Case report

Unexpected neurologic complications following a novel lymphoma treatment 'expected' to give rise to neurologic toxicity

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SUMMARY

Chimeric antigen receptor (CAR) T-cell therapy is a novel and promising form of cellular immunotherapy using genetically engineered, tumour-specific autologous T cells. CD19-specific CAR T-cells have been shown to be very effective as a treatment for relapsed/refractory B-cell acute lymphoblastic leukaemia and aggressive B-cell non-Hodgkin's lymphoma. ICANS (immune effector cell-associated neurotoxicity syndrome) is one of the most frequently occurring toxicities of CAR T-cell treatment. We describe two cases of patients with neurologic symptoms following CAR T-cell infusion who were suspected to have ICANS, but in fact had cerebral toxoplasmosis and venous sinus thrombosis respectively. The focus on CRS and ICANS after CAR T-cell infusion may lead to less vigilance to the 'normal' threats faced by intensively pretreated patients with lymphoma such as infections and thrombosis. Both cases underscore the importance of a broad and thorough examination of patients if they experience neurologic symptoms after CAR T-cell treatment.

BACKGROUND

Chimeric antigen receptor (CAR) T-cell therapy is a novel and promising form of cellular immunotherapy using genetically engineered, tumour-specific autologous T cells. A CAR consists of the antigen recognition part of a monoclonal antibody, a costimulatory domain (4-1BB or CD28) for optimal in vivo expansion and persistence and the intracellular signalling domain of a T-cell receptor. The B-cell-specific CD19 antigen has been demonstrated to be an excellent target for CAR T cells. Recently, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved two CD19 CAR T-cell products: tisagenlecleucel for relapsed/refractory (R/R) acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL), and axicabtagene ciloleucel for R/R DLBCL, transformed follicular lymphoma and primary mediastinal B-cell lymphoma after at least two prior lines of systemic treatment. Overall response rates following this therapy as high as 50%–80% (lymphoma) to 90% (ALL) have been reported in cohorts of heavily pretreated patients.^{1–3} Significant percentages of complete and long-term remissions are induced. Frequently occurring acute toxicities of the treatment comprise cytokine release syndrome (CRS) and immune effector

cell-associated neurologic toxicity (ICANS). CRS occurs in the majority of patients and includes a broad spectrum of symptoms such as fever, hypotension, tachycardia and dyspnoea, sometimes leading to multiorgan failure. Treatment consists of supportive care and, if necessary, the administration of the interleukin (IL)-6 receptor blocking antibody tocilizumab and corticosteroids. Neurologic toxicity usually occurs a few days after CRS and can be seen concurrent with ongoing CRS, but can also be seen in the absence of or following resolution of CRS. Patients may present with confusion, aphasia, tremor, seizures and very seldomly with cerebral oedema. In the case of higher grade neurologic toxicity, treatment with corticosteroids and seizure prophylaxis must be considered.⁴

CASE PRESENTATION

We recently observed unexpected 'neurologic toxicity' following CAR T-cell infusion. Two patients with R/R DLBCL were referred to our centre for participation in a CD19 CAR T-cell trial. The first patient, a 71-year-old man, was diagnosed with DLBCL in 2015. After first-line

Figure 1 Axial T1 MRI with gadolinium: hypointense lesion with incomplete ring enhancement in the left basal ganglia with eccentric target sign surrounded by hypointense perifocal oedema.

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Figure 2 MRI axial 2D time of flight reconstruction, with thrombosis of left sinus transversus.

immunochemotherapy (8 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP)) he had refractory disease. He continued with second-line immunochemotherapy (R-DHAP, R-VIM and R-DHAP), followed by high-dose chemotherapy (BEAM) and an autologous stem cell transplant. A few months later, the lymphoma relapsed and the patient was referred for CAR T-cell therapy in the CTL019 JULIET clinical trial.³ After apheresis, bridging chemotherapy with one cycle of rituximab–bendamustine was given. After lymphodepleting chemotherapy consisting of cyclophosphamide and fludarabine, the CAR T cells were infused. From day +1, the patient had fever considered to be grade 1 CRS, for which because of neutropenia broad-spectrum antibiotics were started, no tocilizumab or steroids were given. The fever resolved on day +5. Seven days after the infusion, the tests that were performed daily for the early recognition of neurologic toxicity presented abnormal results. The patient missed 6 out of a total of 30 points on the mini mental state examination, and in a writing test micrographia was noted and the patient made some mistakes (ie, wrote Amsterdam instead of Amsterdam). We expected that the patient was experiencing ICANS. However, a brain MRI scan demonstrated radiologic findings fitting a diagnosis of cerebral toxoplasmosis (figure 1). The toxoplasma serology tests (Liaison immunoglobulin (IgM)/IgG and Sabin Feltman assay) were negative, probably due to the multiple prior lines of treatment with immunochemotherapy. Already prior to start of conditioning chemotherapy, the patient had hypogammaglobulinaemia (IgG, 2.9 g/L) and a low CD4 count ($0.18 \times 10^9/L$). The patient was treated with pyrimethamine, folic acid and sulfadiazine. His neurologic symptoms improved within a few days and resolved and the patient remains in complete remission 21 months after CAR T-cell infusion. His family has noted that he has developed a mild cognitive disorder.

