of remission.[2] Another study found the median persistence of 41BBCART19 was shorter for those with a CD19+ relapse (2.5 months) as opposed to a CD19− relapse (6 months).[4]

Several studies using CD28-CART19 products have shown limited persistence, but a correlation of outcomes with persistence is less clear.[9,11,12] In the ZUMA-3 trial using CD28-CART19 (KTE-X19), CARTs were no longer detectable in 79% of patients with evaluable samples by 6 months, and B-cell recovery had occurred in all evaluable ongoing responders at 12 months. The experience at Memorial Sloane Kettering Cancer Center using their CD28-CART19 showed median persistence of 14 days (range, 7-138 days), and duration of persistence did not correlate with survival.[9] In 1 study, however, from the National Cancer Institute treating 50 pediatric and AYA patients with a CD28-CART19 product, remissions were durable only with consolidative SCT, which the authors hypothesize may be due to limited persistence.[11]

Given the correlation between 4-1BBCART19 persistence and CD19+ durability of remissions, it is vital to understand correlates with persistence using these CART19 products. The group at the Fred Hutchinson Cancer Research Center found that the addition of fludarabine to cyclophosphamide lymphodepletion improved persistence and disease-free survival.[19] The impact of antigen load on persistence has varied across studies. The group from Seattle Children's found a positive correlation, with >15% bone marrow blasts correlating with prolonged persistence.[2] Conversely, the group from did not find an association with low disease burden and CD19+ relapses.[17] Evaluation of T cells in apheresis and manufactured 4-1BBCART19 products identified phenotypical and functional attributes of CAR CD8 T cells that correlated with persistence.[20]

Most of the studies in Table 1 use CARs containing a murine domain that may be a target for immune-mediated rejection. The development of a CART19 product using a CAR containing a humanized anti-CD19 scFv domain may bypass this rejection, resulting in improved persistence and relapsed free survival (RFS).[7,10] A recent report of outcomes in pediatric and AYA patients with r/r ALL treated with a humanized CART19 based on the backbone of CTL019 (tisagenlecleucel) has shown excellent responses. In 41 CART19-naive patients, CR rate was 98%, and RFS at 1 year was 84%. Similar to prior studies, earlier B-cell recovery as a time-dependent covariate correlated with worse RFS. In an exploratory analysis, time to B-cell recovery was compared with a historical cohort of CTL019 recipients, and there was a trend toward a lower cumulative incidence of B-cell recovery by 6 months (15% vs 29%), but it did not reach statistical significance.[7]

Risk of CD19− relapse

CD19− relapses happen when CD19 antigen loss occurs through mutation or epigenetic alterations, likely in preexisting leukemia subclones.[21-23] An attractive approach to limit the incidence of CD19− relapse is to infuse CARTs that target more than 1 antigen such as CD19 with either CD20 or CD22. One approach is to generate a singular CART product that can target more than 1 antigen vs coadministering 2 distinct products with different targets either concurrently or sequentially.[13,16,24-26] In 1 study, 20 children with r/r ALL who achieved an MRD-CR with CART19 were infused with CART22 at a median of 1.65 months after CART19 infusion.[13] No patients received consolidative SCT, and at 1 year, 85% were in CR, an improvement when compared retrospectively with outcomes from CART19 alone.[13]

Role of consolidative SCT

For a patient without an antecedent SCT with an MRD-CR after CART19, a critical question is whether to consolidate that remission with transplant if the patient is medically fit to consider this approach. As always when considering SCT, treatment-related morbidity and mortality needs to be balanced against risk of relapse. Another consideration is that the CARTs with functional persistence would be destroyed by SCT, losing their benefit of ongoing tumor surveillance. There are no studies to date that randomize patients after CART therapy to allogeneic SCT or observation. Furthermore, the decision is not likely generalizable across different CART19 products. For example, patients taking 4-1BBCART19 products have better persistence (with potentially longer disease-free intervals, although more data are needed) than recipients of CD28-CART19 products. There is considerable variation among clinical trials and retrospective analyses regarding the potential benefit of a consolidative SCT, and again, no randomized trials have formally addressed this question.

