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Chimeric antigen receptor T-cell neuropsychiatric toxicity in acute lymphoblastic leukemia

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Abstract

Chimeric antigen receptor T cells are used in the treatment of B-cell leukemias. Common chimeric antigen receptor T-cell toxicities can range from mild flu-like symptoms, such as fever and myalgia, to a more striking neuropsychiatric toxicity that can present as discrete neurological symptoms and delirium. We report here two cases of chimeric antigen receptor T-cell neuropsychiatric toxicity, one who presented as a mild delirium and aphasia that resolved without intervention, and one who presented with delirium, seizures, and respiratory insufficiency requiring intensive treatment. The current literature on the treatment and proposed mechanisms of this clinically challenging chimeric antigen receptor T-cell complication is also presented.

Keywords

Chimeric antigen receptor; Neurotoxicity; Cytokine release syndrome; Acute lymphoblastic leukemia

INTRODUCTION

Chimeric antigen receptor (CAR) T-cell treatment is a novel option for acute lymphoblastic leukemia (ALL) patients who experience relapse and poor treatment response from the standard chemotherapy and stem cell transplant options (Tasian & Gardner, 2015). While this CAR T-cell option appears promising, providing the potential for a 90% remission rate, it can be associated with such complications as neuropsychiatric toxicity (Maude et al., 2014a). Clinical symptoms may range from mild confusion to aphasia, seizures, psychosis, obtundation, and possibly death (Maus et al., 2014; Maude et al., 2014a).

This is a case report presenting two cases that demonstrate the range in severity of the associated neurotoxic symptoms. An overview of CAR T-cell neuropsychiatric toxicity is also presented.

CASE REPORT 1: MILD NEUROPSYCHIATRIC TOXICITY

A 25-year-old male with acute lymphoblastic leukemia diagnosed in 2009, with a relapse in 2013, requiring allogeneic stem cell transplant (complicated by graft-versus-host disease and liver mass) and chemotherapy agents to which he was unresponsive, presented to Memorial Sloan Kettering Cancer Center in December of 2015 with plans to receive conditioning chemotherapy prior to undergoing CAR T-cell treatment. He was started on a chemotherapy regimen of cyclophosphamide and fludarabine as well as on levetiracetam for seizure prophylaxis. Neurology was consulted to establish the patient's pre-CAR T-cell baseline, and the exam was significant only for baseline neuropathy of the toes and mild right face and arm weakness, both believed to be secondary to previous chemotherapy effects. Baseline MRI showed no significant intracranial abnormalities. CAR T-cell infusion was successfully completed eight days postadmission, and hospital course was complicated by the nasopharynx being positive for parainfluenza with fever. Shortly afterward, he developed bifrontal pressure-like headaches (six days post-CAR T-cell infusion) associated with photophobia, phonophobia with nausea and vomiting, but no neck rigidity. By eight days post-CAR T-cell infusion, he was noted to have word-finding difficulties with rapid eye movements, confusion, and irritability. Head CT was negative, and EEG revealed diffuse slowing with no epileptiform abnormalities. However, out of concern for seizures, the levetiracetam dose was increased.

He was described as being mildly encephalopathic and diagnosed with likely early cytokine release syndrome (CRS), given current symptoms that persisted despite resolution of fever.

Psychiatry was consulted (nine days post-CAR T-cell infusion) as the patient was refusing to participate in the neurological assessments and refusing further EEG monitoring. He was said to be irritable, agitated, and having difficulty coping. He described intermittent episodes of confusion and on interview demonstrated a lag in time when answering questions, but he would not allow formal cognitive testing. Labs were significant for pancytopenia, resolving elevated liver enzymes with normal ammonia (likely from liver mass), elevated ferritin, and mildly elevated C-reactive protein. At this time, given that the disorientation, confusion, and word-finding difficulties aligned with the timeframe of the recent CAR T-cell administration, along with no signs of active infection, the patient was diagnosed with likely mild neurotoxicity secondary to CAR T-cell treatment. In addition, his C-reactive protein and ferritin levels were elevated when symptoms of confusion and word-finding difficulties presented, which is typical for CAR T-cell neurotoxicity. It was recommended that the patient be started on a low-dose antipsychotic for agitation and confusion, and that neurology consider a different antiepileptic given that levetiracetam might increase agitation. While none of these interventions were put into place, by five days after the initial confusion episode, the patient had returned to baseline mental status and no longer had word-finding difficulties.

