Published in final edited form as:

Expert Opin Orphan Drugs. 2018 ; 6(10): 563–566. doi:10.1080/21678707.2018.1529562.

CAR-T immunotherapy: how will it change treatment for acute lymphoblastic leukemia and beyond?

Christian M. Capitini¹

¹Department of Pediatrics and Carbone Comprehensive Cancer Center, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Abstract

Introduction: The recent approval of CD19 chimeric antigen receptor (CAR) T cells for refractory or second relapse of B cell acute lymphoblastic leukemia (B-ALL) has led to a paradigm shift. Besides being an alternative to chemotherapy and antibody-based approaches, CAR-T cells have become the first successful example of “personalized medicine.”

Areas covered: In clinical trials, tisagenlecleucel demonstrated higher response rates than prior therapies, and led to durable remissions lasting up to years for some children. Toxicities like cytokine release syndrome and neurotoxicity, while potentially reversible, have limited usage of CAR-T cells at certified centers with expertise in cellular therapy. Strategies to deal with B-ALL relapse after CAR-T remain an open area of research.

Expert opinion: Going forward, improvements will likely be seen in managing the side effects of CAR-T therapy as well as usage of CAR-T cells upfront as a replacement for chemotherapy or allogeneic bone marrow transplant for B-ALL. Further advances will need to reduce the biomanufacturing time needed to generate CAR-T cells as well as develop biomarkers that predict CAR-T persistence and/or toxicities.

Keywords

CTL019; Tisagenlecleucel; CAR-T cells; ALL; acute lymphoblastic leukemia; cytokine release syndrome

1. Introduction

Chimeric antigen receptor (CAR) T cells are T cells that have been genetically engineered *ex vivo* to express a single chain variable fragment (scFV) that recognizes an antigen on malignant (and often normal) cells, fused with the signaling chain of a co-stimulatory

Corresponding author: Christian Capitini, 1111 Highland Ave, Madison, WI 53705, (608) 262-2415 (phone); (608) 265-9721 (fax), ccapitini@pediatrics.wisc.edu.

Declaration of interest

CM Capitini received honorarium for a one-time Novartis advisory board in 2016 and is presently on an advisory board for Nektar Therapeutics and receives honorarium. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript, apart from those disclosed.

Reviewer Disclosures

Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

molecule (e.g. CD137) and a T cell activation signal (e.g. CD3-zeta)¹. The advantage of expressing a CAR is that the T cell has the antigen recognition capabilities of an antibody [allowing it to bind any molecule on a cell surface in a non-major histocompatibility complex (MHC) restricted manner] directly coupled with the killing capacity of an effector cell. In 2017, Food and Drug Administration (FDA) approval of CAR-T cells that recognize CD19 on normal and malignant B cells to treat refractory or 2nd relapse of B cell acute lymphoblastic leukemia (B-ALL) in children and young adults, as well as refractory or relapsed diffuse large B cell lymphoma in adults, changed the landscape for immunotherapy of high-risk cancers. In this Editorial, we will review the impact of these therapies in the context of B-ALL and then examine how CAR-T immunotherapy can be potentially applied for other cancers.

2. Relapsed ALL in the pre-CAR-T cell era

For children with refractory or relapsed B-ALL, prognosis remains poor². For example, only 17% of patients with refractory disease ever achieve a complete remission (CR)³. Until recently the standard of care for this population was to re-induce patients with intensive combination chemotherapy with the goal of achieving a minimal residual disease (MRD) negative CR in the bone marrow, and then moving forward with an allogeneic bone marrow transplant (alloBMT). Unfortunately there is not a standard of care regimen used for relapsed B-ALL, but most regimens typically utilize combination chemotherapy that mimic induction or consolidation treatments^{4,5}. While sometimes efficacious, chemotherapy-induced remissions are not durable.

In review of the more recent single agent chemotherapies that were FDA-approved for relapsed ALL, namely clofarabine and liposomal vincristine, CR rates were less than 12% and durability of response was 5–6 months (Table 1). Twelve-month survival rates have not been reported but are likely less than 5%. Blinatumomab⁶ and inotuzumab ozogamicin⁷ are both antibody-based approaches that have demonstrated higher response rates than chemotherapy for relapsed/refractory B-ALL, with the added advantage of durability for 30–40% patients after 12 months (Table 1). However for most patients, these drugs are used as a bridge for alloBMT. Thus alloBMT with the best available donor is needed after achieving an MRD negative CR from chemotherapy or antibody-based therapy to achieve a long-term cure. While certainly effective and durable, alloBMT is dependent on the ability to find an MHC matched donor and avoidance of complications like infection and graft-versus-host-disease that can be life threatening.

