

CART-Cell Therapy in Pediatric Acute Lymphoblastic Leukemia: A Review for General Pediatricians

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Chimeric antigen receptor (CAR) T cell therapy has transformed outcomes for children and young adults with relapsed/refractory CD19+ B-cell acute lymphoblastic leukemia (B-ALL), enabling deep remissions even in patients who are refractory to chemotherapy or have relapsed after hematopoietic stem cell transplantation (HSCT). Use of adoptive cellular immunotherapy requires a strict clinical pathway and is delivered at designated CART-cell centers. Initial complete remission rates are high and often MRD (minimal residual disease)-negative, but relapse remains frequent through loss of persistence or antigen escape. Key acute toxicities are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), whereas longer-term issues include prolonged cytopenias, infection risk, B-cell aplasia, and hypogammaglobulinemia requiring immunoglobulin replacement. This narrative review for general pediatricians reviews the current state-of-the-art of CART-cell therapy for ALL and summarizes key principles about CART-cell indications, production, outcomes, complications, and relevant issues for shared-care centers on follow-up in the short and long term.

INTRODUCTION

Successful clinical trials have steadily improved outcomes for childhood acute lymphoblastic leukemia (ALL), with a cure rate now around 85%.¹ However, a subset of patients experience refractory or relapsed disease that requires intensive chemotherapy and hematopoietic stem cell transplantation (HSCT), both of which carry significant toxicity and poorer outcomes.

In recent years, the therapeutic landscape for B-cell ALL (B-ALL), particularly relapsed/refractory B-ALL, has evolved rapidly with the development of immunotherapies.^{2–4} These therapies harness immune cells to enhance tumor recognition and clearance.

Chimeric antigen receptor (CAR) T cell therapy is a form of cellular immunotherapy in which either autologous or allogeneic T lymphocytes are engineered to express a synthetic receptor that recognizes a tumor-associated antigen allowing selective targeting of malignant cells. CD19 CART-cells can induce deep remission in children and young adults with relapsed/refractory B-lineage-ALL both as salvage therapy after HSCT and, in certain subgroups, as a potential alternative to HSCT.^{4–8}

Currently, tisagenlecleucel is the only US Food and Drug Administration (FDA)-licensed product for children and young adults and is indicated for patients aged 25 years or under with B-ALL that is refractory, in second or later relapse, or relapsed post-HSCT.⁹ The CIBMTR (Center for International Blood and Marrow Transplantation Research) post-authorization registry, which holds the largest

abstract

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body of real-world data on its use, recorded 974 such patients across North America and Asia through May 2023 since its approval in 2017.¹⁰ Reporting to the registry is voluntary, so this figure likely understates the true number treated.

As indications expand and use increases, pediatricians outside specialized CART-centers are increasingly likely to encounter children who have received this treatment early post-discharge and during long-term follow-up.

This review summarizes what pediatric oncologists and community pediatricians involved in shared-care need to know about CAR T treatment, including indications, outcomes, key complications, and practical implications for shared and long-term care.

PRINCIPLES OF CART-CELL THERAPY

What is a CAR?

A CAR is a synthetic hybrid receptor engineered into T cells, combining an antibody-derived antigen-binding domain (single-chain variable fragment) with intracellular T cell activation domains. This allows CART-cells to recognize tumor surface antigens without requiring HLA-mediated (HLA antigen) antigen presentation, making the approach applicable to most patients.

An ideal CART-target antigen is selectively expressed on the tumor cells. However, targets shared with normal tissue may still be useful if the associated on-target but off-tumor effects are manageable. CD19-directed CART-cell therapy is a classic example: CD19 is expressed on leukemic and

normal cells of the B-cell lineage. Although targeting CD19 results in B-cell aplasia, this is effectively mitigated with immunoglobulin (Ig) replacement therapy.

Several CAR designs have been proposed over the last 3 decades, but most licensed products are “second-generation” CARs, incorporating an activation domain (CD3 ζ) plus a co-stimulatory domain (commonly CD28 or 4-1BB/CD137).¹¹ Co-stimulation enhances expansion and persistence of CART-cells and is critical for durable antileukemic activity. For example, the CD19-CAR in tisagenlecleucel uses 4-1BB co-stimulation, which support longer persistence than CD28-constructs, enabling use as a standalone therapy¹² (Figure 1).

Clinical Pathway: From Referral to Infusion

In routine practice, CART-cell therapy is delivered at highly specialized academic centers because of the need for expert toxicities management, including access to the pediatric intensive care unit (PICU) and neurology support. Rigorous protocols guide the treatment pathway, from referral and assessment to infusion and post-infusion management (Figure 2).

