Case Reports in Oncology

Case Rep Oncol 2024;17:75–81
DOI: 10.1159/000535426
Received: October 19, 2023
Accepted: November 20, 2023
Published online: January 9, 2024

Case Report

Exacerbations of Persistent Neurotoxicity following Axicabtagene Ciloleucel in a Patient with Relapsed/ Refractory Diffuse Large B-Cell Lymphoma: A Case Report

Graeme A. Fenton[a] Erin A. Dean[b]

[a]College of Medicine, University of Florida, Gainesville, FL, USA; [b]Division of Hematology and Oncology, Department of Medicine, University of Florida, Gainesville, FL, USA

Keywords
Immunotherapy · Chimeric antigen receptor T cell · Neurotoxicity · Diffuse large B-cell lymphoma · Case report

Abstract
Introduction: Neurological toxicity following chimeric antigen receptor T-cell infusion, termed immune cell-associated neurotoxicity syndrome (ICANS), is a common and limiting factor in the expansion of this promising treatment modality. While refractory cases of ICANS have been reported in clinical trials, there is limited description of these presentations and their associated treatment. The use of predictive biomarkers and risk stratification tools offer a means of identifying patients with higher likelihood of developing ICANS; however, their discriminatory sensitivity has been shown to vary depending on disease type. ***Case Presentation:*** In this case report, we present the clinical course of a patient with diffuse large B-cell lymphoma treated with axicabtagene ciloleucel who developed a nonsinusoidal pattern of severe neurotoxicity refractory to steroid treatment, and we evaluate the predictive value of commonly used biomarkers and risk scores in assessing the likelihood of her presentation. ***Conclusion:*** In assessing the efficacy of these scores in the context of our patient's pattern of severe neurotoxicity exacerbations, we aim to provide valuable clinical insight to better manage refractory ICANS and ultimately improve patient outcomes.

Correspondence to:
Erin A. Dean, Erin.Dean@medicine.ufl.edu

Case Rep Oncol 2024;17:75–81
DOI: 10.1159/000535426

Introduction

Although chimeric antigen receptor (CAR) T-cell therapy has emerged as a valuable therapeutic agent for use in the treatment of patients with relapsed or refractory large B-cell lymphoma (LBCL), treatments are frequently complicated by immune cell-associated neurotoxicity syndrome (ICANS) and cytokine release syndrome (CRS) [1]. ICANS is characterized by the acute onset of neurologic deficits with a largely consistent evolution in presentation from initial tremors, dysgraphia, inattention, and apraxia later progressing to global aphasia, seizures, coma, and potentially death [2]. Given the varied clinical presentation and duration of ICANS, broad adoption and application of CAR T-cell therapy will rely on an expanded understanding of ICANS through qualitative description, as well as identification of potential biomarkers and related scoring systems that may better predict the onset of neurotoxicity. Further examination of ICANS can help to better risk stratify patients prior to treatment, reduce morbidity and mortality, and potentially expand our knowledge of the immunologic underpinnings of CAR T-cell expansion and persistence.

Herein, we describe a case of a patient with relapsed/refractory LBCL who received axicabtagene ciloleucel (axi-cel) and subsequently experienced neurotoxicity with atypical exacerbations. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535426).

Case Presentation

A 64-year-old woman with a history of Stage IV diffuse large B-cell lymphoma (DLBCL), activated B-cell (non-germinal center) subtype diagnosed 1 year prior. She received six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone chemo-immunotherapy, achieving a complete response. Three months later, the patient had recurrence of disease after follow-up positron emission tomography/computed tomography (PET/CT) imaging showed an interval increase in the size of a right retroperitoneal lymph node as well as a new osseous lesion in the left iliac bone. The patient received 2 cycles of salvage chemo-immunotherapy with second-line rituximab, gemcitabine, carboplatin, and dexamethasone complicated by delirium with cycle 1. Restaging PET/CT, however, demonstrated interval increase in the maximum standardized uptake value (SUVmax) of the osseous lesion, from 3.7 to 7.6. The lesion was later confirmed to be an atypical CD20+ lymphoid infiltrate on biopsy with unremarkable cytogenetics (46, XX).