3. Emergence of CD19 CAR-T cell therapy

The potential for tisagenlecleucel, formerly known as CART19 and CTL019, for CD19⁺ B-ALL emerged in a description of 2 case reports of children who went into a MRD negative CR for 2 and 11 months after infusion⁸. A CD19 negative relapse was reported in one of the patients. Results from a pilot/phase I trial and a phase I/IIa study reported a 90% MRD negative CR rate one month after CAR infusion, including in patients who had a prior alloBMT. Interestingly a variety of lymphodepletion regimens were used, with fludarabine 30mg/m² daily × 4 days and cyclophosphamide 500mg/m² × 2 days the most common.

Event-free survival at 6 months was 67% and overall survival at 6 months was 78%. CRS occurred in 100% patients, and 27% had severe CRS. All severe CRS required vasopressor support and had coagulopathy. Neurotoxicity occurred in 43% patients. Total followup on this study was up to 2 years. The durability of responses in this report correlated with persistence of CAR-T cells, as evidenced by persistent B cell aplasia. In fact none of the patients with B cell aplasia had a CD19⁺ relapse⁹.

In a followup pivotal phase II, 25 center, global trial with tisagenlecleucel for refractory or 2nd relapse of CD19⁺ B-ALL, an 81% MRD negative CR rate was observed 3 months after CAR infusion, also including in patients who had a prior alloBMT¹⁰. An intent to treat analysis of all enrolled patients, including patients who enrolled but were never infused, showed a 66% CR rate. A single lymphodepletion regimen of fludarabine 30mg/m² daily × 4 days and cyclophosphamide 500mg/m² × 2 days was used. Event-free survival at 6 months was 73% and at 12 months was 50%. Overall survival at 6 months was 90% and at 12 months was 76% (Table 1). In patients who responded, relapse-free survival was 80% at 6 months and 59% at 12 months, and CD19⁺ relapses, CD19⁻ relapses, and combinations of CD19⁺CD19⁻ relapses in the same patient were observed. CRS occurred in 77% of patients, and 48% had severe CRS requiring tocilizumab. Neurotoxicity occurred in 40% patients.

Due to repeated clinical trials showing high response rates that were more than double seen from previous therapies, high rates of durable remissions, and improved overall survival, the FDA approved tisagenlecleucel in August 2017. Now B-ALL patients have an opportunity to use CAR-T cells as a bridge to alloBMT, or as a means to replace alloBMT entirely, particularly if they do not have a potential donor or have already relapsed after alloBMT. In addition, for patients with central nervous system (CNS) relapse, is it debatable whether alloBMT improves outcomes^{11,12}. Since CAR-T cells traffic into the CNS and can effectively clear CNS disease, tisagenlecleucel is a viable option for this patient population and could spare additional long term toxicity seen with intrathecal chemotherapy and cranial radiation.

4. CAR-T cell challenges and potential solutions for moving forward

While there is a great deal of excitement in the field regarding CAR-T cell therapy, there are still several barriers to overcome. First the time for manufacturing tisagenlecleucel is 22 days, which means the time from apheresis to infusion is between 3–4 weeks. B-ALL is a disease that can quickly become rapidly progressive, and while patients can be managed with chemotherapy, there are still washout periods recommended both prior to apheresis and infusion so as not to damage the T cells. And patients are very fragile and could have a life threatening toxicity from the chemotherapy used to keep the B-ALL “in check” during the manufacturing process. Reducing the manufacturing time of CAR-T cells will be a critical goal moving forward¹. Ideally, we may reach a point where T cells do not even have to be expanded *ex vivo*, rather a patient could be apheresed, transduced and then re-infused in a matter of a day or two.

Certainly improvement needs to be made in reducing or minimizing CRS and neurotoxicity. Presently, tisagenlecleucel can only be given at select certified treatment centers under a risk

evaluation and mitigation strategy (REMS) program with elements to assure safe use (ETASU). These centers are all programs that have experience with alloBMT. While certainly tocilizumab and corticosteroids have been effective for managing CRS, being able to avoid CRS entirely would make maximize patient eligibility (particularly older patients with co-morbidities). Either using tocilizumab as CRS prophylaxis or engineering the CAR-T cells to release anti-inflammatory signals will be needed to minimize CRS, recognizing some degree of CRS is needed for the anti-tumor effect⁹. In addition, presently neurotoxicity is managed with supportive care measures, as we are only beginning to understand why patients develop neurotoxicity¹³. Again developing drugs that can minimize neurotoxicity, like anti-IL-1 therapy¹⁴, or engineering the CAR-T cells to avoid causing neurotoxicity entirely will be valuable steps going forward to avoid the need for a REMS/ETASU program.

