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Low incidence, high stakes: BCMA CAR-T and parkinsonism

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AUTHOR CONTRIBUTIONS

O.V.O. drafted the manuscript and developed the figure. S.P. provided critical intellectual input and revised the manuscript. Both authors reviewed and approved the final version of the manuscript.

CONFLICTS OF INTEREST

O.V.O. declares no conflicts of interest. S.P. reports consulting and advisory relationships with Johnson & Johnson, Regeneron, Karyopharm, Genentech/Roche, and Poseida Therapeutics. S.P. has received research support from Johnson & Johnson, Bristol Myers Squibb (formerly Celgene), Caribou Biosciences, and Genentech.

MAIN:

In this issue, Yoshino et al.[1] provide the first detailed clinicopathological description of delayed parkinsonism following idecabtagene vicleucel (ide-cel), offering important insights into the mechanism of BCMA-directed chimeric antigen receptor T-cell (CAR-T) therapy neurotoxicity. The authors describe a 58-year-old man with high-risk multiple myeloma with extramedullary involvement who developed delayed neurotoxicity with features of parkinsonism approximately 25 days after ide-cel infusion, associated with enrichment of CAR-T in the cerebrospinal fluid (CSF). Autopsy demonstrated focal T-cell infiltration and BCMA expression in the basal ganglia, without overt neuronal loss or evidence of intracranial extramedullary myeloma. Together, these observations add important pieces to the puzzle of movement and neurocognitive treatment-emergent adverse events (MNTs) following BCMA-directed CAR-T therapy.

A hypokinetic movement disorder with parkinsonian features, distinct from ICANS (immune effector cell-associated neurotoxicity syndrome), was first described following ciltacabtagene autoleucel (cilta-cel) in 2021.[2] About 5% of CARTITUDE-1 recipients developed MNTs, associated with high tumor burden, grade ≥2 cytokine release syndrome (CRS), ICANS, and increased CAR-T expansion. Improved bridging therapy, earlier aggressive treatment of CRS and ICANS, and increased awareness and monitoring have lowered the incidence below 1% in subsequent trials.[3] Cases with ide-cel are generally rarer, but have been reported, including a patient who developed parkinsonism on day 22, with basal ganglia hypometabolism, suggesting that this toxicity is not unique to a single CAR construct.[4] There has been an increasing interest in CAR-T-associated immune-related adverse events more broadly, a spectrum that not only includes parkinsonism, but also cranial nerve palsies and enterocolitis.[5] Importantly, these adverse events are associated with a fivefold higher hazard of non-relapse mortality.[6] With increasingly durable remissions after BCMA-directed CAR-T therapy, including the potential for cure, better understanding these uncommon toxicities is essential.

The present case shares established features, including substantial pre-infusion disease burden and onset after CRS resolution, but without preceding ICANS or abnormalities on conventional brain imaging. Three observations deserve particular attention. First, at the onset of neurotoxicity, 61.5% of CSF lymphocytes were CAR-T cells (despite low CSF cellularity), of which 76% were CD4+, supporting growing evidence that CD4+ CAR-T cells may be central mediators of delayed immune-related toxicities.[6] Second, autopsy demonstrated focal CD4+ and CD8+ T-cell infiltrates in the basal ganglia without neuronal or white matter injury. Third, peak absolute lymphocyte count (ALC) was only 2,040/μL, below the recently proposed risk threshold of 3,000/μL, or 2,500/μL following a daily twofold increase, suggesting that while ALC is a useful screen, it does not exclude neurotoxicity risk.[7] Direct assessment of CAR-T kinetics, phenotype (including CD4+ fraction), and tissue trafficking may ultimately be more informative.