Patients are typically referred by their primary oncologist to a Foundation for the Accreditation of Cellular Therapy-accredited CART-cell delivery center.¹³ Several online resources can help locate these centers (eg, the Kymriah treatment center locator). Center choice may depend on insurance requirements, product availability, institutional referral relationships, family preferences, and manufacturing slot availability.

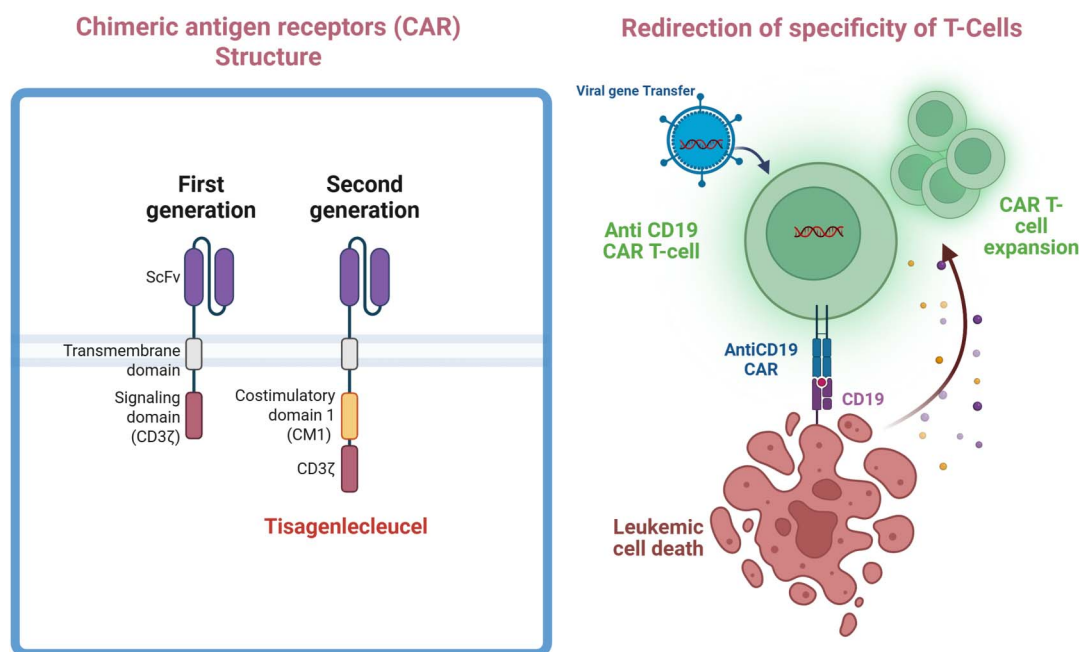


FIGURE 1.

(A) Structure of chimeric antigen receptor and (B) T cells expressing CD19 CAR killing CD19+ target and starting to proliferate.

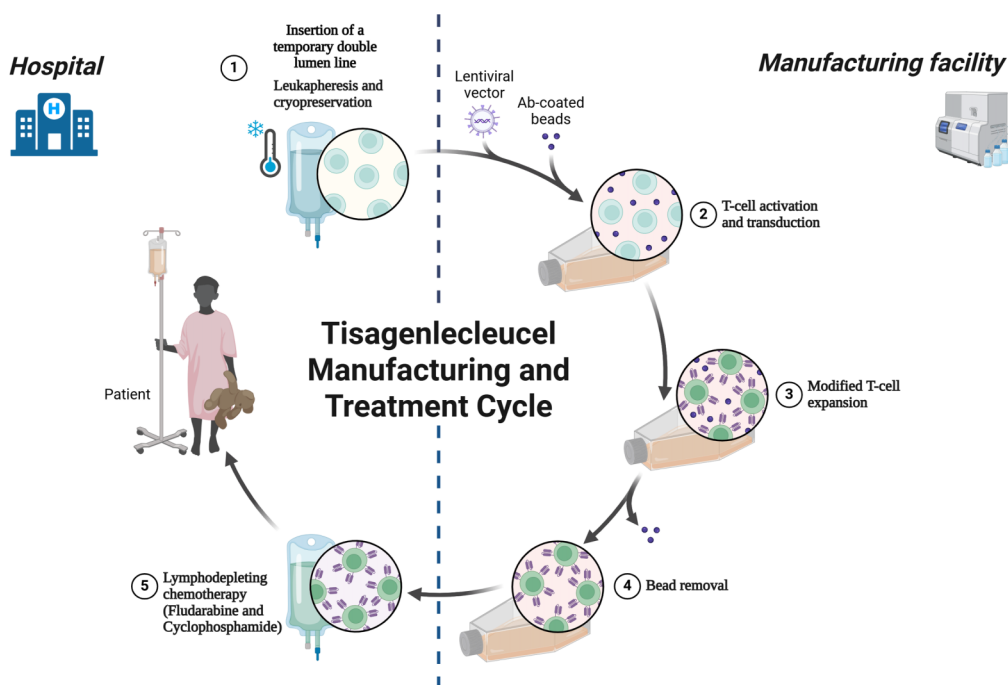


FIGURE 2.
CD19 CAR T manufacturing process.

