CAR T-Cell Therapy Unveiled: Navigating Beyond CRS and ICANS to Address Delayed Complications and Optimize Management Strategies

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Author's disclosures of conflicts of interest are found at the end of this article.

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Abstract

Chimeric antigen receptor (CAR) T-cell therapy has ushered in a transformative era in the management of relapsed/refractory hematologic malignancies. The extensive phase II trials targeting relapsed/refractory non-Hodgkin lymphoma, including diverse subtypes such as diffuse large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma, along with multiple myeloma and B-cell acute lymphoblastic leukemia, have culminated in the endorsement of various CAR T-cell products for these specific indications by the US Food and Drug Administration. Although CAR T-cell therapy has achieved remarkable success, it is important to recognize that this innovative approach often gives rise to notable toxicities and is frequently associated with a distinctive pattern of adverse effects. Advanced practice providers, including advanced practice nurses and physician associates, involved in the care of these patients should be able to recognize these toxicities and be versed in treatment strategies to mitigate their impact.

CASE STUDY 1

CJ is a 60-year-old female patient with a significant past medical history of left kidney sarcoma status post nephrectomy, diabetes mellitus, hypertension, and deep vein thrombosis. Her Eastern Cooperative Oncology Group (ECOG) performance status is 1. She was diagnosed with immunoglobulin G (IgG) kappa multiple myeloma in 2019 after presenting with a hemoglobin (Hgb) of 9.7 and acute kidney injury (AKI; creatinine 1.46). An initial workup revealed Hgb of 8.8, white blood cells (WBC) of 3.7, platelets (PLT) of 177, beta-2 microglobulin (B2M) of 7.1, lactate dehydrogenase (LDH) of 184, albumin of 2.9, total protein of 12.3, creatinine of 1.4, calcium (Ca) of 9.3, ionized Ca of 1.25, IgA of 20,

IgG of 7,700, IgM of 9, free kappa light chain (fKLC) of 1,659, kappa/lambda ratio of 868.59, free lambda light chain (fLLC) of 1.91, serum immunofixation (SIFE) showing IgG kappa, and monoclonal (M) protein of 6.12 g/dL. Her bone marrow biopsy showed 90% plasma cell.

She received induction therapy with KRd (carfilzomib, lenalidomide, and dexamethasone) for 4 cycles with very good partial response. She then proceeded to consolidation with autologous stem cell transplant on clinical trial with elotuzumab (Empliciti) and lenalidomide, achieving complete remission (CR), followed by KRd maintenance until May of 2022 when she progressed. Subsequently, she received multiple lines of therapy including isatuximab (Sarclisa), pomalidomide (Pomalyst), dexamethasone, belantamab mafodotin (Blenrep), selinexor (Xpovio), bortezomib (Velcade), and dexamethasone. The disease was either refractory to these therapies or she experience short remission duration. In July of 2023 she received standard-of-care ciltacabtagene autoleucel (Carvykti). CJ's hospital course was complicated by grade 2 cytokine release syndrome (CRS; fever and hypotension) requiring intravenous fluid, broad-spectrum antibiotics, and tocilizumab on day 8, with resolution of CRS. The infectious workup was negative. CJ did not experience ICANS and was discharged on day 10 to the outpatient fast-track clinic for monitoring.

Chimeric antigen receptor (CAR) T-cell therapy has transformed the management of relapsed/refractory hematologic malignancies, such as non-Hodgkin lymphoma, multiple myeloma, and B-cell acute lymphoblastic leukemia (Shouse et al., 2022; Table 1). While it has demonstrated efficacy, its use is often accompanied by significant toxicities that require careful management. Advanced practice providers (APPs), including advanced practice nurses and physician associates, play an essential role in the multidisciplinary care of patients receiving CAR T-cell therapy.

PRIMARY TOXICITIES

Two of the most prominent toxicities associated with CAR T-cell therapy are cytokine release syndrome (CRS) and neurotoxicity, also known as immune effector cell–associated neurotoxicity syndrome (ICANS). These reactions are triggered by the engagement of CAR T cells with their target, resulting in an excessive release of inflammatory signaling molecules (IL-2, IL-6, IL-8, IL-10, IL-15, TNF-α, IFN-γ, MIP-1α [CCL3], and granulocyte-macrophage colony-stimulating factor) and the subsequent activation of other immune and non-immune cells including macrophages and monocytes, leading to systemic inflammation (Chen et al., 2022; Hayden et al., 2022; Zhou et al., 2020).

Cytokine release syndrome is the most commonly observed toxicity associated with CAR T-cell therapy. The incidence can vary widely depending on the specific treatment and patient population (Shaikh & Shaikh, 2023). It typically presents with symptoms such as fever, myalgias, and rigors, but in more severe cases, can progress to hypotension and breathing difficulties (Hernani et al., 2022). Fulminant CRS can pose a life-threatening risk when accompanied by conditions such as cardiac dysfunction, adult respiratory distress syndrome, liver failure, renal failure, disseminated intravascular coagulation and, in extreme instances, hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS; Hayden et al., 2022). These severe CRS complications can lead to a critical and potentially fatal clinical situation, underscoring the importance of early recognition, intervention, and aggressive management to mitigate these life-threatening outcomes (Table 2). Immune effector cell–associated neurotoxicity syndrome occurs less frequently, and it is often delayed compared to CRS. Table 3 displays ICANS symptoms, which typically exhibits with headaches, agitation, tremors, confusion, motor impairment, and aphasia, but can progress to severe complications, including unmanageable cerebral edema and, in rare instances, death (Hernani et al., 2022).

