CAR T-Cell Therapy

Pediatric patients with relapsed and refractory acute lymphoblastic leukemia

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**BACKGROUND:** Immunotherapy provides a promising treatment option for children and adolescents with refractory or relapsed acute lymphoblastic leukemia (ALL).

**OBJECTIVES:** This article presents a hospital’s experience with providing chimeric antigen receptor (CAR) T-cell therapy, followed by a detailed discussion of the trajectory of treatment provided for pediatric patients and their families.

**METHODS:** Clinical experience in delivering care to pediatric patients undergoing CAR T-cell therapy is described. Care coordination, patient and family assessment and education, and post-CAR T-cell infusion monitoring are presented.

**FINDINGS:** Of 59 patients having been treated with CAR T-cell therapy at the authors’ institution, 93% had a complete response at day 28. The 12-month relapse-free survival rate is 55%. A multidisciplinary team of skilled clinicians is recommended to support patient and family needs throughout screening, treatment, and follow-up while coordinating care with the referring oncologist.

**KEYWORDS**
immunotherapy; CART T-cell therapy; CART-19; acute lymphoblastic leukemia

**DIGITAL OBJECT IDENTIFIER**
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**PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)** is the most common childhood cancer. About 6,000 new cases of ALL are diagnosed in the United States each year, with half of those cases involving children and adolescents (Hunger & Mullighan, 2015). Significant improvements in pediatric ALL survival rates, from less than 10% in the 1960s to as high as 90% today, have occurred because of ongoing clinical and bench scientific research. Factors contributing to improved survival include improvement in the efficacy of multi-agent chemotherapy; development of risk-stratified treatment intensity; and the addition of craniospinal radiation, cranial radiation, and intrathecal chemotherapy (Hunger & Mullighan, 2015).

About 15% of patients with pediatric ALL relapse, and cure rates are much lower after relapse. For patients who relapse after completion of therapy, the cure rate is 50%. For those who relapse while still undergoing therapy, the chance of obtaining a second remission is 50%–70%, and the cure rate is only 20%–30% (Hunger & Mullighan, 2015).

Survival rates based on risk stratification have shown that it is necessary to identify high-risk patients sooner and administer therapy based on risk. With risk-adapted therapy, the goal is to give patients the best chance of cure while minimizing unnecessary toxicity (Shalabi, Angiolillo, & Fry, 2015). Better understanding of the biology of pediatric ALL has aided the development of risk-stratified treatment regimens to administer the appropriate therapy (Tasian & Gardner, 2015). The toxicity of conventional therapy has limited the potential for dose escalations in relapsed and refractory ALL therapy. Poor salvage rates following relapse suggest that this may be because of ALL being refractory to conventional chemotherapy (Maude, Shpall, & Grupp, 2014). The decreased chance of cure because of chemotherapy resistance and poor treatment tolerance indicates the need for novel targeted therapies.

Continued research in genomics, ALL biology, and immunology has affected the discovery of more effective and less toxic targeted therapy for pediatric cancer (Lee, Barrett, Mackall, Orentas, & Grupp, 2012). This research in targeted therapies and immunologic therapies has led to phase 1 and phase 2 trials using targeted immunotherapies. The current article discusses one pediatric tertiary care hospital’s experience with providing chimeric antigen receptor (CAR) T-cell therapy to patients with relapsed or refractory ALL. An
overview of CAR T-cell therapy will be followed by a detailed discussion of the trajectory of treatment provided for the patients and families.

**Overview of CAR T-Cell Therapy**

Cancer immunotherapy uses the body’s immune system to seek out and destroy malignant disease (Lee et al., 2012). Targeted immunotherapy is the process of using tumor-specific antigen recognition. The principle advantages of this therapy is the ability of the T cells to expand and go after target cells, with the potential for surveillance through T-cell memory (Singh, Frey, Grupp, & Maude, 2016). One type of CAR T-cell therapy targets antigen CD19 (CART-19). This antigen is on the majority of all cases of ALL and is highly expressed throughout B-cell development from early pro-B cells to mature B cells (Maude, Barrett, Teachey, & Grupp, 2014).