Following discussion between the primary oncologist and the CART-cell center, patients undergo specialist assessment to confirm eligibility and obtain consent. Patients then undergo leukapheresis, and peripheral mononuclear cells are shipped to a centralized manufacturing facility. T cells are isolated and activated (generally with CD3/CD28 stimulation) and then transduced with a viral vector carrying the CART transgene. The modified cells are expanded to the required dose, cryopreserved, and shipped back to the treating center.¹⁴ This process usually takes 3 to 4 weeks.

To prevent disease progression during this period, most patients need “bridging chemotherapy”¹⁵ to maintain disease control before CART-cell infusion. The CART-cell center typically provides guidance on the regimen, which is often delivered at the referring oncology center. The aim is not necessarily to achieve deep molecular remission but to reduce the leukemic burden before infusion and hence reduce the risk of severe toxicity and disease relapse. Close communication between the primary oncologist and the CART-cell center about complications and disease status is critical during this period.

Before infusion, patients undergo reassessment, including bone marrow and cerebrospinal fluid (CSF) disease assessment, infections screening, and organ function testing. Once the product is ready, the patient is admitted and receives lymphodepleting chemotherapy, most commonly fludarabine and cyclophosphamide before CART-cell infusion. Lymphodepletion creates an immunologic

environment that favors CART-cells expansion and persistence by depleting endogenous lymphocytes, including regulatory T cells, and eliminating cytokine sinks, thereby increasing the availability of homeostatic cytokines such as interleukin (IL)-7 and IL-15 that promote CART-cell proliferation and survival.^{16,17} Importantly, this treatment is not myeloablative, but it contributes to early cytopenia and infection risk.¹⁸

CART-cells are thawed and infused intravenously. Following infusion, CART-cells expand in vivo (often peaking over the first 1–2 weeks), driven by recognition of the target antigen. Persistence is critical in ALL: durable CD19-CAR function is associated with ongoing B-cell aplasia (absence of B-cells in the peripheral blood), which becomes a practical surrogate marker of CAR activity.¹⁹ Most patients remain inpatient for 2 to 4 weeks for toxicity monitoring and disease assessment at 1 month post-infusion. In selected patients, outpatient CART-cell infusion is feasible²⁰ and is increasingly adopted, thus requiring robust infrastructure, reliable caregiver support, close monitoring, and a low threshold for admission.

INDICATIONS

Core Pediatric Indication

Tisagenlecleucel is licensed by the FDA⁹ for children and young adults aged 25 years and under with B-ALL that is refractory or in second or later relapse.

Patients referred for CART-cell therapy are heavily pretreated children with multiple relapsed/refractory diseases, often with previous HSCT and exposure to immunotherapy, such as blinatumomab (bispecific T cell engager) and inotuzumab (antibody drug conjugate), and intensive chemotherapy. For this reason, they may have significant baseline vulnerability to infections, organ toxicity, and psychosocial challenges.

Outcomes

Across trials and real-world data, CD19-directed CART-cell therapy induces high initial complete remission (CR) rates in pediatric B-ALL (80–90%), with most responders achieving minimal residual disease (MRD) negativity.^{6,7,21,22} MRD in leukemia refers to the presence of leukemic cells below the threshold of detection by the conventional morphological methods. Patients who achieve morphological CR may still harbor significant residual disease detected by sensitive techniques like flow cytometry, PCR techniques, and next generation sequencing (NGS). MRD is the most powerful marker of disease response and outcome of B-ALL treatment.²³ In the pivotal ELIANA study,⁴ most responding patients achieved MRD-negative remission within the first month. Real-world data and meta-analyses of pediatric/adolescent and young adult (AYA) studies confirm these high CR and MRD-negative CR rates overall.^{24,25} Importantly, in contrast to chemoradiotherapy, a cytogenetic risk group does not appear to affect CR rates or relapse-free survival after CD19-CART-cell therapy.²⁶ Furthermore, CART-cells traffic to the central nervous system (CNS). Although patients with isolated CNS relapse were excluded from the original licensing study for tisagenlecleucel, subsequent real-world data have confirmed efficacy in this setting,²⁷ and CD19-CART are routinely used in such patients as long as CNS disease has cleared before therapy.

Durability of Response

B-cell aplasia and persistence of circulating CART-cells are markers of ongoing CART-cell activity. Residual disease in the marrow or loss of B-cell aplasia are key early predictors of relapse.²⁸ Specialist centers commonly reassess disease every month in the first 3 months post-infusion and then every 3 to 6 months for 1 to 2 years according to local practice.⁶ Increasingly, the NGS-MRD monitoring^{29,30} is added to flow cytometry to improve sensitivity because MRD re-emergence can be an early sign of relapse.