Across pivotal trials, these adverse effects have consistently emerged, showing similar frequencies across different CAR T-cell products. With CD19-targeting therapy, CRS affects 30% to 100% of patients, whereas grade 3 or higher is reported

Table 1. FDA-Approved CAR T-Cell Therapies

	Idecabtagene vicleucel (Abecma)	Ciltacabtagene autoleucel (Carvykti)	Tisagenlecleucel (Kymriah)	Axicabtagene ciloleucel (Yescarta)	Brexucabtagene autoleucel (Tecartus)	Lisocabtagene maraleucel (Breyanzi)
Target	BCMA	BCMA	CD19	CD19	CD19	CD19
Pivotal trial	KarMMA (*N* = 128)	CARTITUDE-1 (*N* = 97)	JULIET (*N* = 115)	ZUMA-1 (*N* = 101)	ZUMA-2 (*N* = 68)	TRANSCEND (*N* = 269)
FDA approval date	3/26/2021	2/28/2022	5/22/2018	10/18/2017	7/24/2020	2/5/2021
ORR (%)	73	97	53		87	
OR (%)				82	93	73
CR (%)	33		39	54	67	53
sCR (%)		67				
CRS (%, any)	84	95	58	93	91	42
> G3 (%)	5	4	22	13	15	2
Median onset (d)	1	7	3	2	2	5
ICANS (%, any)	18	21	21	64	63	30
> G3 (%)	3	10	12	28	30	10
Median onset (d)	2	8	6	5	7	9
Neutropenia (%)	91	96	1	84	87	63
> G3 (%)	89	95	20	78	86	60
Anemia (%)	70	81	9	66	68	48
> G3 (%)	60	68	15	43	50	37
Thrombocytopenia (%)	63	79	1	58	74	31
> G3 (%)	52	60	12	38	50	27

Note. FDA = Food and Drug Administration; ORR = overall response rate; OR = objective response; CR = complete response; sCR = stringent response; CRS = cytokine release syndrome; ICANS = immune effector cell–associated neurotoxicity; G = grade. Information from Abramson et al. (2020); Berdeja et al. (2021); Munshi et al. (2021); Neelapu et al. (2017); Schuster et al. (2019); Wang et al. (2020).

Table 2. ASTCT Grading and Management of Cytokine Release Syndrome

Signs and symptoms	Grade 1	Grade 2	Grade 3	Grade 4
Fever: temperature ≥ 38°C	Yes	Yes	Yes	Yes
With				
Hypotension: SBP < 90	No	Responds to IVF	Vasopressor support	Multiple vasopressors
And/or				
Hypoxia: saturation < 90%	No	Requires oxygen supplementation FiO2 < 40%	Requires oxygen supplementation FiO2 > 40%	BiPAP or mechanical ventilation
Management	• IVF, antipyretics • Rule out infection • Start empiric antimicrobials • G-CSF if neutropenic (per institutional guidelines) • If no improvement in 24–48 hours, consider tocilizumab[a]	• Supportive care as for G1 • O2 supplement • Tocilizumab • Dexamethasone • Consider/or transfer to ICU	• Supportive care as for G1–2 • Transfer to ICU • Vasopressor support • HF O2 or non-invasive ventilation • Dexamethasone • Tocilizumab	• Supportive care as for G1–3 • ICU monitoring for vasopressor support and positive pressure ventilation • Methylprednisolone[b]

Note. DD = differential diagnosis; MAS = macrophage activation syndrome; HLH = hemophagocytic lymphohistiocytosis; SBP = systolic blood pressure; IVF = intravenous fluid; FiO2 = fraction of inspired oxygen; G-CSF = granulocyte colony-stimulating factor; ICU = intensive care unit; HF = high flow. Information from Hayden et al. (2022); Lee et al. (2019).
[a]8 mg/kg (max 800 mg per dose); max 3 doses in 24 hr.
[b]If no response to steroids, consider DD of MAS/HLH.

in 10% to 30% of patients (Frey & Porter, 2019; Gudiol et al., 2021). Immune effector cell–associated neurotoxicity syndrome affects 30% to 50% of patients with any grade, and grade 3 or higher is seen in 12% to 30% (Hayden et al., 2022). In regard to anti–B-cell maturation antigen (BCMA) therapy, CRS affects 84% to 95% of all patients, whereas grade 3 or greater is noted in less than 5% (Chekol Abebe et al., 2022; Munshi et al., 2021). Additionally, 18% to 21% experienced any-grade ICANS, while only 3% to 10% reported grade 3 or greater (Chekol Abebe et al., 2022; Martin et al., 2023; Munshi et al., 2021). Given the risk of CRS and neurologic toxicities, all CAR T-cell therapies are available only through a Risk Evaluation and Mitigation Strategy (REMS), a restricted program that manages the risk of CRS and neurologic toxicity (Ibrahim et al., 2020).

Case Study 1 Continued

On Day 20, CJ presented to the fast-track clinic reporting diarrhea 5 to 6 times a day for 2 days. The preemptive surveillance cytomegalovirus (CMV) level was 1,250 from a previous level of 142. A CT of the abdomen showed marked diffuse thickening of the colon associated with edema and a small amount of ascites, compatible with pancolitis. Due to a concern for CMV gastroenteritis/colitis, CJ's history of left nephrectomy, and cytopenia (absolute neutrophil count [ANC] 0.07 and platelets [PLT] 5), CJ was admitted to the hospital for intravenous ganciclovir, renally dosed, day 20 through day 26. Stool cultures and gastrointestinal (GI) multiplex were negative. A GI scope was deferred due to pancytopenia. CJ's diarrhea resolved, and CMV titer improved with CMV level decreasing to 176 at day 27. She transitioned to valganciclovir 900 mg po bid and was discharged to continue monitoring CMV twice weekly in the outpatient setting. She remained on antimicrobials levofloxacin and posaconazole since she remained neutropenic with ANC < 500 cells/mm^3. Additionally, she remained on *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis

Table 3. ASTCT Grading and Management of Immune Effector Cell–Associated Neurotoxicity Syndrome