CASE REPORT 2: SEVERE NEUROPSYCHIATRIC TOXICITY

A 33-year-old female with acute lymphoblastic leukemia, diagnosed in 2014, who had undergone chemotherapy and radiation without response, presented to Memorial Sloan

Kettering Cancer Center in February of 2016 with plans to receive conditioning chemotherapy (cyclophosphamide and fludarabine) prior to undergoing CAR T-cell treatment. While psychiatry was consulted eight days into admission for management of anxiety, the patient instead complained of hallucinations. On evaluation, she was found to have a mild delirium and was started on olanzapine 2.5 mg at bedtime. Contributing factors at this time included opiates, steroids, hyponatremia, and possible infection given she had fevers. She underwent CAR T-cell treatment 13 days postadmission and by 4 days post-CAR T-cell infusion, was transferred to the ICU for an episode of worsened mental status, speaking nonsensically with word-finding difficulty, and continued hallucinations while febrile and tachycardic. EEG showed moderate diffuse cerebral dysfunction but no epileptiform activity, and head CT showed stable previous subdural hematoma but no acute process. She eventually became minimally responsive, nonverbal, unable to recognize family, and unable to follow simple commands. Although several factors likely contributed to the initial delirium, she also exhibited signs particular to CRS. These included elevated ferritin and C-reactive protein. Treatment was therefore shifted toward targeting CRS by giving the anticytokine antibody tocilizumab (five days post-CAR T-cell infusion). Unfortunately, there was minimal response to the tocilizumab, and the patient went on to have recurrent seizures, requiring treatment with levetiracetam and lorazepam. Due to wheezing and poor airway control, she twice required intubation. As her symptoms were progressing despite administration of tocilizumab, she was started on dexamethasone to decrease the cytokine storm. Aside from the CRS, her course was complicated by *Klebsiella* bacteremia progressing to septic shock and requiring pressors. The final critical care overall assessment of events was CRS with catastrophic multiorgan system deterioration (respiratory failure, renal insufficiency), including possible CAR T-cell neurotoxicity with seizures. The patient eventually recovered after receiving dexamethasone treatment and was no longer delirious. Although many factors played a role in this medically complex case, the elevated ferritin, elevated C-reactive protein, seizures (occurring prior to bacteremia), as well as the good response to steroids—all indicate that the patient's CAR T-cell treatment was likely complicated by CRS and neurotoxicity.

A REVIEW OF CHIMERIC ANTIGEN RECEPTOR T-CELL NEUROPSYCHIATRIC TOXICITY

Chimeric Antigen Receptor T Cell: Treatment

Chimeric antigen receptor T-cell treatment is a targeted immunotherapy against a B-cell specific antigen (Maude et al., 2014*b*) now being used to treat treatment-refractory B-cell leukemias. During this process, T cells are collected from the patient's blood through the process of leukapheresis. Antibody genes, which are encoded to recognize tumor antigens, are then transferred into the patient's T cells using viral vectors. The outcome is the production of engineered T cells that express the antibody fragment on their receptors, which will then target tumor antigens (Maude et al., 2014*a*). Binding of the tumor antigen will then cause T-cell proliferation and tumor lysis, providing long-term disease control after a single infusion of the engineered cells (Maude et al., 2014*a*; 2014*b*). Patients usually undergo induction chemotherapy prior to infusion with CAR T cells to decrease disease burden (Tasian & Gardner, 2015). Ideal targets for CAR T-cell treatment include antigens

that are universally expressed on tumor cells but not on healthy cells. Therefore, B-cell leukemias are prime for this treatment as they express such an antigen, known as CD19 (Maude et al., 2014*b*).

