ANTICANCER RESEARCH *42*: 3853-3856 (2022)
doi:10.21873/anticanres.15876

Intrathecal Chemotherapy as a Potential Treatment for Steroid-refractory Immune Effector Cell-associated Neurotoxicity Syndrome

PALASH ASAWA[1], URWAT VUSQA[1], CYRUS KHAN[2], YAZAN SAMHOURI[2] and SALMAN FAZAL[2]

[1]*Department of Internal Medicine, Allegheny Health Network, Pittsburgh, PA, U.S.A.;*
[2]*Division of Hematology and Cellular Therapy, Allegheny Health Network Cancer Institute, Pittsburgh, PA, U.S.A.*

Abstract. *Background/Aim: Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of various B-cell malignancies. However, it can cause serious adverse effects like immune effector cell-associated neurotoxicity syndrome (ICANS). ICANS is attributed to disruption of the blood-brain barrier due to inflammatory cytokines and increased levels of immune effector cells (IECs) in the cerebrospinal fluid (CSF). Corticosteroids and supportive management are the mainstays of ICANS treatment. However, no guidelines exist for the treatment of steroid-refractory ICANS. Some reports have shown favorable outcomes with no long-term complications in patients with steroid-refractory ICANS treated with intrathecal (IT) chemotherapy. Case Report: We describe the outcomes of two patients with steroid-refractory ICANS treated with IT chemotherapy. Both patients had refractory large B-cell lymphoma and were not candidates for autologous transplant. They developed steroid-refractory ICANS after CAR T-cell infusion. IT chemotherapy with 12 mg methotrexate and 50 mg hydrocortisone resulted in prompt neurological improvement in both patients. One of them passed away due to multiple other comorbidities, and the other patient continues to do well without any complications. Conclusion: IT chemotherapy could be considered as a potential approach for the management of steroid-refractory ICANS based on our experience. Prospective studies are needed to validate this approach.*

Correspondence to: Palash Asawa, MD, Department of Internal Medicine, Allegheny Health Network, 320 East North Avenue, Pittsburgh, PA 15212, U.S.A. Tel: +1 4123594001, e-mail: asawa.palash@ahn.org

Key Words: ICANS, steroid refractory, intrathecal chemotherapy, CAR T-cell therapy, potential treatment.

Chimeric antigen receptor (CAR) T-cell therapy is a novel therapeutic modality that uses genetically modified T cells to target tumor cells. CAR T-cells get activated after binding to a specific antigen on tumor cells to proliferate, secrete cytokines and kill the targeted cancer cells (1). CD-19 targeting CAR T-cells (tisagenlecleucel/tisa-cel and axicabtagene ciliLeucel/axi-cel) are approved to treat relapsed or refractory (R/R) B cell acute lymphoblastic leukemia (B-ALL) and large B cell lymphomas (2-3).

CAR T-cell therapy has revolutionized the treatment of hematologic malignancies. However, it is associated with adverse events like cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity (ICANS). CRS is caused by the systemic release of inflammatory cytokines through activated lymphocytes and myeloid cells, which can result in a clinical syndrome consisting of fever, hypotension, and widespread organ dysfunction (4). ICANS may occur with or without CRS, and onset is variable ranging from days to weeks after cell infusion. Its presentation is diverse, ranging from encephalopathy (most common), focal weakness/numbness to tremors, seizures, and cerebral edema.

Management of CRS and ICANS depends on the severity of the toxicity, with supportive care, corticosteroids, and IL-6-directed therapy (tocilizumab) being the mainstay of treatment (5). Tocilizumab was approved by FDA in August 2017 for the treatment of CRS as a first-line pharmacotherapy (6). However, it is unclear if it helps treat ICANS without CRS. Corticosteroids are indicated for neurological toxicity, including ICANS and CRS refractory to tocilizumab (5). However, there is only a little information available to guide the treatment of patients with steroid-refractory ICANS (7). A few reports have demonstrated favorable outcomes with no long-term complications in patients with steroid refractory ICANS treated with the novel approach of intrathecal (IT) chemotherapy to target IECs implicated in neurotoxicity (8-9).

Here, we report the outcomes of two cases of refractory DLBCL who developed steroid-refractory ICANS after receiving CAR T-cell therapy and were treated with intrathecal (IT) chemotherapy.