Neurotoxicity criteria	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7–9	3–6	0–2	0
Depressed level of consciousness	Decreased, but awakens spontaneously	Altered, but awakens to voice	Awakens to tactile stimuli; seizures (focal, general, or nonconvulsive)	Unarousable or requires vigorous tactile to arouse, stupor, coma
Seizure activity	Not applicable	Not applicable	Any focal/generalized clinical seizure that resolves with intervention	Prolonged seizure (> 5 min) without return to baseline; cerebral edema; papillary edema; Cushing's triad
Motor findings				Deep focal motor weakness
Management	• Aspiration precaution • Seizure prophylaxis • Consult neurology • CT/MRI brain • Tocilizumab if + CRS • Consider dexamethasone	• Supportive care as for G1 • CT/MRI brain • LP if indicated • Dexamethasone • Consider ICU transfer	• Supportive care as for G1–2 • Benzodiazepines if nonconvulsive seizures are noted on EEG • Transfer to ICU • Dexamethasone	• Methylprednisolone • Consider anakinra, intrathecal or systemic chemotherapy

Note. ICE = immune effector cell-associated encephalopathy; CRS = cytokine release syndrome; LP = lumbar puncture; ICU = intensive care unit. ASTCT Immune Effector Cell Encephalopathy (ICE) Score: 10/10. Orientation: Orientation to year, month, city, hospital: 4 points. Naming: Ability to name 3 objects (e.g., point to clock, pen, button): 3 points. Following commands: Ability to follow simple commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue"): 1 point. Writing: Ability to write a standard sentence (e.g., "our national bird is the bald eagle"): 1 point. Attention: Ability to count backwards from 100 by 10: 1 point. Information from Hayden et al. (2022); Lee et al. (2019).

with pentamidine intravenous every 21 days. Given that she was on valganciclovir for CMV viremia, the prophylaxis antiviral (valacyclovir) for herpes simplex virus (HSV) was held.

At the Day 30 mark, a bone marrow biopsy (BMB) was obtained to rule out infectious causes of bone marrow failure and tested for adenovirus, parvovirus, human herpesvirus 6 (HHV-6), Epstein-Barr virus, CMV, disseminated tuberculosis, and histoplasma. The BMB revealed no infectious process, however, noted a profound hypocellular bone marrow, no increase in blast, and no morphologic support for plasma cell neoplasm. Her myeloma labs at Day 30 revealed a response to CAR T-cell therapy with a noted reduction in free kappa light chain (1.67 < 661) and M protein (0.9 < 2.6). A PET scan showed resolution of previous hypermetabolic bony lesions. CJ continued to be monitored outpatient twice weekly, requiring granulocyte colony-stimulating factors (G-CSF) and platelet transfusion. In addition, she was initiated on weekly romiplostim for refractory thrombocytopenia.

SECONDARY TOXICITIES

While the immediate adverse effects like CRS and ICANS have been extensively documented, other adverse effects, including persistent cytopenia, B-cell aplasia, hypogammaglobulinemia leading to compromised immune function, and increased infection susceptibility, are also noteworthy. Additionally, delayed non-ICANS–related neurotoxicity with features resembling Parkinsonism, referred to as movement and neurocognitive treatment-emergent adverse events (MNTs), has been observed in some patients following anti-BCMA therapies (Berdeja et al., 2021; Martin et al., 2023).

Prolonged Cytopenia

The development of prolonged cytopenia, or biphasic cytopenia, after CAR T-cell therapy is a complex and multifactorial issue, and the exact mechanisms are not fully understood. However, there are several potential factors and contributing causes including baseline cytopenia, lymphodepleting conditioning regimens, which include chemotherapy agents like fludarabine and cyclophosphamide,

and individual factors, such as the patient's overall health and prior treatments, including hematopoietic stem cell transplantation (HSCT), bone marrow involvement, the specific CAR T-cell therapy used, and the development of high-grade CRS or ICANS (Hayden et al., 2022; Jain et al., 2020; Logue et al., 2021). In general, studies have identified cytopenia as the most prevailing adverse reaction, particularly at grade 3 severity. In an analysis conducted by Strati et al. (2021) that focused on 31 patients who underwent treatment with axicabtagene ciloleucel (Yescarta), 48% of the study group experienced severe cytopenia, classified as grades 3 to 4. This severe cytopenia included cases of anemia in 16% of patients, neutropenia in 29%, and thrombocytopenia in 42%. Furthermore, among the patients who maintained remission, grade 3 to 4 cytopenia was observed in one out of nine individuals, accounting for 11% of these patients at the 2-year mark (Strati et al., 2021). Similarly, a retrospective study involving 85 patients post–axicabtagene ciloleucel infusion reported prolonged cytopenia, specifically grade 3 or higher neutropenia in 30% at the 30-day mark and 10% at the 1-year mark (Logue et al., 2021).

Studies involving CAR T-cell therapies targeting BCMA have shown similar findings of prolonged hematologic adverse effects. In the CARTITUDE-1 study at the 2-year follow-up, approximately 30% of patients experienced prolonged grade 3 or grade 4 neutropenia, while a substantial 60% of the patients encountered persistent grade 3 or grade 4 thrombocytopenia that continued beyond the initial 30 days following treatment (Martin et al., 2023). Additionally, beyond the 60-day period following ciltacabtagene autoleucel (Carvykti) therapy, there was evidence of a recurrence of grade 3 or higher lymphopenia, neutropenia, and thrombocytopenia in a subset of patients (Janssen Biotech, Inc., 2022). Specifically, 8% of patients experienced a recurrence of grade 3 or higher lymphopenia, 10% of patients experienced a recurrence of grade 3 or higher neutropenia, and 40% of patients had a recurrence of grade 3 or higher thrombocytopenia (Martin et al., 2023). Cytopenia was also frequently observed in the pivotal phase II KarMMa trial, with notable persistent grade 3 or higher neutropenia and thrombocytopenia in 41% and 49% of patients, respectively (Munshi et al., 2021; Sanoyan et al., 2023). Real-world experience from a retrospective multicenter observational study involving 159 patients across 11 United States medical centers showed persistent grade 3 or higher anemia, thrombocytopenia, and neutropenia at 38%, 59%, and 60%, respectively, beyond the 30-day mark and post idecabtagene vicleucel (Abecma) infusion (Hansen et al., 2023).