Despite excellent initial remission rates, many patients relapse or lose CART-cell persistence; the disease-free survival of patients treated with CD19 CART-cell therapy as a standalone therapy is around 40% to 50%.³¹ Most relapses occur within the first year, so surveillance is highest during this period. Two broad patterns of relapse are recognized (Figure 3)^{14,32}:

- CD19-positive relapse: more common pattern, generally linked to inadequate persistence/early loss of CART-cells. A practical surrogate for CART-cell loss is B-cell recovery. Early loss of B-cell aplasia particularly within 6 months after infusion is associated with high rates of CD19-positive relapses³⁰ unless patients receive further therapy with consolidative HSCT, maintenance low-intensity chemotherapy, or reinfusion of CART-cell.
- CD19-negative relapse/antigen escape or lineage switch: here the leukemic cells evolve to downregulate CD19 so they are no longer vulnerable to the antileukemic effect of persisting CART-cells. In this situation, potentially curative option requires reinduction with chemotherapy or immunotherapy targeting other receptors such as CD22 (inotuzumab) followed by HSCT.¹⁴

Factors that appear predictive of relapse after CD19 CAR T cell therapy include high tumor burden,²⁵ relapse less than 6 months post HSCT,³³ previous nonresponse to blinatumomab,³⁴ and detection of MRD post infusion.³⁰

Positioning of CART-Cell Therapy in the B-ALL Treatment

Tisagenlecleucel is licensed by the FDA and European Medicines Agency (EMA) for children and young adults aged 25 years and under with B-ALL that is the following:

- primary (fails to achieve CR after 2 lines of standard frontline chemotherapy) or secondary (fails to achieve CR after 1 cycle of standard re-induction therapy for relapse) refractory,
- second or later relapse,
- relapsed after SCT, or
- relapsed but not fit for SCT because of comorbidity or lack of a suitable donor.

The excellent outcome achieved with the current frontline chemotherapy for B-ALL, the integration of immunotherapies such as blinatumomab³⁴ and, in addition, the cost and complexity of CAR T cell therapy, make it difficult to justify its use in the front line in most patients with ALL.

Despite this, there is growing interest in moving CART-cell therapy to earlier treatment lines for selected high-risk patients. The National Comprehensive Cancer Network guidelines²⁸ now include tisagenlecleucel as a category 2B option for patients with persistent MRD positivity after consolidation; this indication has been investigated by the Cassiopea study (NCT03876769) which results are awaited. Additionally, CART-cell therapy is increasingly favored over HSCT for relapsed patients in CR2 because of its relatively favorable toxicity profile, which avoids the short-term mortality and late effects of HSCT. In such patients, the decision of which therapy to offer requires multidisciplinary discussion taking into account disease status, fitness for HSCT, the

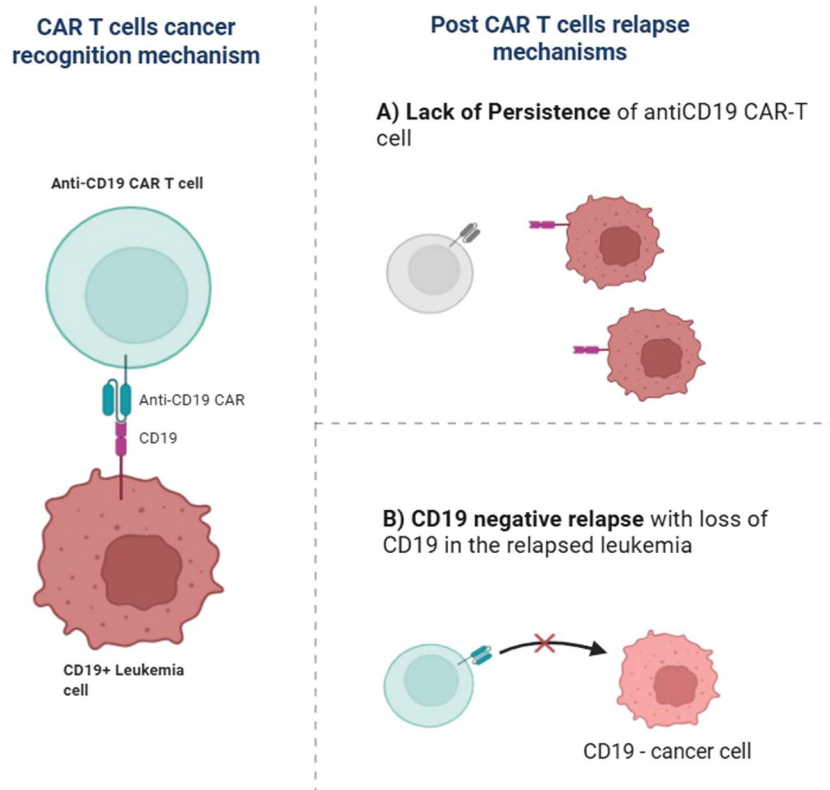


FIGURE 3.
Post CD19 CAR T cell relapse mechanisms.

availability of an HLA-matched donor, and patient and parents' wishes.

