

## EDITORIAL COMMENT

# Cytokines Are at the Heart of It

## Cytokine Release Syndrome Underlies Cardiovascular Effects of CAR T Cell\*



Anna B. Catino, MD

Chimeric antigen receptor (CAR) T cell therapy has emerged as an extremely promising therapy for patients with refractory and relapsing hematological malignancies, primarily B-cell lymphomas that include acute lymphoblastic leukemia and diffuse large B-cell lymphoma. Additionally, CAR T cell is under investigation for chronic lymphocytic leukemia (CLL) and multiple myeloma. Without this therapy, these patients have significantly reduced survival, and therapy is primarily focused on palliation (1). Using CAR T cell therapy, patients' T cells are specifically engineered to target the CD19 antigen, which is expressed on these B-cell malignancies (1). Although use of CAR T cell therapy has led to remarkable improvement in remission, it is associated with significant toxicity, most notably cytokine release syndrome (CRS) and neurotoxicity (1,2). Concerns for cardiovascular (CV) toxicity have also emerged, including troponin elevation, reduced left ventricular (LV) function, heart failure (HF), pulmonary edema, and cardiogenic shock (3). It appears that CV complications often occur in conjunction with CRS (4), but unfortunately, there is a paucity of data regarding direct CV effects of CAR T cell and a general lack of understanding of the pathophysiology.

CAR T cell therapy has been used for several years in the pediatric population, and retrospective data have suggested that a significant number of patients treated with CAR T cell have a transient drop in LV systolic function and/or require vasopressor support for hypotension (5,6). With the growing use and potential applications of this novel hematological therapy, a better understanding of CV toxicities, including how to identify at-risk patients, management, and long-term implications, are highly relevant. In this issue of *JACC: CardioOncology*, Lefebvre et al. (7) published their experience with CART cell therapy and associated CV effects at the University of Pennsylvania (the founding institution for CAR T cell therapy).

In this retrospective review, the investigators reported on CV outcomes for the first 145 patients treated at the University of Pennsylvania. They found a high rate of CRS in their population (72% of patients) and a significant rate of major adverse cardiovascular events (MACE); there were 42 events in 31 (21%) patients, including 2 cardiac deaths. Consistent with other reports (8), the investigators found that those with CV toxicities were exclusively those who experienced CRS. CRS is a common and dangerous side effect of CAR T cell and is characterized by fever, hypotension, and hypoxia. It is a systemic inflammatory response syndrome caused by release of several cytokines and chemokines (in particular, interleukin [IL]-6) from targeted T-cell therapy (9). The increased rate of cardiac complications in patients with CRS was noted by others (4-6,8) although it remains unclear whether this represents direct myocardial injury or is secondary to demand ischemia. It should be noted that the CD19 antigen targeted by the engineered T cells is not expressed on myocardial cells (10).

In this study, the investigators also demonstrated that CRS preceded development of CV complications,

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From the Division of Cardiovascular Medicine, Department of Medicine, University of Utah, Salt Lake City, Utah, USA. Dr. Catino has reported that she has no relationships relevant to the contents of this paper to disclose. The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: CardioOncology* [author instructions page](#).

