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## **Relapsing, steroid-refractory ICANS after CAR T-cell therapy: diagnostic work-up and response to delayed repeated intrathecal chemotherapy**

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Chimeric antigen receptor T-cell (CAR T) therapy has significantly improved survival rates in patients with refractory hematologic malignancies, and its indications have expanded considerably over the past decade. Despite these remarkable advances, cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) remain potentially life-threatening complications. These toxicities can occur in isolation or concurrently, and encompass a wide spectrum of clinical manifestations.(1-3)

Current standard treatment for ICANS consists of high-dose corticosteroids(2), though prolonged exposure is associated with inferior progression-free survival (PFS) in CAR-T-treated diffuse large B-cell lymphoma (DLBCL) patients.(4) Additionally, severe ICANS increases infection risk, posing a significant clinical challenge as high-dose corticosteroids may further raise susceptibility to life-threatening infections such as pulmonary aspergillosis.(5) Moreover, no standard-of-care exists for steroid-refractory ICANS.

We present a case of a 54-year-old male treated with CAR T-cell therapy who suffered relapsing, high-grade ICANS and uniquely achieved near-complete neurological recovery following two late administrations of intrathecal (IT) chemotherapy, 45 days post-CAR-T infusion. This study respects the ethical rules of the Netherlands.

The patient was diagnosed with stage IV DLBCL involving bone, spleen, lymph nodes, and adrenal glands. Following six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy, PET-CT scan demonstrated chemo-refractory disease, indicating CAR T-cell therapy as second-line treatment. Given the high tumor burden, the patient was considered high-risk for both CRS and ICANS.

After leukapheresis, bridging therapy consisted of radiotherapy (4x5Gy) to the adrenal glands because of progressive back pain. However, a subsequent  $^{18}\text{F}$ -Fluorodeoxyglucose (FDG)-PET scan showed marked progression outside the radiation field.

A day to day case description is given in Table 1.

Several significant measures were taken following CAR T-cell infusion. On day 5, patient concomitantly suffered a worsening ICANS (to Grade 2) and a Grade 3 CRS which necessitated ICU admission. He was treated with corticosteroids for ICANS and tocilizumab (600mg) to treat the CRS. On day 19, the patient developed acute respiratory deterioration. At this time, there was significant diagnostic uncertainty as to whether this deterioration reflected occult CRS, pulmonary infection or neurotoxicity-related respiratory compromise. In this acute setting, tocilizumab was again administered address potential occult CRS.

Both, on day 19 and day 41, a full work-up with ancillary testing, including brain MRI, EEG, and CSF analysis was done, to rule out other causes of neurological decline. The day 41 MRI demonstrated pronounced barrier dysfunction with extensive leptomeningeal enhancement (Figure 2A/B). The differential diagnosis included leptomeningeal lymphoma and infection. However, CSF testing showed low leukocyte counts, negative microbiological studies, and no detectable CD19<sup>+</sup> B cells or clonal B-cell population(Table 1), while systemic disease evaluation supported treatment response. Collectively, these findings supported prolonged high-grade ICANS rather than CNS lymphoma.

High-dose corticosteroids and anakinra were administered as ICANS treatment throughout the patients disease course and although transient improvement was observed, steroid-refractory neurological decline developed(Table 1). After this, the patient was treated with IT chemotherapy on days 45 and 47 after CAR-T infusion.

After these IT administrations, clinical improvement was observed.(Table 1) Brain MRI performed on day 81 showed marked reduction of leptomeningeal enhancement.(Figure

2C/D) Despite ongoing neurological recovery, the patient developed multiple nosocomial infections and was found to have progressive lymphoma on an  $^{18}\text{F}$ -FDG-PET performed on day 84 post-CAR-T. The patient died on day 88 after CAR T-cell infusion, due to respiratory failure resulting from combined infectious and oncologic causes.

The exact pathophysiology for ICANS remains incompletely understood. Current hypotheses suggest that systemic inflammation after CAR T-cell therapy leads to endothelial cell activation and disruption of the blood-brain barrier, resulting in cytokine and immune cell infiltration into the CNS and subsequently neuroinflammation. In severe cases, this can progress to cerebral edema.(3)

ICANS typically occurs within one week after CAR T-cell infusion, with a median onset of approximately five days but initiation up to 3 weeks after treatment has been described.(6, 7) Early manifestations commonly include expressive aphasia, dysgraphia and altered mental status(2), all of which were observed in our patient. ICANS most often follows a monophasic course and resolves within 3 weeks after CAR-T.(8) However, as in our case, symptoms may persist and can recur.