Given the relapsed/refractory nature of her DLBCL, the patient presented to our academic center for evaluation of CAR T-cell therapy with commercial axi-cel. She had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 and required a walker for ambulation support. Baseline PET/CT redemonstrated a left iliac lesion with an SUVmax of 5.45 as well as a new large retroperitoneal mass involving the great vessels located at the level of the kidneys measuring 6.4 cm × 5.4 cm with an SUVmax of 37. Bridging therapy with a 4-day course of high-dose dexamethasone was completed following apheresis 2 weeks prior to infusion. After undergoing a 3-day course of lymphodepleting chemotherapy with fludarabine and cyclophosphamide, she received axi-cel at a dose of 2×10^6 cells/kg on day 0. The patient received prophylactic corticosteroids, dexamethasone 10 mg PO daily, on day 0, +1, and +2. Ferritin was noted to be elevated at 1,381 ng/mL prior to infusion on day −1. C-reactive peptide (CRP) was elevated at 17.2 mg/L. Lactate dehydrogenase (LDH) was also high at 240 U/L. On day +2 post-infusion, the patient developed grade 2 CRS characterized by low-grade fever and hypotension. She was noted to have grade 1 ICANS with an immune effector

Case Rep Oncol 2024;17:75–81
DOI: 10.1159/000535426

cell-associated encephalopathy (ICE) score of 9, characterized by mild confusion on exam with errors on a neurocognitive functional screening assessment. The patient subsequently received 400 mg tocilizumab and 10 mg dexamethasone per institutional protocol. As she was neutropenic and febrile, prophylactic cefepime and fluconazole were started. CRP was noted to be uptrending to 169.4 mg/L. Day +4 was complicated by overnight fevers with a maximum temperature of 102.7 Fahrenheit (F) and mild hypotension consistent with grade 2 CRS. Later that afternoon, she began speaking word salad and was noted to have ICANS 2/ICE 5. She received 400 mg tocilizumab and 1 g methylprednisolone per protocol prior to being transferred to the medical intensive care unit where she underwent neurological workup and stroke evaluation. CT head and magnetic resonance brain revealed no intracranial abnormalities or findings suggesting the presence of ICANS or metastatic disease. Electroencephalogram demonstrated abnormal background slowing consistently with mild encephalopathy without seizure activity. Seizure prophylaxis with levetiracetam 750 mg twice daily starting day 0 was continued. Lumbar puncture fluid analysis showed xanthochromia, and gram stain demonstrated no evidence of organisms or white blood cells. LDH and ferritin were uptrending to 350 U/L and 3,870 ng/L, respectively. Interleukin (IL) panel, measured in pg/mL, was notable for elevated levels of the following: IL-2R at 6.8, IL-5 at 218.8, IL-6 at 2,008.3, IL-8 at 8, IL-10 at 155.4, and IL-13 at 22.1. Interferon-gamma was also elevated at 261.2 pg/mL. On day +5, the patient displayed expressive aphasia and was unable to swallow medications, requiring Dobhoff tube placement. At that time, ICANS grade was 3 and ICE score 0. On day +6, while CRS resolved, grade 3 ICANS remained unresponsive to initial steroid treatment, prompting an increase in methylprednisolone dosing to 1 g twice daily. The patient became progressively more alert over the next 4 days; however, she continued to experience ICANS grade 3 with ICE score of 0, as she was unable to speak or follow commands. During this time period, ferritin and LDH were noted to be downtrending from peak levels but remained persistently elevated above reference range.

On day +11, the severity of neurological symptoms grew acutely worse; the patient had no purposeful movements and was completely mute, consistent with grade 4 ICANS. Neurological decompensation was preceded by grade 2 CRS in the setting of tachycardia, tachypnea, and development of a fever; she received a third dose of 400 mg tocilizumab. Ferritin and LDH had increased to levels comparable to those observed at the onset of neurotoxicity. ICANS was downgraded to grade 2 on day +13, characterized by a significant improvement in neurological symptoms with the patient becoming more interactive and responsive to commands. Methylprednisolone tapering from 1,000 mg twice daily back to 1,000 mg daily was begun given improved neurological function. She transitioned out of the intensive care unit to the general medicine floor on day +14, where she continued to regain neurological function over the next 4 days with ICE scores ranging from 4 to 7, corresponding to grade 2 ICANS.