The management of patients with prolonged cytopenia involves supportive care with close monitoring of the patient's blood counts, assessing for nutritional deficiency and supplementing with folic acid and vitamin B12 if needed (Sanoyan et al., 2023). Anemia and thrombocytopenia are managed through the replacement of erythrocytes and platelets. In general, red blood cell transfusion is recommended for hemoglobin less than 7.0 and platelet transfusion for less than 10,000. All patients post–CAR T-cell infusion should receive leukoreduced and irradiated blood products support per local institutional guidelines. The use of G-CSF to sustain an ANC above 1,000 cells/mm^3 can be considered (National Comprehensive Cancer Network, 2023). Nevertheless, it is crucial to approach this decision with caution and a thorough evaluation of the potential risks and benefits performed given the theoretical concern that using G-CSF in the early post–CAR T-cell period (< 14 days) might elevate the risk of CRS (Bupha-Intr et al., 2021; Jain et al., 2019; Kambhampati et al., 2022). Advanced practice providers should carefully assess individual patient circumstances, follow institutional guidelines, and monitor patients closely when making decisions about G-CSF administration in the early post–CAR T-cell period (Gea-Banacloche, 2023; Kambhampati et al., 2022).

Thrombocytopenia that is refractory to platelet transfusion presents a clinical challenge, with no unanimous consensus regarding the safety of using thrombopoietin (TPO) receptor agonists in this context (Chakraborty et al., 2021). While there is no definitive consensus, reports suggest that TPO receptor agonists such as eltrombopag and romiplostim could be considered as a potential treatment option for managing refractory thrombocytopenia (Beyar-Katz et al., 2022; Hansen et al., 2023). Anecdotally, prolonged, persistent cytopenia after anti-BCMA therapy has been

managed with the transfusion of autologous or allogeneic stem cells (Hansen et al., 2023; Sanoyan et al., 2023). The decision to use TPO receptor agonists or stem cell boost in the management of refractory cytopenia should be made on a case-by-case basis. Moreover, the use of TPO receptor agonists in the management of CAR T-cell–induced cytopenia should be approached with caution and individualized based on the patient's clinical condition (Gudiol et al., 2021). Further research and studies are needed to better understand the role and safety of these agents in this specific context. In the setting of prolonged cytopenia, it is advisable to consider a BMB to assess whether there might be an underlying secondary bone marrow condition, which could include myelodysplastic syndrome, infections affecting the bone marrow, primary malignancies, or another contributing factor (Shaikh & Shaikh, 2023).

Case Study 1 Continued

At the Day 48 mark, CJ remained cytopenic (WBC of 0.8, ANC N/A, Hgb of 7.9, PLT of 5K) and continued to have intermittent diarrhea. She also reported new dental pain. The stool culture for *Clostridium difficile* colitis was positive and was treated with vancomycin. Her CMV level remained undetected. A CT maxillofacial was obtained and showed no acute findings, specifically no significant periodontal disease or dental abscess. The dental service identified pain associated with two posterior mobile molars. Since she remained neutropenic and thrombocytopenic, she was not eligible to have these teeth extracted. CJ was discharged with amoxicillin/clavulanic acid for 10 more days, high-fluoride toothpaste, and an antibacterial mouth rinse. At Day 58, given that the CMV polymerase chain reaction levels remained undetected, valganciclovir was stopped (restarted valacyclovir prophylaxis) without further rebound viremia. CJ continued to be monitored in the fast-track clinic twice weekly.

B-Cell Depletion and Hypogammaglobulinemia

CAR T-cell therapy that targets CD19 effectively eliminates both malignant B cells and normal B cells expressing CD19. This "on-target, off-tumor" effect of CAR T-cell therapy targeting CD19 results in a condition known as B-cell depletion (aplasia), where the population of B cells in the patient's bloodstream is profoundly reduced or eliminated leading to hypogammaglobulinemia (Hill et al., 2019). B-cell aplasia frequently persists for an extended period, often exceeding 6 months and, in some cases, lasting for years (Hill et al., 2018; Wat & Barmettler, 2022; Wilson Dib et al., 2023). Similarly, BCMA is expressed on the surface of both normal and malignant plasma cells and to a subset of mature B-cells, thus, the "on-target, off-tumor" activity of anti-BCMA CAR T-cell therapy eliminates both normal plasma cells and malignant plasma cell and subsequently leads to profound and lasting humoral immune deficiency (Chakraborty et al., 2021; Raje et al., 2019; van de Donk et al., 2021). The rate of hypogammaglobulinemia is variable across studies. In general, hypogammaglobulinemia (IgG < 400 mg/dL) was reported in 35%, 27%, and 46% of adult patients at approximately day 30, 60, and 90, respectively, following CAR T-cell infusion (Wat & Barmettler, 2022). Kambhampati et al. (2023) conducted a retrospective analysis of 55 patients with relapsed/refractory multiple myeloma post–anti-BCMA therapy and noted hypogammaglobulinemia in 70% and 41% at 3 months and at the 1-year mark, respectively. These findings underscore the long-lasting nature of B-cell aplasia and hypogammaglobulinemia in some individuals following CAR T-cell therapy.