Chimeric Antigen Receptor T Cell: Cytokine Release Syndrome and Neuropsychiatric Toxicity

While CAR T-cell treatment is a remarkable source of hope for cancer patients who are refractory to treatment, it is not without potential complications. Cytokine release syndrome is the most significant CAR T-cell-associated toxicity and can be potentially life-threatening (Maude et al., 2014*a*). It is an overactive inflammatory process associated with elevated cytokines, ferritin, and C-reactive protein levels, and produces symptoms that range from mild flu-like symptoms of fevers and myalgias, to more severe reactions of vascular leakage, hypotension, respiratory distress, cardiac dysfunction, multiorgan failure (including renal/hepatic), and neurological toxicity (Maus et al., 2014; Maude et al., 2014*a*; 2014*b*; Lee et al., 2014; Tasian & Gardner, 2015). Neurotoxic effects typically present with mental status changes believed to be secondary to inflammation and released cytokines (Maus et al., 2014). Neurotoxicity can present as a wide range of neurological and psychiatric manifestations, including seizures, delirium, aphasia, and hallucinations (Tasian & Gardner, 2015).

While CRS is usually manifested as mild to moderate fever and myalgia during the first 7 to 10 days post T-cell infusion, currently there does not seem to be a consensus in terms of when neurotoxicity may occur or what percentage of patients will go on to develop it (Tasian & Gardner, 2015). The best approach for now in terms of anticipation of CRS is to identify high-risk patients such as those with greater pretreatment blast burden, those with fevers, and those with elevated levels of C-reactive protein (Davila et al., 2014; Maude et al., 2014*a*; Tasian & Gardner, 2014). Potentially helpful is the CRS diagnostic criteria developed by Davila et al. (2014), which include fevers for at least three consecutive days, dramatic increases from baseline cytokine levels, and at least one clinical sign of toxicity (hypotension [requiring IV vasoactive pressor], hypoxia [$PO_2 < 90\%$], and neurological findings [cognitive changes, obtundation, and seizures]) (Davila et al., 2014). Furthermore, beyond diagnostic criteria, Lee et al. (2014) created a grading system that classifies CRS symptoms based on severity for a more targeted treatment that will allow for maximizing therapeutic benefit of cancer treatment while minimizing risks from CRS (Lee et al., 2014).

Chimeric Antigen Receptor T Cell: Mechanisms of Neuropsychiatric Toxicity

While the exact mechanism of how CAR T cells cause neurotoxicity is not yet known, the consensus is that it is likely related to the surge of cytokines in CRS. Maus et al. (2014) proposed that perhaps neurotoxicity may be based on systemic cytokines crossing the blood/brain barrier and engaging cytokine receptors in the brain or from direct cytokine production in the central nervous system (CNS) (Maus et al., 2014; Tasian & Gardner, 2015). Another suggested mechanism is that hyperthermia and IL-6 released during CRS may enhance trafficking of CAR T cells to the cerebrospinal fluid (CSF) in an antigen-independent mechanism, since CAR T cells have been found in the CSF of patients (Fisher et al., 2011; Maus et al., 2014; Tasian & Gardner, 2015; Lee et al., 2015). Also proposed is that there

may be crossreactivity or yet-to-be-detected expression of CD19 in the brain (Maus et al., 2014).

While CRS involves a surge of cytokines (including IL-10, IFN- γ , and several others), one of the major cytokines often targeted in the treatment of CRS is IL-6, which is said to be a possible biomarker of CRS (Maude et al., 2014*b*; Tasian & Gardner, 2015). While IL-6 is usually thought of as a part of the peripheral immune system responsible for proliferation and differentiation of B cells, it is also produced by CNS astrocytes, microglia, and neurons, and elevated levels have been identified in disease processes associated with altered cognitive function (Gruol, 2015). Since targeting IL-6 often resolves neurotoxic symptoms, it is likely that it plays one of the major roles in the development of neuropsychiatric symptoms, but this has not been clarified in detail (Tasian & Gardner, 2015).

