Long-term follow-up of CD19-CAR T-cell therapy in children and young adults with B-ALL

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The tremendous successes of CD19-directed CAR T cells in children and young adults with B-cell acute lymphoblastic leukemia (B-ALL) has led to the more widespread use of this important treatment modality. With an ability to induce remission and potentially lead to long-term survival in patients with multiply relapsed/chemotherapy refractory disease, more children are now receiving this therapy with the hope of inducing a long-term durable remission (with or without consolidative hematopoietic cell transplantation). While overcoming the acute toxicities was critical to its broad implementation, the emerging utilization requires close evaluation of subacute and delayed toxicities alongside a consideration of late effects and issues related to survivorship following CAR T cells. In this underexplored area of toxicity monitoring, this article reviews the current state of the art in relationship to delayed toxicities while highlighting areas of future research in the study of late effects in children and young adults receiving CAR T cells.

LEARNING OBJECTIVES

- Review the current landscape of subacute/delayed toxicities following CAR T-cell therapy
- Identify approaches to evaluation and management of delayed toxicities following CAR T cells
- Recognize the need for study of late effects in long-term survivors following CAR T-cell therapy

Introduction

The advent of CD19-targeted chimeric antigen receptor (CAR) T cell therapy is changing the approach to the management of relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL) in pediatric patients. Over the past decade, early clinical studies have established a remarkable initial efficacy profile that led to FDA approval of tisagenlecleucel for pediatric B-ALL.[1] Cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) have been recognized as potentially severe acute toxicities of CAR T-cell therapy. Standardized grading systems, consistent monitoring, and informative correlative studies have led to improved management strategies for these acute toxicities and supported the integration of CAR T-cell therapies into standard of care.[2] In contrast, there is still limited knowledge of longer-term toxicities after CD19-CAR T-cell therapy.

As the field continues to evaluate where CAR T-cell therapy should fit in current treatment paradigms, investigating beyond the acute toxicities of these novel therapies will be critical in making informed treatment decisions. Based primarily on the experience with CAR T-cell therapy in B-ALL, this review focuses on describing the current landscape of subacute/delayed toxicities and late effects following CAR T cells in children and young adults. (Figure 1)

CLINICAL CASE 1

A 19-year-old man with relapsed/refractory B-ALL is referred for CD19-CAR T-cell therapy. He was initially diagnosed at age 15 and relapsed after completing therapy. Reinduction therapy induced a second remission, but he subsequently experienced a second bone marrow relapse. He was then referred for CAR T-cell therapy, with 50% leukemic burden in bone marrow prior to infusion. He was treated with a single infusion of tisagenlecleucel after lymphodepletion with fludarabine and cyclophosphamide. During his acute CAR T-cell treatment course, he developed grade 3 CRS, which was fully reversible with a single dose of tocilizumab. He had no evidence of ICANS. At day 30 after CAR T-cell infusion, bone marrow studies demonstrated MRD-negative remission, and he had B-cell aplasia with hypogammaglobulinemia. However,