The practice of proactive IgG replacement remains a topic of debate due to the absence of data stemming from randomized clinical trials (Wat & Barmettler, 2022). Nonetheless, because persistent B-cell aplasia is associated with sinopulmonary infections, notably with encapsulated bacteria, it is recommended to obtain a baseline assessment of lymphocyte subsets and immunoglobulin levels in all adult patients before lymphodepleting chemotherapy and subsequent monthly monitoring within the initial 3 months following CAR T-cell therapy (Hayden et al., 2022; Kampouri et al., 2022; Wat & Barmettler, 2022). In cases of sustained severe hypogammaglobulinemia (IgG ≤ 400 mg/dL) coupled with persistent or recurring respiratory bacterial infections, the consideration of prophylactic intravenous immunoglobulin (IVIG) is warranted as described in Table 4 (Bupha-Intr et al.,

Table 4. Prophylaxis Antimicrobials After CAR T-Cell Therapy

Pathogen	Prophylaxis duration	Antimicrobial	Consideration
Gram-negative organism prophylaxis *(Pseudomonas)*	Continue until ANC is > 500 cells/mm^3 for at least 3 days	Levofloxacin 500 mg po daily or equivalent	• Dose adjust for renal function, monitor QTc, tendinopathies, including tendon rupture
		Alternative: Cefpodoxime 200 mg po daily	
Candida prophylaxis	Continue until ANC is > 500 cells/mm^3 for at least 3 days	Fluconazole 200–400 mg po daily	• Monitor LFTs
		Alternative: Caspofungin 50 mg IV daily	• Infuse slowly, over ~1 hour • Do not administer by IV bolus
Mold active prophylaxis	Start if persistent ANC < 0.5 × 10^9/L (> 3 weeks) or patient treated with tocilizumab or high-dose steroids. Continue until ANC is > 500 cells/mm^3 for at least 3 days	Posaconazole 300 mg daily	• Inhibitor of CYP3A4 • Monitor LFTs, monitor QTc
HSV/VZV prophylaxis	Start with LDC and continue until 1 year after CAR T-cell therapy, and until CD4+ per mm^3	Acyclovir 400–800 mg bid	• Dose adjust for renal function
		Valacyclovir 500–1,000 mg daily	
Pneumocytis jiroveci pneumonia (PJP) prophylaxis	Start with LDC and continue until 1 year after CAR T-cell therapy, and until CD4+ per mm^3	Trimethoprim-sulfamethoxazole 160/800 MWF	• Sulfa allergy, myelosuppression, dose adjust for renal function
		Alternative: Pentamidine 300 mg IV or inhalation monthly	• Pancreatitis
		Alternative: Dapsone 100 mg daily	• Check G6PD
		Alternative: Atovaquone 1500 mg once daily	• Take with fatty meal
Hepatitis B infection prophylaxis (+ HBsAg or +HBcAb)	Recommended for minimum duration of 18 months. Monitor viral load every 3–6 months during the first year after discontinuation	Entecavir 0.5 mg po daily	• Monitor hepatitis B polymerase chain reaction once per month while on prophylaxis and for 1 year after stopping • Consider infectious disease consult
		Alternative: Tenofovir	
Respiratory bacterial infections coupled with hypogammaglobulinemia (IgG ≤ 400 mg/dL) prophylaxis		IVIG 400 to 600 mg/kg every 3 to 4 weeks, or subcutaneous immunoglobulins 100–200 mg/kg/weekly	• Anaphylactic reaction • Hemolysis • Transfusion-related acute lung injury • Thromboembolic events (myocardial infarction, stroke, venous thromboembolism) • Increased risk of sinusoidal obstructive syndrome

Note. HSV/VZV = herpes simplex/varicella zoster; ANC = absolute neutrophil count; CD = cluster of differentiation; LDC = lymphodepleting chemotherapy; LFTs = liver function tests. Information from Bupha-Intr et al. (2021); Jain et al. (2019); Wudhikarn et al. (2020).

2021; Jain et al., 2019; Wat & Barmettler, 2022). Anaphylactic reaction, hemolysis, transfusion-related acute lung injury, thromboembolic events (myocardial infarction, stroke, venous thromboembolism), and acute kidney injury are adverse effects that should be monitored while the patient receives IVIG infusion (Hill et al., 2019).

Infection Risk

Infections are a significant complication that can occur after CAR T-cell therapy and can have a negative impact on patient outcomes. In some cases, these infections are associated with a decrease in the 2-year survival rate for individuals who have undergone CAR T-cell therapy (Kampouri et al., 2022). A systematic review of 45 studies found the overall frequency of infections and grade 3 or greater infections to be 34% and 16%, respectively (Gea-Banacloche, 2023). Factors that increase the likelihood of infection, such as those depicted in Figure 1, include prolonged neutropenia, impaired host defenses, the administration of immunosuppressive drugs such as tocilizumab and systemic corticosteroid to treat CRS or ICANS, and subsequent hypogammaglobinemia due to prolonged B-cell aplasia (Bupha-Intr et al., 2021; Gudiol et al., 2021; Wudhikarn et al., 2020).

Most infections, approximately 23% to 42%, occur within the initial 30 days following CAR T-cell infusion. Approximately 80% manifest within the first 10 days (Baird et al., 2021; Hill et al., 2018; Wat & Barmettler, 2022). With CD19-targeting therapy, bacterial infections are more predominant during the first 30 days and include multidrug-resistant strains like *Clostridium difficile* and coagulase-negative staphylococcus and emerge during the neutropenic phase (Kampouri et al., 2022; Logue et al., 2021). Whereas, beyond day 30, viral infections tend to be more prevalent and include respiratory syncytial virus, influenza, and polyomaviruses (Hayden et al., 2022; Jain et al., 2019; Wudhikarn et al., 2020). Currently, there is a lack of long-term infection studies in the anti-BCMA-treated patient population. A retrospective analysis following anti-BCMA therapy with a cohort of 55 patients reported 47 total infections up to 1 year after CAR T-cell therapy (Kambhampati et al., 2022). Real-world experience reported an infection rate in 31% and 29% of patients following idecabtagene vicleucel and ciltacabtagene autoleucel, respectively (Sanoyan et al., 2023). Unlike for anti-CD19 therapy, anti-BCMA therapy infectious complications were predominantly viral (53%), followed by bacterial (40%) and fungal (6%) infections (Kambhampati et al., 2022).

