

CLINICAL CASE CHALLENGES

CardioMEMS-Guided CAR T Cell Therapy for Lymphoma in a Patient With Anthracycline-Induced Cardiomyopathy



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CASE REPORT

A 66-year-old woman with advanced diffuse large B-cell lymphoma (DLBCL) was referred for chimeric antigen receptor (CAR) T cell therapy. She was diagnosed with DLBCL 6 years prior to presentation and had no significant past medical history. She received a total of 10 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), with a lifetime exposure of doxorubicin >500 mg/m². She underwent an autologous hematopoietic stem cell transplant after 4 cycles of R-CHOP. Four years later, her DLBCL recurred, requiring 6 more cycles of R-CHOP. One month after she completed the last cycle, her transthoracic echocardiogram (TTE) demonstrated a left ventricular ejection fraction (LVEF) of 55% to 60% and global longitudinal strain of -12% (normal: -19% to -22%). Two months following therapy, she was admitted to the hospital with acute decompensated heart failure (HF). Repeat TTE demonstrated an LVEF of 25% with global left ventricular (LV) dysfunction.

Positron emission tomography scan imaging demonstrated progression of her DLBCL with new pulmonary nodules. She was referred to our center for consideration of CAR T cell therapy. Coronary computed tomography demonstrated mild coronary artery disease, and cardiac magnetic resonance imaging showed no evidence of infiltrative or inflammatory disease. She was presumed to have anthracycline-induced cardiomyopathy and was initiated on furosemide and guideline-directed medical therapy (GDMT), including lisinopril 2.5 mg and metoprolol succinate 12.5 mg daily. Up-titration of GDMT was limited, and spironolactone or eplerenone could not be added, secondary to hypotension.

She was referred to a cardio-oncologist for risk stratification prior to CAR T cell therapy. She had good exercise tolerance, riding a stationary bike for 10 to 15 min at a time. A right heart catheterization (RHC) demonstrated mildly elevated biventricular filling pressures with normal cardiac output (right atrium 10 mm Hg, pulmonary artery 36/20/27 mm Hg, pulmonary capillary wedge pressure 16 mm Hg, Fick cardiac output 5.1 l/min, Fick cardiac index 2.9 l/min/m², and a mixed venous oxygen saturation 57.4%).

It was felt that CAR T cell therapy was her only therapeutic option. Multidisciplinary discussions between her hematologist/oncologist, cardio-oncologist, and advanced HF team were held to determine feasibility. Given the recent onset of her cardiomyopathy, the decision was made to give her a 3-month trial of GDMT for HF optimization. Of particular concern was how she would be able to withstand cytokine release syndrome (CRS), a common complication of CAR T cell, in which a rapid release of cytokines occurs from the CAR T cells when they engage with the target antigen expressed on malignant cells. Manifestations of CRS include fevers and derangements in blood pressure and oxygenation, ranging from mild hypotension and hypoxemia to

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**ABBREVIATIONS
 AND ACRONYMS**

- CAR** = chimeric antigen receptor
- CRS** = cytokine release syndrome
- GDMT** = guideline-directed medical therapy
- DLBCL** = diffuse large B-cell lymphoma
- HF** = heart failure
- LVEF** = left ventricular ejection fraction
- PA_d** = pulmonary artery diastolic pressure
- R-CHOP** = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
- RHC** = right heart catheterization
- TTE** = transthoracic echocardiogram

vasodilatory shock requiring vasopressors and severe hypoxemia necessitating intubation. The hypoxemia typically results from capillary leak syndrome, a low-pressure pulmonary edema. Other possible cardiac complications include atrial or ventricular arrhythmias and ventricular dysfunction. Invasive pulmonary artery catheter monitoring was considered as an option to facilitate appropriate volume management. However, the risk of infection was considered prohibitive given that lympho-depleting chemotherapy is administered prior to CAR T cell therapy. Considering these circumstances, the decision was made to implant a CardioMEMS (Abbott, Abbott Park, Illinois) device that was approved under compassionate use criteria.

