Current Hematologic Malignancy Reports (2019) 14:561–569
https://doi.org/10.1007/s11899-019-00544-6

CART AND IMMUNOTHERAPY (M RUELLA AND P HANLEY, SECTION EDITORS)

Driving the CAR to the Bone Marrow Transplant Program

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Published online: 23 October 2019

Abstract

Purpose of Review The US Food and Drug Administration (FDA) approved two commercially available chimeric antigen receptor (CAR) T cell therapies for the treatment of relapsed B cell acute lymphoblastic leukemia (B-ALL) children and young adults less than 25 years of age and non-Hodgkin lymphoma in adults after promising results from early-phase single and multi-institutional clinical trials. In this review, we provide an overview of the practical aspects of a chimeric antigen T cell receptor (CAR-T) program development and the steps necessary for its successful implementation.

Recent Findings CAR-T therapy is a complex process and poses significant challenges as institutions prepare to deliver this therapy as a standard of care for the eligible patients. It requires a rigorous infrastructure with specific clinical, administrative, and regulatory demands. Institutions that led the clinical trials for CAR-T have adopted various approaches to integrate commercial CAR-T products into their program.

Summary Delivering commercial CAR-T cells outside the scope of clinical trials requires careful planning, allocation of resources, and utilization of existing infrastructure. Institutions may need to adapt the existing recommendations and guidelines and tailor them to meet the needs of their program and ensure appropriate financial reimbursement for this expensive but promising immunotherapy.

Keywords Chimeric antigen receptor · CAR · CD19 · CD22 · Tocilizumab · Cytokine release syndrome · Cytokine-related encephalopathy syndrome · Cellular therapy program · Acute lymphoblastic leukemia · Non-Hodgkin lymphoma · T cells · Tocilizumab · Gene therapy · Program development

Introduction

Chimeric antigen T cell receptor (CAR-T) therapy has revolutionized the field of hematologic malignancies offering a promising option for patients with relapsed/refractory disease. CARs are genetically engineered receptors consisting of antibody-mediated recognition site for the antigen of interest, T cell signaling moieties, and T cell costimulatory domains [1]. Introducing the CAR into the T cells allows recognition of the antigen expressed on the tumor cell and elimination of the tumor cell by CAR-T cell–mediated cytotoxicity, thereby harnessing the power of both the innate and adaptive immune systems [2•]. To date, clinical trials have primarily focused on CD19 expressing B cell hematological malignancies and more recently CD22 alone or both CD19/CD22 as dual targets [3••, 4, 5••, 6, 7••, 8]. The Food and Drug Administration (FDA) recently approved two CAR-T products for relapsed B cell acute lymphoblastic leukemia (B-ALL) for patients up to 25 years of age and for adults with B cell non-Hodgkin lymphomas (NHL) [9–11]. Tisagenlecleucel (CTL019), a CD19-directed CAR-T product from Novartis was the first CAR-T cell gene therapy approved in 2017 for a pediatric indication before its approval in adults [12]. Subsequently, a different CAR-T product axicabtagene ciloleucel manufactured by Kite Pharma was approved for use in adults with diffuse large B cell lymphoma (DLBCL) and aggressive B cell malignancies [13, 14]. These approvals have culminated from years of effort in clinical development and testing in single- and multicenter clinical trials. Given the FDA approvals, it is now a

This article is part of the Topical Collection on *CART and Immunotherapy*

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challenge and a task for centers as they start delivering this novel therapy outside the scope of clinical trials as an "off-the-shelf" therapy [15]. The adverse events of CAR-T cell therapies, notably cytokine release syndrome (CRS) and neurotoxicities associated with immune effector cell therapy (ICANS) are common and have been fatal in few clinical trials and with the two approved drugs [16••, 17]. Given the intricacies involved in the administration of CAR-T therapy, it is more complex to prescribe this therapy than other forms of immunotherapies or even stem cell transplant. It involves painstaking understanding of the FDA label for each patient, evaluating the availability of resources and infrastructure at the treatment centers and educating the clinicians, trainees, and nursing staff to deliver this novel therapy. In this review, we discuss the logistics of building a CAR-T cell program based on our experience at the Children's National Health System, Washington, DC pertaining to the commercial product tisagenlecleucel in the pediatric population. Furthermore, we highlight the key points related to the infusion and management of the side effects of CAR-T cell therapy.