Case 1

Our first patient is a 66-year-old male with stage III R/R DLBCL (non-germinal center subtype), positive for c-myc, BCL2 and BCL6 rearrangements. He had received three lines of treatment and was not a candidate for an autologous transplant. Due to his progressive disease, he was treated with CAR T-cell therapy (axi-cel). On day 2 post-infusion, he developed a fever of 39.4˚C and hypoxia needing 2 l of oxygen (grade 2 CRS based on ASTCT consensus grading of CRS) along with disorientation to time and difficulty counting 100 backward by 10 (grade 1 ICANS based on ASTCT consensus grading of ICANS for adults). He was treated with tocilizumab and dexamethasone, to which he initially responded well. However, while being tapered on dexamethasone, he developed persistent fevers despite antipyretics, worsening hypoxia needing 6l of oxygen (grade 3 CRS), and worsening orientation (grade 3 ICANS) on day 5. A workup with MRI Brain was unremarkable for acute abnormality, and an EEG was negative for seizure activity. On day 7, a lumbar puncture (LP) was performed, which showed an opening pressure of 32 cm water (H2O) along with 12 lymphocytes. Treatment with IV solumedrol was initiated, and tocilizumab was resumed. Symptoms of CRS improved, whereas ICANS progressed to grade 4. Due to his worsening mental status, he was intubated on day 8. Given refractory ICANS, intrathecal chemotherapy with methotrexate 12 mg and hydrocortisone 50 mg was administered on day 9. The patient's mental status improved on day 12, and ICANS improved to grade 1. He was weaned off the ventilator and extubated on day 13. The patient showed disease response, however, he had a lengthy hospital stay due to deconditioning and vocal cord paralysis, secondary to prolonged intubation. He was eventually discharged, however, he passed away due to his multiple co-morbidities.

Case 2

Our second patient is a 69-year-old female with stage IV DLBCL (non-germinal-center subtype) with leptomeningeal involvement. FISH for c-myc, BCL2, and BCL6 rearrangement was negative. She had disease progression after three lines of treatment. She was not a candidate for an autologous transplant. She was then treated with CAR T-cell therapy. On day 4 of CAR T-cell (axi-cel) infusion, she developed a fever of 38.7˚C without other systemic signs (grade 1 CRS based on ASTCT consensus grading of CRS). Dexamethasone and tocilizumab were initiated, to which she initially responded. However, on day 9, she developed hypotension, fever (grade 2 CRS), tremors, and altered mental status (grade 3 ICANS based on ASTCT consensus grading of ICANS for adults). Due to the worsening of CAR T-cell toxicity, dexamethasone was changed to pulse dose solumedrol while tocilizumab was continued. A CT scan of the head did not show any acute intracranial abnormalities and an EEG was negative for epileptiform activity. An LP was performed which revealed an opening pressure of 21 cm H_2O and 84 lymphocytes. Eventually, the symptoms of CRS resolved by day 11; however, encephalopathy worsened, and she became increasingly somnolent and did not follow commands. (ICANS grade 4). Due to concerns for steroid-refractory ICANS, she was treated with 12 mg methotrexate and 50 mg of hydrocortisone intrathecally. The patient showed prompt significant neurological improvement a day later and eventually had resolution of ICANS by day 16. Since her discharge on day 28, she continues to do well without any complications. A brain MRI follow-up, after CART-infusion and intrathecal chemotherapy, showed no new intracranial enhancement and improvement of prior areas involved (10).

Discussion

Attempts at engineering CAR T-cells to target tumor antigens began 30 years ago. Following refinements, current CAR T-cells targeting CD19 represent a promising approach for various hematologic malignancies. Despite their careful design, CAR T-cell therapies are associated with life-threatening toxicities, including ICANS (11). The mechanism of development of ICANS remains unclear. It has been attributed to blood-brain barrier (BBB) dysfunction secondary to elevated cytokines like IL-6, IL-2, IFN-γ and Granulocyte-monocyte colony-stimulating factor (GM-CSF) (12). An animal study showed high levels of CAR T-cells and endogenous T cells in the brain parenchyma, as well as CSF in rhesus monkeys with CART associated ICANS (13). However, there is a paucity of clinical data to affirm a clear relationship between CAR T-cell counts/white cell counts in CSF and ICANS (14). Another study by Faulhaber *et al*. using an immunocompetent mouse model demonstrated evidence of neurovascular unit injury and leukocyte plugging of the cerebral vasculature associated with CD19 CAR T-cell therapy. The underlying mechanism was thought to be secondary to increased leukocyte-endothelial adhesion (15). Risk factors for ICANS include antecedent severe CRS, higher disease burden, CAR T- cell dose and presence of a pre-existing neurologic disorder. It is also more common with axi-cel as compared to tisa-cel (7). Both of our patients were noted to have CRS before developing severe ICANS and had received axi-cel.

