



The Pharmacist's Role in CAR-T Cell Therapy: From Protocol Development to Toxicity Reduction

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Abstract

Background: CAR-T cell therapy is cutting-edge immunotherapy for hematologic malignancies, and the pharmacist has a crucial role to play in its safe delivery.

Aim: Through this review, the pharmacist's role in CAR-T therapy, ranging from protocol development to toxicity management, is evaluated with consideration of real-world evidence and the future direction.

Methods: A Systematic literature review was conducted on PubMed, Embase, and Web of Science using searches for studies between 2017–2025. Relevance to pharmacist roles in CAR-T therapy informed study selection, synthesizing data on protocol management, product handling, and toxicity mitigation.

Results: Pharmacists enable regulatory compliance, manage product logistics, and guide toxicity interventions, reducing adverse events by up to 40% in some settings. Case studies illustrate outpatient care (85% ambulatory care) and tocilizumab early start (90% severe CRS prevention). Complications are supply chain interruption and limited specialist roles (20% of centers).

Conclusion: Pharmacists are the key to the success of CAR-T therapy, improving safety and outcomes. Dedicated positions and standardized training would be necessary to cope with emerging challenges, especially in outpatient and solid tumor settings.

Keywords: CAR-T therapy, pharmacist role, toxicity management, protocol development, pharmacovigilance

1. Introduction

The era of chimeric antigen receptor T-cell (CAR-T) therapy has transformed oncology, especially for hematologic cancers that are resistant to traditional therapies. CAR-T cells are genetically engineered autologous T lymphocytes with a chimeric antigen receptor directed against specific tumor antigens, e.g., CD19 for B-cell malignancies (June et al., 2018). FDA-approved since 2017, drugs including axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and brexucabtagene autoleucel (brexu-cel) have demonstrated complete response rates of greater than 50% in phase III trials (Neelapu et al., 2017). Despite these successes, CAR-T therapy is fraught with certain challenges like high costs, logistics issues, and deadly toxicities like CRS and ICANS (Lee et al., 2019).

As ATMPs, CAR-T products are governed by stringent regulatory guidelines like the FDA's Risk Evaluation and Mitigation Strategy (REMS) and the European Medicines Agency's advanced therapy guidelines (Iglesias-López et al., 2019). Hospital pharmacists form the core of this process, with product procurement, storage, preparation, dispensing, and pharmacovigilance being their duties (Booth et al.,

2020). Their drug reconciliation knowledge, patient education, and toxicity minimization ensure guideline adherence and patient outcomes (Marzal-Alfaro et al., 2021). This review addresses the pharmacist's multifaceted role, ranging from management of protocols to toxicity minimization, according to contemporary literature. It focuses on the need for trained CAR-T pharmacists and interdisciplinary training to address evolving challenges in outpatient and non-outpatient settings. The scope addresses clinical, operational, and safety aspects, focusing on evidence from clinical trials, real-world evidence, and expert guidelines.

Background on CAR-T Cell Therapy

CAR-T therapy involves patient T cell isolation by leukapheresis, viral vector transduction using a construct that encodes CAR, ex vivo expansion of engineered cells, and administration after lymphodepleting chemotherapy (Parikh & Lonial, 2023). The CAR would typically include an extracellular antigen-binding component (e.g., single-chain variable fragment against CD19), a transmembrane part, and intracellular signaling components (e.g., CD3ζ with CD28 or 4-1BB

costimulation) (June & Sadelain, 2018). Upon interaction with tumor antigens, CAR-T cells are activated, proliferate, and exhibit cytotoxicity that is not major histocompatibility complex presentation dependent (Stern & Stern, 2021). CAR generations have evolved: first-generation lacked costimulatory domains, resulting in poor persistence; second-generation (e.g., CD28 in axi-cel) induces rapid expansion but heightened toxicity; third generation possess two costimulation domains for enhanced efficacy (Geyer et al., 2018).

