Development of a successful immune effector cell therapy program at an academic medical center: the role of the pharmacist

Chimeric antigen receptor T cell (CAR T) therapy is a form of immune effector cell therapy utilizing patients' T cells through an adoptive cell transfer process to create antitumor activity.[1] As of October 2017, two products, tisgenlecleucel and axicabtagene ciloleucel are approved by the Food and Drug Administration (FDA) to treat certain types of leukemia and lymphoma and the University of Kansas Health System is accredited to provide both treatments[2,3] The FDA requires compliance with the Risk Evaluation and Mitigation Strategy (REMS) for treatment centers to be authorized to administer these products. This innovative therapy was first of its kind and required centers to develop robust practices to support successful treatment of patients. Our program was the third institution in the country to complete all requirements to administer axicabtagene ciloleucel commercially. This treatment involves lymphocyte collection, lymphodepleting chemotherapy, cell infusion, and management of unique side effects. Developing a successful IEC program requires a multidisciplinary team. As this is a first in class treatment modality, there were no established best practice processes for the foundational development of procedures, however we were able to complete all requirements within 4 months utilizing innovative technologies. We describe the role of the pharmacist in the development of a successful IEC therapy program including efforts to streamline processes related to administrative and financial logistics, pre-treatment, cell-infusion and side effect management.

When the products were FDA approved, they were reviewed and approved at the hematology/oncology subcommittee of the health system Pharmacy and Therapeutics (P&T) Committee. Our health system is a LEAN institution; therefore, Standard Work documents were designed to ensure consistency.[4] The pharmacy and finance teams worked to develop a proactive financial workflow given the high cost of these treatment modalities. Upon approval from the patient's insurance provider the pharmacy clinical coordinator was deemed responsible for completing a clinical eligibility review based on established criteria and requesting final approval from the executive leadership team and facilitating the purchase order process.

Patient's receiving this therapy must first undergo a leukapheresis procedure to collect the mononuclear cells. A computerized order entry plan was developed in our EMR's oncology module to maintain consistent practices with other chemotherapy plans by our pharmacy information technology (IT) team. After leukapheresis the patient's cells are sent for the manufacturing process which takes approximately 2-3 weeks depending on the processing facility. In the meantime, patients are monitored closely in the ambulatory hematopoietic stem cell transplant clinic (HSCT) clinic. This clinic is open seven days a week and is staffed by a team of three pharmacists through the week and one pharmacist on the weekends. The pharmacists are essential to daily functions and work with the clinical team to monitor patient's labs and medications, provide treatment recommendations, and provide essential patient counseling. Because our HMCT clinic is well established, outpatient administration of this chemotherapy is feasible and routinely recommended to save inpatient admission days and decrease therapy costs.

Prior to the reinfusion of CAR T cells, lymphodepleting chemotherapy may also need to be initiated. Our pharmacy IT team created four individual EMR treatment plans to support use. Once ordered by the provider, the treatment plans are validated by two individual clinical pharmacists. Due to the variability of the bridging chemotherapy and the lymphodepleting chemotherapy our HSCT pharmacists are closely involved in the decision-making process as well as the chemotherapy order entry, verification and patient education. After completion of lymphodepleting chemotherapy patients are then ready for their CAR T cell infusion. To aid in the admission process we created a CAR T admission order set that contains specific nuances for CAR T patients. The products presented a unique challenge for the department of pharmacy as it has a national drug code (NDC) number but is handled outside of the pharmacy. Our apheresis team was deemed responsible for the infusion, therefore our pharmacy IT team created an electronic drug entry for each product that does not print a label to the pharmacy.

Besides the financial toxicities the primary risk of this treatment modality is the considerable risk of side effects, including cytokine release syndrome (CRS) and neurotoxicity.[5] Symptoms can range from mild to life threatening and timely monitoring is critical. In our established process, patients are directly admitted to a telecapable bed and if an intensive care unit (ICU) transfer is needed patients are admitted to a pre-specified ICU service. There are two clinical pharmacists that round seven days a week with the two HMCT teams and ICU clinical pharmacists that round with the ICU teams. Our clinical pharmacy team works directly with providers to make treatment recommendations for complex patients. Additionally, our pharmacy team completes medication reconciliation within 24 hours of admission, patient counseling during admission and discharge counseling with bedside medication delivery.