The ICE score grades the severity of ICANS-related encephalopathy, while the overall grade is further influenced by the presence of additional neurological features such as seizures.(2) Guidelines recommend continuous neurological reassessment and to adjust treatment accordingly. More severe ICANS (>Grade 2) may necessitate diagnostics (e.g., brain MRI, CSF analysis, and EEG) to rule out other causes of neurological deterioration or to evaluate ICANS-associated abnormalities.(9)

Brain MRI abnormalities in ICANS are variable and may be absent even in severe cases; however, patterns including leptomeningeal enhancement and mesial temporal or hippocampal abnormalities, have been reported and may reflect neuroinflammation and blood-brain barrier dysfunction.(1, 3, 6, 8) CSF analysis, including flow cytometry and microbiological testing, can differentiate between alternative diagnoses (i.e. leptomeningeal lymphoma or infection) fitting radiological findings or new neurological decline. EEG in ICANS commonly reveals diffuse slow activity, as observed in our patient, and may be employed to detect seizure activity or to evaluate unexplained changes in consciousness.(1, 3, 6)

High-grade ICANS ( $\geq$ Grade 3) occurs in 10% of CAR T-treated patients.(10) Risk factors for neurotoxicity include treatment with axi-cel, high tumor burden, early and severe CRS, and pre-existing neurological disorders.(2, 3, 10) Our patient exhibited several of these risk factors.

Standard management consists of high-dose corticosteroids and supportive care(1), yet no standardized treatment exists for steroid-refractory ICANS. Tocilizumab, an IL-6 receptor antagonist, is effective for CRS but has limited efficacy in ICANS, possibly due to poor blood-brain barrier penetration.(1, 3) Moreover, peripheral IL-6 receptor blockade may even worsen ICANS by increasing IL-6 levels in the CSF.(3) Guidelines thus recommend tocilizumab only in the presence of concomitant CRS, limiting its role ICANS treatment.(10) Anakinra, an IL-1 receptor antagonist, shows promise in steroid-refractory cases. In a retrospective cohort study (n=40), high-dose anakinra was associated with faster neurological recovery without compromising CAR T-cell efficacy.(11) In our patient, improvement was initially observed following its introduction, although symptoms later recurred.

IT chemotherapy administered early after ICANS onset has shown encouraging results in case studies. This treatment is hypothesized to mitigate neurotoxicity through suppression of

CNS inflammation and reduction of neurotoxicity-driving CAR T-cells in the CSF.(12)Two independent case reports described rapid improvement in patients with high-grade, steroid-refractory ICANS treated with IT hydrocortisone in combination with chemotherapeutic agents.(12, 13) Furthermore, a 2024 case series reported 12 lymphoma patients who received IT chemo (methotrexate, cytarabine, or both) a median of three days after ICANS onset. All patients had previously been treated with systemic corticosteroids, and neurotoxicity resolved in all but one case, with a median time to improvement of two days. Notably, only half of the patients had high-grade ICANS, similar to our patient. The patient who did not recover neurologically suffered grade 3 ICANS and was treated the latest after symptom onset (23 days).(14) In contrast, our patient showed marked improvement even 42 days after onset in high-grade ICANS.

Another case series described seven patients who received IT hydrocortisone within five days of developing high-grade, steroid-refractory ICANS, four of whom also received IT chemotherapy.(15) Amongst those treated with IT chemo, no patient received chemotherapeutic agents later than 15 days after ICANS onset. All seven patients recovered, showing improvement to low-grade ICANS within a median of two days. In contrast, eight patients who either did not receive IT therapy or were treated later after onset (i.e., with IT hydrocortisone day 24 after ICANS onset) exhibited higher cumulative steroid exposure and significantly lower PFS. Among these, four patients with steroid-refractory ICANS had an estimated one-year PFS of 0%, and half experienced no resolution of neurotoxicity. This study suggests a clear benefit of early IT treatment in promoting neurological recovery and reducing systemic steroid exposure, potentially contributing to preserved CAR T-cell function.

Of note, all previous reports are retrospective in nature and limited by the heterogeneity of CAR T-cell indications, treatment modalities and concomitant systemic treatment. The beneficial effect attributable solely to IT chemotherapy cannot be fully determined from these findings, however, the consistent temporal relationship between IT administration and clinical improvement across reports is compelling.

