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EDITORIAL COMMENT

Guarding the Heart in an Era of "Tachy-CAR-T"

The Rapid Proliferation of a Transformative Therapy*

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In this issue of *JACC: CardioOncology*, Lefebvre et al[1] report the first single-center prospective observational study designed to evaluate the cardiac events profile of patients undergoing contemporary chimeric antigen receptor T-cell (CAR-T) therapy targeting CD19. CAR-T therapy has revolutionized the treatment of some hematologic malignancies in recent years. In this treatment modality, a patient's T cells are equipped with artificial antigen receptors (ie, the chimeric antigen receptor) to allow killing of cancer cells upon activation following binding to certain cell surface antigens. Although efficacy is excellent, toxicity syndromes such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome, as well as organ toxicities such as cardiotoxicity, are both common and exhibit a wide range of clinical presentation.[2,3] CAR-T indications continue to expand, and CAR-T products are currently approved for the treatment of blood malignancies such as acute myelogenous leukemia, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, and multiple myeloma. The number of CAR-T treatments is rapidly proliferating (ie, "Tachy-CAR-T"), and a better understanding of cardiac risks is necessary.

Lefebvre et al[1] sought to prospectively describe the incidence of major adverse cardiac events (MACE) after CAR-T therapy. The investigators collected and reported clinical, electrocardiographic, echocardiographic, and laboratory data from patients treated with CD19-directed CAR-T therapy. The primary endpoint was the incidence of MACEs, which were defined as 1 or more of the following: symptomatic heart failure, nonfatal acute coronary syndrome, nonfatal ischemic stroke, new onset arrhythmia, and cardiac death. Forty-four patients were enrolled with a median follow-up of 1.3 years. MACEs were uncommon (4.5%) and included 1 patient with heart failure and preserved ejection fraction and 1 patient with atrial fibrillation.

One of the major immune-mediated acute side effects of CAR-T, CRS, has been linked to cardiac events.[4] In 1 study, the rates of any grade and grade ≥2 CRS were 52% and 27% with a median time to CRS of 4 days. Although prior studies reported cardiac events largely with the occurrence of CRS grade 2 or higher, the 2 events in this study occurred during grades 1 and 2. During CRS, patients had a higher mean heart rate, inflammatory markers as measured by C-reactive protein and ferritin values, and higher N-terminal pro-B-type natriuretic peptide compared with baseline. During the follow-up period, a small and temporary worsening in the left ventricular global longitudinal strain was noted, without a significant change in the left ventricular ejection fraction. In addition, right ventricular function was slightly decreased during follow-up as measured by S' in patients who developed CRS. These findings are welcomed because they suggest that attention to cardiac function, with careful consideration of echocardiography, should be added to recommendations of current surveillance strategies after CAR-T therapy.

It is now well recognized that most cardiac events in patients receiving CAR-T therapy occur in those who develop CRS, which is a systemic inflammatory condition characterized by the hallmark of high fever,

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and the possibility of hypotension and hypoxia. The incidence, timing, and likely severity of CRS events are variable depending on the diagnosis and CAR-T product.[5-7] A prior retrospective study suggested utilization of tocilizumab, an interleukin-6 receptor blocking antibody, may mitigate cardiotoxicity. Specifically, there was a notable increase in the event rates with every 12-hour delay in tocilizumab administration.[4] In the prospective study by Lefebvre et al,[1] the median time from CRS diagnosis to tocilizumab utilization was 1 day. The low rate of MACEs is encouraging and may point to the overall recognition of the deleterious effects of CRS and the field's move to aggressively treat it, as evidenced by the short duration of CRS onset to tocilizumab's administration.

The report has several limitations. As acknowledged by the authors, the study was conducted in part during the coronavirus disease-2019 pandemic, which limited patients' participation and follow-up frequency. Another limitation is that the study is specific to CD19-targeted CAR-T, whereas anti-B-cell maturation antigen CAR-T products have more recently gained regulatory approval with limited cardiac data.[3] The findings of this study may not apply to anti-B-cell maturation antigen or other CAR-T treatments in development. In addition, the study did not prospectively report the incidence of nonmajor adverse cardiac events such as arrhythmias other than atrial fibrillation, and the lack of uniformity on defining MACEs may limit the comparison of event rates with other studies.[8,9]

Moreover, there are racial disparities in health care outcomes in patients with leukemia, lymphoma, and multiple myeloma,[10] and these have remained despite innovations like CAR-T therapy; currently, there are racial disparities in access, toxicities, and clinical outcomes.[11] Recently, it was found that Black patients have higher levels of baseline inflammatory markers, including C-reactive protein and ferritin.[12] It is believed that these differences in baseline characteristics may contribute to Black patients having higher rates of CRS, longer hospital stays, and more prolonged cytopenia.[12] Lefebvre et al[1] noticed cardiac effects associated with contemporary CAR-T therapy; therefore, it is important to highlight disparities in cardiovascular health among various populations. Recent data show Black men and women have a 70% and 50% elevated risk for the development of heart failure compared to their White counterparts, and approximately 45% of Black adults have a cardiac risk factor such as hypertension.[13] Importantly, the onset of cardiac risk factors and overt cardiac disease occurs at an earlier age in the Black population.[14]

Current guidelines, based on expert consensus, recommend obtaining a baseline echocardiogram for patients undergoing CAR-T therapy, particularly in those with pre-existing cardiovascular disease or risk factors.[15] This study adds to our knowledge of the immediate and short-term cardiac toxicities of CAR-T therapy, including more details regarding the echocardiographic parameters clinicians should monitor beyond left ventricular ejection fraction. As "Tachy-CAR-T" continues, more patients will be treated and at risk for cardiac events. Larger prospective studies are needed to better understand the long-term adverse cardiac events and optimize surveillance programs.

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