Chimeric Antigen Receptor T Cell: Neuropsychiatric Toxicity Treatment and Prognosis

Treatment of CRS-associated neuropsychiatric toxicity starts with the direct targeting of cytokines. As mentioned, IL-6 specifically is targeted by using the monoclonal antibody to the IL-6 receptor known as tocilizumab (Barrett et al., 2014; Maude et al., 2014*b*; Tasian & Gardner, 2015). Tocilizumab is used in an effort to lessen the immune activation and associated sequelae of CRS (Tasian & Gardner, 2015). Adjuvant use in severe CRS has correlated with decreased IL-6 levels and has demonstrated clinical improvement without terminating CAR T-cell activity or persistence (Lee et al., 2015; Tasian & Gardner, 2015). For this reason, it is seen as a preferred first-line treatment for CRS and thus for the neurotoxic effects of CAR T-cell treatment (Tasian & Gardner, 2015). Thus far, there does not appear to be a clear indication for prophylactic use of tocilizumab or other anticytokine receptor antibodies in patients prior to CAR T-cell treatment to prevent or lessen CRS effects (Tasian & Gardner, 2015). If IL-6 blockade does not reverse neurotoxic symptoms, the next option is the use of steroids to counteract the overactive inflammatory response. However, it has been shown that steroids can be lymphotoxic and in turn can decrease the proliferation of CAR T cells, thereby decreasing the efficacy of the originally intended treatment (Maude et al., 2014*b*; Tasian & Gardner, 2015). Beyond these measures, symptomatic treatment would include antiepileptics, antipyretics, mechanical ventilation for respiratory support, and vasoactive pressors for hemodynamic instability.

While mild symptoms are usually self-limiting, resolving within days, and may require only observation or supportive care, more severe conditions may require hemodynamic support and mechanical ventilation (Maude et al., 2014*a*; Tasian & Gardner, 2015).

DISCUSSION

Currently there does not appear to be a solid consensus on the length of persistence of the CAR T-cell line, and so long-term treatment outcomes unfortunately are not yet uniform. While up to a 90% complete remission rate has been demonstrated, some patients still choose to proceed with stem cell transplantation following CAR T-cell treatment in fear of recurrence (Maude et al., 2014*a*).

Reducing complications associated with CAR T-cell neurotoxicity may start with treatment teams identifying high-risk patients, such as those with greater pretreatment blast burden, fevers, or elevated C-reactive protein levels (Tasian & Gardner, 2015). Alternatively, such diagnostic criteria as those created by Davila and colleagues (2014) that highlight the critical aspects contributing to the diagnosis may be helpful in early targeting of symptoms.

Routine assessments of mental status, as seen in the cases presented herein, help to track mental status change to assess whether it coincides with CAR T-cell treatment. Brain imaging should be utilized if lesions are suspected that may increase susceptibility to seizures with treatment. EEGs are advised if seizures are suspected. If after these workups the patient is still not improving, particularly if fever is present, then a lumbar puncture may be implicated.

CONCLUSIONS

We conclude that psychosomatic medicine psychiatrists should be familiar with the diagnosis and treatment of CAR T-cell-associated CRS given the potential for neuropsychiatric toxicity whose symptoms may progress if not treated early. While treatments for the cytokine storm do exist, psychiatrists can play an integral role in managing the distress that can occur when patients are in a delirium and experiencing altered mental status and potential psychoses. Given the success rates in providing remission for patients with treatment-refractory acute lymphoblastic leukemia, CAR T-cell studies have begun for a number of other cancer types, including chronic lymphocytic leukemia, acute myeloid leukemia, multiple myeloma, prostate cancer, and breast cancer (Giordano et al., 2011; Ritchie et al., 2013; Deng et al., 2015; Porter et al., 2015; Cao et al., 2016; Drent et al., 2016). It is therefore expected that neurotoxicity will be found at greater rates, which may lead to increased routine integration of psychiatry, in addition to neurology, to assist in symptom management.

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