Commercial CAR-T Products

Tisagenlecleucel (Formally Known as CTL019 and Branded as Kymriah)

Tisagenlecleucel is a second-generation CAR utilizing a single costimulatory molecule 4-1BB to promote proliferation, persistence, and efficacy. It has a murine single-chain variable fragment (scFv) to recognize human CD19 [15]. Single-center early trials in pediatric and young adults showed complete response rates up to 90%with 1-year event-free survival of 50% [3••]. ELIANA was the first pediatric global CAR-T trial of tisagenlecleucel in children and showed remission rate of 83% (95% confidence interval, 70.9 to 91%) within 3 months after a single infusion, and 62% relapse-free survival at 24 months [18••, 19•]. All patients with complete remissions had negative minimal residual disease as detected by flow cytometry. Persistence of T cells and B cell aplasia was seen for as long as 20 months in some patients. Grade 3 or 4 adverse events related to T cells were seen in 73%, and cytokine release syndrome (CRS) seen in 77% patients, 48% of whom received tocilizumab. Neurological events were seen in 40% of the patients, all of whom recovered with supportive care with no reported cases of cerebral edema. Similarly, the JULIET (Study of Efficacy and Safety of CTL019 in Adult DLBCL Patients) study (NCT02445248) evaluated the efficacy and safety of tisagenlecleucel in adult patients with relapsed/refractory diffuse large B cell lymphoma (DLBCL) in an international Phase 2a trial [19•]. A total of 93 patients received an infusion and were included in the evaluation of efficacy. The best overall response rate was 52% (95% confidence interval, 41 to 62); 40% of the patients had complete responses, and 12% had partial responses. At 12 months after the initial response, the rate of relapse-free survival (RFS) was estimated to be 65% (79% among patients with a complete response). The most common grade 3 or 4 adverse events included CRS (22%), neurologic events (12%), cytopenias lasting more than 28 days (32%), infections (20%), and febrile neutropenia (14%). Three patients died from disease progression within 30 days after infusion. No deaths were attributed to tisagenlecleucel, CRS, or cerebral edema.

Axicabtagene Ciloleucel (Yescarta)

Kite Pharma (Santa Monica, CA) recently acquired by Gilead developed CAR technology after obtaining the licensed technology from the National Cancer Institute. Axicabtagene ciloleucel also has a murine CD19-binding domain similar to Kymriah but contains both a CD28 spacer and a CD28 costimulatory signaling domain [20•]. ZUMA-1, a single-arm, multicenter, registrational trial at 22 sites in the USA and Israel recently reported the long-term outcomes in adult patients with relapsed/refractory mature B cell CD19+ malignancies [20•]. One hundred one patients were assessable for activity after a single CAR-T cells infusion with a median follow-up of 27.1 months. Eighty-four (83%) had an objective response, and 59 (58%) had a complete response with a median duration of response of 11.1 months. The median progression-free survival (PFS) was 5.9 months (95% CI 3·3–15·0). Forty-eight percent had grade 3 or worse serious adverse events. Grade 3 or worse CRS occurred in 12 (11%) patients, and grade 3 or worse neurological events in 35 (32%). Two treatment-related deaths (due to hemophagocytic lymphohistiocytosis and cardiac arrest) were previously reported in the 1-year analysis, but no new treatment-related deaths occurred during the additional follow-up.

CAR-T Clinical Trials There are over 30 clinical trials in the USA registered on clinicaltrials.gov that are currently active and/or recruiting children and adults with hematological malignancies. It is important for the clinicians to have a cross-talk between the research investigators at their institution to be aware of the clinical trials that are active or in the pipeline. This helps understand the availability and distribution of the shared resources between the clinical and the research programs prior to building the CAR-T program. The details of the clinical trials targeting CD19 and other antigens such as CD22, CD20, and CARs using humanized constructs is not in the scope of this review.

Building a CAR-T Program

Understanding the CAR-T Delivery Process

CAR-T administration is a complex process involving screening the patient for eligibility, collecting the T lymphocytes for manufacturing, shipping of the apheresis material fresh or cryopreserved to the manufacturing facility for the genetic manipulation, receiving the manufactured product, preparing the patient and the clinical team for the CAR-T infusion, and monitoring the patient for adverse events in the immediate- and short-term follow-up [15]. All patients require long-term follow-up as mandated by the FDA. Given this lengthy and complex process, the first step is to identify the key stakeholders and experts essential at each step described above and establish a multidisciplinary task force (Table 1). The purpose of this task force is to assess the resources that are required, evaluate the existing resources within the institution, and conduct a gap analysis to identify needs. This gap analysis helps justify additional staffing and collaborations required within and outside the institution and are helpful for negotiations with the hospital administration to get sufficient resources allocated for the CAR-T program. Based on our gap analysis and the moderate size of our pediatric stem cell transplant program and experience with manufacturing and administering cellular therapy including hematopoietic stem cells, ex vivo-expanded cytotoxic virus, and tumor antigen-specific T cells and mesenchymal stroma cells, we established that the CAR-T therapy would be administered by the blood and marrow transplant (BMT) program in collaboration with the apheresis program, the cellular therapy laboratory, and the immunotherapy research program..