On day +17, approximately 2 weeks after the initial onset of severe neurotoxicity, the patient again developed grade 3 ICANS and was unable to respond to commands. CRS was grade 0 at the onset of the exacerbation. LDH levels were again noted to be uptrending to levels previously observed during prior ICANS exacerbations; however, ferritin levels remained stable and CRP was within normal limits. Methylprednisolone dosing was subsequently increased back to 1 g twice daily. Neurological function slowly improved over the next 8 days, prompting the reduction of methylprednisolone dosing back to 1,000 mg daily on day +21 and initiation of steroid tapering on day +25. Neurological symptoms resolved with ICANS 0/ICE 10 on day +40, and the patient was tapered off steroids on day +41, 39 days after the initial development of fever and neurotoxicity.

Hospital admission was further complicated by the identification of pulmonary nodules on CT chest, later found to be fungal pneumonia following bronchoscopy, and subsequently treated with amphotericin B. Transbronchial biopsy found no evidence of lymphoma

Case Rep Oncol 2024;17:75–81
DOI: 10.1159/000535426

involvement. She also developed and required treatment for aspiration pneumonia, CMV viremia, pseudomonal urinary tract infection, and hypogammaglobulinemia. She was discharged on day +87 to a rehabilitation facility given severe deconditioning associated with her treatment complications and duration of stay. Restaging PET/CT 4 months after infusion demonstrated good disease response without evidence of recurrence. Subsequent restaging PET/CT performed 10 months after infusion, however, identified a soft tissue osseous lesion concerning for progression of disease that was later confirmed as relapsed lymphoma on biopsy. Given that the patient experienced recurrent infections requiring hospitalization, she was transitioned to supportive care and passed away shortly thereafter.

Discussion

In this case, we observed a nonsinusoidal pattern of refractory neurotoxicity exacerbations within the first month following administration of axi-cel in a patient with relapsed/refractory DLBCL. Our patient experienced three distinct episodes of severe neurotoxicity during her clinical course.

The patient's initial ICANS presented with concurrent CRS 2 days following CAR T-cell therapy. Neurotoxicity developed despite a 3-day course of prophylactic corticosteroids, a management strategy employed for patients in cohorts 4 and 6 of the ZUMA-1 trial associated with a reduced rate of severe grade 3 or 4 neurologic events following infusion [3, 4]. ICANS is typically preceded by the onset of CRS, but can develop concomitantly when presenting with more severe grades of toxicity [5]. ICANS that occurs concurrently with CRS is generally found to have shorter duration and lower grade than ICANS occurring independently [6]. Notably, the relationship between our patient's CRS and ICANS did not follow this trend as her initial ICANS became severe and persisted despite corticosteroid treatment.

Patient-specific factors and management strategies of therapy-related toxicities may explain at least partially her unusual neurotoxicity course as well as the lack of durability of treatment response. The patient's previous history of delirium following chemotherapy might have been a risk indicator for future neurologic toxicity. In addition, other known risk factors, including age greater than 52 years, aggressive histologic subtype, higher disease burden, elevated baseline inflammatory markers including ferritin and CRP, as well as early onset of CRS, may have all played a role in her case [7]. While high-grade neurotoxicity (grade 3–4) characterized by intermittent symptom-free intervals and acute exacerbation following initiation of a steroid taper have been noted in the literature, the qualitative description of this nonsinusoidal pattern of recurrence and subsequent management remains limited [8, 9]. Our patient also received 3 doses of tocilizumab for repeated episodes of CRS. Data from a small cohort of patients enrolled in the ZUMA-1 trial suggested that early tocilizumab treatment for CRS increased the frequency and severity of high-grade ICANS, likely in the setting of increased circulating IL-6 in the central nervous system following peripheral IL-6 receptor blockade; however, larger clinical trials are needed to confirm these findings [10]. To date, administration of tocilizumab has not been associated with reduced CAR T-cell efficacy or overall response rate [6]. The prolonged (>10 days) and early use of corticosteroids following development of CAR T-cell-associated toxicities has, however, been correlated with significantly shorter overall survival in a cohort of 100 patients with DLBCL [11]. To this end, the required prolongation of high-dose steroid use must be considered as a potential contributing factor to the patient's relapsed disease 10 months following treatment.