An ideal target antigen would be universally tumor-specific and not expressed on normal cells, minimizing off-tumor toxicity (Shalabi et al., 2015). These unique antigens are difficult to find. The CD19 antigen is an excellent target for relapsed and refractory ALL because it is expressed on nearly all B-cell ALL cases and is not expressed on stem cells. However, the normal B cell expresses CD19; therefore, treatment with CART-19 therapy can result in B-cell aplasia. B-cell aplasia is treatable with immunoglobulin replacement. Unfortunately, CAR T cells cannot distinguish between a normal cell expressing the antigen and a malignant cell (Grupp, 2014).

CARs are synthetic genetically engineered molecules consisting of signal domains and an extracellular antigen binding domain derived from either murine or humanized monoclonal antibodies (Maus, Grupp, Porter, & June, 2014). This customized receptor on the T cell targets antigens expressed on malignant cells. Goals for this therapy include engineering cells to recognize and attack cancer cells, expansion of the cells in the laboratory, and proliferation after infusion in the patient. A final goal is to have the engineered cells persist for long-term surveillance, providing immunologic memory (Grupp, 2014). They have been described as a type of living drug, persisting and surveilling to hunt down any CD19-positive malignant cells. CD19 is a useful target antigen because it is expressed on almost all cases of ALL. Successful CARs in current trials include a co-stimulatory domain that results in improved T-cell proliferation and persistence (Maude, Teachey, Porter, & Grupp, 2015).

CAR T cells are personalized medicine created from T lymphocytes collected from the patient during leukapheresis, followed by a process of genetic modification and cell expansion in a manufacturing facility to produce a clinical dose of CAR T cells. The genetic modification is achieved using viral vectors to modify the T-cell DNA, with two different virus types currently in use (i.e., lentiviral and retroviral). This genetic modification allows the T cells to express the CAR, and the manufacturing process takes three weeks. Chemotherapy is given for antileukemia effect and lymphodepletion prior to the infusion. Once the CAR T cells are infused into the body, they home to and recognize the CD19 antigen expressed by B cells, resulting in a therapeutic response.

**Table 1. CAR T-CELL THERAPY CLINICAL TIMELINE AFTER DIAGNOSIS OF RELAPSED OR REFRACTORY ALL**

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<th>TIMELINE</th>
<th>PATIENT/FAMILY EXPERIENCE</th>
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| Initiation of referral | ■ Referring team and/or family contact CART T-Cell team.  
| Prior to initial consultation | ■ Nurse navigator and social worker contact family via telephone.  
| Initial consultation: First on-site meeting; outpatient stay of 3–4 days | ■ Meet with multidisciplinary team.  
| Manufacturing of CART-19 cells | ■ Manufacturing of cells can take three weeks.  
| Week 1: Prior to CAR T-cell infusion; outpatient clinic; stay locally | ■ Lymphodepleting chemotherapy for four days in outpatient setting.  
| Week 2: Infusion of therapy; outpatient clinic; return to local housing | ■ Preinfusion disease assessment: diagnostic lumbar puncture, bone marrow aspirate, and biopsy  
| Weeks 3–4: Stay locally for assessment | ■ Preinfusion assessment and laboratory testing.  
| Week 5: Stay locally for assessment | ■ Premedication with acetaminophen and antihis- tamine.  
| Week 6: Return home | ■ CART-19 IV infusion.  
| Monthly postinfusion assessment | ■ Postinfusion monitoring and laboratory testing.  
| Quarterly postinfusion monitoring and testing | ■ Possible admission with fever  
| Monthly postinfusion assessment | ■ Monitoring and laboratory testing at home hospital or CAR T-cell therapy institution.  
| Long-term follow-up | ■ Quarterly follow up with CAR T-cell therapy institution for as many as two years for monitoring and laboratory testing.  
| FDA-mandated follow-up for 15 years postinfusion | ■ FDA-mandated follow-up for 15 years postinfusion.  