The CAR-T Task Force

We assembled a team of clinicians, nurses, and allied health personnel from the divisions of BMT, hematologic malignancies, pediatric intensive care unit, neurology, neurosurgery, infectious disease, ophthalmology, pharmacy, apheresis, cellular therapy laboratory, interventional radiology, nursing education, and program coordinator. A lead clinician was identified whose primary role was to facilitate and harmonize the interactions between all the specialties and assign roles for each specialist in the workflow (Table 1). It is very imperative to involve the hospital's financial team from the planning phase; given the high price of this T cell therapy, they can provide their input in the workflow when dealing with public and private insurers. The task force reviewed and discussed the current literature and guidelines for management of patients receiving CAR-T therapy and built checklists for intake and apheresis, consent forms, order sets for admission and infusion, and algorithms for management of toxicities from the CAR-T cells [15, 21••]. We also reviewed the number of line placements done by our interventional radiologists and the number of stem cell harvests to ascertain the number and timing of the T cell collections that would be feasible without impacting the other aspects of the bone marrow transplant program. We created a group email system to alert all stakeholders when a patient was identified for T cell collection so as to start the financial authorization process and prepare the clinical units for the patient.

Conceptualization of Workflow

The above task force met on a weekly basis to discuss every step required from the first point of contact of an eligible patient requiring CAR-T. We reviewed our current practices and standard operating procedures and conceptualized the CAR-T delivery to mirror our autologous stem cell program. We also reviewed the literature to find current practices among larger academic CAR-T programs [15, 22]. We divided the workflow into six major processes/steps: patient intake, pre-infusion collection of material for CAR-T cell manufacturing, bridging chemotherapy, infusion, post-infusion management including mandatory reporting to governing bodies, and long-term monitoring. We hereby describe our steps which we believe are essential for the successful roll-out of a CAR-T program and depicted in Fig. 1.

Step 1: Patient Intake

We created a CAR-T referral phone line and an email to receive referrals from within and outside the institution. The program (nurse) coordinator receives the referrals and sends the patient intake form to the referring physicians to gather all the information required for screening the eligibility of the patients and insurance information to seek advice from the financial administrators to ensure eligibility to receive the therapy at our institution. Each patient is then assigned a primary CAR-T team comprised of a BMT physician and advanced practice practitioner (APP), oncology physician, and APP and a social worker. It is important that all the members of this team receive the REMS training and are registered and certified with the manufacturers to prescribe the CAR-T products and manage their side effects [15]. The CAR-T team reviews the medical history to determine eligibility for the CD19 CAR-T products. This includes confirming the presence of CD19 antigen at the time of relapse, timing of the relapse in relation to the most recent chemotherapy or allogeneic stem cell transplant received and presence of graft versus host disease and assessing toxicities from all prior chemotherapy. Patients/families must be available for in-person (preferred) or phone consultation to determine eligibility and commitment to stay within 2 h of the institution for 4 weeks

following the CAR-T cell infusion. The demand for CAR-T is high and hence it is important to assess the timely availability of the resources prior to accepting patients. The oncology team weighs in on the disease burden to determine the timing of leukapheresis and CAR-T infusion and any other chemotherapy that maybe required to be continued prior to and after the T cell collection. Patients with low disease burden are likely to receive the most benefit from CAR-T therapy both from the standpoint of efficacy and risk of cytokine release syndrome and neurological toxicities from CAR-T infusion [23]. If patients do not meet the FDA labeling of the commercial products (example, age criteria and underlying disease), then the team reviews the eligibility of the investigational CAR-T trials available at the institution. Institutions must establish a process to identify this triage process to decide the appropriate CAR-T product for the patient [7••]. In order to facilitate this intake process, we established a weekly CAR-T case conference with the CAR-T experts, oncologists, bone marrow transplant team, and the administrative staff.