Across all studies, fungal infections accounted for less than 6% of cases and primarily manifest during the initial neutropenia or CRS period (Haidar et al., 2020; Kambhampati et al., 2022; Logue et al., 2022). Among these, candidemia is the main concern, although various mold species like *Aspergillus*, *Fusarium*, and *Mucorales* have been implicated in lung diseases (Haidar et al., 2020; Jain et al., 2019; Kambhampati et al., 2022). The primary risk factors for fungal infections include the duration of neutropenia and the extended use of systemic corticosteroids to manage severe adverse reactions (Wudhikarn et al., 2020). As noted previously, many patients exhibit CD4 lymphopenia linked to prolonged B-cell aplasia, which can lead to the reactivation of latent DNA viruses, such as CMV, BK polyomavirus, hepatitis B, and HHV-6 approximately 6 to 12 months after the infusion of CAR T cells (Bupha-Intr et al., 2021).

Guidelines pertaining to infection prevention and management post–CAR T-cell therapy are largely drawn from the protocols established for recipients of HSCT as listed in Table 4 (Jain et al., 2019; Shaikh & Shaikh, 2023). Recommendations include instructing all patients to undergo prophylactic measures against herpes simplex virus, varicella-zoster virus, and PJP within the first week of conditioning chemotherapy and continuing up to 1 year following CAR T-cell therapy or until the CD4+ count exceeds > 200/μL (Gea-Banacloche, 2023; Gudiol et al., 2021; Shaikh & Shaikh, 2023). Furthermore, individuals with chronic or resolved hepatitis B are recommended to continue antiviral therapy for a minimum duration of 18 months (Bupha-Intr et al., 2021; Hill & Seo, 2020; Jain et al., 2019). Additionally, it is advisable to check pretreatment serology for human immunodeficiency virus (HIV), hepatitis B, hepatitis C, CMV, and HHV-6, and implement regular monitoring and stringent preventive strategies to manage potential CMV-related complications (Hill et al., 2018; Jain et al., 2019; Kampouri et al., 2022).

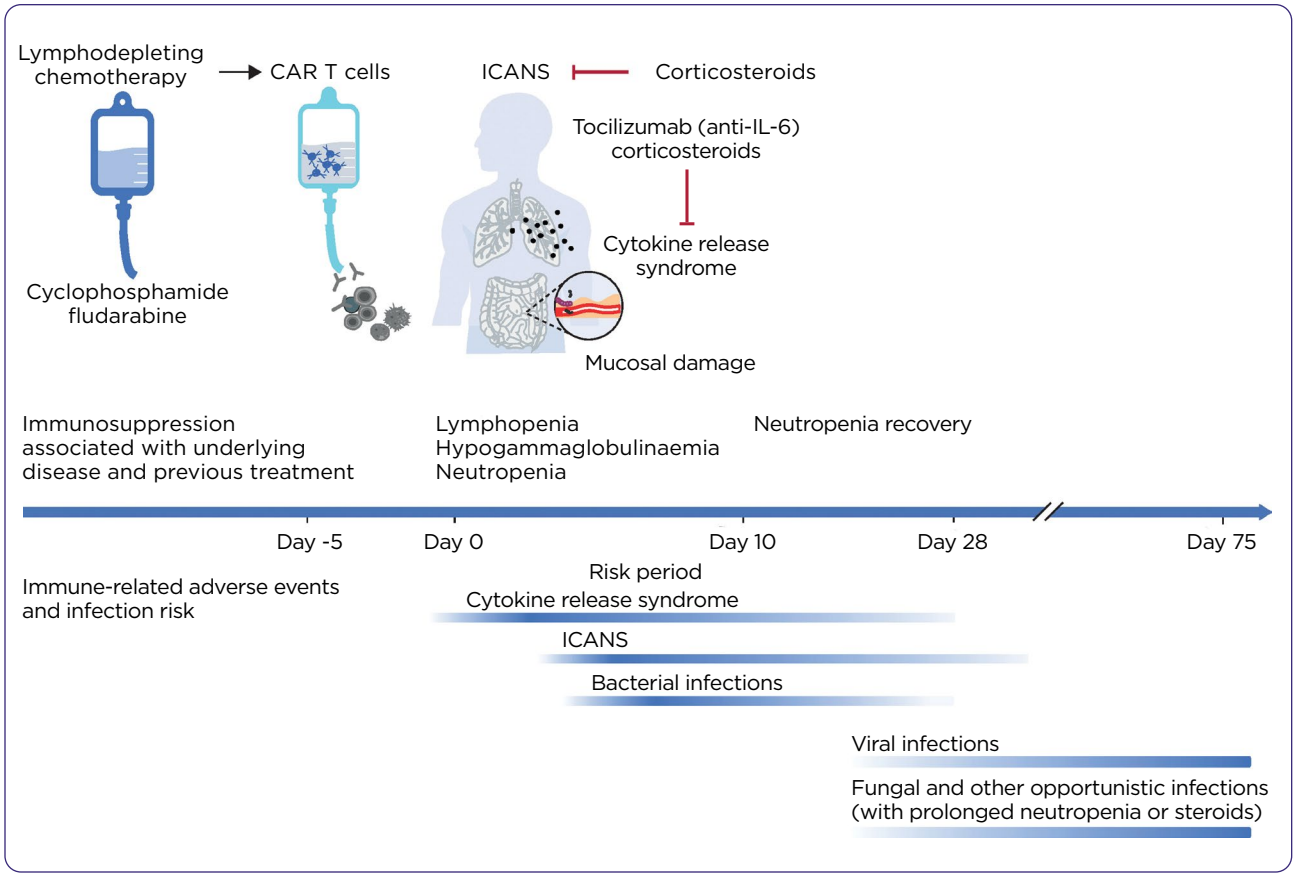

Figure 1. Risk factors associated with infections. Reprinted with permission from Gudiol et al. (2021). CAR = chimeric antigen receptor; ICANS = immune effector cell–associated neurotoxicity syndrome.