The role of consolidative SCT in CD28-CARTs

Recently, the National Cancer Institute reported long-term follow-up of 50 children and young adults (median age, 13.5 years; range, 4.3-30.4 years) treated with their CD28-CART19 product who clearly benefited from a consolidative SCT. Of the 28 patients who achieved an MRD-CR, 21 (75%) proceeded to SCT with a median OS of 70.2 months. The cumulative incidence of relapse after SCT was 9.5% at 24 months. All patients who did not proceed to SCT relapsed at a median of 152 (range, 94-394) days.[11] However, data from Memorial Sloane Kettering Cancer Center provided long-term outcomes from 51 adults (median duration, 18 months) treated with a different CD28-CART19. Of the 32 patients in MRD-CR, no difference in OS was seen in patients who did or did not receive SCT after CARTs.[9] Recently, results from the ZUMA-3 multicenter trial using KTE-X19 (a CART19 with CD28) have been reported. In this study, 55 patients were treated and 39 patients (71%) achieved CR. Ten patients (18%) proceeded to SCT, and with sensitivity analyses, the median duration of remission was unchanged by SCT consolidation.[12]

The role of consolidative SCT in 4–1BB CARTs

It is clear that a subset of patients with initial response to some 41BBCART19 products has ongoing durable remissions without consolidative SCT, which correlates with persistence.[2,5-8] Even when a particular CART19 product has been shown to have good functional persistence, however, that persistence is not observed across all patients treated, and CD19+ relapses remain a significant challenge that may be mitigated by SCT in some patients.[1] In addition, even if one anticipates and observes ongoing persistence, CD19− relapses from antigen escape occur despite CART19 persistence. Only a minority of the young adult and pediatric patients with relapsed ALL treated with tisagenlecleucel on the ELIANA study received a consolidative SCT. The EFS of 50% at 12 months is therefore representative of remission durability with this 4-1BBCART19 product.[6] When CTL019 (the precursor to tisagenlecleucel) was used to treat older adults, those who proceeded to SCT in MRD-CR had an improved EFS compared with those who were not, although durable remissions

were seen in each group.[1] Similarly, in another study using a different 4-1BBCART19, there was a trend toward an improved EFS in patients bridged to SCT (*P*=.088). In another study using a 41BBCART19 for r/r ALL, 21 of the 47 patients who achieved MRD-CR were bridged to SCT. Although there was no difference in OS between the 2 groups, EFS and RFS were significantly prolonged in the SCT group.[4]

Toxicity

Due to their mechanism of action, CART19 is associated with cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), which are both potentially life-threatening.[27] The incidence of these complications across selected trials for adult ALL is summarized in Table 1. It should be noted that different grading scales were used across trials, challenging any comparison of toxicity.

CRS

Fever, hemodynamic instability, and hypoxia are the core clinical features of CRS and used in the American Society for Transplantation and Cellular Therapy consensus grading scale.[28] The incidence of CRS is high across all CART19 studies compared with other B-cell malignancies. The syndrome can be self-limited (requiring only supportive care with antipyretics and intravenous fluids) or more serious, requiring intervention with tocilizumab (an antibody to the interleukin 6 receptor) or corticosteroids. The biology and risk factors for CRS are well understood and continue to inform management strategies, and further approaches to mitigate CRS are being explored in clinical trials. In ALL, disease burden is a strong predictor for the severity of CRS.[2,5,9,12,19] Some centers have adopted a risk-adapted approach in which a lower dose of cells is given for patients with higher disease burdens.[9,19] Others have used more intensive cyto-reduction for patients with higher disease burdens.[10] Several centers are evaluating the benefit of intervening with tocilizumab for earlier grades of CRS compared with the approach in early clinical trials that treated at more severe CRS due to concerns that earlier intervention may mitigate response. In 1 study from the Children's Hospital of Philadelphia, patients were assigned to high and low (<40%) tumor burden cohorts. Those with high disease burden received tocilizumab for persistent fevers. Of 70 patients treated, 15 received early tocilizumab, which, when compared retrospectively with a similar group from an earlier study, showed a reduction in grade 4 CRS from 50% to 27%.[29] Seattle Children's reported their experience with earlier tocilizumab intervention resulting in a lower incidence of severe CRS without an impact on response.[2] We and others have used a fractionated dosing scheme in which the total planned CART dose is infused over 3 days. This approach, in which subsequent doses are held for early signs of CRS, allows for real-time dose modification in response to toxicity without an impact on efficacy.[1,8]