CART Vs HSCT: Bridge, Alternative, or Both?

A major dilemma is whether CART-cell therapy should be used as definitive therapy or as a bridge to allogeneic HSCT. Evidence remains limited, lacking randomized prospective trials.^{35,36} Around 35% to 40% of children achieve long-term remission with CAR T cell therapy as a standard treatment, but the risk of relapse is substantial. The decision to proceed to transplant is tailored to the individual patient and is influenced by whenever they have had a previous HSCT, the level of disease burden, and how refractory the disease has been previously. In general, patients who have had a previous HSCT and those that have low disease burden before CAR are often treated with CART-cells alone, proceeding to HSCT if they lose CAR T cell persistence in the first 6 months post infusion, whereas in patients with high disease burden or other high-risk features, CART-cells may be used as a bridge to HSCT, especially if HSCT-naïve.³⁵

POTENTIAL COMPLICATIONS

CART toxicities can be divided into early immune effector toxicities (days/weeks) and later complications (months/years), particularly immune dysfunction and cytopenias.

Cytokine Release Syndrome

Cytokine release syndrome (CRS) is an acute systemic inflammatory syndrome driven by a self-perpetuating cycle of inflammation after CAR engagement and target cell killing.^{8,12} Clinically, it typically presents with fever and can progress to hypotension, capillary leak, hypoxia, and multi-organ dysfunction, often in the first week after infusion (timing can vary by product and disease burden). Because of the possibility of CRS, CART-cell centers require onsite PICU, and close liaison between CART and ICU teams is critical. The severity is assessed by American Society for Transplantation and Cellular Therapy (ASTCT) criteria³⁷ and correlates with a high pre-infusion disease burden. Most patients (60%) will experience only fever (CRS grade 1) whereas some will need an escalation of supportive care (O₂ therapy or management of hypotension with fluid replacement). Patients that have a partial or no response to the supportive care (persistent O₂ requirement or hypotension requiring several fluid boluses or inotropes) are treated with tocilizumab, an IL-6 receptor blocking antibody. Prompt use of tocilizumab improves symptoms and does not compromise the efficacy and persistence of CART-cells.⁸ Early recognition of CRS is critical, and close monitoring of oxygen requirement, hypotension, and capillary leak is mandatory. Although the pattern of the CRS is

usually predictable, it is difficult to differentiate it from sepsis, so patients are usually treated also with broad-spectrum antibiotics from the onset of fever.³⁷ In patients where severe CRS is refractory to tocilizumab, steroids are used as second line therapy.

Immune Effector Cell–Associated Neurotoxicity Syndrome

Immune effector cell–associated neurotoxicity syndrome (ICANS) is a neurological syndrome that can follow immune-activating therapies, including CART therapy. It often follows CRS but can occur independently. Presentations range from mild confusion/aphasia to seizures and, rarely, cerebral edema. A baseline neurological assessment of the patient is important, and several scores (Cornell Assessment of Pediatric Delirium for <12 years

old, ICE for >12 years old) can help the clinicians in their evaluation of the severity of ICANS, whereas the grading is done according to ASTCT criteria (Table 1).³⁷

Supportive care includes clinical neurological assessment, Electroencephalogram (EEG), neuroimaging, close metabolic monitoring, and exclusion of infection. Steroids are the mainstay of treatment. Tocilizumab is used when ICANS occurs with CRS but is not reliably effective for isolated neurotoxicity because of poor penetrance through the blood-brain barrier. Death by cerebral edema and severe sequelae (eg, profound weakness/quadruparesis) have been reported in adults but are very rare with the licensed product in children. Although typically occurring in the second week post infusion, ICANS can happen later when the patient is already at home. For this reason, any new confusion, speech disturbance, focal neurological deficit, severe