Step 2: Pre-Infusion

This entails the processes necessary for the collection of T lymphocytes and storage, shipping for manufacturing, and receipt of the CAR-T product. We met with our transfusion medicine team to review the apheresis manual provided by Novartis and other investigational manufacturing sites to identify gaps in our existing SOPs for non-mobilized stem cell collections and any additional training required by the apheresis personnel, stem cell laboratory technologists, financial and nursing coordinators and then established the apheresis workflow. We followed the same model as our autologous stem cell transplant collection, for scheduling the patients for apheresis, assessing need for central line placement for the harvest, coordinated care between the CAR-T team and the pediatric intensive care unit (PICU), and post-collection chemotherapy recommendations to the patient's referring team. Our current practice is to admit the patients for the apheresis the night prior as most pediatric patients require a central line and some degree of sedation. It is also important to identify if

Table 1 Need assessments to deliver CAR-T therapy

Team	Training/oversight provided
Program administration	• Provide program oversight, resource allocation and business planning
CAR-T task force: providers from Oncology/BMT/Neurology/ PICU/Emergency Medicine/Interventional Radiology/Neurosurgery/ Nursing/Pharmacy	• Develop workflow to coordinate care at various steps of CAR-T therapy • Develop algorithms for management of CAR-T-related toxicities in compliance with ASCT guidelines and institutional practices • Develop order sets for lab monitoring and supportive care • REMS training for all providers • Develop education curriculum for all staff
Coordination: nurse coordinator	• Develop checklists to obtain referral documents • Develop workflow to coordinate with clinical/finance/referral team
Clinical team: primary CAR-T physician and nurse practitioner	• Documentation templates to deliver direct patient care in inpatient and outpatient setting
Apheresis	• Address citations or recommendations from Novartis (manufacturer) • Determine appropriate charges for clinical and research • Coordinate timing of apheresis with clinical team
Cellular therapy laboratory (CTL)	• ISBT 128 labeling • Address any citations or recommendations from Novartis (manufacturer) audit • SOP for CAR-T process • Work with finance to determine billing • Work with finance to determine who gets revenue (pharmacy vs CTL) • Validate freezing of MNC product if not within Novartis (manufacturer) specifications • Perform dry runs with Novartis • REMS training • Get training and access to CellChain
Financial services	• Insurance contracts and agreements with payors on case-by-case basis • Coordinate with clinical team with timing of treatment and insurance approvals
Legal and compliance	• Contractual agreements with manufacturer • HIPAA compliance and language for consent
Pharmacy	• Develop order sets for chemotherapy, CAR-T infusion, and treatment algorithms • Formulary oversight, verification of tocilizumab supply, and billing
Research team	• Enrollment on CAR-T trials • Capture information for reporting

cells are being collected for storage alone, or storage and shipment to manufacturing facilities, shipped as fresh or frozen. There are minimum requirements for the leukapheresis for CAR-T products including the number of CD3+ T cells to be collected, be it commercial or investigational and hence this needs to be reviewed by the CAR-T and the apheresis teams ahead of the collection. For tisagenlecleucel, there is a recommended minimum absolute lymphocyte count of 500 μl/L and absolute CD3+ T cell count of 150 μl/L [24]. The CAR-T team also needs to review the washout period from prior therapies that have been recommended by Novartis as well as published guidelines [21••, 23]. This can be a moving target in patients who have received several cycles of chemotherapy and hence leukopenic and therefore good communication between the clinical and financial teams in imperative. Tisagenlecleucel can be collected and cryopreserved for later use up to 9 months from collection, per the "at-risk collection" strategy employed by Novartis. The apheresis product can be collected at any apheresis center if the patient is not able to travel, as long as it is a Novartis-approved site for the tisagenlecleucel product. Once the T cells are collected, they are prepared for shipment per the manufacturer's guidelines. Novartis has an extensive process prior to engaging in an agreement with collection centers and cell processing facilities to ensure the harvested product meets the technical and quality standards for a high-quality CAR-T cell product. For our institution, the collection and processing happens at our own institution but other hospitals may have different practices and hence these agreements need to be thoroughly reviewed to ensure harmonization between different sites. Both investigational and commercial manufacturers have processes established to track and identify their products and use an electronic system, which requires training of clinical and non-clinical staff and on-site inspections by the manufacturers [22]. Prior to the collection, the cellular processing laboratory must ensure they have all the packaging and shipping equipment and courier setup for the pick-up of the shipment. A key focus of the FACT standards is establishing a regulated chain between the manufacturer and the treating facilities to receive the CAR-T product. This requires additional training, time, and financial resources.

Step 3: Bridge Between Collection and Infusion

Depending on the manufacturer, it may take 2–4 weeks before the CAR-T product is ready and shipped back for infusion. There are several essential steps that need to happen to ensure that the patient is ready for the infusion. In the ELIANA trial, of the 92 patients enrolled, 10 patients had severe adverse event or death precluding tisagenlecleucel infusion. Of the