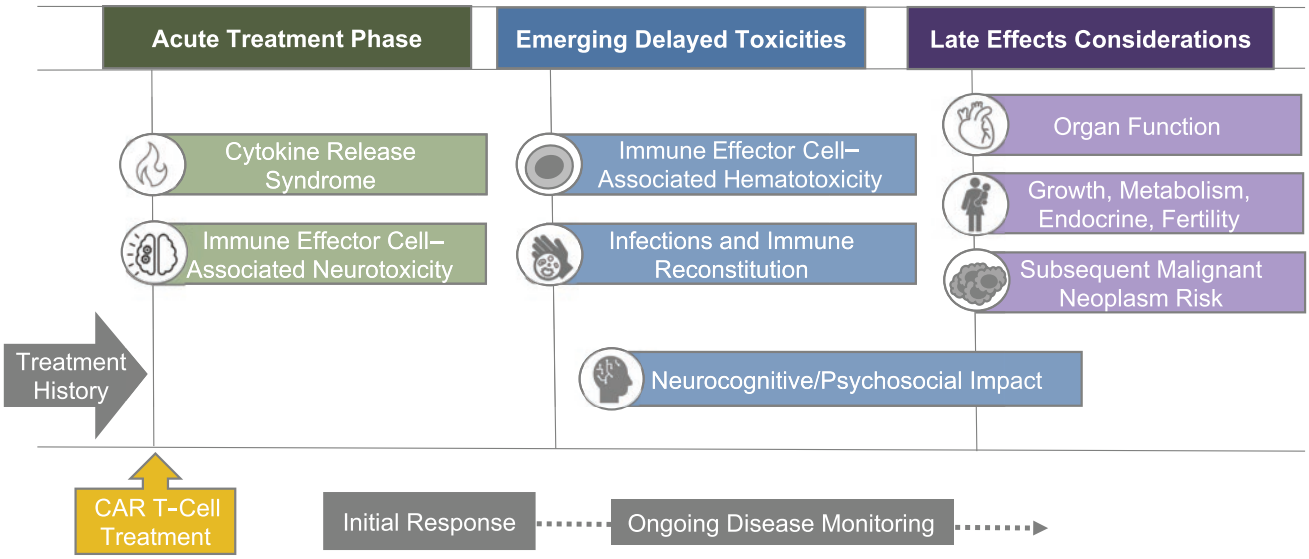

Figure 1. General approach to follow-up after CAR T-cell infusion. CAR, chimeric antigen receptor.

Table 1. Delayed and subacute CAR T-cell toxicities (≥ 30 days post infusion)

Toxicity	Presentation	Risk factors or alternate etiologies
Immune effector cell–associated hematotoxicity	Generalized cytopenias (anemia, thrombocytopenia, neutropenia) with bone marrow hypocellularity and/or transfusion dependence Bimodal pattern of presentation	CRS severity Medication effects Viral or other infection Disease relapse Delayed IEC-HS
Immune reconstitution	B-cell aplasia Persistent hypogammaglobulinemia Recurrent infections (particularly sino-pulmonary) Vaccination responses (prior titers)	On-target, off-tumor targeting
Neurocognitive function	Difficult to assess without formal testing, which would need to be done prospectively. Changes may be subtle and not consistent across domains.	ICANS, severity and association with long-term outcomes unknown
Other end organs	Organ specific (eg, persistent cardiopulmonary compromise)	CRS severity and acute impact on end-organ function during event Site of extramedullary disease

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; IEC-HS, immune effector cell–associated hemophagocytic lymphohistiocytosis-like syndrome.

he also had cytopenias with decreased bone marrow cellularity (5–10%), an absolute neutrophil count of 250 cells/μL, and platelet and red blood cell transfusion dependence. At 3 months, his repeat bone marrow confirms ongoing remission, but he remains with severe neutropenia although transfusion requirements are starting to decrease. He has not had any serious infections during this period.

Delayed toxicities of CAR T-cell therapy

Navigating the management of acute CAR T-cell–related toxicities such as CRS, ICANS, and more recently immune effector cell–associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS)[3] has been imperative in the ability to broadly use these novel immunotherapies. However, implications from these inflammatory conditions, or the treatment thereof, can impact the manifestations of delayed toxicities that occur beyond 30 days following CAR T-cell infusion (Table 1). Emerging experience has revealed bone marrow dysfunction, immune reconstitution, and neurologic impact as key areas of interest for delayed toxicities.[4]

Bone marrow dysfunction

Newly termed as immune effector cell–associated hematotoxicity (ICAHT),[5] there is an increasing appreciation that prolonged cytopenias are a delayed CAR T-cell–associated toxicity, particularly in those with severe CRS.[6] Based primarily on literature from adults with lymphoma receiving CAR T cells, hematologic recovery after lymphodepletion and CD19-CAR T-cell therapy generally follows a bimodal distribution.[7,8] While most patients

recover neutrophil, platelet, and red blood cell counts within the first month after CAR T-cell therapy, early clinical studies have reported that 40%–50% of patients have persistent grade 3–4 neutropenia or thrombocytopenia 30 days after CAR T-cell infusion.[9] While some patients recover spontaneously, up to 15% have persistent severe cytopenias beyond 3 months.[10] While prior treatment, disease burden, and baseline inflammatory status are thought to predispose to early cytopenias, risk factors for delayed cytopenias in pediatric and young adult CAR T-cell recipients have not been well described.[9]