TABLE 1. ASTCT ICANS Consensus Grading

Age, years		Grade 1	Grade 2	Grade 3	Grade 4
<12	CAPD score	1–8	1–8	≥9	Unable to perform CAPD
≥12	ICE score	7–9	3–6	0–2	Unable to perform ICE
All ages	Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimuli	Requires vigorous or repetitive tactile stimuli
All ages	Seizure	N/A	N/A	Any clinical seizure that resolves quickly or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
All ages	Motor weakness	N/A	N/A	N/A	Hemiparesis, paraparesis
All ages	Elevated ICP/cerebral edema	N/A	N/A	Focal edema on neuroimaging	Decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, Cushing's triad or signs of diffuse cerebral edema
CAPD score (children <12 years)	Never (4 points)	Rarely (3 points)	Sometimes (2 points)	Often (1 point)	Always (0 point)
Eye contact with the caregiver					
Actions deliberated					
Aware of their surroundings					
Communicate their needs and wants					
	Never (0 points)	Rarely (1 point)	Sometimes (2 points)	Often (3 points)	Always (4 points)
Is the child restless?					
Is the child inconsolable?					
Is the child underactive?					
Does it take the child a long time to respond to interactions?					
ICE score (adults and children ≥12 years)	Never (4 points)	Rarely (3 points)	Sometimes (1 point)	Often (1 point)	Always (1 point)
	Orientation to year, month, city, hospital	Naming three objects	Following simple commands	Writing a standard sentence	Counting backwards from 100 to 10

Abbreviations: ASTCT, American Society for Transplantation and Cellular Therapy; CAPD, Cornell Assessment of Pediatric Delirium; ICANS, immune effector cell-associated encephalopathy; ICE, immune effector cell-associated encephalopathy score; ICP, intracranial pressure; N/A, not applicable.

headache, or persistent vomiting needs prompt evaluation and an urgent escalation to the CART center and pediatric critical care.

Immune Effector Cell–Associated HLH-Like Syndrome

A rare subset of patients develops a hyperinflammatory syndrome, now termed immune effector cell–associated HLH-like syndrome (IEC-HS). The IL-1 receptor anakinra and steroids are the mainstay of treatment. Coagulopathy can occur in severe inflammatory states; monitoring for hypofibrinogenemia and replacing fibrinogen when indicated is important.

Cytopenias: Early, Prolonged, and Late

Cytopenias are common after CART-cell therapy. Early cytopenias are expected following lymphodepletion; however, prolonged (30–90 days) and late (>90 days) cytopenias also occur, with multifactorial mechanisms including inflammation, infections, marrow suppression, and (rarely) secondary marrow pathology.³⁸ In pediatric/AYA tisagenlecleucel cohorts, significant proportions have thrombocytopenia/neutropenia at day 28 and some have cytopenias persisting beyond 3 months. Cytopenias can show a “biphasic” pattern, with a second nadir around weeks 3 to 4 in some patients. Severity of CRS/ICANS often correlates with prolonged cytopenias in observational data.³⁹

The presence of prolonged neutropenia and thrombocytopenia drives infection and bleeding, increases transfusion needs, and complicates returning to a normal life. Neutropenia is the most common cytopenia, requiring antifungal and antibacterial prophylaxis and use of G-CSF in some cases. When the cytopenia is severe or prolonged, a work-up for infections and medication-related marrow suppression is advisable. If cytopenias are prolonged or late, marrow evaluation is often recommended to assess for relapse and secondary marrow disorders.

Infection Risk and Immune Dysfunction

Infection risk is increased by previous therapies, lymphodepletion, cytopenias, and the B-cell depleting nature of CD19-directed CART-cell therapy. Studies in children support antimicrobial prophylaxis aligned to local epidemiology and proactive early management of febrile episodes, recognizing that CRS-related fever can be difficult to distinguish from bacterial sepsis. A longer-term issue is hypogammaglobulinemia as a natural consequence of the prolonged B-cell aplasia correlated with CAR T cell persistence, which necessitates Ig replacement. Many institutions administer intravenous Ig replacement on a monthly-basis or subcutaneous Ig weekly starting when the IgG level drops below 4 g/L to mitigate the potential risks associated with long-term hypogammaglobulinemia, such as recurrent respiratory tract infections. Up to 50% of pediatric patients have partial or full recovery of normal B-cells 6 to 12 months

after infusion. Vaccinations are generally recommended to commence at least 2 months after Ig replacement has ceased, except for the COVID and seasonal influenza vaccine that can be given earlier.

Genotoxicity

Finally, because viral transduction introduces the CART transgene throughout the genome, there is a theoretical risk of insertional mutagenesis resulting in transformation of CART-cells in T-lineage leukemia/lymphoma originating from the infused product. However, T cells are terminally differentiated, so this risk appears very low: in a global survey of centers treating children and young adults with CART no cases of insertional mutagenesis were reported after 3582 infusions.⁴⁰ Importantly, because CART are transduced ex vivo, there is essentially no risk of genotoxicity in the gametes. Nonetheless, patients are routinely counselled before consent about the potential risk of genotoxicity, and those of child-bearing age are recommended to use contraception during and immediately after CART treatment.

