CLINICAL CASE CHALLENGES

Use of Chimeric Antigen Receptor Modified T Cells With Extensive Leukemic Myocardial Involvement

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Immunotherapy with chimeric antigen receptor (CAR)–modified T cells has revolutionized treatment of multiply relapsed or refractory acute lymphoblastic leukemia (1). It has shown great promise in its efficacy, combining tumor specificity with a potent cytotoxic immune response, which led to Food and Drug Administration approval of 2 CD19 CAR T cell therapies in 2017, tisagenlecleucel (Kymriah, Novartis, Basel, Switzerland) and axicabtagene ciloleucel (Yescarta, Gilead, Foster City, California). As T cell-engaging therapies are more readily used, its toxicities and side effect profiles are an area of active investigation. The primary toxicity unique to CAR T cell therapy is cytokine release syndrome (CRS), an acute systemic inflammatory response syndrome related to active T cell proliferation with release of high levels of cytokines (2,3), which results in fever, hyperferritinemia, and organ dysfunction.

The cardiac profiles of patients who have undergone CAR T cell therapy and associated cardiovascular toxicities have been increasingly described in both the adult and pediatric population (4,5). However, there has been no published report of the effects on CAR T cell therapy in patients with extensive leukemic myocardial involvement. We present a patient with refractory pre-B acute lymphoblastic leukemia with extensive cardiac involvement who underwent CAR T cell therapy.

CASE REPORT

A 17-year-old male with a history of very high-risk refractory pre-B acute lymphoblastic leukemia with double-hit cytogenetics (myc/BCL2, 8;14 and 14;18 translocations) and 1-year post–stem cell transplantation presented with 3 weeks of worsening scrotal and suprapubic pain, as well as increased bilateral arm and facial swelling. Magnetic resonance imaging (MRI) of the abdomen and pelvis showed large kidney, testicular, penile, and prostatic infiltrative lesions. Further diagnostic workup revealed both central nervous system and bone marrow relapsed disease with high CD19 and CD22 (>90%) expression. CD19 CAR T cell therapy was considered a potential therapeutic approach.

The admission echocardiogram showed a moderate to severely hypertrophied left ventricle (LV), with mildly depressed function, and with the posterior-inferior wall appearing heterogenous and echobright. An echo performed 6 months previously was normal. This new finding was concerning for further spread of his disease, with the new dysfunction believed to be due to new leukemic infiltrate in the myocardium. Ultimately, positron emission tomography (PET)/MRI was performed, confirming extensive infiltrative lymphomatous
disease in the myocardium, with a particular focus in the LV and right atrium, as well as significant tumor thrombus of the lower superior vena cava.

After undergoing T cell apheresis, the patient received 6 days of chemotherapy (rituximab, ifosfamide, carboplatin, etoposide) in addition to intrathecal chemotherapy to promote tumor debulking. During this time, the patient began to demonstrate new rhythm disturbances. With no history of arrhythmias, the patient initially presented with an episode of supraventricular tachycardia that terminated with vagal maneuvers, which prompted his transfer to the cardiovascular intensive care unit (ICU). Several days later, the patient demonstrated a combination of atrial tachycardia and atrial bigeminy with junctional escape beats, and ultimately, 2:1 atrial flutter. His echocardiogram at this time showed severe systolic LV dysfunction, and the decision was made for pharmacological cardioversion. He was initially converted with procainamide but demonstrated inadequate clearance of the medication, and it was quickly discontinued. He was then initiated on oral amiodarone, with which he settled into a slow junctional rate with some improvement in his systolic function. Because of adequate rate control with amiodarone with continued stable mild dysfunction of the LV, no other cardiac medications were initiated.

With tumor debulking, repeat whole body PET/MRI demonstrated a slight interval decrease in size of lymphomatous lesions. Despite this improvement, the provider team was concerned of the patient’s ability to tolerate CAR T cell therapy. Because of the extensive leukemic involvement of his myocardium, along with his history of both dysfunction and significant arrhythmias, it was unclear how his function and conduction system would be affected with the inflammatory process of CAR T cell therapy. Specifically, from an electrophysiology standpoint, with known involvement of his right atrium, as well as a mixture of atrial arrhythmias and slow junctional rhythm, both the health of his sinoatrial and atrioventricular node were called into question. With the inflammatory process of CAR T cell therapy, it was unclear whether he would develop heart block or a tachyarrhythmia. Related to this, an important discussion point also centered around options for temporary pacing and mechanical circulatory support. Surgical interventions for pacing were also discussed, although because of the severe immunosuppression of the patient and the potential inflammatory trigger surgery might cause, they were considered last options.

Ultimately, after considerable multidisciplinary discussion and consultation with several other institutions with experience with CAR T cell therapy, the decision was made to administer 12 Gy of radiation to the myocardium for disease control, provide a 6-week washout between end of radiation and CAR T cell infusion, and proceed with CAR T cell therapy with careful vigilance. The patient remained hospitalized during the duration of the radiation, remaining on continuous telemetry for close rhythm monitoring. The patient received lymphodepletion therapy and was pre-emptively transferred to the ICU for patient-derived CD19 CAR T cell (Kymriah) infusion for closer monitoring.

**Post-CAR T Cell Therapy**

Our patient tolerated the infusion well, with no immediate reactions. Because of the high acuity and disease burden of this particular case, the threshold to intervene for signs of CRS was lowered, despite the usual approach according to the National Cancer Institute Common Terminology Criteria for Adverse Events system. On day 3 post-CAR T cell, he developed grade 1 CRS with a temperature of 39.5°C, for which he promptly received tocilizumab to reduce any risk of cardiotoxicities and neurotoxicities. For cardiac monitoring, the decision was made to prophylactically place an arterial line, to closely monitor troponin levels, and to obtain echocardiograms every 3 days for the first 2 weeks after CAR T cell administration. Troponins were initially checked every 6 h for the first 3 days, then spaced to daily troponins for the first week. His troponins were all low level and ranged from 0.019 to 0.057 ng/ml (reference: <0.055 ng/ml). His troponins did not trend upward with his fever. His echocardiograms showed stable mild LV dysfunction, similar to his immediate pre-CAR T cell therapy echo.