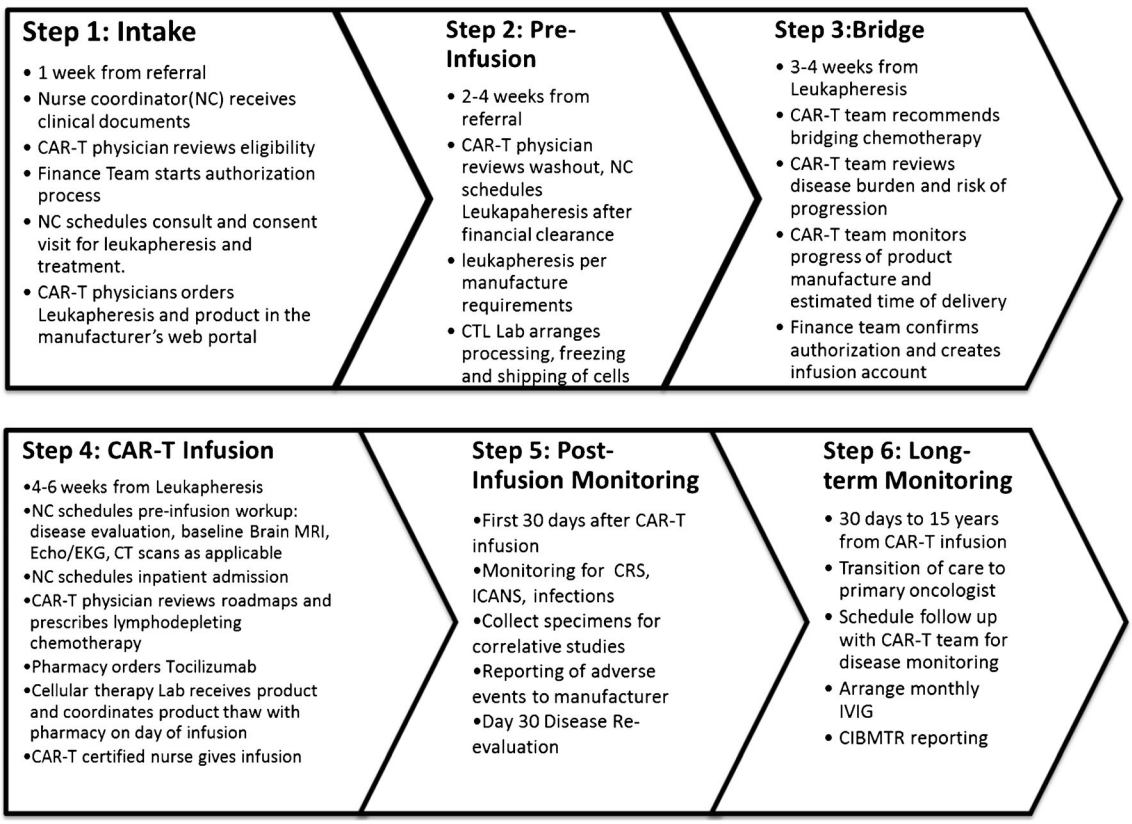

Fig. 1 Six steps identified for the building of a CAR-T program with roles and responsibilities and timeline

75 patients who received the CAR-T infusion, 65(87%) received bridging chemotherapy after T cell collection prior to CAR-T infusion. Hence, clinicians need to evaluate the likelihood of disease progression, potential for short-term complications, and time to recover from chemotherapy and the date of infusion. We also reviewed the guidelines published by the American Society of for Transplantation and Cellular Therapy (ASTCT) regarding the revised grading criteria and management of CAR-T-related toxicities [25••]. The CAR-T task force critically reviewed the recent literature on past experiences of various single and multi-institutional CAR-T trials in children and young adults for B-ALL and aggressive lymphomas [21••, 25••]. Evaluations and supportive care differ between clinical trials and vary from the institutional practices and guidelines. Hence, after rigorous discussions with all the specialists in the task force, we formulated our checklists to assess readiness for CAR-T infusion, bridging chemotherapy, work-up required prior to infusion, disease evaluation, and algorithms for the grading and management of CAR-T-related toxicities. Although there is no definitive lymphodepleting chemotherapy, clinical trials using various CAR-T products have all proved that aggressive lymphodepletion does affect the CAR-T cell expansion, persistence, and toxicities [6, 18••, 26]. We used the fludarabine-cyclophosphamide-based lymphodepletion regimen as stated in the tisagenlecleucel package insert and modified it based on the patient's absolute lymphocyte counts and CAR-T product. We developed roadmaps and order sets for the lymphodepleting chemotherapy regimen which would be given two to 7 days prior to CAR-T infusion. The order sets were reviewed by the oncology pharmacists, nursing educators, and clinicians. We also developed order sets to include all the supportive care required to manage the toxicities of CAR-T, medications, laboratory studies required for the monitoring of CRS, electronic entry of CAPD, and ICE scales for neurotoxicity management, order set for tociluzumab, and ensuring the availability of two doses per patient per tisagenlecleucel REMS requirement.