Certain biomarkers in the peripheral blood of patients receiving CAR T cells provide invaluable predictive information regarding the trajectory of ICANS. Biomarkers reflecting endothelial activation and inflammatory response are of particular interest, as neurotoxicity has been postulated to develop as a result of endothelial dysfunction and increased

blood-brain barrier permeability following CAR T-cell infusion. ICANS grade ≥3 is associated with elevated median peak levels of the acute phase reactants CRP and ferritin, with CRP levels peaking prior to the onset of neurologic symptoms and ferritin levels peaking shortly after [1, 12]. Likewise, elevated serum levels of the pro-inflammatory markers interferon-gamma, CXCL19, IL-1R, IL-10, IL-15, granulocyte-macrophage colony-stimulating factor, and monocyte chemoattractant protein-1 following infusion have also been associated with increased risk of severe neurotoxicity [13]. Finally, ICANS has been observed prior to peak CAR T-cell levels in the blood [14] and its timing depends on the type of CAR T-cell therapy product [2].

In the case of our patient, elevated levels of CRP, ferritin, and LDH, which is typically used as a surrogate marker of tumor burden, were noted prior to CAR T-cell infusion, findings that would place her at greater risk for high-grade ICANS. CRP displayed a singular peak preceding the development of initial toxicity (shown in Fig. 1a). In contrast, we observed a bimodal ferritin peak following infusion, with uptrending levels of ferritin preceding distinct exacerbations in neurotoxicity (shown in Fig. 1b). LDH likewise displayed uptrending values preceding exacerbations as well a delayed bimodal peak following onset of acute neurotoxicity exacerbation (shown in Fig. 1c). IL and cytokine panels were collected following the initial onset of neurotoxicity, with all values above normal limits, as expected, except for IL-15. Despite confirming the initial acute toxicity, these panels were not trended to allow possible prediction of the subsequent exacerbations. The patient's CAR T-cell expansion was also not measured, which could have been helpful if done in real time. Associated expense and turnaround time are limitations of these potential blood biomarkers. Detection of IL-1 in the cerebrospinal fluid, which is targetable by anakinra, is a less convenient biomarker requiring lumbar puncture for collection [14]. Despite being routinely obtained, brain imaging studies are typically insignificant, as in this case [15].

The limited predictive power of individual biomarkers has prompted the development of more comprehensive risk scores that account for the interplay between the patient's clinical condition, systemic inflammation, tumor burden, endothelial function, and CAR T-cell proliferation post-infusion. Use of the Endothelial Activation and Stress Index (EASIX) score, calculated using the formula ([creatinine × LDH]/platelets) prior to lymphodepleting chemotherapy, for example, has successfully identified patients at greater risk of grade 2–4 ICANS, with scores correlating to observed outcomes following CAR T-cell administration [12]. EASIX, as well as the simplified EASIX, which omits creatinine, and the modified EASIX (m-EASIX), which replaces creatinine with CRP, has demonstrated moderate efficacy correlating with severe ICANS shortly after infusion [16]. Notably, the predictive value established by Greenbaum et al. [12] using EASIX scores calculated prior to infusion is contradicted by Pennisi et al. [16], as the latter study's data suggest only post-infusion EASIX scoring appropriately discriminates associated risk of neurotoxicity [12, 16].

In assessing the EASIX, simplified EASIX, and m-EASIX scores in our patient, her pre-lymphodepletion EASIX score of 2.69 did not meet the cutoff criteria established by Greenbaum et al. [12] (EASIX >4.6) for high risk of severe (grade 2–4) neurotoxicity. Following infusion, m-EASIX did peak sooner prior to the onset of initial neurotoxicity, with all three scores consistently increasing following subsequent exacerbations (shown in Fig. 1d). Comparing the risk-stratified m-EASIX scoring of patients with ICANS described by Pennisi et al. [16], our patient's m-EASIX score of 7.15 on day +1 put her within the reported interquartile range for increased risk of both grade 1–2 (2.17–28.90) and severe, grade ≥3 neurotoxicity (4.30–30.60); however, her m-EASIX score of 8.86 was well below the day +3 interquartile range for severe neurotoxicity (15.76–146.56). These findings, coupled with the discordant results published in the literature, stress the importance of continued development of new risk stratification scoring tools [16] with the goal to more consistently capture neurotoxicity and its exacerbations.