IMPLICATIONS FOR SHARED AND LONG-TERM CARE

CART-cell therapy changes the “aftercare” landscape. Many children will transition back from high-intensity tertiary oncology care to a shared-care model involving the primary oncology center, primary care physicians, and community services and immunology input. Patient care is typically transitioned from the CART-cell center to the referring/primary oncology centers around day 30. During the first year, visits are usually monthly and subsequently spaced out based on patient characteristics and institutional practice. These visits alternate between the CART-cell center and the primary oncology center, coordinated with the scheduled disease surveillance assessments performed at the CART-cell center. During visits with primary oncologist, serial blood counts, lymphocyte subpopulation with absolute CD19 positive B-cell quantification, and serum Ig levels are obtained. Results are reviewed in coordination with the CART-cell center. Intravenous Immunoglobulin (IVIG) replacement is coordinated with the shared-care model between the CART-cell and the primary oncology centers.

CONSIDERATIONS FOR PRIMARY ONCOLOGIST

The transition of care requires clear communication about the date of CART-cell infusion/reinfusion, type of product infused (commercial use of tisagenlecleucel or CART as a part of a clinical trial), and whether the patient had significant CRS/ICANS or ICU admission. Additional information is the plan for MRD surveillance, presence of ongoing B-cell aplasia, the patient’s antimicrobial prophylaxis and IVIG schedule, recent blood counts, need for Granulocyte Colony Stimulating Factor (G-CSF) or blood products, and scheduled follow-up at CART-cell center.

CART-cell therapy–related complications tend to follow a broad temporal pattern. In the early period (first 3–6 weeks), patients may develop late CRS or immune effector cell–associated neurotoxicity syndrome (ICANS), as well as acute complications such as febrile neutropenia. During the intermediate phase (approximately 2–6 months), cytopenias, infections, and immune dysfunction are common. In the later phase (>6–12 months), attention shifts to immune reconstitution, vaccination planning, and monitoring for persistent cytopenias in a minority of patients, along with addressing psychosocial and neurocognitive recovery.

FEVER AND ACUTE ILLNESS: A PRACTICAL APPROACH FOR GENERAL PEDIATRICS

CART-cell recipients are immunocompromised because of the underlying leukemia, previous exposure to multiple lines of chemotherapy including HSCT, lymphodepletion before CART-cell infusion, neutropenia, B-cell aplasia, and hypogammaglobulinemia associated with CART-cell therapy. Hence, fever is treated as significant in these patients, especially in the first months. In clinical practice, children presenting with fever are typically evaluated and managed according to the local febrile neutropenia/immunocompromised child pathway. Outside of the early post-infusion period when the patient is already at the CART center, CRS is uncommon and infectious complications are more frequent. In this context, communication with the tertiary CART-cell center is often part of the management of unwell patients.

MONITORING AFTER CART-CELL THERAPY

Following CART-cell therapy, ongoing monitoring is typically coordinated between the CART-cell center and the patient's primary pediatric oncology team. In addition to disease surveillance, follow-up commonly includes monitoring of blood counts and management of cytopenias.

Monitoring of Ig levels and B-cell aplasia is also an important component of follow-up. Hypogammaglobulinemia frequently persists while B-cell aplasia remains present, and Ig replacement varies with institution. Some centers administer monthly replacement regardless of IgG levels, whereas others aim to maintain serum IgG concentrations above approximately 4 g/L. Some patients with longer hypogammaglobulinemia will switch to subcutaneous IG with liaison with immunology team.

Infectious risk remains an important consideration during this period. Many patients continue antiviral or antifungal prophylaxis after CART-cell therapy, although the specific regimen varies between institutions and according to individual patient factors.

Vaccination after CART-cell therapy can be complex because immune reconstitution occurs at variable rates, and Ig replacement therapy may attenuate vaccine responses; therefore most vaccines (with the exception of

seasonal influenza and COVID-19, where T cell responses may be beneficial) are not indicated while on Ig replacement. Vaccination, coordinated with the CART center, is resumed after B-cell recovery and return of endogenous IgG production, typically 3 to 6 months after Ig replacement has been discontinued. National guidelines on revaccination post chemotherapy/HSCT should be adhered to.⁴¹

LONG-TERM PLANNING: VIGILANCE FOR RELAPSE AND TRANSITION

Relapse risk is highest early but persists beyond 1 year for some patients; mechanisms include antigen escape and loss of CART-cell persistence. Although B-cell aplasia serves as a useful marker of ongoing CART-cell activity, it does not guarantee sustained disease control, and bone marrow MRD surveillance remains important. Although MRD monitoring is individualized according to patient's risk of relapse, these are usually performed 1, 2, 3, 6, 9, and 12 months post-infusion with subsequent monitoring of blood counts and lymphocyte subsets every 3 months until 2 years post-infusion.⁴

For older adolescents and young adults, early planning for transition to adult services is often considered, particularly for patients requiring ongoing Ig replacement, monitoring of late cytopenias, second malignancies, fertility, and endocrine follow-up related to previous therapies, and continued mental health support.

