ASSOCIATION OF COMMUNITY CANCER CENTERS

IMMUNO-ONCOLOGY INSTITUTE

Optimizing Care Coordination

Part of the Bringing CAR T-Cell Therapy to Community Oncology Series

As the fusion of medicine, bioengineering, and multidisciplinary cancer care has meant new immunotherapies and renewed hope for patients with aggressive hematologic malignancies, chimeric antigen receptor (CAR) T-cell therapy is quickly emerging as one of the most promising treatments for B-cell acute lymphocytic leukemia, lymphoma, and multiple myeloma. The number of active clinical trials involving CAR T-cell therapy for both hematologic and solid tumor malignancies has surpassed 600 globally,[1] with no signs of slowing down. According to the National Cancer Institute, the U.S. Food and Drug Administration (FDA) has approved six CAR T-cell therapy products with more expected on the horizon.[2]

In the last five years, more than 100 institutions across the country (particularly those with existing blood and marrow transplantation programs) have become FDA-certified treatment centers for CAR T-cell therapy.[3] To do so, these institutions underwent rigorous certification under the Risk Evaluation and Mitigation Strategy (REMS) due to the risk of treatment-related adverse events, as well as accreditation by the Foundation for the Accreditation of Cellular Therapy (FACT). Yet, for patients, accessibility to these treatment centers has been difficult due to many barriers, including limited availability of delivery sites, exorbitant costs, and inadequate reimbursement.

To bridge this gap, oncologists and community-based cancer programs have built collaborative referral relationships with certified treatment delivery centers to bring these innovative therapies to their patients. However, with this rapid increase of referrals, care coordination through the complex stages of therapy can be arduous and the roles between the referring, treating, and community providers can often become blurred.

Through its initiative *Bringing CAR T-cell Therapies to Community Oncology*, the Association of Community Cancer Centers (ACCC) examines how to optimize care coordination between community oncology providers and treatment centers for seamless, integrated CAR T-cell therapy.

Understanding Collaborative Care Roles

Optimized care coordination begins with understanding the distinct roles of the collaborative care relationship and multidisciplinary engagement. The referring provider, typically a primary oncologist and their multidisciplinary care team, should be involved throughout the patient's CAR T-cell journey and effectively co-manage therapy with the treating provider (i.e., the CAR T-cell specialists at the FDA-approved treatment facility).

Considerations must also be made for community providers, the people and institutions responsible for providing care

for patients outside of the oncology treatment setting, such as primary care physicians or emergency providers, due to the risk of treatment-related adverse events, such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome. Studies from a five-year period (between 2015 and 2020) revealed approximately 80 percent of patients undergoing CAR T-cell therapy developed cytokine release syndrome, while a smaller percentage (10 percent) experienced immune effector cell-associated neurotoxicity syndrome.[4]

Due to the number of transitions and handoffs involved as patients progress through CAR T-cell therapy, it is vital that electronic health records (EHRs) are easily accessible and continuously updated with the patient's diagnosis, indication for CAR T-cell therapy, expected outcomes (including toxicities), and treatment plans. Multidisciplinary team members—the physicians, nurses, pharmacists, advance practice providers, navigators, administrative staff—who support patient referral and treatment, as well as community providers, must engage collaboratively to ensure that communication is ongoing, instructions are specific, and information is transparent throughout the continuum of care.

The care coordination process, from initial referral through CAR T-cell infusion to the final stages of patient monitoring and follow-up, should be orchestrated to optimize patient health and efficiency and minimize treatment delays.

Workflow should include the following steps but may also include additional steps to cater to specific product requirements or or individual specific product requirements or individual patient/institutional needs:

Step 1. Initial Referral
Step 2. Patient Eligibility & Selection Process
Step 3. Enrollment
Step 4. Leukapheresis (Cell Collection)
Step 5. Bridging Therapy
Step 6. Lymphodepleting Chemotherapy
Step 7. Cellular Infusion
Step 8. Post-Infusion Monitoring and Follow-Up Care

Referral, Patient Selection, and Enrollment

The first phase of treatment, encompassing referral, patient identification, and enrollment is complex. During these stages, patients are evaluated for CAR T-cell therapy eligibility and undergo consultations and clinical workup to gauge disease status and clinical qualification criteria, financial eligibility, and logistical requirements. Thereafter, lengthy processes, such as insurance pre-authorization, communicating with the manufacturer for CAR T-cell product ordering, preparative treatment, and scheduling for cell collection must be meticulously aligned between the referral and treatment provider teams.

For optimal efficiency and precision, referring providers should be well-versed in the eligibility criteria for CAR T-cell therapy and should ensure that their patients and caregivers are educated on the proposed treatment plan as well as the roles of the referring, treating, and community providers. Typically, before leukapheresis, financial authorization and pre-CAR T evaluation tests are performed.

Leukapheresis (Cell Collection)

During the leukapheresis stage, an apheresis catheter is placed and white blood cells—specifically non-mobilized CD3-positive T lymphocytes—are collected from the patient (the target number of cells is specific to each CAR T-cell product).[5] As leukapheresis can be performed in outpatient, community-based, apheresis centers registered with the FDA (typically centers that already perform stem cell transplant and cellular therapy), referring community oncology providers may opt to conduct this stage at a local apheresis facility rather than send patients directly to treatment centers, which may add unnecessary costs and/or logistical burdens for patients. Collected cells, which can usually be harvested in one session, are subsequently sent to the manufacturing facility for genetic modification to express the specific CAR, resulting in CAR T-cells.