There is no consensus about antibacterial or antifungal prophylaxis in late-onset cytopenia cases, and this practice is not universally mandated (Gea-Banacloche, 2023). Nevertheless, it is advisable to consider this approach for patients experiencing neutropenia, in conjunction with the use of G-CSF (Hill et al., 2018; Jain et al., 2019). Individuals classified as low risk without a history of invasive fungal infections are recommended to receive fluconazole treatment during periods of neutropenia (Jain et al., 2019). Conversely, patients at high risk, such as prior fungal history, severe CAR T-cell–associated complications, prolonged steroid exposure, or patients with prolonged (> 14 days) or severe neutropenia (ANC < 500 cells/mm^3), are better suited for a mold-active agent, such as posaconazole (Bupha-Intr et al., 2021; Jain et al., 2019; Shaikh & Shaikh, 2023).

The precise role of vaccinations in this context remains uncertain, warranting further investigations to shape forthcoming recommendations (Ibrahim et al., 2020; Jain et al., 2019). Given the potential for long-term B-cell depletion following CAR T-cell therapy, standard national immunization schedules should be evaluated on an individual basis, considering the patient's history of infections and laboratory assessments of cellular and humoral immunity (Ibrahim et al., 2020). If vaccines are administered, the specific antibody responses should be closely monitored (Ibrahim et al., 2020). The annual influenza A and B vaccines are recommended 2 to 4 weeks prior to starting lymphodepleting chemotherapy or 3 months after CAR T-cell infusion (Jain et al., 2019; Wilson Dib et al., 2023). Both the Center for International Blood and Marrow Transplant Research (CIBMTR) and the National Marrow Donor Program (NMDP) recommend SARS-CoV-2 vaccination as early as 3 months following CAR T-cell therapy, independent of prior vaccination history

(El Chaer et al., 2022; Wilson Dib et al., 2023). Additionally, APPs should strongly advise all family members and any close contacts to receive the influenza and COVID-19 vaccines.

Case Study 1 Continued

On day 83, CJ presented with L-facial hemiparesis and diplopia on gaze to the right. Her physical exam demonstrated cranial nerve VII paralysis and R cranial nerve VI weakness. She did not have any CRS or ICANS, her immune effector cell–associated encephalopathy (ICE) score was 10/10, and no movement disorders, cognitive impairment, or personality changes were noted. There were no abnormal or extraneous movements noted on exam. A CT of the brain did not show any acute intracranial hemorrhage or infarction. An MRI of the brain with and without contrast was obtained and showed no intracranial leptomeningeal enhancement and no stroke. An electroencephalography obtained was negative. Per neurology recommendations, a lumbar puncture was deferred given cytopenia. She was initiated on methylprednisolone pack 4 mg and advised to use an eye patch to help with the diplopia.

Non-ICANS Neurotoxicity

Delayed non-ICANS neurotoxicity has been reported with anti-BCMA CAR T-cell therapy. It includes Parkinsonism, Guillain-Barré syndrome, immune-mediated myelitis, peripheral neuropathies, and cranial nerve palsies (Janssen Biotech, Inc., 2022). Table 5 displays MNTs, which are late-onset neurotoxicities that manifest with a subtle yet distinct set of symptoms consisting of movement, cognitive, and personality alterations that do not align with the current definition of ICANS and often are not responsive to conventional ICANS or Parkinson's therapy (Van Oekelen et al., 2021). In the CARTITUDE-1 study, a subset of patients developed signs and symptoms of Parkinsonism (n = 5), with a median onset of 43 days (Janssen Biotech, Inc., 2022; Martin et al., 2023). Moreover, a new case of Parkinson's syndrome was reported at 914 days post–ciltacabtagene autoleucel infusion in the 2-year follow-up for CARTITUDE-1. The patient developed cognitive slowing, tremors, and gait instability (Martin et al., 2023). In addition, there is one documented case of progressive bilateral facial nerve palsy with anisocoria (right pupil larger than the left pupil) following ciltacabtagene autoleucel infusion (Patrick et al., 2023).

Risk factors associated with MNTs are the presence of two or more of the following criteria: male sex, high tumor burden, previous grade ≥ 2 CRS, previous ICANS, high level of IL-6 at baseline, and high CAR T-cell expansion and persistence (Cohen et al., 2022; Van Oekelen et al., 2021). Biomarkers associated with CAR T-cell expansion and persistence, such as absolute lymphocyte count (ALC) and CD4+ T cells, were notably high on Days 14, 21, and 28 in patients who later develop MNTs (Cohen et al., 2022). These underscore the importance of monitoring ALC and CD4+ T cells to identify individuals at risk of MNTs.