Step 4: CAR-T Infusion

In our case, tisagenlecleucel is received by the cellular therapy laboratory in collaboration with the hospital pharmacy. It is cryopreserved in a patient-specific single or double bags containing CAR-T cells ranging from 0.2 to 5.0×10^6 CAR-positive viable T cells per kilogram of body weight for patients 50 kg or less, or 0.1 to 2.5×10^8 CAR-positive viable T cells for patients more than 50 kg. The administration requires premedications with acetaminophen and diphenhydramine, priming of the tube with normal saline, and infusion within 30 min of thawing the product. The administration recommendations in the tisagenlecleucel package insert were matched with our institutional practice; the product is removed from the freezer by the cellular therapy laboratory and verified to contain the proper identifiers by at least two trained staff members. The product is then taken to the pharmacy where they print a label to accompany the product. The infusion order sets were appropriately built to reflect these practices. Hence, the cellular therapy lab needs to coordinate the thaw of the infusion to generate the patient label that matches with the CAR-T purchase order for billing before the product is brought over to the patient-care area for infusion. Appropriate time should be taken into consideration for these additional steps as the CAR-T product should be infused within 30 min of thawing. Once the CAR-T infusion is complete, the patient will need to be monitored closely either as an outpatient three times a week for the first 1 month after infusion or as an inpatient until no evidence of toxicity and/or resolution of all CAR-T cell–related toxicities. At our institution, we elected to admit the patients for the lymphodepleting chemotherapy and monitor them for at least 2 weeks following the CAR-T infusion.

Step 5: Immediate Post-infusion Care

The two common and well-described complications of CAR-T therapy are CRS and neurotoxicity, also termed as cytokine-related encephalopathy syndrome (CRES) or immune effector cell-associated neurological symptoms (ICANS) [16••, 25••, 27]. CRS is characterized by a clinical spectrum of high-grade fevers, myalgias, vascular leak, hypotension, respiratory and renal insufficiency cytopenias, coagulopathy, and cardiac dysfunction [28]. Severe CRS requiring intensive care intervention with vasopressors and respiratory support has been reported in 27 to 44% across different trials with a median onset ranging from 6 h to 22 days following CAR-T infusion [18]. The mainstay of CRS is anti-IL6receptor antibody, corticosteroids, vasopressors, and supportive care [29, 30].

CRES is potentially a life-threatening neurotoxicity, occurring in 25 to 50% of patients with symptoms ranging from headaches, mild confusion to encephalopathy, seizures, nerve palsies, and cerebral edema [18, 25••]. The severity, frequency, and patterns of CRES have differed by different CAR-T products and hence it is important to harmonize the recognition, grading, and management between commercial products and clinical trials. Our CAR-T task force reviewed the literature and the published guidelines for grading the severity and management and after discussion with all the involved sub-specialists established a treatment algorithm to reflect there commendations provided by the clinical trials and the commercial products and to match with our institutional practice [25••]. This was an important step as the choice of vasopressors, anti-epileptics, and infectious disease prophylaxis varies between institutions and clinical judgment must be used in applying these algorithms.

Step 6: Long-Term Monitoring

Patients will need to have monitoring for their underlying malignancy as well as evaluated for long-term side effects of their disease. Patients undergo disease re-evaluation at 30 days post-infusion and transitioned back to the primary oncology team for further care including monitoring for B cell recovery and need for monthly intravenous immunoglobulin replacement.

There is wide variation in the durability of CAR-T responses and lack of specific recommendations regarding the role of subsequent BMT. For patients with eligible donors and no prior BMT, the risks and the benefits of BMT must be reviewed with the patients as it can offer improvement in the 1-year event-free survival offered by CAR-T therapy alone [31], although randomized trials are needed to show the benefit of BMT over no therapy after CAR-T therapy. Hence, donor availability, history of prior transplant, preparative regimen options for the BMT, and other comorbidities must be reviewed prior to scheduling the date of CAR-T infusion.

Education of Staff and Providers

Educating the nurses, medical technologists, residents and fellows, physicians, and mid-level providers caring for patients with hematologic malignancies and stem cell transplant about CAR-T-related complications is of paramount importance [22]. This should be done prior to the roll-out of the CAR-T program and at periodic intervals to give refresher training to existing and new staff. All physicians and advanced practice practitioners, pharmacists, and nurses are required to undergo training in the FDA-mandated risk evaluation mitigation strategy provided by the manufacturers regarding CAR-T-specific toxicity and management and knowledge assessment [15, 32, 33, 34••].

Families and caregivers must also be educated regarding the toxicities and provided with the wallet-card describing the symptoms warranting urgent medical care. Many families would also require temporary housing as they are required to stay within 60 min of the treating institution for the first 4 weeks.