ALL—acute lymphocytic leukemia; CAR—chimeric antigen receptor; CART-19—CAR T-cell therapy that targets CD19 antigen; FDA—U.S. Food and Drug Administration.
patient, they engage with cells expressing the CD19 antigen (in the case of CART-19). This engagement leads to activation of the T cell, resulting in T-cell proliferation and expansion, tumor killing, and persistence (Maude, Shpall, & Grupp, 2014).

**Clinical Timeline of a Pediatric Patient**

CAR T-cell therapy for pediatric relapsed or refractory ALL provides a new potential treatment where none existed before. The process of accessing this therapy is complex, requiring careful screening, preparation of the family, guidance for referring physicians, temporizing treatment to keep the disease under control prior to CAR T-cell infusion, and transfer of the patient for the actual cell therapy. Table 1 provides a clinical timeline for CART-19 therapy at the Children’s Hospital of Philadelphia (CHOP) in Pennsylvania.

**Screening Phase**

Following referral for CART-19 therapy, each patient undergoes a detailed review of eligibility for treatment. Eligibility screening entails evaluation of organ function, including renal, cardiac, liver, and pulmonary function. Serum chemistries, echocardiogram, and pulmonary function testing may be required to assess and document adequate organ function, particularly because all patients are currently treated on clinical trials. Similar to consideration for stem cell transplantation, patients with active, uncontrolled infections are not appropriate candidates for this treatment. Any uncontrolled active medical conditions (e.g., renal insufficiency, uncontrolled seizures) may deem a patient ineligible for the CART-19 clinical trials.

For early-phase trials at the authors’ institution, patients must have documented relapsed or refractory CD19-positive B-cell malignancies with no other curative options for therapy. The age range for inclusion in early phase trials is 1–24 years. Based on clinical experience treating children and young adults enrolled on CART-19 trials, patients with active disease should optimally have stable disease or disease that is responding to recent treatment. Patients with rapidly progressing disease may not be appropriate candidates for CART-19 therapy because the CAR T cells are expected to begin expanding 7–10 days after infusion.

Some patients considering CART-19 for relapsed ALL have undergone allogeneic stem cell transplantation as part of their prior treatment. These patients must have no evidence of active graft-versus-host disease (GVHD) and must not require immunosuppressive therapy for treatment of GVHD. Immunosuppressing agents, such as steroids, may negatively affect the ability to collect a sufficient number of T cells and may affect the ability of the reprogrammed T cells to proliferate and persist once infused (Maude et al., 2015).

**Pretreatment Phase**

Once eligibility is established, an informed consent meeting is scheduled. This meeting between the family and healthcare team outlines the CART-19 treatment plan. The risks and benefits are reviewed in detail prior to obtaining consent.

The patient must undergo leukapheresis to collect the necessary T cells that will be manufactured into the CART-19 product. Leukapheresis involves withdrawing whole blood from the patient, separating white blood cells collected, and reinfusing remaining blood components back into the patient. The ability to harvest sufficient numbers of T cells for manufacturing varies among patients. The collection of T cells is influenced by the disease and prior treatments (Miller & Maus, 2015). To increase the likelihood of success, an absolute lymphocyte count of 500 (ideally with at least 40% T cells) is recommended before proceeding with collection.

The majority of pediatric and young adult patients require the placement of a temporary apheresis catheter for T-cell collection. Prior to the placement of the apheresis catheter, the family tours the apheresis center and meets with the apheresis team to review what to expect during the collection process. The actual collection process takes about three to four hours. Once T cells are collected, the patient and family return home, and the patient usually receives bridging chemotherapy at home.