In addition to providing transfusion support, patients with persistent cytopenias should be evaluated for any contributing destructive or consumptive etiologies.[11,12] While there are no standard definitions for bone marrow dysfunction after CAR T-cell therapy, patients meeting criteria for aplastic anemia in at least two of three cell lines or with single lineage involvement and evidence of bone marrow hypoproduction may be suspected of abnormal marrow function. While growth factors are generally used with caution after infusion due to potential for exacerbating inflammatory side effects, the benefit of granulocyte-colony stimulating factor may outweigh this risk in patients with prolonged neutropenia, particularly with active infections.[12] For recipients of prior hematopoietic cell transplant (HCT), administration of a CD34+ hematopoietic progenitor cell boost from the prior HCT donor may improve cytopenias.[13,14] Further investigation is needed to understand the etiology of prolonged bone marrow dysfunction observed in a subset of patients after CD19-CAR T-cell therapy, as this is beyond the expected recovery duration from lymphodepleting chemotherapy and not explained by direct on-target off-tumor effects. Particularly, with increasing utilization of alternative CAR T-cell constructs, monitoring for these delayed cytopenias across new trials will remain critical. Future directions seek to develop consensus grading and management approaches.[8] The impact on quality of life in patients with persistent cytopenia and utilization of health care resources are other areas of ongoing research.[11]

Immune reconstitution

With CD19-CAR T-cell therapy, B-cell aplasia is an expected on-target off-tumor effect and can serve as a surrogate marker of CAR T-cell persistence. The duration of B-cell aplasia is variable, ranging from weeks to years.[15] While sustained CAR T-cell persistence is valuable for relapse prevention, B-cell aplasia and hypogammaglobulinemia produce a humoral immune defect. While immune globulin supplementation is discontinued in some adult patients in the absence of recurrent infections despite persistent hypogammaglobulinemia, this approach has not been evaluated in pediatrics.[16] Because immune reserve is dependent on plasma cell mass, which increases with age, the adult experience cannot be directly extrapolated to pediatrics.[17] In addition to immune globulin support, prophylactic antimicrobial agents are considered for patients undergoing CAR T-cell therapy. In general, Pneumocystis jiroveci pneumonia (PJP) and herpes viral prophylaxis are recommended at a minimum until CD4+ lymphocyte counts are greater than 200/μL, though optimal duration is not well defined.[12,18,19] Practices for additional antifungal and antibacterial prophylaxis are variable and may include considerations for duration of neutropenia.

Current recommendations are to continue immune globulin supplementation in pediatric patients unless there is evidence of *de novo* production.[12,20] With this supportive care practice, the limited initial experience of late infections is low, with mild upper respiratory infections occurring most frequently.[21] Ongoing immune globulin supplementation limits the ability to assess potential vaccine response after CD19-CAR T-cell therapy. While live vaccinations should be avoided due to safety considerations in patients without immune recovery, further investigation is needed to determine whether there is any clinical benefit for attempting other re-vaccination in patients with indefinite B-cell aplasia.[16,22]

Neuropsychiatric and neurocognitive impact

In the acute setting, ICANS can have variable presentations, ranging from headache and confusion to seizures and somnolence.[23-25] While the most obvious symptoms of ICANS typically resolve within the first month, patients have not been routinely assessed for the persistence of more subtle neurocognitive changes. In quality-of-life measures, patients report that CAR T-cell therapy carries a notable symptom burden in the acute phase but improves over time after therapy.[26] However, in adult cohorts, CAR T-cell recipients report an increased incidence of neuropsychiatric symptoms compared with the general population[27] and concerns for persistence of some cognitive delay, despite generalized improvements.[28] While history of ICANS is identified as a potential risk factor for ongoing neurocognitive and neuropsychiatric effects, these have also been identified in patients who did not experience ICANS.[27,28]

Routine neurocognitive assessments and evaluation for persistent or delayed-onset neurologic toxicities incorporating patient-reported outcomes will be required to better profile the neurologic and psychosocial impact of CAR T-cell therapy. Identifying factors such as persistent anxiety, stress, or depression related to the CAR T-cell treatment experience that impact social function will be necessary to provide optimal psychosocial support to patients and families. This evaluation is complex in a cohort historically exposed to other potentially neurotoxic therapies with delayed-onset symptoms, including intrathecal chemotherapy, radiation, and HCT.[29] Capturing prior treatment exposures will be necessary to isolate which neurocognitive outcomes may be attributed to CAR T-cell therapy and will be vital for decision-making as CAR T cells are increasingly integrated into the care of children with B-ALL.