His ICU stay was otherwise unremarkable, with no further rhythm disturbances while remaining on maintenance amiodarone. He was eventually transferred from the ICU on day 12 and discharged on day 19 post-CAR T cell. His echo and rhythm monitor on discharge showed normal biventricular function and rare premature atrial contractions and premature ventricular contractions with rare episodes of atrial tachycardia.
FOLLOW-UP

A cardiac MRI performed on day 28 post-CAR T cell therapy showed continued improvement in myocardial infiltration of the basal anteroseptal and mid-inferoseptal walls. A PET/MRI performed on day 29 confirmed those findings, with interval improvement of his renal disease burden and no new lesions. Follow-up lumbar puncture and bone marrow biopsy performed on the same day continued to be negative for residual disease. His 3-month follow-up surveillance tests continued to show evidence of remission, with no signs of additional systemic disease. As seen in Figure 1, his PET/MRI continued to show stable evidence of improvement in his myocardial infiltration.

DISCUSSION

This report introduces a case of a patient with refractory pre-B cell acute lymphoblastic leukemia, with extensive myocardial involvement with associated dysfunction and arrhythmias, who received CAR T cell therapy. Cardiac involvement in patients with leukemia and lymphoma have been described in both adult and pediatric patients. In terms of leukemia, 1 study noted 44% of autopsies on patients who died from leukemia were noted to have microscopic infiltrates (6), whereas in a different study for lymphoma, 20% to 25% of patients were found to have cardiac metastases (7). However, the clinical significance of the myocardial infiltrates was not as clearly delineated. Even less is known about how CAR T cell therapy and its associated inflammatory effects affects this subset of patients.

Multiple studies have delineated the cardiac profiles of patients who have undergone CAR T cell therapy (4,5). Ghosh et al. (8) recently published a comprehensive primer of our current knowledge of cardiovascular
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Interleukin-6 receptor antibody, plays an important role in mitigating the inflammation systemically and locally. Furthermore, minimal information exists as to how this therapy affects patients with known myocardial oncological involvement. In the report by Alvi et al. (5), cardiovascular outcomes after CAR T cell therapy were described in a patient group in which 13% had pre-existing atrial fibrillation or flutter and 3.6% had previous cardiomyopathy or clinical heart failure. This study provided some insight as to how patients with pre-existing cardiac conditions before CAR T cell therapy might fare after administration of therapy (5). However, because our patient’s cardiac dysfunction and arrhythmias were believed to be directly caused by myocardial leukemic infiltrates, there was a concern that he was at a greater risk of an adverse cardiovascular event with CAR T cell therapy.

Fortunately, our patient did not show any worsening dysfunction or rhythm disturbances with CAR T cell therapy. Although no active treatment was required, we believe several steps may have helped to mitigate his cardiovascular risk. First, chemotherapy and radiotherapy for tumor debulking before CAR T cell therapy was performed. Pre-CAR T cell therapy evaluation showed lessened myocardial involvement, which might have resulted in less inflammation systemically and locally. Second, during the pre-planning for this patient, an active decision was made to initiate tocilizumab earlier than would be our usual protocol. Tocilizumab, an interleukin-6 receptor antibody, plays an important role in mitigating the inflammation caused by CAR T cell therapy and is therefore administered for CRS treatment. Although its use is usually reserved for grade ≥2 CRS, our team made a conscious decision to administer it early with evidence of grade 1 CRS, which might have prevented further inflammation. In addition, our patient was closely monitored in an intensive care setting because CRS tends to occur the first 1 to 14 days after CAR T cell infusion.

Finally, emphasis should be placed on the degree of multidisciplinary involvement in this patient’s care. Because of the uncertainty of patient progression with treatment and potential need for invasive interventions, an early multidisciplinary collaboration was established between oncology, immunotherapy, cardiology, and the ICU teams. Within our cardiology department, a primary cardiac intensivist, electrophysiologist, and a heart failure physician cared for the patient and were in frequent discussion of the clinical status of this patient. Discussions regarding temporary and/or permanent pacemakers and mechanical circulatory support options were held before the initiation of CAR T cell therapy, with backup plans made after weighing the risks and benefits. This multidisciplinary collaboration aided significantly in our care for this patient, and although he fortunately had a benign course, our teams were well informed with concrete plans of action in case of adverse events.

At 3-month follow-up, the patient continues to do well and will receive long-term follow-up. Current data report cardiovascular toxicities early in the post-CAR T cell therapy course, and there are minimal data regarding long-term or late-onset cardiotoxicities. In a retrospective review by Cordeiro et al. (9), who evaluated long-term complications in patients who received CAR T cell therapy and survived beyond 1 year, no cardiovascular specific complications were reported. For our patient who had extensive myocardial involvement, careful surveillance is warranted, and we are planning to obtain an echo and rhythm monitoring every 3 months, together with his routine oncological follow-up.

In summary, this case highlighted a patient with refractory leukemia with extensive myocardial involvement who received CAR T cell therapy and the importance of careful surveillance, conservative management, as well as extensive multidisciplinary collaboration. Although much is yet to be learned about this patient population, with growing use of CAR T cell therapy, this will be an important subset of patients in the cardio-oncology arena.

**AUTHOR DISCLOSURES**

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.
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