Approved indications are pediatric/young adult B-ALL (tisa-cel), relapsed/refractory DLBCL (axi-cel, liso-cel, tisa-cel), mantle cell lymphoma (brexu-cel), and multiple myeloma (ide-cel, cilta-cel) (U.S. Food and Drug Administration, 2024). Pivotal trials like ZUMA-1 in axi-cel had 83% ORR and 58% complete response in DLBCL, and 40% were in durable remission at 5 years (Locke et al., 2022). ELIANA for tisa-cel in B-ALL had 81% ORR and 59% event-free survival at 12 months (Maude et al., 2018). In myeloma, CARTITUDE-1 for cilta-cel had 98% ORR (Berdeja et al., 2021). These findings are corroborated by real-world data, albeit with heterogeneity based on the comorbidities of patients (Jacobson et al., 2022). While CAR-T can be potent, it is not without risk: failure of production (up to 10%), expense (\$373,000–\$475,000 per dose), and toxicities (Salter et al., 2018).

70–90% of patients develop CRS as a result of massive unheralded release of cytokines (e.g., IL-6, IFN- γ), which correlate with fever, hypotension, and organ failure (Lee et al., 2014). ICANS, in 20–60%, is the presence of neuroinflammation, seizures, and cerebral edema (Santomasso et al., 2018). Other complications include cytopenias, infections, and on-target/off-tumor effects (Brudno & Kochenderfer, 2019). Pharmacists minimize these by adhering to protocol and supportive care because REMS mandates training to handle and manage toxicity (Fala, 2018).

The Pharmacist's Role in CAR-T Protocol Management

A CAR-T program requires FACT accreditation, and multidisciplinary teams involve pharmacists to plan infrastructure and protocols (Okamoto et al., 2023). Pharmacists participate in policy, EMR integration, and order set creation (Booth et al., 2020). In one U.S. survey, 72% of centers reported involvement by pharmacists in multidisciplinary committees (Mahmoudjafari et al., 2019). Pharmacists pre-screen for readiness, including comorbidities, prior therapy, and washout times (e.g., 2–4 weeks with ibrutinib) to optimize T-cell quality (Moreno-Martínez et al., 2020). Prescribe bridging therapy like corticosteroids or radiation to control disease without T-cell depletion (Amini et al., 2022). Medication reconciliation for interactions, such as live

vaccines off-limits because of immunosuppression (Dioverti et al., 2022).

During leukapheresis, pharmacists offer anticoagulation orders and coordinate transport to manufacturers (e.g., Novartis for tisa-cel) (Paroder et al., 2020). To lymphodepletion (e.g., fludarabine/cyclophosphamide), they verify dosing based on renal/hepatic function and hypersensitivity screening (Jacobson et al., 2022). Protocols also include pre-medicating with acetaminophen and antihistamines to prevent infusion reactions (Awasthi et al., 2023). Table 1 & Figure 1 summarize the pharmacist's responsibilities in CAR-T protocol management.

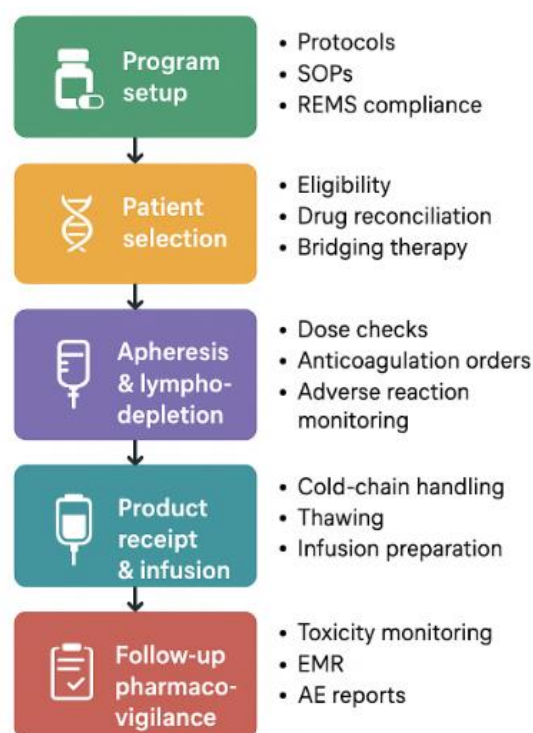


Figure 1. Pharmacist's Role in CAR-T Protocol Management.