Why does BCMA CAR-T therapy provoke basal ganglia dysfunction with T cell infiltration in a small subset of patients? The occurrence of a parkinsonian syndrome with similar neuropathological findings after both cilta-cel and ide-cel supports it being a BCMA-directed CAR-T class effect. Consistent with earlier observations implicating the basal ganglia, Yoshino et al. detected BCMA protein expression in the caudate nucleus with two antibodies and none in the cortex or cerebellum, supporting this hypothesis.[1] Nevertheless, BCMA expression in the adult brain remains disputed, with another study demonstrating little or no convincing evidence of expression.[8] Interindividual variation in low-level striatal BCMA expression (as shown in this case using transcriptomic data from the Human Protein Atlas) could contribute to the rarity of MNTs, but it is unclear if antigen expression alone provides the complete explanation. An alternative, potentially complementary, model is that rapid CAR-T expansion and/or a particular CAR-T phenotype permit central nervous system (CNS) trafficking, followed by local inflammatory activation and reversible disruption of striatal circuits (Figure 1). The absence of

overt neuronal loss or structural injury in the present case, despite clinically significant parkinsonism, and reports of neurological improvement following CAR-T depletion or intrathecal chemotherapy argue against a purely destructive neurodegenerative process, at least initially, in a subset of patients. If excessive expansion and tissue trafficking of CAR T cells drive these syndromes, early identification of patients at risk may permit intervention before the neurological injury becomes established. Peak absolute lymphocyte count (ALC), CAR-T kinetics, CD4/CD8 composition, and CSF CAR T cell monitoring warrant prospective evaluation as biomarkers.

Differences across T cell-engaging platforms further argue against an overly simplified mechanistic model. BCMA-directed bispecific antibodies have not been associated with parkinsonism at a comparable rate. Furthermore, in the phase 1 study of anitocabtagene autoleucel (anito-cel), a BCMA-directed CAR-T product incorporating a distinct D-domain binder with a faster off-rate, delayed neurotoxicity has not been reported so far.[9] Although cross-trial comparisons and limited follow-up in a small cohort preclude firm conclusions, CAR design, antigen-binding kinetics, and cellular expansion may modify neurotoxicity risk. Conversely, GPRC5D-directed (CAR-T cell) therapy has been associated with a distinct cerebellar syndrome.[10]

Treatment evidence for MNTs after BCMA-directed CAR-T is supported largely by case reports and small series. Unlike idiopathic Parkinson disease, CAR-T-associated parkinsonism is generally unresponsive to levodopa, while corticosteroids often provide limited benefit. Early recognition and intervention may mitigate neurological progression, whereas CAR-T depletion with cyclophosphamide or intrathecal chemotherapy have produced responses in selected patients, sometimes tracking with reduction in CSF lymphocytosis. Indiscriminate immunosuppression, however, carries substantial infectious risk; this patient died of septic shock, as have others with CAR-T-associated immune-related adverse events and related

toxicities. Additional prospective studies evaluating immune-related adverse events, including implementation of systematic monitoring and rational, mechanistic treatment strategies, are needed.

By providing the first detailed CNS neuropathological assessment of ide-cel-associated parkinsonism, Yoshino et al. extend previous observations following cilta-cel and strengthen the evidence for a potential BCMA CAR-T class-related neurotoxicity. As BCMA-directed CAR T-cell therapy moves into earlier lines of treatment for multiple myeloma, rare but potentially devastating delayed toxicities will assume greater importance. Prospective neurological assessment, longitudinal CAR T-cell measurements, paired blood and CSF immune profiling, and, when available, tissue-based investigation will be needed to elucidate what attracts and retains these cells in vulnerable tissues and how neuronal function is disrupted. Such insights may enable earlier detection and safer interventions while preserving CAR-T efficacy.

REFERENCES

1. Yoshino H, Imi T, Nukii Y, et al. Parkinsonism-like delayed neurotoxicity after idecabtagene vicleucel therapy for multiple myeloma: clinicopathological, cerebrospinal fluid, and autopsy analyses. Haematologica. xxx

2. Van Oekelen O, Aleman A, Upadhyaya B, et al. Neurocognitive and hypokinetic movement disorder with features of parkinsonism after BCMA-targeting CAR-T cell therapy. Nat Med. 2021;27(12):2099-2103.