The hospital visit for T-cell collection is often the initial encounter for patient and families to the authors’ institution. This includes three to four outpatient visits and serves as a starting point to prepare families for what to expect during T-cell collection and upcoming CART-19 treatment. Typically, the first day involves meeting with the CART-19 team, along with an anesthesia visit in preparation for the apheresis line placement the following day. During this initial visit, detailed past medical, family, medication, and social histories are reviewed. The patient undergoes a physical examination, laboratory specimens are obtained, and the plan for the next few days is discussed. The third day is the T-cell collection day, and the fourth day involves removal of the apheresis catheter. Education is an essential component for preparing patients and families undergoing CART-19 therapy. This education and collaborative relationship between the team and patient/family is important to building a trusting relationship and ensuring that the patient and family are comfortable in knowing when to call for questions and concerns.
Treatment Phase
The patient receives chemotherapy prior to the CART-19 infusion to provide disease control and lymphodepletion. A typical lymphodepleting chemotherapy regimen is cyclophosphamide (Cytoxan®) and fludarabine (Fludara®). Chemotherapy reduces regulatory T cells, which may enhance the effectiveness of cell therapies (Barrett, Singh, Porter, Grupp, & June, 2014). Immunosuppressive effects of chemotherapy can help prevent the theoretical risk of immunoreactivity to CART-19, and it supports cellular expansion and proliferation (Wieczorek & Uharek, 2013).

Before the infusion and following chemotherapy, a baseline disease evaluation, including bone marrow aspirate, biopsy, and diagnostic lumbar puncture, is completed. At CHOP, CART-19 cells are infused the week after the administration of the lymphodepleting chemotherapy in the outpatient setting. Acetaminophen and diphenhydramine (Benadryl®) are administered 30 minutes prior to infusion. The CART-19 cells are infused over a few minutes, and the patient remains in the clinic following administration for observation and monitoring for about one to two hours postinfusion. To date, none of the patients have experienced allergic reactions or anaphylaxis following infusion.

Steroids may affect the efficacy of the CART-19 cells (Maude et al., 2015). Therefore, the use of steroids is strongly discouraged, including as premedications for blood products and other infusions during active treatment while the CART-19 cells persist. The reprogrammed T cells begin expanding 7–10 days after the CART-19 infusion (Grupp et al., 2013).

Anticipated Toxicities and Management
Primary anticipated sequelae after CART-19 infusion is cytokine release syndrome (CRS), which is experienced to some degree by about 90% of patients undergoing CART-19. CRS is a systemic inflammatory response produced by elevated levels of cytokines, resulting from T-cell activation and proliferation. CRS is a constellation of symptoms that can range from mild and moderate to severe. Patients may experience high fevers, myalgias, headaches, nausea, anorexia, and fatigue, but those with more severe CRS may also experience hypotension, vascular leak leading to respiratory compromise, renal insufficiency, and coagulopathy (Maude, Frey, et al., 2014).

Fever is an expected side effect following CART-19 infusion and is typically observed any time from the day of the infusion to about day 10 postinfusion. Once a fever occurs, patients are admitted to the hospital. At CHOP, standard fever criteria are used for a patient with cancer that would require admission. Nurses are often the first providers to notice a critical change in patient status and are at the forefront in providing supportive care; therefore, frequent and targeted assessments are necessary for early identification of acute changes. Other complications may include neurologic side effects, such as encephalopathy and seizures, and the long-term side effect of B-cell aplasia. A more in-depth discussion regarding the side effects and complications related to CART-19 therapy can be found in this supplement in the article by Smith and Venella (2017).

Logistics of Care During Active Treatment
To monitor and manage symptoms associated with CART-19 therapy, patients are required to stay locally for six weeks during treatment at the institution. This includes the week of chemotherapy, the infusion week, and the four observation weeks following the infusion. Patients are then followed closely and monitored frequently in the days and weeks following CART-19 infusion. Patients return to clinic multiple times the week of the infusion to monitor for side effects and then two to three days per week in the subsequent weeks if not hospitalized. These visits are a great opportunity to continue to review the expected side effects and reactions with patients and their families. Four weeks following the infusion, the patients have follow-up diagnostic procedures to evaluate disease response.

One week after completion of diagnostic procedures, the patient and family meet with the multidisciplinary team, review all results, discuss future plans and options, and then are able to return home. They are required to follow up with a combination of visits with their local oncology team and the team at CHOP. They follow up with their primary oncologist at least monthly but more frequently, if needed, for examinations or laboratory monitoring and follow up every three months for the first two years at the institution that did the CART-19 infusion. These follow-up appointments are important, particularly because this is a new engineered T-cell therapy, and any complications or issues need to be monitored and reported.