After 3 months of GDMT, repeat RHC demonstrated normal filling pressures with preserved cardiac output (right atrium 2 mm Hg, pulmonary artery 25/12/18 mm Hg, pulmonary capillary wedge pressure 15 mm Hg, Fick cardiac output 4.7 l/min, Fick cardiac index 2.8 l/min/m², and mixed venous oxygen saturation 61.5%). During the RHC, she had successful placement of the CardioMEMS device. Repeat TTE demonstrated no improvement in her LVEF (24.6%), but did show that her right ventricular performance improved from mildly to moderately reduced to normal.

The following week, she was admitted for pre-treatment with a lympho-depleting chemotherapy regimen consisting of fludarabine and cyclophosphamide. During pre-treatment, she developed neutropenic fever and hypotension, and was started on intravenous antibiotics. GDMT was held. On day 1, 2 days later, she received the infusion of axicabtagene ciloleucel (Yescarta, Kite Pharma/Gilead, Los Angeles, California) CAR T cells. On day 2, she developed mild CRS with fevers, sinus tachycardia to the 150s, and systolic blood pressures in the 90s. The CardioMEMS demonstrated an elevated pulmonary artery diastolic pressure (PA_d) of 20 mm Hg (Figure 1). She was given intravenous furosemide 20 mg and a dose of tocilizumab, an interleukin-6 receptor antagonist used in the treatment of CRS. By day 3, she had worsening tachypnea and a new oxygen requirement of 2 l nasal cannula, requiring a second dose of tocilizumab. Chest x-ray revealed diffuse pulmonary opacities (Figure 2), with a PA_d of 10 mm Hg on CardioMEMS, suggestive of noncardiogenic pulmonary edema. Given the normal PA_d, the treatment team held diuretic agents to prevent hypotension. Monitoring the patient's volume status required significant coordination between the oncology and cardiology services. The oncology nurses performed the CardioMEMS measurements 3 to 4 times/day. The advanced HF consult service rounded on the patient daily, and made recommendations based on the CardioMEMS readings.

On day 6, her course was complicated by atrial flutter with rapid ventricular rates in the 140s. She developed acute hypoxic respiratory failure secondary to cardiogenic pulmonary edema, as evidenced by a PA_d of 23 mm Hg. She required intubation and initiation of low-dose norepinephrine. She was started on amiodarone for the atrial flutter, converted, and remained in sinus rhythm thereafter.