Other organ toxicities

Additional organ-specific toxicities have been identified in the acute phase after CAR T-cell therapy, particularly cardiac, pulmonary, and renal toxicities in the setting of cytokine release syndrome.[30-33] In the observed experience to date, primarily in adult patients, these effects generally improve with resolution of the acute inflammatory state.[7] With B-ALL, local inflammation at sites of extramedullary disease (eg, pulmonary, periocular) may also be associated with manifestations of unique toxicities.[32,34,35] Accordingly, as approaches in CAR T cells tar geting brain tumors evolve, recognition of tumor inflammation–associated neurotoxicity[36] necessitates both unique monitoring and treatment strategies. Evaluation of novel CAR T-cell targets for a range of malignancies will also require a high index of suspicion for new on-target, off-tumor effects. Further systematic evaluation will be required to determine the delayed toxicities of CAR T-cell therapy on systems

Table 2. Future study of late effects following CAR T-cells

	Recommendations
Long-term monitoring guidelines	At present guidelines specific to CAR T-cell long-term follow-up do not exist. Recommend use of existing guidelines for post HCT (if indicated) or completion of therapy follow-up for specific end-organ monitoring (eg, endocrinopathies, neurocognitive function, cardiac) as related to impact of therapy a patient may have received prior to CAR T-cells. Continue monitoring for B-cell aplasia, hypogammaglobulinemia, and responses to vaccination.
CAR T-cell–associated mutagenesis	To date, CAR T-cell–induced malignancies have not been seen with use of standard approaches to transduction and manufacturing approaches. Continue ongoing monitoring as novel strategies are implemented.
Second malignant neoplasms	Risk is likely not higher with use of CAR T-cells above and beyond what would be anticipated in patients with comparable lines of prior therapy. Close monitoring will be needed as patients receive fewer lines of therapy and get CAR T-cells earlier in the treatment paradigm.
Fertility	The impact of CAR T-cells on fertility is unknown. Systematic studies of patients who go on to father a child/become pregnant and have a live birth are needed. Improved strategies for implementing fertility discussion in the peri CAR T-cell setting are needed (beyond those advising on avoiding pregnancy in the immediate CAR T-cell infusion period).

HCT, hematopoietic cell transplant.

especially relevant to children and young adults, including psychosocial considerations, endocrine, growth, and metabolism, and to evaluate how the long-term risk profile of CAR T-cell therapy compares with other therapeutic options.[4]

CLINICAL CASE 2

A 23-year-old woman with a history of relapsed/refractory B-ALL is now 5 years status post tisagenlecleucel infusion. Her history is notable for a prior myeloablative total body irradiation–based allogeneic HCT from a matched sibling donor. She received CAR T cells for relapsed disease 1 year post HCT. Following infusion, she achieved a complete remission, has not received any subsequent intervention or reinfusions, and remains with B-cell aplasia requiring immunoglobulin replacement. She recently moved to a new state and is establishing care with a survivorship clinic. Her new provider asks her about recommendations for long-term follow-up after CAR T cells.

Late effects of CAR T-cell therapy

As the earliest cohorts of children and young adults who received CAR T-cell therapy for B-ALL are entering into a decade post their initial infusion, there is an emerging need to understand late effects for children and young adults who receive this novel therapy. With the goal of improving long-term durable remissions, extended follow-up from initial studies confirm that CD19-directed CAR T cells may be used as a singular therapy in a subset of patients[37] or as a bridge to HCT for others.[38,39] Experience accumulated over the past decade has generated important insights into clinical factors important for maintaining long-term durable remissions.[40,41] Evolving strategies will likely serve to help differentiate patients in whom CAR T cells will be curative as standalone therapy versus those at highest risk of treatment failure where risk-mitigation strategies to prevent relapse, such as a preemptive consolidative HCT, may be indicated, particularly for an HCT naïve patient.[42] Accordingly, the number of children and young adults who receive CAR T cells will continue to increase, as will the proportion of patients who live into the survivorship phase.

Long-term monitoring following CAR T cells

At present, there are no standard guidelines specific to long-term monitoring in recipients of CAR T cells (Table 2). As patients who are referred for CAR T cells are those with relapsed/refractory disease and have generally received multiple lines of prior therapy (including HCT) or will be receiving HCT, referral to survivorship clinics and/or adopting use of guidelines applicable to monitoring organ-specific toxicities in the post-HCT or completion of therapy setting will be critical until CAR T-cell–specific late toxicities are more well-established.[43,44] Similarly, current recommendations for screening and monitoring neurocognitive function in long-term survivors of B-ALL therapy could be evaluated for use in ongoing follow-up for patients receiving CAR T cells.[45,46]

As recent data have shown that contemporary survivors of standard-risk ALL have reduced late mortality and morbidity,[44] it will be imperative to evaluate whether long-term morbidity and mortality continue to decrease with earlier utilization of CAR T cells prior to receiving multiple lines of salvage therapy and potentially reducing the need for HCT.