Response to Treatment
Response to treatment is evaluated at day 28 after the CAR T-cell infusion with a bone marrow aspirate, biopsy, and diagnostic lumbar puncture. Those procedures are repeated every three months for the first year to examine the presence of CART-19 cells and disease remission. CART-19 cells are found in the peripheral blood, bone marrow, and cerebral spinal fluid (even in patients without central nervous system disease) (Grupp et al., 2013).

Results from a CART-19 clinical trial in adult patients with chronic lymphocytic leukemia showed signs of clinical efficacy in two adult patients who experienced a long-term complete response (Porter, Levine, Kalos, Bagg, & June, 2011), and the first pediatric trial at CHOP showed high levels of proliferation and long-term persistence (Maude, Frey, et al., 2014). CART-19 therapy has been shown to be effective in previously treated pediatric patients with relapsed and refractory ALL, including those who relapsed after bone marrow transplantation. Of the first 59 evaluable patients treated on the first clinical trial at CHOP, the complete remission rate was 93% at day 28 after CART-19 infusion,
with a 12-month relapse-free survival rate of 55% (Maude et al., 2016).

A 100- to 100,000-fold CART-19 cell expansion is routinely observed in responding patients (Teachey et al., 2016). One of the most important predictors of response to CART-19 is expansion of the engineered T cells (Grupp, 2014). CART-19 cells are expected to achieve peak expansion at about 7–10 days postinfusion. Patients who receive this therapy have varying tumor burdens, ranging from very little disease to large tumor burdens with peripheral blasts. CART-19 cells are capable of high proliferative potential and can overcome large tumor burdens (Lee et al., 2012). Because B-cell aplasia is a continued effect of CART-19, the presence or absence of normal B cells is a way to measure the functional persistence of CART-19 cells (Maude et al., 2015). B-cell aplasia indicates CART-19 cell persistence; conversely, return of B cells indicates lack of persistence of CART-19 cells. Early B-cell recovery could be concerning for the risk of disease recurrence.

Two major goals for CART-19 therapy are proliferation and persistence. Persistence is needed for surveillance and long-term disease control. In patients not eligible for stem cell transplantation, lack of persistence of CART-19 cells is less likely to produce long-term remission (Maude, Frey, et al., 2014). CART-19 cells have the capability of inducing remission for patients with refractory disease to initial therapy, re-inducing remission for patients with relapsed disease, consolidating patients with persistent minimal residual disease, bridging to stem cell transplantation, or, in cases of long-term persistence and disease control, replacing transplantation (Grupp, 2014).

**Relapses**

Two different mechanisms of relapse have been observed and are associated with reappearance of CD19-positive or CD19-negative ALL. Relapses with CD19-positive ALL result from short-term persistence of the CART-19 cells. The disappearance of CART-19 cells can be indicated by research tests detecting CART-19 cells or by the evidence of normal B-cell recovery. Therefore, CD19 markers should be monitored monthly to determine presence or absence of CART-19 cells. CD19-negative relapses are not prevented by the persistence of CART-19 cells. Single-target therapy may lead to escape variants, a CD19-negative population of ALL cells that are not recognized by the remaining CART-19 cells (Maude et al., 2015). In the initial trial at CHOP, 20 of 59 patients relapsed, 13 of which were CD19-negative relapses (Maude et al., 2016). Therapies are being discussed to prevent CD19-negative relapses.

**Psychosocial Care Needs During CAR T-Cell Treatment**

Relapse after treatment or refractory disease adds significantly to the stress of patients and families, and this is almost always the case for children treated with this therapy. Adding to the stress is the need for families to seek treatment in a different location from their home and treatment hospital. Potential loss of community support and treatment hospital relationships built over the years since original diagnosis and treatment for ALL compounds family stressors. However, the overriding hope attached to success for CART-19 treatment is a powerful mitigator of that stress.