Importantly, previous studies have focused exclusively on early IT chemotherapy, typically initiated within days of ICANS onset. In contrast, our report provides the first evidence of clinical benefit even when administered as late as 42 days after initial symptoms. This finding directly extends the currently recognized therapeutic window for IT intervention and suggests that even in prolonged and refractory ICANS, intrathecal treatment may still meaningfully modulate CNS-driven neurotoxicity. In our experience, repeated dosing was well tolerated and IT chemotherapy effectively managed relapsing, steroid-refractory ICANS leading to near-complete symptom resolution.

IT chemotherapy may induce meaningful neurological improvement in high-grade ICANS unresponsive to systemic therapy, even when administered weeks after CAR-T infusion. A second dose appeared safe and proved to be effective in relapsing ICANS, suggesting its utility beyond acute presentations. This case highlights a broader therapeutic window for IT treatment than previously recognized and underscores the need for prospective studies to define its role in ICANS management.

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| Day        | Symptoms   | Diagnostics   | Initiated treatment   |
|------------|--|---|---|
| -10-<br>-6 | Pre-CAR-T. No neurological symptoms  | <b>CSF:</b> CC < 7 x10 <sup>6</sup> . TP 0.37 g/L. <b>FCM:</b> No B-lymfocytes, 7% T-cells CD4/CD8 ratio of 0.10. <b>Blood:</b> CRP 176.2 mg/L. Ferritin 4046 ug/L.   | Lymphodepletion: CTX + fludarabine<br>DEX (40mg)  |
| 0          | Day of CAR T-cell infusion   | ICE score: 10. <b>Blood:</b> CRP 263.3 mg/L, Ferritin 7933 ug/L   | Axi-cel. prophylactic DEX (10mg)  |
| 1-2        | Fever (38.4-38.7 °C) (grade 1 CRS)   | ICE score: 10. <b>Blood:</b> CRP 201.9 mg/L, Ferritin 9329 ug/L   | prophylactic DEX (10mg)   |
| 3          | Dysgraphia (grade 1 ICANS)   | ICE score: 9. <b>Blood:</b> CRP 131.4 mg/L, Ferritin 11413 ug/L   | DEX (10mg)  |
| 5          | Fever (38.6 °C), SpO2 95%, BP (78/55 mmHg) (grade 3 CRS).<br>Bradyphrenia, mild aphasia (grade 2 ICANS). | ICE score: 5. <b>Blood:</b> CRP 103.6 mg/L. Ferritin 14491 ug/L.  | ICU admission. Tocilizumab(600mg)<br>DEX (10mg 4 times daily)   |
| 7          | Aphasia, bradyphrenia (grade 3 ICANS)  | ICE score: 1. <b>CSF:</b> CC <7 x10 <sup>6</sup> , TP 0.36 g/L, glc 5.6 mmol/L. lactate 2.98 mmol/L. <b>Culture CSF:</b> no bacterial or fungal growth. <b>CSF PCR:</b> negative (CMV; EBV; HSV 1,2; L. monocytogenes; N. meningitides; S. pneumoniae; VZV). <b>CT brain:</b> No hemorrhage. <b>Blood:</b> CRP 57.3 mg/L  | High-dose MPS (1000mg daily for three days)   |
| 8          | Focal epileptic seizures (grade 3 ICANS)   | ICE score 0-2. <b>Blood:</b> CRP 26.7 mg/L  | Levetiracetam (500mg twice daily)   |
| 10         | No improvement despite MPS (grade 3 ICANS)   |   | Anakinra SC (100mg daily). DEX (40mg daily)   |
| 12         | Partial improvement (Grade 1 ICANS)  | ICE score 8-9   | Anakinra SC discontinued. ICU dismissal.  |
| 13         | Worsening bradyphrenia, ongoing aphasia  | ICE score 7   | Anakinra SC (100mg daily) restarted   |
| 15-<br>19  | Recurrent generalized seizures. Decreased consciousness. Respiratory insufficiency. GCS: E3M1V1 - E4M5V1 | ICE score 0-1. <b>EEG:</b> no epileptic status. <b>MRI brain:</b> mild cytotoxic edema around hippocampi, attributed to postictal changes. <b>CSF:</b> CC <7 x10 <sup>6</sup> , TP 0.51 g/L, glc 5.6 mmol/L, lactate 3.1 mmol/L. 65.7% of T-lymfocytes were CAR T-cells. <b>CSF PCR</b> negative. (Enterovirus; HSV 1,2; Listeria monocytogenes; N. meningitides; Parechovirus; S. pneumoniae; VZV) <b>Bacterial culture CSF:</b> no growth. <b>Blood</b> CRP 2.5 mg/L  | Day 15 Readmission ICU. Levetiracetam increased to 1000mg twice daily<br>Day 19 Intubation. Tocilizumab 600mg |
| 25-<br>40  | Gradual increasing bradyphrenia, varying degree of drowsiness and aphasia. GCS E3-4M6V3-4                | Day 30: <b>Blood</b> CRP 1.6 mg/L<br>Day 31: <b>PET-CT:</b> Good PMR of malignant lymphoma. Adrenal localizations show residual necrotic/cystic lesions. Only few small foci with Deauville 4.  |   |
| 41         | Sudden decrease in the level of consciousness. GCS E1M1V1. Recurrent seizures (grade 4 ICANS)            | <b>Brain MRI:</b> Pronounced BBB disruption; persistent hippocampal swelling, extensive leptomenigeal enhancement. <b>EEG:</b> Diffuse slow activity. <b>CSF:</b> CC <7 x10 <sup>6</sup> . TP 0.62 g/L. Glc 5.3 mmol/L. No B-lymfocytes. 6% NK-lymfocytes, 31% T-lymfocytes CD4/CD8 ratio of 1.96. <b>CSF PCR:</b> negative (CMV; Cryptococci; EBV; HSV 1,2; JC polyomavirus, L. monocytogenes; N. meningitides; S. pneumoniae; VZV). <b>CSF culture:</b> No bacterial, cryptococcal or fungal growth. <b>Blood:</b> CRP 2.3 mg/L, ferritin 4143 ug/L | levetiracetam increased to 1250mg twice daily<br>MPS (1000mg daily for three days)                            |
| 45         | Limited effect of MPS. GCS E1M3V1  |   | IT MTX 15mg), Ara C(40mg), HC (20mg)  |
| 47         | Slight improvement in GCS E3M4Vtube  | <b>CSF:</b> CC <7 x10 <sup>6</sup> . TP 0.69 g/L, glc 4.7 mmol/L. Lactate 2.41 mmol/L. 43.5% of T-Lymfocytes are CAR T-cells  | IT MTX (15mg), Ara C(40mg), HC (20mg)   |
| 49-<br>88  | GCS E4M6Vtube. Adequate non-verbal responses. Short sentences after extubation.                          |   | Day 74 dismissed from ICU. Anakinra discontinued. DEXA tapered from 10mg/day.                                 |