ECONOMICS OF CART-CELL THERAPY

One major barrier to the broader adoption of the currently approved CART-cell product is the cost, largely reflecting its bespoke manufacturing process. The list price of tisagenlecleucel (Kymriah) in the United States is \$475 000 per 1-time administration.⁴² However, the total cost of the care from leukapheresis through 2 months post-infusion is estimated at \$612 779, with about 22.5% (\$137 636) representing costs beyond the drug itself. These additional costs largely relate to management of adverse events (\$70 968; 51.6%), inpatient and intensive care unit admissions not attributed to adverse events (\$57 952; 42.1%), and laboratory tests and procedures (\$5209; 3.8%).⁴³

In the United States, insurance coverage also influences access to CART-cell therapy. Medicare provides coverage for CART-cell therapy, whereas Medicaid coverage varies by state, with some states applying more restrictive eligibility policies.^{44,45}

Despite the high upfront cost, tisagenlecleucel is considered cost-effective in pediatric relapsed/refractory B-cell ALL. Because it can produce durable remissions in children who would otherwise have a very poor prognosis, the incremental cost per quality-adjusted life-years (QALY) gained ranges from roughly \$25 000 to \$65 000, far below the commonly cited \$100 000 to \$150 000/QALY willingness-to-pay threshold in the United States. The high upfront cost

is offset by large lifetime health gains and avoidance of ongoing treatment costs.^{43,46,47}

FUTURE DIRECTIONS

The major challenges in CART-cell therapy for B-lineage-ALL are to improve the persistence of CART-cells and prevent CD19-negative relapse. New approaches, including strategies that preserve early stem cell memory T cells and vaccinations, are being developed to improve CART-cell persistence. At the same time, a method to target CART-cells to multiple antigens (eg, CD19 and CD22)^{48,49} is being developed to overcome these challenges. If such approaches can improve disease-free survival rates so that they are equivalent to blinatumomab followed by HSCT, CART-cell therapy has the potential to obviate the need for HSCT with its toxicity and late effects. More broadly, the current methodology for ex vivo generation of CART-cells is costly and logistically complex, limiting access in many countries and restricting its use in ALL to patients with relapsed/refractory disease. In the future, in vivo CART approaches, in which the patient's T cells are converted into CART-cells inside the body using delivery systems that carry gene-transfer or gene-editing machinery, may streamline production with off-the shelf reagents, lowering the cost of manufacturing, shortening the time to treatment, and enabling broader access. Proof-of-principle for generating CART in vivo has recently been demonstrated in adult patients with myeloma using infusion of a lentivirus encoding a CAR that specifically targets T cells, eliminating the logistical issues associated with ex vivo CART production.⁵⁰ If this approach can be extended to ALL, it has the potential to reshape the indications for future CART-cell therapy and enable its extension to use in frontline therapy, particularly for the highest-risk patients.

Finally, use of CART therapy, originally conceived for treatment of malignant diseases, is quickly expanding its application in the context of immune diseases like scleroderma and systemic lupus erythematosus with good results and will likely become part of the treatment pathway for refractory diseases going forward.⁵¹

CONCLUSION

CART-cell therapy has transformed outcomes for children and young people with relapsed/refractory CD19+ B-ALL, achieving high rates of deep remission and offering the possibility of durable disease control in a population with few alternatives. Tisagenlecleucel is currently the only FDA-approved licensed CART-cell therapy for children and young adults with relapsed/refractory B-ALL.

Primary oncologists and general pediatricians play a key role in management of these patients and close communication with the CART center both during bridging therapy and after infusion, clear family education on red flags, and proactive preventive care (vaccines, Ig replacement

coordination, school reintegration) are critical for effective shared care and safe and optimal outcomes. As experience with CART-cell therapies grows and indications expand, increasing numbers of pediatric oncologists and eventually community pediatric providers will encounter these patients in routine clinical practice. This evolving landscape highlights the importance of coordinated shared care and familiarity with the unique clinical issues that arise after CART-cell therapy.

ABBREVIATIONS

ASCT: autologous stem cell transplantation
B-ALL: B-cell acute lymphoblastic leukemia
CAR T: chimeric antigen receptor T cell
CRS: cytokine release syndrome
FDA: US Food and Drug Administration
HLA: HLA antigen
HSCT: hematopoietic stem cell transplantation
ICANS: immune effector cell-associated neurotoxicity syndrome
ICER: incremental cost-effectiveness ratio
MRD: minimal residual disease
PICU: pediatric intensive care unit
QALY: quality-adjusted life-year

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