Neurologic toxicity

The ASTCT consensus grading for ICANS requires assessment of a patient's immune effector cell–associated encephalopathy score, level of consciousness, seizure activity, focal motor weakness, and cerebral edema.[28] Similar to CRS, neurologic events occur within the first few weeks of therapy and have been reported in all the studies summarized in Table 1. Our understanding and ability to mitigate neurologic toxicity after CART19 is limited. Current management strategies are based on intervention with corticosteroids. Risk factors for severe ICANS are less clear but correlate with product used, higher interleukin 6 levels, high disease burden, and more severe systemic CRS.[9,12,19] CART19 cells readily cross the blood-brain barrier (BBB, a potential benefit for disease targeting as discussed above) and are detectable in the cerebral spinal fluid (CSF) in most treated patients. Their presence in the CSF, however, does not predict for toxicity.[5] Further studies are needed to determine the mechanism of action, risk factors, and optimal management strategies of neurologic toxicity after CAR T-cell therapy.

Role of CART19 vs other therapies

Clinicians may have several salvage options available to treat a patient with r/r ALL. Treatment decisions need to be individualized based on prior therapy, goals of therapy, role of potential consolidative SCT, and features of the CART19 product available (see Table 2). Comparing outcomes of CART19 studies with outcomes from inotuzumab (INO-VATE study) and blinatumomab (TOWER study) should be done with caution given differences in trial design, patient populations, disease burden, and role of consolidative SCT in the different studies. In addition, most efficacy outcomes reported from CART19 studies are for those who made it to infusion, discounting failures of treatment from manufacturing or inability to tolerate the treatment delay that is inherent in autologous CART19 treatment. Randomized controlled trials are lacking and needed to appropriately compare outcomes. Acknowledging these limitations, outcomes from mature multicenter CART19 trials (CR=71%-81%; median OS of 11 months not reached; median duration of CR=12.8 months not reached) compare favorably with outcomes with blinatumomab (CR=35.1%; median OS=7.7 months, median duration of CR=7.3 months) and inotuzumab (CR=80.7%; median OS=7.7 months; median duration of CR=4.7 months).[6,8,12,30,31]

Table 2. Challenges of CART19 and solutions under investigation

Challenge	Solutions under investigation
Relapse	
CD19− relapse due to antigen escape	Dual targeted approach (CD19 and CD22)
CD19+ relapse due to loss of persistence	41BB costimulatory domain
Immune mediated rejection	Humanized CARTs
Exhaustive phenotype	Manufacturing changes to select for nonexhaustive phenotype
Logistics	
Window for leukapheresis	Collect and store cells early in disease course
Disease control during manufacturing	Develop more rapid manufacturing time
	"Off-the-shelf" or allogeneic CARTs
Toxicity	
CRS and ICANS	Earlier intervention with tocilizumab or corticosteroids
	Fractionated dosing scheme: dose modification in response to early toxicity
	Dose modifications by disease burden
	Novel anticytokine approaches

CART19, inotuzumab, blinatumomab, and chemotherapy in patients who are not refractory all have the potential to successfully induce an MRD− remission that can serve as a successful bridge to SCT. Although successful, there is no evidence that an MRD− remission from a CART product vs chemotherapy or other targeted approach improves RFS after SCT. One report compared outcomes from patients with r/r ALL who achieved MRD− CR with CART19 or chemotherapy and were bridged to SCT. No difference in cumulative incidence of relapse (11.1% vs 12.8%) or nonrelapse mortality was identified.[32]

The toxicity of a specific CART19 product needs to be considered on an individualized basis and used to inform treatment decisions with CART19 vs another available product. Patients with high disease burden, advanced age, and comorbid cardiovascular disease, for example, may not tolerate anticipated severe CRS or ICANS, and another approach may be more appropriate. On the other hand, a patient with minimal disease burden would be anticipated to have lower risk of these toxicities from CART19. Other specific factors may influence a clinician's decision to treat with CART19. For a patient with a low likelihood or desire to proceed to an SCT if a CR is obtained, CART19 products that have been shown to have durable remissions without consolidative SCT may be favored over other products. A patient with CNS disease history may benefit from CART19, which has been shown to cross the BBB and treat disease in the CSF.