Potential social and emotional challenges faced when contemplating entry into immunotherapy for relapsed or refractory ALL should be evaluated through a family-centered psychosocial lens (Kearney, Salley, & Muriel, 2015), as well as through the broader view from the integrative model of pediatric medical traumatic stress (Price, Kassam-Adams, Alderfer, Christofferson, & Kazak, 2016). Of the many documented stressors identified in the extensive pediatric oncology psychosocial care literature, specific ones may be most relevant to CART-19 therapy. Emotionally, patients and their families may have fear about whether the treatment will help and concern that this is the child’s last chance to get better. In terms of financial stressors, patients and families experience short-term relocation (six weeks) to another town that may be far from home. Incomes may be decreased with one or both parents unable to work. Patients and their families may also experience social stress, with loss of proximity to an established support community because of relocation and isolation. Role relationship may also be a stressor, with job loss, parenting changes, family disruption with having to relocate and potentially split the family unit, sibling issues, and caregiver burden. Finally, patients and families may experience stress related to relationships with the care team because of new providers, unfamiliar hospital environments, prior experiences that may affect building trust, and clarity of communication and expectations (Gage-Bouchard, LaValley, Panagakis, & Shelton, 2015; Price et al., 2016; Rodriguez et al., 2012; Rosenberg et al., 2013).

From referral through treatment, a number of interventions and systems are in place to address potential challenges. The social worker on the team assesses financial hardships for the family and helps with local housing and identification of additional resources (Pelletier & Bona, 2015). Research grant funding covers travel and lodging reimbursement to help defray financial concerns. A strong parent–provider relationship, with clear communications about treatment goals, risks, and prognosis, is known to decrease family stress (Kearney et al., 2015). Balancing giving information with discussion to support shared decision making with the patient and family, along with assessment and support of previous coping strategies, provide key supports (Kazak et al., 2015).

**Implications for Practice**

- Become familiar with targeted immunotherapy for relapsed or refractory acute lymphoblastic leukemia as a novel therapy with the potential to provide curative treatment for children and adolescents.
- Use a multidisciplinary approach to support patient and family needs throughout screening, treatment, and follow-up while coordinating care with the referring oncologist.
- Prepare patients and families to receive chimeric antigen receptor T-cell therapy with ongoing education.
Multidisciplinary Approach to Patient Management

A multidisciplinary team approach is imperative for the support of patients and their families throughout CAR T-cell therapy. The multidisciplinary team at CHOP has expanded based on understanding the complex needs of patients and families. Currently, the individuals on the team include an intake coordinator, insurance specialist, nurse navigator, social workers, nurse practitioners, and physicians. The nurse navigator and intake coordinator roles were added to manage increasing referrals over time. While patients are at the institution for T-cell collection, they interface with other departments, including anesthesia, interventional radiology, and apheresis. When patients and families are at the institution, the CAR T-cell therapy team, inpatient and outpatient nurses, child life specialists, bone marrow transplantation team, pediatric intensive care unit, and emergency department staff provide ongoing care. With increasing numbers of patients being treated, it has also been necessary to assemble a research team at the hospital to help families and meet complex regulatory and study requirements. Research study team members include a program manager, team managers, data coordinators, and clinical research coordinators.

Clear and open communication among all team members is necessary for a successfully functioning team. In addition, frequent communication from the CAR T-cell therapy team to the referral team is needed to provide ongoing feedback about treatment and synchronize care when the patient is ready to return home. Care coordination is vital.

Conclusion

CART-19 therapy is an exciting novel targeted immunotherapy, with the benefits of targeting a specific antigen on a tumor cell, potential for expansion in the patient, and potential for long-term persistence for disease surveillance. This therapy has shown encouraging responses in patients with relapsed and refractory ALL who have otherwise limited treatment options.

Patients and families seek out treatment following their own searches for viable options and come to the consultation visit with numerous questions and expectations. Nurses play a significant role in providing family-centered education, safe care for patients, effective, age-appropriate communication, and anticipatory guidance and education for pediatric patients and their families.

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