Pharmacist Involvement in Product Handling and Administration

Pharmacists manage ordering from producers under cold chain supply (e.g., cryopreserved at $\leq -150^{\circ}\text{C}$) (Nezvalova-Henriksen et al., 2023). Upon receipt, they verify the chain of identity (patient-individual labeling) and custody and document temperature deviations (Black, 2018). The EU's ATMP law mandates pharmacist control for traceability (Iglesias-López et al., 2019). Storage requires liquid nitrogen dewars with continuous monitoring; personnel are trained by the pharmacist in handling to prevent loss of viability (up to 20% if mishandled) (Perica et al., 2018). Thawing follows product-specific protocols (e.g., 35–37°C water bath for axi-cel), cell count, and viability confirmed by the pharmacist through certificate of analysis (Mohty et

al., 2023). Pharmacists formulate infusion bags in laminar flow, adding dextrose/saline without a filter to avoid cell damage (Benedetti & Latchford, 2019).

Infusion rates start slowly (≤ 50 mL/min) to monitor reactions, with the pharmacists also making supportive drugs such as tocilizumab (8 mg/kg IV) available (Elsallab & Maus, 2023). Outpatient patients make them arrange 24/7 access and instruct self-

administration of rescue therapy (Owusu et al., 2022). Only 20% of U.S. centers have CAR-T specialist pharmacists, yet they reduce errors by 30% (Mahmoudjafari et al., 2019). Pharmacists monitor pharmacokinetics post-infusion, documenting peak CAR-T expansion at day 7–14, and adjust antimicrobials for cytopenias (4–8 weeks duration) (Garfall et al., 2019).

Table 1. Pharmacist Responsibilities in CAR-T Protocol Management

Phase	Key Responsibilities	Supporting Evidence
Program Setup	Develop SOPs, EMR order sets, REMS compliance; ensure tocilizumab stocking (2 doses/patient)	Booth et al. (2020); Marzal-Alfaro et al. (2021)
Patient Selection	Screen for eligibility, reconcile medications, recommend bridging (e.g., steroids)	Moreno-Martínez et al. (2020); Amini et al. (2022)
Apheresis/Lymphodepletion	Oversee anticoagulation, dose lymphodepleting agents, monitor for adverse reactions	Paroder et al. (2020); Jacobson et al. (2022)
Product Receipt/Infusion	Verify chain of identity/custody, thaw product, prepare infusion bags	Kamisetti (2023)

Toxicity Mitigation: Pharmacist-Led Strategies

CRS is due to CAR-T activation, cytokine release like IL-6, endothelial damage, and capillary leak (Giavridis et al., 2018). Incidence: grade ≥ 3 15–25% for axi-cel (Neelapu et al., 2018). ICANS involves disruption of the blood-brain barrier, aphasia, and seizures; pathophysiologically involves monocyte infiltration (Norelli et al., 2018). Other toxicities: cytopenias (weeks duration 90%), infections (50%), hemophagocytic lymphohistiocytosis-like syndrome (1–5%) (Frey & Porter, 2019). Risk factors include high disease burden, early CRS onset, and CD28-costimulated products (Logue et al., 2021). Figure 2 represents the pharmacist-led toxicity mitigation in CAR-T therapy.

Pharmacist Role in Monitoring and Intervention

Pharmacists deliver REMS training, educating ASTCT grading (Lee et al., 2019). Pharmacists also provide tocilizumab (FDA requirement: 2 doses/patient) and develop order sets for emergent use (Marzal-Alfaro et al., 2021). For CRS grade 1–2, supportive care (fluids, antipyretics); grade ≥ 3 , tocilizumab $\pm$ corticosteroids (dexamethasone 10 mg IV q6h) (American Society of Clinical Oncology, 2022). For ICANS, the preferred treatment by pharmacists is steroids (methylprednisolone 1–2 g/day) over tocilizumab, which has poor CNS penetration, and antiepileptics like levetiracetam (Santomasso et al., 2018). New agents: anakinra for IL-1 blockade in refractory patients (Strati et al., 2020). Pharmacists also perform medication reconciliation to rule out drug-induced symptoms and management of polypharmacy (e.g., excluding NSAIDs for fever because of bleeding risk) (Adkins, 2019).

In outpatient guidelines, wallet cards for toxicity identification and 24/7 hotlines are provided by pharmacists (Gatwood et al., 2024). Pharmacovigilance encompasses reporting to FAERS; pharmacists aggregate adverse event monitoring (Escudero-Vilaplana et al., 2021). Prophylactic IL-6 blockade (siltuximab) reduces CRS incidence by 50% in trials (Mushtaq et al., 2022). For infections, pharmacists maximize prophylaxis (e.g., acyclovir, posaconazole) during B-cell aplasia (up to 2 years) (Hill et al., 2020). Table 2 represents an overview of ASTCT grading and pharmacist management of key CAR-T toxicities.