Corticosteroids such as dexamethasone and methylprednisolone, along with supportive management, remain the mainstay of treatment (14). Tocilizumab has a large molecular

size and hence does not cross BBB, which is postulated to be the reason for its ineffectiveness in treating ICANS (5). IL-1 antagonist anakinra, on the other hand, does cross BBB and has shown promise in preventing ICANS in animal models (7). In a series by Strati *et al*., four out of six patients with R/L large B-cell lymphoma who developed high-grade ICANS after receiving CAR T-cell therapy experienced clinical benefits after treatment with anakinra. (16) A multicenter retrospective study analyzed 26 patients with B-cell/plasma cell malignancies who developed ICANS/CRS after CAR T-cell therapy and were given either low-dose or high dose anakinra after failing steroids/tocilizumab. High dose anakinra was associated with rapid resolution of symptoms with a manageable toxicity profile. (17) In another retrospective single-center experience, 14 patients who developed steroid/tocilizumab refractory ICANS with or without CRS after administration of CD19 CAR T-cell therapy were treated with anakinra. Anakinra was associated with improvement of clinical and laboratory markers of inflammation, however, the correlation was more so for CRS than for neurological toxicity. (18) Hence, large-scale clinical studies to establish the efficacy of this option are warranted.

Steroid-refractory ICANS could be life-threatening and has no second-line treatment established yet. Here we present a novel potential approach to managing ICANS refractory to corticosteroids by using IT corticosteroids in combination with a cytotoxic agent. This approach has shown promising results only in a few case reports/series before. In a series, seven patients with non-Hodgkin lymphoma received anti-CD 19 CAR T-cell therapy and subsequently developed steroid-refractory ICANS. Treatment with IT chemotherapy (15 mg methotrexate, 40 mg cytarabine, and 50 mg hydrocortisone) resulted in a complete response and improvement of ICANS in five (71%) patients. The median duration of steroid treatment in these patients was 11 days. Two patients out of the seven did not respond (9). Another report of two patients with chemo-refractory DLBCL who received anti CD-19 CAR T-therapy demonstrated rapid and sustained response in both patients after treatment with IT chemotherapy for steroid-refractory ICANS (8). Recently, a series of patients with R/R B-cell non-Hodgkin lymphoma with high grade (>3) and steroid-refractory ICANS reported a difference in outcomes in those who received early IT therapy with steroids and those who did not. Out of the total of 15 patients who had high-grade ICANS, 7 were refractory to steroids and were given early IT therapy (within 5 days) of developing high grade ICANS, all these recovered. The estimated 1-year survival progression free survival (PFS) and overall survival (OS) was 57.1% for this group of patients. Amongst these patients, three did receive anakinra additionally for steroid-refractory ICANS, and all of them died of infectious complications Remaining patients either did not receive IT chemotherapy (7) or received late IT therapy. Out of these, four patients (50%) had steroid-refractory ICANS and had 0% progression free survival and overall survival. The median duration of corticosteroid usage in patients with steroid-refractory ICANS receiving IT therapy was 35 days (22-43 days) when compared to 50 days (23-62) in patients with steroid-refractory ICANS not receiving IT therapy. This study suggested utility of IT treatment in high grade steroid-refractory ICANS and as a possible alternative to systemic immunosuppression which could help in reducing treatment-related complications and mortality with CAR T-cell therapy. (19)

In our report, IT chemotherapy in the form of methotrexate 12 mg and hydrocortisone 50 mg was given to our two patients who had developed high grade ICANS after axi-cel infusion refractory to high dose systemic steroids. They showed rapid neurological recovery without any complications attributable to this approach.