Understanding how to best overcome relapse after CAR-T cell therapy still needs to be addressed. For CD19+ relapses, one reason is because patients lose their CAR-T cells, as evidenced by recovery of normal B cells. One reason may be related to the co-stimulatory domain within the CAR-T cells, with CD137 CAR-T cells having less capacity for exhaustion than CD28 CAR-T cells¹⁵. In these patients, re-infusion of CAR-T cells may be helpful. For CD19- relapses, re-infusion would not be useful since the B-ALL no longer expresses the target. Some patients have gone on to receive CD22 CAR-T cells and gone back into a CR¹⁶.

B cell aplasia is an “on target, off tumor” toxicity that is managed with monthly intravenous immunoglobulin infusions for probably the rest of the patient’s life. While it can be performed as an outpatient, or even at home subcutaneously, there are still increased potential risks of infection or complications from the infusions. More data is needed in terms of how long one needs CAR-T cells in their system, and whether the CAR-T cells could be safely inactivated after some period of time, allowing normal B cell recovery. It will be difficult to test this as families may be hesitant to allow the CAR-T cells to be inactivated or eliminated.

Lastly, usage of tisagenlecleucel is currently limited to B-ALL patients who are refractory or in second relapse. By definition these patients are heavily pre-treated and may have organ dysfunction or toxicities that could be exacerbated by the lymphodepletion chemotherapy or CRS associated with CAR-T cell therapy. Thus usage of tisagenlecleucel either for first relapse, as a bridge to transplant or to replace alloBMT entirely, needs to be addressed. In addition, it is easy to envision using tisagenlecleucel upfront, perhaps during induction or consolidation as a means of avoiding subsequent years of chemotherapy altogether. These questions, while intriguing, will need to be addressed through carefully designed, multi-center phase II or III clinical trials through the Children’s Oncology Group.

5. Expert Opinion

The recent FDA approval of tisagenlecleucel has converged the field of gene therapy and adoptive cellular therapy for patients with B-ALL, resulting in a real paradigm shift in how

we manage refractory and relapsed disease. The combination of high CR rates and durable remissions has led to improvements in event-free and overall survival for B-ALL.

Once a patient is identified and pre-approved as a candidate for tisagenlecleucel, leukocytes are collected by apheresis. Manufacturing is expected to take 22 days, and could be longer if there are delays. It is unclear how to best manage these heavily pre-treated and often chemo-refractory patients during this waiting period, but future research should focus on reducing the time for manufacturing and quality assurance/quality control such that cells are ready sooner (ideally less than a week).

CRS is a potentially life threatening toxicity that can be treated with tocilizumab and/or corticosteroids, but further research will need to determine if patients can use tocilizumab as CRS prophylaxis or if CAR-T cells can be engineered to avoid CRS entirely. Similarly, the need for biomarkers that can predict neurotoxicity are needed, as well as effective drugs that can prevent or treat life threatening cases. While B cell aplasia is an expected toxicity from successful persistence of tisagenlecleucel, it is unclear how long patients need to maintain B cell aplasia (and remission from leukemia) to be considered cured. A test that can measure CAR-T cells in the blood is needed so that clinicians can measure persistence in lieu of using B cell aplasia as a surrogate marker. If CAR-T cells and/or B cell aplasia do not persist, particularly within the first 12 months from infusion, future clinical trials need to determine if re-infusion an additional dose of CAR-T cells is useful or if patients need alternative therapy (e.g. alloBMT) to maintain disease remission.

CD19 negative relapse remains a major complication after tisagenlecleucel. Going forward either CAR-T cells will have to target multiple antigens, or be combined with therapies (e.g. CD22 CAR-T cells, inotuzumab, etc) that target alternative antigens, on B-ALL. Lastly more research into the late effects of CAR-T cell therapy beyond B cell aplasia (e.g. pregnancy, neurocognitive, etc) will need to be conducted. As further improvements are made in when we use CAR-T cells, how we manage the side effects and eventually how we better engineer CAR-T cells, continued progress will be made for this common cancer of childhood.

Acknowledgments

Funding

This paper was supported by grants from Stand Up To Cancer St. Baldrick's Pediatric Dream Team Translational Research Grant SU2C-AACR-DT1113, the National Institutes of Health (NIH)/National Cancer Institute (NCI) K08 CA174750, NIH/NCI P30 CA014520 to the University of Wisconsin Carbone Cancer Center and the National Science Foundation EAGER CBET-1645123. Stand Up To Cancer is a program of the Entertainment Industry Foundation administered by the American Association for Cancer Research. The contents of this article do not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.