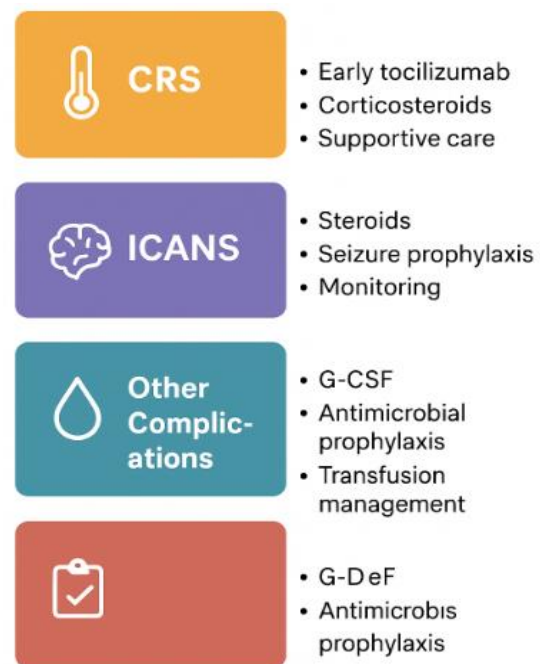


Figure 2. Pharmacist-Led Toxicity Mitigation in CAR-T Therapy.

Table 2. ASTCT Grading and Pharmacist Management of Key CAR-T Toxicities

Toxicity	Grade 1 Symptoms	Grade 2–3 Management (Pharmacist Role)	Grade 4 Management	Citation
CRS	Fever $\geq 38^{\circ}\text{C}$	Monitor cytokines; tocilizumab 8 mg/kg IV; fluids; order sets	ICU transfer; high-dose steroids; vasopressors	Lee et al. (2019); Neelapu et al. (2018)
ICANS	Mild aphasia	Dexamethasone 10 mg q6h; levetiracetam if seizures; EEG monitoring	Methylprednisolone 1 g/day; consider anakinra	Santomasso et al. (2018); Strati et al. (2020)
Cytopenias	ANC $<1.0 \times 10^9/\text{L}$	G-CSF (filgrastim); antimicrobial prophylaxis	Transfusions; monitor for HLH	Frey & Porter (2019); Hill et al. (2020)

Case Studies and Real-World Evidence

Pharmacists' involvement in CAR-T cell therapy is increasingly visible in real-life practice, where pharmacovigilance, patient information, and protocol optimization result in improved outcomes. What is provided below illustrates some of the most significant case studies and real-world experience showcasing their influence, together with the challenges of implementation faced. In a Spanish multicenter study, the pharmacists' pharmacovigilance programs strongly influenced reporting on adverse events (AEs) among CAR-T treatments.

Through the use of standardized monitoring protocols and collaboration with clinicians, pharmacists were able to reduce unreported AEs by 40%, notably CRS and ICANS. This program involved electronic medical record (EMR) documentation of real-time AE in real time and mandatory reporting to the Spanish Agency of Medicines for alignment with European Medicines Agency (EMA) standards (Revuelta-Herrero et al., 2022). Active involvement of pharmacists in educating healthcare professionals on early detection of subtle signs of toxicity, for example, early fever or neurological changes, to enable early interventions such as tocilizumab or corticosteroids was highlighted in the study. At MD Anderson Cancer Center, an American outpatient CAR-T program demonstrated the pivotal role of pharmacists in ambulatory care.

By developing comprehensive patient education protocols, pharmacists enabled 85% of patients to be treated outside of inpatient settings, reducing hospitalizations by 25%. Education focused on the identification of toxicity, rescue medication self-administration (e.g., acetaminophen for fever), and proper follow-up schedules. Pharmacists coordinated 24/7 telepharmacy support and provided wallet cards containing emergency contact numbers and toxicity grading charts, empowering the patient and caregiver to respond quickly to symptoms (Jain et al., 2023). The model proved cost-saving in reducing health expenditure and improving the quality of life of patients but required robust infrastructure support for outpatient monitoring. In Greece, a one-center

experience showed the pharmacists' role in enabling early intervention for CRS.