**Table 1: Day by day case description** Abbreviations: Ara C: cytarabine; BBB: Blood-brain barrier; CAR-T: Chimeric antigen receptor T-cell; CC: cell count; CTX; cyclophosphamide, CMV: Cytomegalovirus; CRS: Cytokine release syndrome; CSF: Cerebrospinal fluid; DEX: dexamethasone; EBV: Epstein-Barr Virus; EEG:

Electroencephalography; GCS: FCM; Flow cytometry ;Glasgow Coma Scale; Glc: Glucose; HC; Hydrocortisone; HSV: Herpes simplex virus; ICANS: Immune effector cell-associated neurotoxicity syndrome; ICE: Immune effector Cell-associated Encephalopathy; ICU: intensive care unit; IT: intrathecal; MPS: methylprednisolone; MRI: Magnetic resonance imaging; MTX: Methotrexate, PMR: Partial metabolic response; SC: subcutaneous; TP: total protein; VZV: Varicella zoster virus. CRS and ICANS grading according to the American Society for Transplantation and Cellular Therapy (ASTCT). (2)

## **Legends to figures**

### **Figure 1:**

**Title:** Timeline of patients ICANS trajectory and treatment for CRS/ ICANS

Abbreviations: CRS; Cytokine release syndrome, ICANS; Immune effector cell-associated neurotoxicity syndrome, ICU; Intensive Care Unit, MTX-Ara-C: Methotrexate and cytarabine (Intrathecal), PD; Progressive disease, PMR; Partial metabolic response

### **Figure 2:**

**Title:** Brain MRI T1 with gadolinium

**Text:** A+B axial MRI T1 with gadolinium day 41, leptomeningeal enhancement in the cerebellar and occipital cerebrospinal fluid

C+D axial MRI T1 with gadolinium day 81, leptomeningeal enhancement resolved

Figure 1