3. Cohen AD, Parekh S, Santomasso BD, et al. Incidence and management of CAR-T neurotoxicity in patients with multiple myeloma treated with ciltacabtagene autoleucel in CARTITUDE studies. Blood Cancer J. 2022;12(2):32.

4. Karschnia P, Miller KC, Yee AJ, et al. Neurologic toxicities following adoptive immunotherapy with BCMA-directed CAR T cells. Blood. 2023;142(14):1243-1248.

5. Kethidi N, Pothukuchi S, Aleman A, et al. Persistence of mucosal CAR-T cells and inflammatory remodeling in enterocolitis associated with BCMA CAR-T cell therapy. Nat Med. 2026 Sep 23. doi: 10.1038/s41591-026-04632-y. [Epub ahead of print]

6. Ho M, Paruzzo L, Noll JH, et al. CD4+ T cells mediate CAR-T cell-associated immune-related adverse events after BCMA CAR-T cell therapy. Nat Med. 2026;32(2):702-716.

7. Hosoya H, Velayati A, Dima D, et al. Rapid peak cilta-cel expansion is associated with delayed neurotoxicity in multiple myeloma. Blood. 2026;148(16):1961-1972.

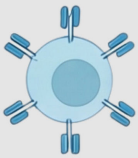
8. Marella M, Yao X, Carreira V, et al. Comprehensive BCMA expression profiling in adult normal human brain suggests a low risk of on-target neurotoxicity in BCMA-targeting multiple myeloma therapy. J Histochem Cytochem. 2022;70(4):273-287.

9. Frigault MJ, Dhakal B, Jakubowiak AJ, et al. Phase 1 Study of anito-cel, a d-domain BCMA CAR T cell for refractory or recurrent myeloma. N Engl J Med. 2026;395(12):1180-1192.

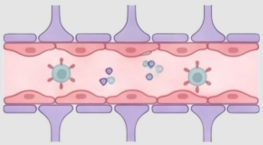
10. Mailankody S, Devlin SM, Landa J, et al. GPRC5D-targeted CAR T cells for myeloma. N Engl J Med. 2022;387(13):1196-1206.

FIGURE LEGENDS

Figure 1. Proposed mechanisms of delayed neurotoxicity following BCMA-directed CAR T-cell therapy. Peripheral CAR T-cell expansion, influenced by host susceptibility, tumor burden, and CAR construct characteristics, may promote trafficking into and persistence within the central nervous system (CNS). Within the basal ganglia, two potentially complementary mechanisms may contribute to neurological dysfunction: (1) on-target, off-tumor recognition of low-level B-cell maturation antigen (BCMA) expression on neural cells, and (2) antigen-independent inflammation mediated by cytokines and local innate immune activation. These pathways may converge on disruption of neuronal circuits, resulting in delayed parkinsonism and neurocognitive symptoms, typically emerging weeks after infusion. Neurological dysfunction may be partially reversible with interventions targeting CAR T cells or CNS inflammation. Although cerebrospinal fluid CAR T-cell enrichment, basal ganglia T-cell infiltration, and BCMA expression support elements of this model, the relative contributions of antigen-dependent recognition and bystander inflammation remain uncertain. Figure created with BioRender.com.

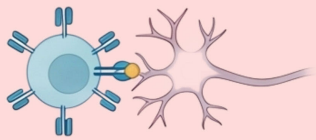


Peripheral CAR-T expansion
susceptible host, tumor and construct factors

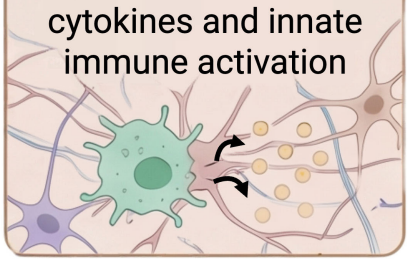


CNS trafficking and persistence
CAR-T cells in CSF and tissue

On-target, off-tumor recognition
low-level BCMA expression



Antigen-independent inflammation
cytokines and innate immune activation



Basal ganglia dysfunction

Delayed parkinsonism and neurocognitive symptoms
weeks after infusion;
sometimes reversible with early depletion