with median time from CAR T cell infusion to CRS of 6 days and a median time to MACE of 11 days. The predominant MACE was HF, followed by atrial fibrillation and other arrhythmias. The investigators analyzed baseline characteristics, including various echo parameters, and found that elevated baseline creatinine and severe CRS (grade 3 or 4) during therapy were most predictive of MACEs. Because HF is the predominant MACE and patients with CRS and renal insufficiency are at highest risk, perhaps fluid resuscitation in the setting of CRS with diffuse capillary leak and altered salt/water hemostasis may contribute in the setting of diastolic dysfunction. The investigators also found a trend between increased estimated left atrial pressure by echocardiography ( $E/e'$ ) and left atrial volume index and MACE. In this context, as HF was the predominant CV complication, the study emphasizes the importance of pre-CAR T cell therapy echocardiograms in identifying at risk patients for cardiac complications. In contrast, pre-existing LV function was not associated with increased risk of MACEs; however, the investigators did demonstrate a modest decline in LV function post-CAR T cell, which raises the question of whether abnormal global longitudinal strain assessment pre-treatment could be a helpful predictor of HF and LV dysfunction. Because systematic cardiac surveillance with serial echocardiograms was not done at the time of HF development or at follow-up, the true incidence of LV dysfunction or resolution of LV dysfunction was not known. This was a shortcoming of this study because in previously reported studies, CAR T cell therapy-associated LV dysfunction appeared to be transient (5,6). An additional limitation of the current study was the lack of cardiac biomarkers. Another recently published retrospective study that assessed the CV adverse events of CAR T therapy showed troponin elevations occurred in 54% of patients and were associated with increased risk of MACEs (8).

The investigators also pointed out that at baseline, their patient population had slightly higher rates of HF, hypertension, atrial fibrillation, and coronary artery disease compared with the general population. As cardiologists trying to assess risk of this novel therapy, it is important to understand the patient population treated. The adult patient population in which this therapy was used had refractory and relapsed lymphomas that were often treated with multiple rounds of anthracycline-based chemotherapy and chest radiation, which are well-established as having delayed cardiotoxic effects. In addition, patients might be exposed to other potentially cardiotoxic therapies and stem cell transplants that are associated with increased CV events. In the

CLL population, in particular, patients are often treated with bruton tyrosine kinase inhibitors (e.g., ibrutinib) that are associated with atrial fibrillation and subsequent HF. Interestingly, neither baseline CV disease or a history of cardiotoxic therapies were predictive of cardiotoxicity in this study.

The actual process of CAR T cell therapy itself may also contribute to CV toxicity by way of conditioning chemotherapy. Before CAR T cell infusion, patients' T cells are collected and genetically modified to engineer the T cells to recognize CD19 expressing tumor cells. These cells are then multiplied to create a sufficient amount for infusion (1,4). Before infusion, patients are treated with lymphodepleting chemotherapy (often fludarabine and cyclophosphamide) to suppress their own T cells to allow for proliferation of engineered T cells once infused. Notably, cyclophosphamide itself can be associated with significant CV toxicity specifically HF and LV dysfunction (4,11).

Although the pathophysiology of CAR T cell-associated CV toxicity may be rather complex and much remains unknown, it is clear that the association between CRS and CV complications is prominent (5-8). Early markers of cardiac toxicity, such as abnormal myocardial strain or elevated cardiac biomarkers, may potentially serve to help predict who will develop CV complications or who even may benefit from tocilizumab, a monoclonal antibody to IL-6 that has been approved by the Food and Drug Administration for severe cases of CRS (9,12). In addition, systematic measurement of inflammatory markers and cytokines such as IL-6 and tumor necrosis factor-alpha may also help us gain a better understanding into the pathophysiology linking CRS and CV complications. Ultimately, prospective data with systematic cardiac monitoring (imaging and inflammatory and cardiac biomarkers) is the next step in helping to understand the frequency and pathophysiology of CAR T cell therapy-related CV adverse events. This study is an excellent report of the founding institution's experience and demonstrates the high rate of CRS-associated CAR T cell therapy and its clear association with CV toxicity. Because the predominant associated adverse CV effect appears to be HF, CAR T cell therapy and CRS, in turn, may offer further insight to a greater understanding of HF, myocardial injury, and cardiac recovery.

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**ADDRESS FOR CORRESPONDENCE:** Dr. Anna Catino, University of Utah Health Science Center, 30 North 1900 East, Room 4A100, Salt Lake City, Utah 84132. E-mail: [anna.catino@hsc.utah.edu](mailto:anna.catino@hsc.utah.edu). Twitter: [@abcatino](https://twitter.com/abcatino).

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