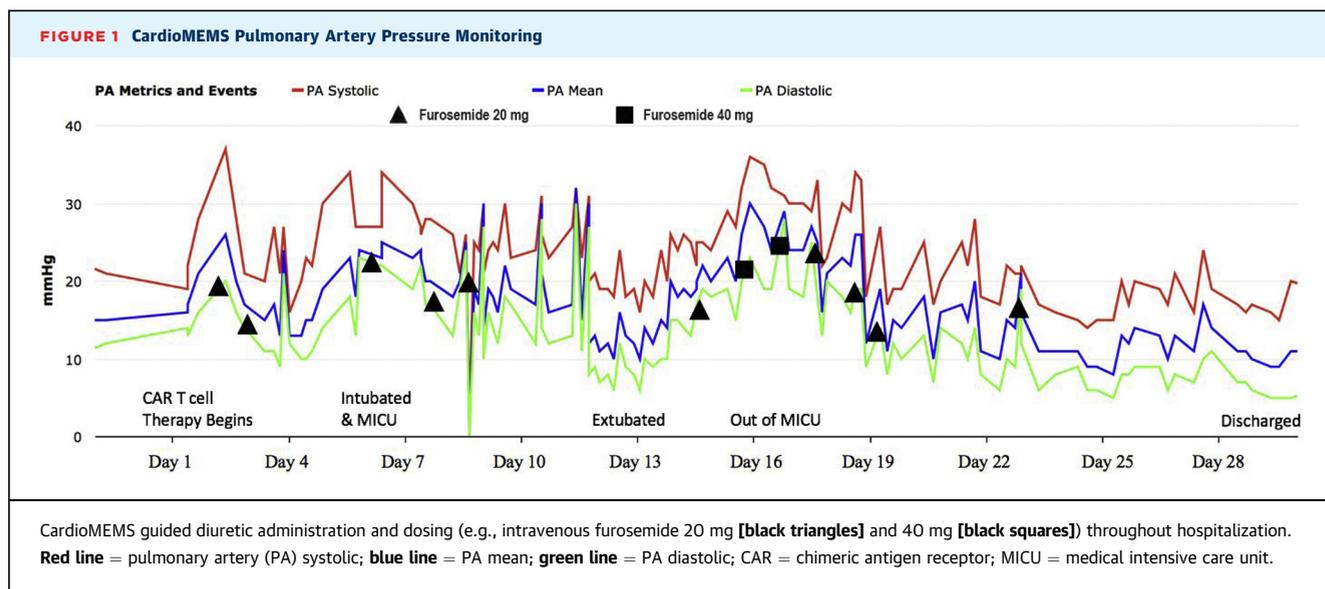
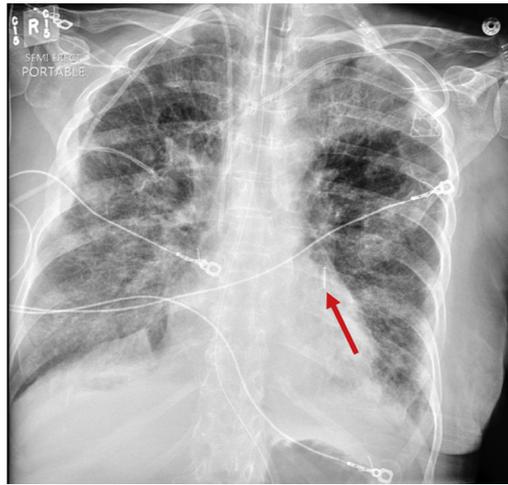


FIGURE 2 Chest X-Ray Demonstrating Capillary Leak Secondary to Cytokine Release Syndrome



Diffuse pulmonary opacities on chest x-ray, but normal pulmonary artery diastolic pressure of 10 mm Hg based on the CardioMEMS device (denoted by the red arrow).

With continued guidance from the CardioMEMS device she received intermittent doses of intravenous furosemide 20 to 40 mg to keep her PA_d between the range of 10 to 20 mm Hg. She was weaned off vasopressors and extubated on day 12. Daily discussions amongst the many teams involved throughout her hospital course were paramount in preventing discordant care, especially when her clinical status had many rapid changes while she was in the intensive care unit. She completed CAR T cell therapy and was discharged to acute rehabilitation after a one-month hospitalization. She was unable to be restarted on GDMT due to hypotension. Her PA_d was 6 mm Hg at discharge. The plan was to obtain a positron emission tomography scan after acute rehabilitation to reevaluate her cancer.

Her initial course at the facility was uncomplicated, and she was able to participate in physical therapy. She had weekly appointments in the oncology clinic and an appointment with the advanced HF team. The providers at rehabilitation continued to transmit CardioMEMS readings to the advanced HF team. Furosemide 20 mg daily by mouth was restarted when her PA_d was 18 mm Hg, which occurred 3 weeks after hospital discharge. At that time, the physician at the facility reported that she continued to do well. Fifteen days later (34 days after hospital discharge) the patient woke up with acute shortness of breath, and was found to have an oxygen saturation of 88%. Prior to this episode she had not reported any dyspnea, but had noted nausea for the past 3 days. She was taken by ambulance to an outside hospital. Initial chest x-ray was interpreted as pulmonary edema and a possible left lower lobe infiltrate. PA_d at the time of hospitalization was 22 mm Hg. She was intubated for progressive hypoxic respiratory failure. Per outside hospital records, a bedside TTE showed severe LV dysfunction but normal right ventricular function. She was treated with multiple vasopressors for presumed mixed septic and cardiogenic shock. She experienced a cardiac arrest due to ventricular tachycardia and expired later that day.