The logistics of autologous CAR T-cell therapy, including identifying an appropriate window to perform leukapheresis and the need to control disease while cells are being manufactured, confer a significant disadvantage compared with other approaches to care, such as inotuzumab or blinatumomab. Several investigations are under way to explore the potential benefit of using allogeneic CARTs from healthy donors in whom the potential for graft-versus-host disease is abrogated by T cell receptor knockout with gene editing techniques. In early studies with this approach, responses have required high immunosuppressive therapy to minimize immune-mediated rejection.[33]

Real-world experience with CART19 for ALL

There is only 1 CART19 product approved in the United States and Europe for r/r B ALL, although more products are likely to be approved for this indication over the next few years. Tisagenlecleucel is approved to treat patients up to 25 years of age with B-cell ALL that is refractory or in second or greater relapse. This approval is based on outcomes from the multicenter phase 2 ELIANA study discussed above.[6]

Real-world registry data collected after the commercialization of tisagenlecleucel have substantiated these outcomes and represent a larger number and more diverse group of patients than those treated in the pivotal trial. Information from 255 pediatric and young adult patients with relapsed ALL obtained from the Center for International Bone Marrow Transplant Registry found a CR rate of 86% with an EFS and OS of 68.6% and 88.5%, respectively, at 6 months.[34] This compares favorably to the ELIANA trial, which had a CR rate of 81% and an EFS and OS of 72% and 87%, respectively, at 6 months. Importantly, treatment in the real world has been shown to be safe, with fewer patients having grade 3 or higher CRS (16% vs 48%) and similar numbers having grade 3 or higher neurotoxicity (9% vs 12.7%).[34] The lower incidence in CRS may reflect progress in management or less advanced disease at time of treatment. In addition to validating efficacy and safety outcomes, real-world data have provided information on populations not eligible for the registration trial. For example, 6% of patients from the Center for International Bone Marrow Transplant Registry were younger than 3 years, and 15% of patients had prior blinatumomab; both subgroups would have been excluded from ELIANA.

Conclusion

At the time of this writing, there is only 1 CAR T-cell product, tisagenlecleucel, approved to treat r/r ALL for patients 25 years and younger, but more approvals over the next few years are anticipated. Treatment with CART19 yields high and durable response rates for adult and pediatric patients with r/r ALL. The decision to treat a patient with CART19 depends on several patient-, disease-, and product-related factors in conjunction

Table 3. Clinical scenarios that favor CART19 vs other therapies

Clinical scenario	CARTs vs alternative approach
Recent CNS disease	Consider CART19 due to ability to cross BBB and treat the CNS compartment. Patients treated with chemotherapy, blinatumomab, or inotuzumab are at risk for extramedullary relapse or progression.
Allogeneic SCT not possible or desirable Relapse occurs after prior SCT High risk for complications from SCT No donor option Patient defers SCT	CART19 should be considered if product with durable remission without SCT is available.
Rapidly progressive disease	CART19 may not be feasible due to need to identify a window for leukapheresis and control disease while awaiting manufacture. Other approaches should be considered.
Frail or older patient with comorbid disease and high disease burden	Patient may not tolerate anticipated severe CRS or ICANS with CART19. Consider alternative approaches.
Frail or older patient with comorbid disease and minimal disease burden	Patient is likely to do well with blinatumomab, inotuzumab, and CART19. With CART19, side effects of lymphodepletion need to be considered, although low CART-related toxicity is anticipated. Decision may be influenced by durability of remissions observed with CART19 product available.

with consideration of other therapies available and the potential role of a consolidative SCT. Approaches are being explored to minimize CD19+ and CD19− relapses and prevent or mitigate toxicity, which will continue to affect the treatment paradigm for ALL over time (see Table 3).

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