Before leukapheresis, referring providers should educate patients and caregivers on the leukapheresis process, as well as assess patients for vascular access, complete blood count, current medications, and any history of stem cell transplantation. Clinical staff from the certified treatment center should also provide detailed patient and caregiver education on the leukapheresis stage, including discussions on potential side effects (e.g., cytopenia [low blood cell counts], hypocalcemia [low calcium levels], cardiovascular events).[6]

Bridging Therapy

As manufacturing of CAR T-cells takes at least two to eight weeks (depending on the manufacturer), there is a risk for disease progression in aggressive malignancies that, if left uncontrolled, could preclude the patient from safely receiving the CAR T-cells. Therefore, careful patient monitoring is needed by the referring community oncology center and bridging therapy may be required to control disease, debulk tumors, and maintain performance status. Specific bridging therapies are dependent on diagnosis and patient-specific factors; options include high-dose steroids, chemotherapy, targeted therapy/immunotherapy, or radiation therapy.[5]

While monitoring and bridging therapy may take place at either the referring or treating center, close communication among providers throughout this period is essential to ensuring that patient status is maintained and disease is controlled while the manufacturing of CAR T-cells progresses.

At the end of this stage, patients should transition to the treatment center (if leukapheresis and bridging has taken place at an outpatient apheresis center) for the subsequent infusion and monitoring stages. To optimize continuity of care between centers and ensure a seamless patient experience, patients and caregivers should be educated on the role the referring provider will continue to play during infusion, post-infusion, and long-term follow-up care.

Lymphodepleting Chemotherapy

During lymphodepletion, the patient's natural T-cells are depleted to promote a favorable immune environment for optimal CAR T-cell expansion. This process could require restaging the patient (particularly in cases where the patient has undergone chemotherapy in the bridging stage) and delivering lymphodepleting chemotherapy in an inpatient or outpatient ambulatory setting. If chemotherapy is delivered in an ambulatory setting, it is strongly recommended that caregivers are present 24 hours a day and that patients are located within a 2-hour/ 30-mile radius of the treating facility, in the event hospitalization is necessary.

While lymphodepletion is conducted at the treatment center, it can be beneficial for the referring provider to remain in communication with the treating team for updates on the treatment plan, patient status, and follow-up care. This includes medication reconciliation between providers before lymphodepletion to evaluate for potential drug interactions and collaboration between pharmacy and information technology departments to create electronic order sets for optimized drug delivery and safety.

Infusion, Monitoring, and Long-Term Follow-Up Care

Infusion of CAR T-cells typically takes place in an inpatient setting at the treatment center for optimal patient supervision and access to immediate care in case of adverse reactions. In some cases, CAR T-cell infusion can be conducted in outpatient settings, depending on the product and patient's risk for complications.[7]

The infusion of manufactured CAR T-cells and immediate monitoring for infusion/post-infusion toxicities should follow product-specific REMS requirements and accreditation standards as outlined by FACT. For commercially-approved CAR T-cell products, REMS requires having immediate access to two doses of tocilizumab per patient for acute cytokine release syndrome. Providers, caregivers, and patients must be trained to recognize and manage adverse reactions. Best practice guidelines recommend daily patient monitoring for the initial seven days post-infusion and weekly for a period of one month thereafter.[8]

As patient care transitions back to the referring provider from the treating provider, meticulous handoff processes with a delineated plan for follow-up care are recommended.[9] The treatment center should provide detailed medical records to the referring provider, as well as comprehensive patient education on potential treatment-related adverse events and long-term toxicities.

Patients should also be provided with immuno-oncology wallet cards (in July 2020 ACCC began offering wallet cards to cancer programs[10]) that identify them as recipients of CAR T-cell therapy and outline signs and symptoms of severe adverse reactions, as required by the FDA as part of REMS for all CAR T-cell products.[11] These cards are essential to helping community providers (primary care physicians and emergency room personnel) react quickly and administer care appropriately.

Expanded Access to CAR T-Cell Therapy

While there continue to be formidable barriers to expanded access to CAR T-cell therapy, including stringent eligibility requirements, limited FDA-approved treatment facilities, and

financial and reimbursement hurdles, close collaboration of referring oncology providers, treating CAR T-cell specialists, and local community providers and hospitals is making CAR T-cell therapy more accessible each year. Central to this collaboration is close communication, multidisciplinary engagement, and comprehensive patient and caregiver education. It is critical that referring, treating, and community providers reinforce this collaborative approach through each stage of the complex CAR T-cell journey, ensuring that patients experience seamless continuity of care as they move between providers and treatment settings.

This educational project is sponsored by Bristol Myers Squibb, Janssen Oncology, and Legend Biotech.

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This publication is produced by the education project "*Bringing CAR T-Cell Therapies to Community Oncology*", which is part of the **ACCC Immuno-Oncology Institute**. Learn more at accc-cancer.org/CAR-T-Cell.

The Association of Community Cancer Centers (ACCC) is the leading education and advocacy organization for the cancer care community. For more information, visit accc-cancer.org.