By tocilizumab dosing regimen confirmation and optimization (8 mg/kg IV within 24 hours of fever onset), pharmacists avoided severe (grade ≥ 3) CRS in 90% of cases. This involved pre-stocking tocilizumab as per FDA Risk Evaluation and Mitigation Strategy (REMS) guidelines (2 doses/patient) and training nurses regarding rapid infusion protocols. Pharmacists also titrated prophylactic antimicrobials, such as acyclovir, to manage risk of infection in prolonged cytopenias, which occur in as many as 90% of patients (Gavrilaki et al., 2025). This proactive intervention minimized transfers to intensive care units and improved survival. Despite these successes, logistical challenges persist. For instance, during the COVID-19 pandemic, supply chain deficits impacted CAR-T product delivery, so pharmacists needed to adapt thawing processes in decentralized settings. Liquid nitrogen storage facilities were not available in small hospitals, so surrogate cryopreservation methods (e.g., -80°C freezers) needed to be validated with cell viability by pharmacists (Weiss et al., 2021). These steps ensured continuity of care but revealed that standardized logistics procedures between centers were needed.

New applications of CAR-T in solid tumors also point to the evolving role of the pharmacist. Pharmacists coordinate novel CAR constructs in trials for GD2 antigens for neuroblastoma, handling proper handling and dosing of investigational product. Pharmacists also deal with rare toxicities, such as tumor lysis syndrome, that differ from hematologic indications (Majzner & Mackall, 2018). Pharmacists are required to adapt protocols for combination therapy (e.g., CAR-T with checkpoint inhibitors) in these trials, offering sophisticated polypharmacy and drug interaction management abilities.

Real-world implementation challenges include personnel shortages—only 20% of U.S. centers have CAR-T pharmacists, which hinders scalability (Mahmoudjafari et al., 2019). Equitable access is also challenging due to high costs (\$373,000–\$475,000 per infusion) and regional disparities in limiting therapy access (Salter et al., 2018). These can

be addressed by pharmacists through sponsorship of cost-saving biosimilars (e.g., tocilizumab generics) and supply chain optimization.

Future Directions and Challenges

Allogeneic CAR-T (e.g., UCART19) may reduce production time but risk graft-versus-host disease and requires pharmacist-managed immunosuppression (Benjamin et al., 2020). Expansion in the outpatient setting necessitates telepharmacy for monitoring (Gatwood et al., 2024). Challenges: staff shortages (only 20% dedicated pharmacists), access equity, and long-term effects such as secondary malignancies (Fraietta et al., 2018). Research priorities: AI for predicting toxicity and combination therapies (e.g., CAR-T + checkpoint inhibitors) (Seago, 2024). Training courses, like ASTCT, need to emphasize certification of pharmacists (Dioverti et al., 2022).

Conclusion

Pharmacists are key professionals in the effective launch of CAR-T cell therapy, combining clinical knowledge with operational skills to optimize patient results. Their responsibilities range from protocol design, adherence to stringent regulatory frameworks like FDA REMS and EMA ATMP guidelines, to hands-on handling of product logistics, like cryopreservation and infusion preparation. In mitigation of toxicity, pharmacists lead interprofessional efforts, from stockpiling life-saving medications like tocilizumab to designing rapid-response order sets for CRS and ICANS, reducing severe adverse events by up to 40% in some settings.

Real-world evidence, such as MD Anderson's ambulatory model (85% ambulatory care, 25% reduced hospitalizations) and Greece's early tocilizumab programs (90% severe CRS reduction), illustrates their impact on safety and outcomes. Patient education programs, including wallet cards and telepharmacy, also empower patients with enhanced adherence and quality of life. As CAR-T therapy is being taken to outpatient sites and solid tumors, standardized protocols are necessary to address practice variation. Low numbers of specialized CAR-T pharmacists (20% of centers) and logistical challenges, such as supply chain disruption, highlight the need for expanded training and infrastructure. Future developments, such as allogeneic CAR-T and AI-based toxicity prediction, hold greater promise of broader uses, but equitable access and long-term safety monitoring are urgent issues. Pharmacists should advocate for affordable solutions and interprofessional collaboration to ensure CAR-T's transformative potential is maintained.

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