References

Papers of special note have been highlighted as:

* of interest

** of considerable interest

1. Piscopo NJ, Mueller KP, Das A et al. Bioengineering Solutions for Manufacturing Challenges in CAR-T Cells. *Biotechnol J*. 2018;13(2).
2. Nguyen K, Devidas M, Cheng SC et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. *Leukemia*. 2008;22(12):2142–2150. [PubMed: 18818707]
3. von Stackelberg A, Volzke E, Kuhl JS et al. Outcome of children and adolescents with relapsed acute lymphoblastic leukaemia and non-response to salvage protocol therapy: a retrospective analysis of the ALL-REZ BFM Study Group. *Eur J Cancer*. 2011;47(1):90–97. [PubMed: 20970323]
4. Parker C, Waters R, Leighton C et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. *Lancet*. 2010;376(9757):2009–2017. [PubMed: 21131038]
5. Tallen G, Ratei R, Mann G et al. Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug chemotherapy: results of trial ALL-REZ BFM 90. *J Clin Oncol*. 2010;28(14):2339–2347. [PubMed: 20385996]
6. von Stackelberg A, Locatelli F, Zugmaier G et al. Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia. *J Clin Oncol*. 2016;34(36):4381–4389. [PubMed: 27998223]
7. Kantarjian H, Thomas D, Jorgensen J et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. *Lancet Oncol*. 2012;13(4):403–411. [PubMed: 22357140]
- *8. Grupp SA, Kalos M, Barrett D et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med*. 2013;368(16):1509–1518. [PubMed: 23527958]
- *9. Maude SL, Frey N, Shaw PA et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med*. 2014;371(16):1507–1517. [PubMed: 25317870]
- **10. Maude SL, Laetsch TW, Buechner J et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med*. 2018;378(5):439–448. [PubMed: 29385370]
11. Harker-Murray PD, Thomas AJ, Wagner JE, Weisdorf D, Luo X, DeFor TE, Verneris MR, Dusenbery KE, MacMillan ML, Tolar J, Baker KS, Orchard PJ. Allogeneic hematopoietic cell transplantation in children with relapsed acute lymphoblastic leukemia isolated to the central nervous system. *Biol Blood Marrow Transplant*. 2008;14(6):685–692. [PubMed: 18489994]
12. Eapen M, Zhang MJ, Devidas M et al. Outcomes after HLA-matched sibling transplantation or chemotherapy in children with acute lymphoblastic leukemia in a second remission after an isolated central nervous system relapse: a collaborative study of the Children's Oncology Group and the Center for International Blood and Marrow Transplant Research. *Leukemia*. 2008;22(2):281–286. [PubMed: 18033318]
- *13. Santomasso BD, Park JH, Salloum D et al. Clinical and Biologic Correlates of Neurotoxicity Associated with CAR-T Cell Therapy in Patients with B-cell Acute Lymphoblastic Leukemia (B-ALL). *Cancer Discov*. 2018.
- **14. Norelli M, Camisa B, Barbiera G et al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR-T cells. *Nat Med*. 2018;24(6):739–748. [PubMed: 29808007]
15. Long AH, Haso WM, Shern JF et al. 4–1BB costimulation ameliorates T cell exhaustion induced by tonic signaling of chimeric antigen receptors. *Nat Med*. 2015;21(6):581–590. [PubMed: 25939063]
- **16. Fry TJ, Shah NN, Orentas RJ et al. CD22-targeted CAR-T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. *Nat Med*. 2018;24(1):20–28. [PubMed: 29155426]

Article highlights box

- CAR-T cells are the first gene therapy approved by the FDA, and were approved for the treatment of refractory or 2nd relapse of B-ALL in children and young adults.
- Tisagenlecleucel recognizes and eliminates cells expressing CD19, resulting in higher, durable remission rates and survival rates from B-ALL than reported for previously approved drugs.
- Short term toxicities from CAR-T cell therapy include CRS and neurotoxicity, which can be life threatening but potentially reversible. Infusion of CAR-T cell therapy is required to be performed in certified centers through a REMS/ETASU program.
- B cell aplasia is an on target, off tumor toxicity from tisagenlecleucel that requires patients to receive immunoglobulin replacement indefinitely.
- Areas of active research include reducing the manufacturing time of CAR-T cells, CRS prophylaxis, mitigating neurotoxicity, and re-engineering CAR-T cells to recognize multiple antigens.
- Usage of tisagenlecleucel for 1st relapse or as part of upfront therapy will also need to be tested in multi-center clinical trials, and the field needs to determine when CAR-T cells should be a bridge to alloBMT or can replace it entirely.

Table 1:

Comparison of agents used for treatment of relapsed B-ALL

Agent	Response rate	Median Duration of Response	12 month survival rate
Clofarabine	CR 11.5%	5 months	Not reported
Liposomal Vincristine	CR 4.6%	5.75 months	Not reported
Blinatumomab	CR 17.1%	6 months	40%
Inotuzumab	CR 35.8%	8 months	30%
Tisagenlecleucel	CR 82.5%	Not yet been reached	79%

CR = complete remission