The second patient is a 49-year-old man who was first diagnosed with DLBCL in 2011. Complete remission was reached after first-line chemotherapy (8 cycles of R-CHOP). In 2016, a first relapse was diagnosed and the patient completed salvage chemotherapy (R-DHAP, R-VIM and R-DHAP) and an autologous stem cell transplant after BEAM chemotherapy. Six months later, a second relapse occurred and the patient was referred to our centre for the KTE-C19 ZUMA-1 CAR T-cell trial.² Eight days after infusion of the cells, the patient complained of a severe

headache. As in the previous case presented, ICANS seemed the most likely explanation, but to rule out other causes of the severe headache, a brain MRI scan was performed. Remarkably, the scan demonstrated a cerebral venous sinus thrombosis (figure 2). The patient was treated with therapeutically dosed low-molecular-weight heparin (LMWH) after which the symptoms disappeared. No underlying hypercoagulability could be demonstrated. A few days later the patient did develop signs and symptoms consistent with ICANS (severe confusion, tremor and aphasia, limiting instrumental activities of daily living, grade 2 as per CTCAE V.5.0 criteria).⁵ The dose of levetiracetam (which was started prophylactically as per protocol) was increased and treatment with dexamethasone was started. The symptoms resolved completely after several days. The evaluation demonstrated complete remission of the lymphoma at 1 and 3 months after infusion, but unfortunately, the lymphoma relapsed after 6 months.

OUTCOME AND FOLLOW-UP

The first patient, diagnosed with cerebral toxoplasmosis, was treated with pyrimethamine, folic acid and sulfadiazine. His neurologic symptoms improved within a few days and resolved fully and the patient remains in complete remission 21 months after CAR T-cell infusion. The second patient, who was diagnosed with cerebral sinus thrombosis, was treated with therapeutically dosed LMWH after which the symptoms of headache disappeared. Whether or not the thrombosis was elicited by CRS is unclear. No other cases of cerebral sinus thrombosis were identified in the ZUMA-1 clinical database. The patient subsequently developed signs of ICANS, which resolved with dexamethasone treatment. The evaluation demonstrated a complete remission of the lymphoma at 1 and 3 months after infusion, but unfortunately the lymphoma relapsed after 6 months.

Patient's perspective

First patient: I first noted numbness in the legs, balance problems and a tremor of the hands. I also had flu-like symptoms. These symptoms have resolved, but my family has noted that I tend to forget things and feel like I have to do things without delay. This is sometimes difficult to handle, because I get upset more easily.

Second patient: I remember having the headache, but I do not remember much of how the neurotoxicity started. I do remember that it progressed and my family has told me I did not recognise them anymore. After that, the first thing I remember was being in the ICU and not being able to express myself, which frustrated me. I was in and out of conscience and had hallucination-like experiences. The whole experience was rather frightening for me and for my family. I have fully recovered however from those symptoms.

Learning points

- ▶ Immune effector cell-associated neurotoxicity syndrome is one of the most frequently occurring toxicities of chimeric antigen receptor (CAR) T-cell treatment.
- ▶ Patients with neurologic symptoms following CAR T-cell infusion should be examined broadly and thoroughly to exclude other causes.

DISCUSSION

CAR T-cell-associated toxicities (CRS and ICANS) can be severe and require intensive monitoring and prompt intervention if needed. CRS is triggered by the activation of T cells and bystander cells such as monocytes/macrophages, resulting in the release of many cytokines and chemokines. The aetiology of ICANS is less well understood but may be caused by passive diffusion of cytokines, trafficking of T cells into the central nervous system, and/or endothelial activation and blood–brain barrier disruption.^{4,6} The use of consensus criteria for diagnosing and grading CRS and ICANS as recently published by the American Society for Transplantation and Cellular Therapy (ASTCT) facilitates recognition and uniform reporting of complications of this novel immunotherapy.⁷ However, the focus on CRS and ICANS after CAR T-cell infusion may lead to less vigilance to the ‘normal’ threats faced by intensively pretreated patients with lymphoma such as infections and thrombosis, which require totally different management. Both cases underscore the importance of a broad and thorough examination of patients who experience neurologic symptoms after CAR T-cell treatment. Additionally, it is of the utmost importance that less frequently occurring complications of immune effector cell treatment, also when administered in the ‘real world’, are captured in registries such as those initiated by the CIBMTR (Centre for International Blood and Marrow Transplant Research) and EBMT (European Association for Blood and Marrow Transplantation).

Contributors MJK: planned the case study. All authors treated the patients and acquired and interpreted the data and wrote the manuscript.

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