Regulatory Requirements Given that CAR-T is a gene therapy using lentivirus constructs, it carries the risk of malignant transformation and hence the FDA requires monitoring of these patients for 15 years after their administration [35, 36]. Hence, centers will have to prepare the administrative and clinical personnel for this reporting. Administrative staff will also be required for reporting the outcomes including all CRS and neurotoxicity as well as any other serious adverse events. For tisagenlecleucel, Novartis recommends reporting directly to the FDA via MedWatch [15]. Programs are encouraged to use the Center for International Blood and Marrow Transplantation cellular therapy data forms for the purposes of reporting [37]. To facilitate capturing the follow-up data, the patients will be required to be seen every 3 months for the first year at the least and then annually at the CAR-T treating site with regular follow-up with their primary oncology team.

Financial Implications The cost of CAR-T therapy for both the commercial products is close to half a million dollar and the total cost of care including apheresis, inpatient hospital stay including intensive care for complications is much higher. Hence, it is imperative to work closely with the hospital's financial administration. We conducted several meetings for mutual education between clinicians and non-clinicians to understand the implications of CAR-T therapy and established a workflow from the time of referral until post-infusion follow-up. Apart from the cost of the product, hospitals need to plan for the management of complications leading to hospitalizations including intensive care, which can be a huge financial risk to the institution. Novartis has a unique outcomes-based agreement wherein Novartis gets reimbursed only if patient shows significant improvement within a month of the CAR-T cell infusion. Hence, it becomes even challenging for providers to choose the patients to ensure the ability to provide a potentially life-saving therapy to a patient and the financial risk [15].

Conclusions

CAR-T therapies have changed the treatment paradigm for patients with multiply relapsed hematologic malignancies and provide a horizon in site for many patients. The delivery of CAR-T therapies is very complex and given that it stemmed from few academic centers, it will be a challenging task to deliver this therapy as a standard of care across institutions. It will require careful planning, education, and closed-loop communication between the administrative staff and the clinicians from multiple disciplines to navigate this complex process and deliver a powerful treatment to a broader population in need.