Collectively, this timeline of neurological events illustrates the many questions that remain regarding recurrence of severe ICANS and its effective management during the course of a CAR

Case Rep Oncol 2024;17:75–81
DOI: 10.1159/000535426

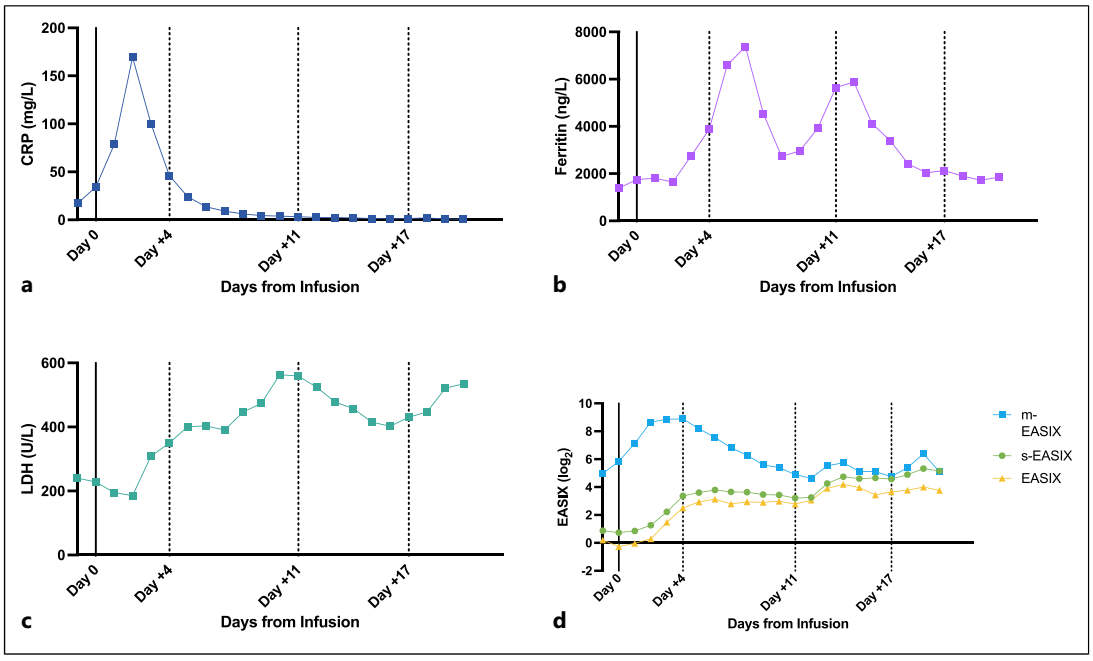

Fig. 1. Biomarkers and risk scores for ICANS due to CAR T-cell therapy in a patient with relapsed/refractory DLBCL. In **a–d**, the solid line represents axi-cel administration on day 0, with the dashed lines marking worsening neurotoxicity on day +4, day +11, and day +17. To estimate the influence and predictive power of individual biomarkers on associated neurotoxicity, we trended CRP (**a**), ferritin (**b**), and LDH (**c**) over the duration of our patient's clinical course following axi-cel infusion. CRP peaked prior to the development of ICANS only, ferritin after the initial episode and first exacerbation, while LDH uptrended with all three episodes. EASIX/s-EASIX/m-EASIX scores were plotted on the same axis (**d**) to compare their relative predictive value of ICANS. Log transformation using base 2 (log_2) was applied to all the EASIX/s-EASIX/m-EASIX scores to reduce skewness. All scores were able to predict the first neurotoxicity exacerbation on time with the m-EASIX score, which replaces CRP with creatinine, performing superiorly; but all peaked after the subsequent two exacerbations. s-EASIX, simplified EASIX.