For the management of these acute toxicities the pharmacy team developed a clinical treatment algorithm after researching published literature and discussions with other institutions regarding clinical management. The algorithm was submitted for a toxicity order set within our EMR. This order set contains monitoring parameters and treatment for CRS Grades 1-4 and neurotoxicity Grades 1-4 and is a vital tool to the management of these critical patients. The CARTOX-10 assessment has been recommended for patients undergoing this treatment modality.[5] This assessment is comprised of a 10-point score and was developed electronically in our EMR flowsheet to automatically calculate the patient's score and severity of CRS based on the answers the patient provides. The development of this tool was a collaborative effort between pharmacy, nursing and the IT team. Additionally, our pharmacy IT team has also created a custom summarized report within the EMR to streamline the clinical team

process for monitoring and aid in assessment of these toxicities to quickly and accurately assess patient's symptoms for CRS and neurotoxicity as well as standardized grading documentation tool in our EMR.

With the approval of tisgenlecleucel, tocilizumab was concurrently FDA approved for the management of CRS due to clinical efficacy in trials.[6] Per the FDA REMS requirements, the pharmacy must stock a minimum of two doses of tocilizumab for each patient, available for administration within two hours.[2,3] At our organization, each patient admitted for CAR T therapy has documentation in their chart confirming these two doses being readily available by the team clinical pharmacist. Symptoms of CRS can occur quickly, therefore to ensure timely administration we created a PRN entry for tocilizumab that is released concurrently with the CAR T product order in the EMR treatment plan. To prepare for possible future admissions, we created a "prepare and give now" entry for tocilizumab within the toxicity order set. This helps providers in dosing and ensures prompt administration. Each time tocilizumab is needed BMT attending is required to call the inpatient pharmacy directly to provide the verbal order to dispense a dose. This safety step ensures that the BMT attending is knowledgeable of the patient's symptoms and agrees with use. Additionally, a second agent is available that has a similar mechanism of action, siltuximab. It is not FDA indicated for the management of CRS; however, it was added to our formulary and stocked if tocilizumab was ineffective in managing patient's acute toxicities.

Corticosteroids present a unique challenge to this patient population as they have been shown to rapidly reverse severe toxicities such as CRS but also run the risk of limiting long-term anti-leukemia effect.[7,8] It is therefore reserved for second line use after tocilizumab for CRS. To prevent unnecessary administration of steroids to CAR T patients we developed several safety mechanisms: 1) patient specific FYI in the EMR with pertinent clinical information informing staff members that the patient received CAR T therapy, 2) corticosteroid allergy placed in the patients EMR that is placed by the pharmacist 3) steroid omission from our toxicity order set 4) alert designed for staff when a steroid is being ordered that it should be reserved for life saving purposes. This alert is defaulted to avoid the steroid in the event the alert is overridden due to alert fatigue. We also built in safety mechanisms where the BMT attending must order the corticosteroids to bypass this alert. We created an alert for the emergency department staff in case the patient presented to the emergency room with delayed toxicities to inform them that the patient received CAR therapy and the BMT attending should be notified.

Lastly, in compliance with the REMs requirements, all staff who prescribe, dispense, and administer must receive direct training and this was one of the largest undertakings. Each manufacturer provides training materials, and this training must be documented and available for auditing and is the responsibility of the institution's REMs Authorized Representative. At our institution this individual is the pharmacy clinical coordinator. Live training was completed for all pertinent staff and subsequent training utilized an online learning module created by this pharmacist for institutional use. To date, over 500 staff members have received this training. Additionally, both physicians and pharmacists completed individualized competency training to ensure they were familiar with institutional practices.

To ensure success of our IEC program efforts, we worked with physicians, nurses, IT, and financial teams. The pharmacist provides a unique vantage point with their knowledge of financial, operational and clinical processes across the continuum of care from patient referral, patient education to toxicity management. We have been able to provide vital education and maintain consistent practices. We continue to develop novel ideas as the use of these therapies evolves. This new treatment modality challenged the pharmacy team to think outside the box and practice at the top of their license to develop ground-breaking tools for education, financial and clinical management to ensure successful outcomes for our patients. We are proud to serve as an example to other institutions nationally who are designing their own IEC programs.

References:

1. June CH, Sadelain M. Chimeric Antigen Receptor Therapy. *New England Journal of Medicine*. 2018;379:64-73.
2. Kymriah (tisagenlecleucel) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018.
3. Yescarta (axicabtagene ciloleucel) [prescribing information]. Santa Monica, CA: Kite Pharma Inc; 2017.
4. Liker JK, Meier D. Toyota Talent: Developing your people the Toyota way. 2007. New York:McGraw-Hill Education.
5. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy-assessment and management of toxicities. *Nat Rev Clin Oncol.* 2018;15: 47-62.
6. Actemra (tocilizumab) [prescribing information]. San Francisco, CA. Genentech Inc. 2017.
7. Brentjens RJ, Davila ML, Riviere I, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. *Sci Transl Med.* 2013;5(177):177ra38.
8. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med.* 2014;6(224):224ra25.