Conclusion

Currently, there are no guidelines available for the treatment of ICANS refractory to steroid therapy. The outcome of our report demonstrates a potential approach for the management of steroid-refractory ICANS with the use of IT chemotherapy. Early initiation of IT chemotherapy can help in faster resolution and decrease complications of high-dose systemic steroids. Larger scale studies are needed to determine the efficacy of this approach and identify adverse effects.

Conflicts of Interest

All Authors have no conflicts of interest to declare.

References

1 Song EZ and Milone MC: Pharmacology of chimeric antigen receptor-modified T cells. Annu Rev Pharmacol Toxicol *61*: 805-829, 2021. PMID: 33035447. DOI: 10.1146/annurev-pharmtox-031720-102211

2 Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, Bader P, Verneris MR, Stefanski HE, Myers GD, Qayed M, De Moerloose B, Hiramatsu H, Schlis K, Davis KL, Martin PL, Nemecek ER, Yanik GA, Peters C, Baruchel A, Boissel N, Mechinaud F, Balduzzi A, Krueger J, June CH, Levine BL, Wood P, Taran T, Leung M, Mueller KT, Zhang Y, Sen K, Lebwohl D, Pulsipher MA and Grupp SA: Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med *378(5)*: 439-448, 2018. PMID: 29385370. DOI: 10.1056/NEJMoa1709866

3 Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, Jäger U, Jaglowski S, Andreadis C, Westin JR, Fleury I, Bachanova V, Foley SR, Ho PJ, Mielke S, Magenau JM, Holte H, Pantano S, Pacaud LB, Awasthi R, Chu J, Anak Ö, Salles G, Maziarz RT and JULIET Investigators: Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med *380(1)*: 45-56, 2019. PMID: 30501490. DOI: 10.1056/NEJMoa1804980

4 Riegler LL, Jones GP and Lee DW: Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag *15*: 323-335, 2019. PMID: 30880998. DOI: 10.2147/TCRM.S150524

5 Rivera AM, May S, Lei M, Qualls S, Bushey K, Rubin DB and Barra ME: CAR T-cell-associated neurotoxicity: Current management and emerging treatment strategies. Crit Care Nurs Q *43(2)*: 191-204, 2020. PMID: 32084062. DOI: 10.1097/CNQ.0000000000000302

6 Le RQ, Li L, Yuan W, Shord SS, Nie L, Habtemariam BA, Przepiorka D, Farrell AT and Pazdur R: FDA approval summary: Tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. Oncologist *23(8)*: 943-947, 2018. PMID: 29622697. DOI: 10.1634/theoncologist.2018-0028

7 Freyer CW and Porter DL: Cytokine release syndrome and neurotoxicity following CAR T-cell therapy for hematologic malignancies. J Allergy Clin Immunol *146(5)*: 940-948, 2020. PMID: 32771558. DOI: 10.1016/j.jaci.2020.07.025

8 Shah NN, Johnson BD, Fenske TS, Raj RV and Hari P: Intrathecal chemotherapy for management of steroid-refractory CAR T-cell-associated neurotoxicity syndrome. Blood Adv *4(10)*: 2119-2122, 2020. PMID: 32407473. DOI: 10.1182/bloodadvances.2020001626

9 Yucebay F, Maakaron J, Grana A, Jaglowski S and Roddy J: Intrathecal chemotherapy: An alternative treatment strategy to prolonged corticosteroids for severe CAR T associated neurotoxicity. Biology of Blood and Marrow Transplantation *26(3)*: S312, 2021. DOI: 10.1016/j.bbmt.2019.12.390

10 Vusqa U, Asawa P, Rai M, Samhouri Y, Mewawalla P, Koget A, Sadashiv S, Kahn C, Fazal S and Lister J: Intrathecal chemotherapy as a potential alternative treatment for steroid-refractory immune effector cell-associated neurotoxicity syndrome. Blood *138(Suppl 1)*: 4816-4816, 2021. DOI: 10.1182/blood-2021-151113