DISCUSSION

CAR T cell therapy is a newer treatment for hematological malignancies and a form of immune therapy that uses a patient's immune system to detect and kill tumor cells (1). T cells are collected from the patient via apheresis and are then genetically engineered in a laboratory to produce CAR proteins on their surface, which allow them to recognize antigens and kill targeted tumor cells when reintroduced into the patient. Importantly, CAR T cell therapy can be effective in chemotherapy-refractory lymphoma, inducing durable complete remissions lasting >2 years in some patients with DLBCL (1).

The side effects of CAR T cell therapy, such as CRS and arrhythmias, can be challenging to manage in patients with HF. CRS, which is predominantly mediated by interleukin-6, can occur in up to 70% to 90% of

patients (2). Hypotension is typically treated with intravenous fluids to maintain systolic blood pressure >90 mm Hg. Third-spacing of fluids with capillary leak is common, and this can lead to noncardiogenic pulmonary edema. A single-center retrospective study demonstrated that 12% of patients developed the composite outcome of arrhythmias, decompensated HF, or cardiovascular mortality (3).

The cardiac toxicities associated with CAR T cell therapy have led many centers to view significant cardiovascular disease as a relative contraindication (4). In 2 of the main clinical trials for CAR T cell therapy in patients with refractory DLBCL, patients were excluded if their LVEF was $\leq 45\%$ to 50% (4). Our team decided to proceed with CAR T cell therapy in the patient described in this report because of her lack of other comorbidities, preserved performance status, and normal invasive hemodynamics. It was also her only treatment option for refractory DLBCL.

The CardioMEMS device—which is typically used to manage outpatients with HF—was an essential component of our patient’s medical treatment (5). For example, at 2 periods in the patient’s hospitalization she was found to have diffuse pulmonary infiltrates, hypoxemia, and hypotension. Her PA_d was 10 and 23 mm Hg during these respective episodes. Hemodynamic monitoring by means of CardioMEMS allowed proper utilization of diuretic therapy, i.e., avoidance in the setting of hypovolemia and administration in the setting of volume overload. Diuretic management on the basis of physical examination and chest x-rays alone would have been challenging due to marked fluctuations in volume status with third spacing of fluids both peripherally and in the pulmonary vasculature. To our knowledge, this is the first study documenting the use of CardioMEMS to monitor the hemodynamic variation with CAR T cell therapy. Investigators are exploring other novel applications for CardioMEMS, especially in patients with rapid changes in hemodynamics. For example, HEMO-VAD (Design and rationale of haemodynamic guidance with CardioMEMS in patients with a left ventricular assist device: the HEMO-VAD pilot study) is a single-center prospective study evaluating the safety and feasibility of CardioMEMS for optimization of LV assist device pump settings (6).

This case demonstrates that CAR T cell therapy is feasible in patients with symptomatic heart failure, when there is close collaboration between oncologists and cardiologists, and there is reliable hemodynamic data to guide treatment decisions. However, the fact that our patient died 1 month after discharge highlights how vulnerable these patients are, and that long-term success may be difficult to achieve in patients with severe LV dysfunction. It is not clear what precipitated the patient’s acute decompensation with possible mixed septic and cardiogenic shock. Some have questioned whether there could be a latent period with continued circulation of CAR T cells after treatment, leading to delayed cardiac toxicities such as arrhythmias and decompensated HF; this warrants further study (3). Also, risk assessment using cardiopulmonary exercise testing in addition to RHC may help to identify suitable patients better. The use of hemodynamic monitoring with CardioMEMS may enable oncologists and cardiologists to offer potentially life-saving therapy to a broader population of patients, but more research is warranted.

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