CAR T-cell–associated mutagenesis (or lack thereof)

Beyond single CAR T-cell infusions, reinfusion of the same CAR T-cell product[47,48] or use of an alternative CAR T-cell construct[49] for preventing or treating post–CAR T-cell relapse is increasingly being employed. How this utilization, with receipt of multiple doses of genetically modified therapy, impacts long-term outcomes remains to be seen. Reassuringly, extensive data over numerous CAR T-cell trials have shown no evidence of replication competent retrovirus/lentivirus using standard CAR T-cell manufacturing and transduction methodologies.[50,51] However, with technological advances, ongoing monitoring will be needed—as shown in a recent case of CAR T-cell–associated lymphoma using a piggyBac-modified CD19-CAR T-cell construct.[52]

Second malignant neoplasms

In addition to considerations of CAR T-cell–associated malignancies, patients remain at risk of developing second malignant neoplasms based on their prior therapies. The additive impact of CAR T cells in this setting is unknown but reassuring, suggesting that the incremental risk of CAR T cells (and the associated lymphodepletion chemotherapy with fludarabine and cyclophosphamide) on second malignant neoplasms is not higher than what would be expected in patients who are heavily pretreated.[53,54] Earlier incorporation of CAR T cells prior to multiple lines of therapy and/or HCT may improve the risk of second malignancies overall and warrants further study.

Lineage switch, which is an immunophenotypic switch of the underlying genomic clone, as to be differentiated from a second malignant neoplasm, remains problematic—particularly in B-ALL following immunotherapy. While the overall incidence remains unknown, a recent study suggests that it comprises 7.2% of all the relapses seen following CD19-CAR T cells in a pediatric population—all of whom had poor outcomes.[55] As most cases occurred acutely (much earlier than 2 years post infusion), it remains unclear whether patients will remain at risk of lineage switch when they are several years out from CAR T cells.

Fertility following CAR T cells

As children and adolescents move into the phase of cancer survivorship, issues of fertility often move into the forefront. Guidelines for fertility preservation,[56,57] generally implemented prior to initiation of therapy—as feasible and if age appropriate—establish a critical foundation for enhancing long-term quality of life in cancer survivors. In acute leukemia, however, fertility preservation may not be possible prior to initiation of therapy, and concern for residual disease in sanctuary sites like the ovary[58] (eg, for ovarian cryopreservation) remain problematic. Additionally, in individuals undergoing myeloablative HCT with use of TBI or busulfan, gonadal toxicity is substantial, leading to permanent infertility in most patients.[59-61] In the context of CAR T cells in patients with refractory disease who have received multiple lines of prior therapy, potentially including myeloablative HCT, concerns for preexisting infertility and the need to get to CAR T cells urgently often precludes discussions regarding fertility.

Nonetheless, with increasing use of CAR T cells to spare HCT and/or additional chemotherapy, several patients who have had children after using CAR T cells (either fathered a child or became pregnant with a live birth) have been briefly reported.[62] Indeed, as CAR T cells are used earlier, the proportion of patients in whom fertility could be preserved may increase—making it imperative to systematically address fertility issues in the peri–CAR T-cell setting moving forward.

Discussion

The transformative impact of CAR T cells for children and young adults with B-ALL is undisputed. Indeed, those with chemotherapy refractory disease and whose hope of cure was dismal are now surviving. As the CAR T-cell use becomes more prevalent and moves earlier into the treatment paradigm, understanding both the subacute and delayed toxicities, alongside identifying issues unique to CAR T cells in the study of late effects and survivorship, will become paramount. As CAR T cells continue to expand in scope with novel antigen targeting, combinatorial strategies and across different diseases, issues of delayed toxicities and post–CAR T-cell survivorship will increase, particular as the therapeutic index of these novel strategies improves. We outline current considerations and anticipate tremendous growth in the study of delayed toxicities and late effects over the next decade.

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Off-label drug use

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