11 Yakoub-Agha I, Chabannon C, Bader P, Basak GW, Bonig H, Ciceri F, Corbacioglu S, Duarte RF, Einsele H, Hudecek M, Kersten MJ, Köhl U, Kuball J, Mielke S, Mohty M, Murray J, Nagler A, Robinson S, Saccardi R, Sanchez-Guijo F, Snowden JA, Srour M, Styczynski J, Urbano-Ispizua A, Hayden PJ and Kröger N: Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). Haematologica *105(2)*: 297-316, 2020. PMID: 31753925. DOI: 10.3324/haematol.2019.229781

12 Santomasso BD, Park JH, Salloum D, Riviere I, Flynn J, Mead E, Halton E, Wang X, Senechal B, Purdon T, Cross JR, Liu H, Vachha B, Chen X, DeAngelis LM, Li D, Bernal Y, Gonen M, Wendel HG, Sadelain M and Brentjens RJ: Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. Cancer Discov *8(8)*: 958-971, 2018. PMID: 29880584. DOI: 10.1158/2159-8290.CD-17-1319

13 Taraseviciute A, Tkachev V, Ponce R, Turtle CJ, Snyder JM, Liggitt HD, Myerson D, Gonzalez-Cuyar L, Baldessari A, English C, Yu A, Zheng H, Furlan SN, Hunt DJ, Hoglund V, Finney O, Brakke H, Blazar BR, Berger C, Riddell SR, Gardner R, Kean LS and Jensen MC: Chimeric antigen receptor T cell-mediated neurotoxicity in nonhuman primates. Cancer Discov *8(6)*: 750-763, 2018. PMID: 29563103. DOI: 10.1158/2159-8290.CD-17-1368

14 Ruff MW, Siegler EL and Kenderian SS: A concise review of neurologic complications associated with chimeric antigen receptor T-cell immunotherapy. Neurol Clin *38(4)*: 953-963, 2020. PMID: 33040871. DOI: 10.1016/j.ncl.2020.08.001

15 Faulhaber LD, Phuong AQ, Hartsuyker KJ, Cho Y, Mand KK, Harper SD, Olson AK, Garden GA, Shih AY and Gust J: Brain capillary obstruction during neurotoxicity in a mouse model of anti-CD19 chimeric antigen receptor T-cell therapy. Brain Commun *4(1)*: fcab309, 2021. PMID: 35169706. DOI: 10.1093/braincomms/fcab309

16 Strati P, Ahmed S, Kebriaei P, Nastoupil LJ, Claussen CM, Watson G, Horowitz SB, Brown ART, Do B, Rodriguez MA, Nair R, Shpall EJ, Green MR, Neelapu SS and Westin JR: Clinical efficacy of anakinra to mitigate CAR T-cell therapy-associated toxicity in large B-cell lymphoma. Blood Adv *4(13)*: 3123-3127, 2020. PMID: 32645136. DOI: 10.1182/bloodadvances.2020002328

17 Gazeau N, Barba P, Iacoboni G, Kwon M, Bailen R, Reguera JL, Corral LL, Hernani R, Ortiz-Maldonado V, Perez-Martinez A, Maziarz RT, Williamson S, Nemecek ER, Shadman M, Coman A, Green DJ, Chow VA, Hirayama AV, Maloney DG, Turtle CJ and Gauthier J: Safety and efficacy of two anakinra dose regimens for refractory CRS or Icans after CAR T-cell therapy. Blood *138(Suppl 1)*: 2816-2816, 2021. DOI: 10.1182/blood-2021-147454

18 Wehrli M, Gallagher K, Chen YB, Leick MB, McAfee SL, El-Jawahri AR, DeFilipp Z, Horick N, O'Donnell P, Spitzer T, Dey B, Cook D, Trailor M, Lindell K, Maus MV and Frigault MJ: Single-center experience using anakinra for steroid-refractory immune effector cell-associated neurotoxicity syndrome (ICANS). J Immunother Cancer *10(1)*: e003847, 2022. PMID: 34996813. DOI: 10.1136/jitc-2021-003847

19 Zurko JC, Johnson BD, Aschenbrenner E, Fenske TS, Hamadani M, Hari P and Shah NN: Use of early intrathecal therapy to manage high-grade immune effector cell-associated neurotoxicity syndrome. JAMA Oncol *8(5)*: 773-775, 2022. PMID: 35266965. DOI: 10.1001/jamaoncol.2022.0070

Received May 2, 2022
Revised June 15, 2022
Accepted June 29, 2022