Although the KarMMa study did not specifically address non-ICANS neurotoxicity, it is worth noting that grade 3 Parkinsonism and grade 3 myelitis were observed as neurological complications associated with idecabtagene vicleucel (Celgene Corporation, 2021). Movement and neurocognitive treatment-emergent adverse events often display a progressive course with a subtle onset. Therefore, there should be vigilant and thorough

Table 5. Movement and Neurocognitive Treatment-Emergent Adverse Events in CARTITUDE-1

Category	Preferred term
Movement disorder	Ataxia, balance disorder, bradykinesia, cogwheel rigidity, dysgraphia, dyskinesia, dysmetria, essential tremor, gait disturbance, hand-eye coordination impaired, micrographia, motor dysfunction, myoclonus, Parkinsonism, posture abnormal, resting tremor, stereotypy, tremor
Cognitive impairment	Amnesia, apraxia, bradyphrenia, cognitive disorder, confused state, depressed level of consciousness, disturbance in attention, encephalopathy, incoherent, leukoencephalopathy, loss of consciousness, memory impairment, mental impairment, mental status changes, noninfective encephalitis, psychomotor retardation
Personality changes	Flat affect, personality change, reduced facial expression

Note. Information from Cohen et al. (2022).

monitoring, along with prompt intervention, to mitigate the potential development of life-threatening or long-lasting neurological complications. Recommendations include extending the patient's monitoring period beyond 100 days, conducting a complete history and physical at every clinic visit, and assessing the patient's handwriting to detect early signs of neurotoxicity such as micrographia, dysgraphia, or agraphia post–ciltacabtagene autoleucel therapy (Berdeja et al., 2021; Cohen et al., 2022; Hayden et al., 2022).

Case Study 1 Conclusion

On day 90, a repeat BMB showed a profound hypocellular bone marrow, no increase in blast, and no morphologic support for plasma cell neoplasm. On day 110, CJ had ongoing left facial hemiparesis and diplopia, with 50% improvement. She underwent evaluation by ophthalmology, and her physical exam revealed large-angle left exodeviation and hypodeviation during left gaze only and small esodeviation during right gaze. There was no sign of optic neuropathy. To date, she remains cytopenic, requiring G-CSF, blood and platelet transfusion, as well as supplementation with vitamin B12 and folic acid. Per infectious disease recommendations, she continued with CMV monitoring weekly. CJ's myeloma remains in complete response with free kappa LC 1.64, ratio unable to calculate, and M protein 0.3.

Case Study 2

SR is a 68-year-old male patient with a significant past medical history of hypertension, hyperlipidemia, right lower extremity deep vein thrombosis, chronic pain, and Revised International Staging System (R-ISS) stage II IgG kappa multiple myeloma presents with lytic lesions and high-risk cytogenetics (*TP53*) at diagnosis. He received four lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, with disease progression. His fourth line of therapy consisted of high-dose cyclophosphamide, doxorubicin, and dexamethasone for 2 cycles, achieving stable disease followed by autologous stem cell transplant with standard-of-care melphalan 200 mg/m^2. A PET-CT post-transplant showed slightly decreased intensity and extent of uptake involving diffuse osseous myeloma. There were no new or progressive suspicious foci. His bone marrow biopsy showed 1% plasma cells.

Subsequently, SR proceeded with standard-of-care ciltacabtagene autoleucel. His hospital course was complicated by CRS grade 2. His CRS was treated with tocilizumab with resolution of CRS. An infectious workup was positive for rhinovirus and CMV DNA, while the HLH workup was negative. A CT chest obtained was consistent with a viral infection. He was discharged on cefpodoxime. The prophylaxis antifungal was discontinued due to rising liver function tests. He did not have ICANS.

SR was readmitted on Day 15 due to complaints of a headache, right facial droop, slurred speech, and inability to close eyelids completely. His physical exam was notable for right facial palsy, right lid lag, and exposure keratopathy of the right eye. Both CT and brain MRI were conducted and did not show any acute intracranial abnormality. Specifically, there was no evidence for acute ischemic stroke. In comparison with a prior scan, there was new enhancement along the bilateral facial nerves, interval decreased conspicuity of the bilateral third cranial nerve enhancement, and absent enhancement of the bilateral trigeminal nerves. Diffuse calvarial and skull base myelomatous lesions were stable. A magnetic resonance angiogram obtained was unremarkable. A diagnostic lumbar puncture was performed and ruled out malignancy. His infectious workup was negative. He continued to have right facial palsy, numbness, and slurred speech, which worsened. He was subsequently started on steroids, and his neurological symptoms improved. He was discharged on Day 18 with a prednisone taper, posaconazole, and *Aspergillus* level monitored weekly. The ophthalmology service recommended over-the-counter preservative-free artificial tears and artificial tear gel at bedtime to seal the lids. While he was inpatient, he received IVIG given his recent history of viral infection and IgG level of 399 mg/dL. His facial palsy resolved completely by day 28.

LONG-TERM FOLLOW-UP

Given the long-term effects of CAR T-cell therapy, ongoing close communication with the community referring physician for a smooth transition of care and long-term monitoring are imperative. Both the patient and referring medical team need

to be alerted of potential long-term effects of CAR T-cell therapy, what to be vigilant of, and potential management strategies. Education efforts should include both patients and caregivers on the risk of infections related to prolonged cytopenia and hypogammaglobulinemia. Prevention strategies, including hand washing hygiene and appropriate vaccinations, should be reinforced. Additionally, APPs must ensure that patients remain adherent to taking the prophylaxis PJP and antiviral medications as prescribed for 1 year after CAR T-cell infusion. Patients post–CAR T-cell therapy should continue to be monitored, as they may require interventions such as growth factors, transfusions, immunoglobulin infusions, and antimicrobial prophylaxis to manage potential late effects and maintain their overall health and well-being.

The role of APPs in monitoring patients post–CAR T-cell therapy is paramount to ensure comprehensive and individualized care. Primary and secondary toxicities require vigilant and ongoing attention. As patients navigate the complexities of recovery, APPs play a crucial role in not only detecting and addressing these potential complications but also in tailoring interventions to each patient's unique needs. Their expertise in managing the nuanced aspects of post–CAR T-cell therapy care, coupled with a patient-centered approach, contributes significantly to improving outcomes and enhancing the quality of life for individuals who have undergone this innovative but complex treatment. Continuous education, collaboration with multidisciplinary teams, and a commitment to staying abreast of evolving research are vital components of the APP's contribution to the long-term well-being of CAR T-cell therapy recipients. ●

Disclosure

The author has no conflicts of interest to disclose.

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