Compliance With Ethical Standards

Conflict of Interest H. D has received funding from the Lymphoma Research Foundation. L. J, none, D. J, none, P.J.H is a cofounder of Mana Therapeutics and is on the board of directors of Mana Therapeutics, C.M.B. is on the scientific advisory board (SAB) for Cellectis, has stock options in Neximmune, Torque Therapeutics, and Cabaletta Bio and is a cofounder and Scientific Advisory Board member of Mana Therapeutics.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Porter DL, Kalos M, Zheng Z, Levine B, June C. Chimeric antigen receptor therapy for B-cell malignancies. J Cancer. 2011;2:331–2.
2.• Maude SL, Teachey DT, Porter DL, Grupp SA. CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Blood. 2015;125(26):4017–23**. A comprehensive review of CD19 CAR-T clinical trials**.
3.•• Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371(16):1507–17. **Two-year follow-up of the 30 patients treated with CTL019 CD19 CAR-T cells.**
4. Davila ML, Bouhassira DC, Park JH, Curran KJ, Smith EL, Pegram HJ, et al. Chimeric antigen receptors for the adoptive T cell therapy of hematologic malignancies. Int J Hematol. 2014;99(4):361–71.
5.•• DW L, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Feldman SA, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet. 2015;385(9967):517–28**. Phase 1 clinical trial of 21 children and adults with CD19+ malignancies treated at the National Cancer Institute**.
6. Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherian S, Hudecek M, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest. 2016;126(6):2123–38.
7.•• Gardner RA, Finney O, Annesley C, Brakke H, Summers C, Leger K, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood. 2017;129(25):3322–31. **Describes the impact of lymphodepleting regimens and CD19 antigen burden on sustained CAR engraftment and durable remissions.**
8. Fry TJ, Shah NN, Orentas RJ, Stetler-Stevenson M, Yuan CM, Ramakrishna S, 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):20–8.
9. FDA approval brings first gene therapy to the United States. 2017.
10. FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma. 2017.
11. at USFaDAFatfawrorlB-clA. www. fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm606540.htm. 2018.
12. Rosenbaum L. Tragedy, perseverance, and chance - the story of CAR-T therapy. N Engl J Med. 2017;377(14):1313–5.
13. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019;20(1):31–42.
14. Locke FL, Neelapu SS, Bartlett NL, Siddiqi T, Chavez JC, Hosing CM, et al. Phase 1 results of ZUMA-1: a multicenter study of KTE-C19 anti-CD19 CAR T cell therapy in refractory aggressive lymphoma. Mol Ther. 2017;25(1):285–95.
15. Perica K, Curran KJ, Brentjens RJ, Giralt SA. Building a CAR garage: preparing for the delivery of commercial CAR T cell products at Memorial Sloan Kettering Cancer Center. Biol Blood Marrow Transplant. 2018;24(6):1135–41.
16.•• Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188–95.
17.• Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15(1):47–62. **This review describes the recommendations for monitoring and treatment for CAR-T related toxicities by the CAR-T-cell-associated TOXicity working group (CARTOX) which included experts from various institutions and disciplines with expertise in delivering CAR-T therapy in adults with leukemia or lymphoma**.
18.•• Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-Cell lymphoblastic leukemia. N Engl J Med. 2018;378(5):439–48. **Results of the phase 2 trial assessing the efficacy, safety, and cellular kinetics of tisagenlecleucel in 75 patients with at least 3 months of follow-up.**
19.• Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380(1):45–56. **JULIET trial contributing to the approval of CAR-T cells in DLBCL**.
20.• Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531–44.
21.•• Mahadeo KM, Khazal SJ, Abdel-Azim H, Fitzgerald JC, Taraseviciute A, Bollard CM, et al. Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy. Nat Rev Clin Oncol. 2019;16(1):45–63**. Guidelines for management of pediatric patients with CAR-T-related toxicities**.
22. Taylor L, Rodriguez ES, Reese A, Anderson K. Building a program: implications for infrastructure, nursing education, and training for CAR T-cell therapy. Clin J Oncol Nurs. 2019;23(2):20–6.
23. Kansagra AJ, Frey NV, Bar M, Laetsch TW, Carpenter PA, Savani BN, et al. Clinical utilization of chimeric antigen receptor T-cells (CAR-T) in B-cell acute lymphoblastic leukemia (ALL)-an expert opinion from the European Society for Blood and Marrow Transplantation (EBMT) and the American Society for Blood and Marrow Transplantation (ASBMT). Bone Marrow Transplant. 2019.
24. Pehlivan KC, Duncan BB, Lee DW. CAR-T cell therapy for acute lymphoblastic leukemia: transforming the treatment of relapsed and refractory disease. Curr Hematol Malig Rep. 2018;13(5):396–406.
25.•• Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625–38. **Most recent guidelines for grading and management of CRS and ICANS**.
26. Klebanoff CA, Khong HT, Antony PA, Palmer DC, Restifo NP. Sinks, suppressors and antigen presenters: how lymphodepletion enhances T cell-mediated tumor immunotherapy. Trends Immunol. 2005;26(2):111–7.
27. Teachey DT, Lacey SF, Shaw PA, Melenhorst JJ, Maude SL, Frey N, et al. Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Cancer Discov. 2016;6(6):664–79.
28. Fitzgerald JC, Weiss SL, Maude SL, Barrett DM, Lacey SF, Melenhorst JJ, et al. Cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. Crit Care Med. 2017;45(2):e124–e31.
29. Frey NV, Porter DL. Cytokine release syndrome with novel therapeutics for acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2016;2016(1):567–72.
30. Le RQ, Li L, Yuan W, Shord SS, Nie L, Habtemariam BA, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. Oncologist. 2018;23(8):943–7.

31. Taraseviciute A, Broglie L, Phelan R, Bhatt NS, Becktell K, Burke MJ. What is the role of hematopoietic cell transplantation (HCT) for pediatric acute lymphoblastic leukemia (ALL) in the age of chimeric antigen receptor T-cell (CART) therapy? J Pediatr Hematol Oncol. 2019;41(5):337–44.
32. Administration. USFaD. Approved risk evaluation and mitigation strategies (REMS). Kymriah (tisagenlecleucel). . 2018.
33. Administration. USFaD. Approved risk evaluation and mitigation strategies (REMS). Yescarta (axicabtagene ciloleucel). 2018.
34.•• Park JH, Riviere I, Gonen M, Wang X, Senechal B, Curran KJ, et al. Long-term follow-up of CD19 car therapy in acute lymphoblastic leukemia. N Engl J Med. 2018;378(5):449–59. **Long-term follow-up data of the CAR-T experience at Memoral Sloan Kettering Cancer Center.**
35. Wang GP, Levine BL, Binder GK, Berry CC, Malani N, McGarrity G, et al. Analysis of lentiviral vector integration in HIV+ study subjects receiving autologous infusions of gene modified CD4+ T cells. Mol Ther. 2009;17(5):844–50.
36. Services USDoHaH. Long term follow-up after administration of human gene therapy products. July 2018.
37. Pasquini MP, Real World M. Data on CAR T-cell recipients: are we there yet? The hematologist. 2019;16(2).