T-cell treatment in a patient with DLBCL. Further understanding of the pathologic mechanisms of ICANS is needed to allow identification of novel biomarkers and construction of comprehensive toxicity models that can more accurately predict ICANS incidence and refractoriness. This will prove to be an important next step in stratifying patients and reducing the morbidity and mortality associated with CAR T-cell therapy as it becomes more widely used.

Statement of Ethics

Ethical approval is not required for this retrospective review of patient data in accordance with local and national guidelines. Written informed consent was obtained from the patient's family regarding publication of the details of her medical case and any accompanying images.

Conflict of Interest Statement

G.A.F. has no conflicts of interest to declare. E.A.D. reports unlicensed patents in the field of cellular immunotherapy (no royalties) held by Moffitt Cancer Center, and is a speaker, Clinical Education Alliance.

Funding Sources

This study, including all associated research, data preparation, and manuscript composition relevant to the study, was not supported by any sponsor or funder.

Author Contributions

E.A.D. conceived of the idea for the manuscript. E.A.D. and G.A.F. participated in data curation and wrote the manuscript. Both authors reviewed and edited the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

References

1 Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531–44.
2 Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transpl. 2019;25(4):625–38.
3 Oluwole OO, Bouabdallah K, Muñoz J, De Guibert S, Vose JM, Bartlett NL, et al. Prophylactic corticosteroid use in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol. 2021;194(4):690–700.
4 Topp MS, van Meerten T, Houot R, Minnema MC, Bouabdallah K, Lugtenburg PJ, et al. Earlier corticosteroid use for adverse event management in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol. 2021;195(3):388–98.
5 Maziarz RT, Schuster SJ, Romanov VV, Rusch ES, Li J, Signorovitch JE, et al. Grading of neurological toxicity in patients treated with tisagenlecleucel in the JULIET trial. Blood Adv. 2020;4(7):1440–7.
6 Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy: assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15(1):47–62.
7 Rubin DB, Al Jarrah A, Li K, LaRose S, Monk AD, Ali AB, et al. Clinical predictors of neurotoxicity after chimeric antigen receptor T-cell therapy. JAMA Neurol. 2020;77(12):1536–42.
8 Gust J, Hay KA, Hanafi LA, Li D, Myerson D, Gonzalez-Cuyar LF, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. Cancer Discov. 2017;7(12):1404–19.
9 Badar T, Johnson BD, Hamadani M. Delayed neurotoxicity after axicabtagene ciloleucel therapy in relapsed refractory diffuse large B-cell lymphoma. Bone Marrow Transpl. 2021;56(3):683–5.
10 Siegler EL, Kenderian SS. Neurotoxicity and cytokine release syndrome after chimeric antigen receptor T cell therapy: insights into mechanisms and novel therapies. Front Immunol. 2020;11:1973.
11 Strati P, Ahmed S, Furqan F, Fayad LE, Lee HJ, Iyer SP, et al. Prognostic impact of corticosteroids on efficacy of chimeric antigen receptor T-cell therapy in large B-cell lymphoma. Blood. 2021;137(23):3272–6.
12 Greenbaum U, Strati P, Saliba RM, Torres J, Rondon G, Nieto Y, et al. CRP and ferritin in addition to the EASIX score predict CAR-T-related toxicity. Blood Adv. 2021;5(14):2799–806.
13 Gust J, Ponce R, Liles WC, Garden GA, Turtle CJ. Cytokines in CAR T cell-associated neurotoxicity. Front Immunol. 2020;11:577027.
14 Santomasso BD, Park JH, Salloum D, Riviere I, Flynn J, Mead E, et al. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. Cancer Discov. 2018;8(8):958–71.
15 Amidi Y, Eckhardt CA, Quadri SA, Malik P, Firme MS, Jones DK, et al. Forecasting immune effector cell-associated neurotoxicity syndrome after chimeric antigen receptor t-cell therapy. J Immunother Cancer. 2022;10(11):e005459.
16 Pennisi M, Sanchez-Escamilla M, Flynn JR, Shouval R, Alarcon Tomas A, Silverberg ML, et al. Modified EASIX predicts severe cytokine release syndrome and neurotoxicity after chimeric antigen receptor T cells. Blood Adv. 2021;5(17):3397–406.