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EDITORIAL COMMENT

Chimeric Antigen Receptor T-Cells and Cardiovascular Toxicity

Cause for Concern?*

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Immunotherapy is an expanding resource in treating cancer patients, with impressive beneficial effects on survival in several advanced malignancies (1). Cancer activates multiple mechanisms that co-opt host-tumor immune interactions, thus inducing immune evasion. Novel therapeutic approaches have been developed by manipulating and engineering immune cells, which has created great expectations in the oncology community. To date, at least 2 immunotherapeutic strategies, checkpoint inhibition and cellular therapy with autologous chimeric antigen-receptor T cells (CAR-T cells), have clearly demonstrated their efficacy in treating solid tumors and in a few hematologic malignancies. In contrast, checkpoint inhibitors can produce a wide spectrum of immune-related adverse complications, also involving the heart, and episodes of fulminant myocarditis or fatal heart failure have been described in patients treated with these drugs (2). Adverse events related to CAR-T cells involve mainly cytokine-related syndrome (CRS) and neurotoxicity (3), but little is known about the occurrence of cardiovascular (CV) complications.

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The study by Alvi et al. (4) in this issue of the *Journal* adds valuable information to this issue through a study of 137 patients treated with CAR-T cells, most of whom had relapsed diffuse large B-cell lymphoma (5). The definition of cardiotoxicity was based on a troponin increase or a left ventricular ejection fraction (LVEF) decrease compared to the pre-treatment period. CV events were composites of arrhythmias, decompensated heart failure, and CV death. The study by Alvie et al. (4) clearly demonstrated that cardiac damage and CV events represent relatively frequent complications of CAR-T cell therapy, as shown by 21% to 59% of the treated patients who experienced cardiac damage, 12% of whom had CV events and 4% of whom had cardiac-related death.

The present study pointed out several observations that need commentary. First, CAR-T cell cardiotoxicity occurred mainly in elderly patients (>60 years old), often characterized by a high CV risk profile and prior anticancer treatment including anthracyclines and radiotherapy. Second, there was a strong association between troponin elevation post-CAR-T cell therapy (>0.03 ng/ml or high-sensitivity troponin >14 ng/l) and subsequent CV events. Troponin elevation was observed in 95% (16 of 17) of the patients experiencing CV events and was commonly seen in patients with CRS development (defined as the first appearance of fever after CAR-T cell therapy). CRS of any grade (using a CRS grading system of 1 to 5) was common, occurring at a median of 5 days after CAR-T cell therapy. Of note, an isolated elevation of troponin without CRS was not associated with the occurrence of CV events. Notably, a clinically significant decrease of LVEF (reduction of at least 10% points to a value below 50%) was detected in 28% of the patients treated with CAR-T cell, but only 29 of the 135 patients had echocardiographic data pre- and during CAR-T cell therapy. For this reason, a parallel between troponin increase and LVEF reduction could

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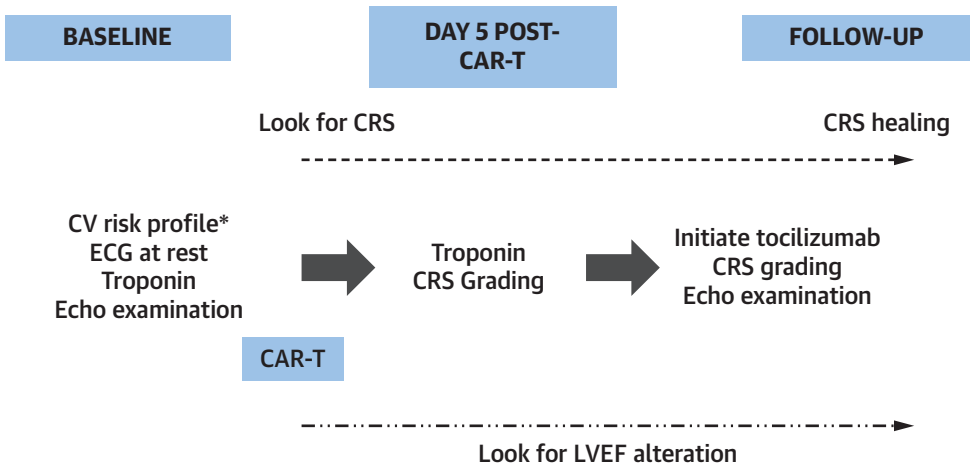
FIGURE 1 Diagnostic Work-Up and Management of CAR-T Cell-Related Cardiotoxicity



After a baseline comprehensive cardiovascular assessment, determination of troponin level within 5 days after CAR-T cell therapy should guide patient management. If a significant rise in troponin is detected, echocardiography should be repeated, the CRS grade determined, and tocilizumab initiated promptly. Timing of cardiological follow-up should be established in individual patients according to clinical judgment. *Baseline assessment including a 24-h ECG and an inducible ischemia test, when needed. CAR-T = chimeric antigen-receptor T cell; CRS = cytokine-related syndrome; CV = cardiovascular; ECG = electrocardiography; Echo = echocardiography; LVEF = left ventricular ejection fraction.

not be formally established, although a reduction in LVEF was observed only in patients with increased troponin and higher CRS grade after CAR-T cells were administered. Lack of data for global longitudinal strain and B-type natriuretic peptide release does not support this relationship either. Also, all CV events occurred in patients with a CRS grade ≥2, known to be associated with significant organ toxicity. Finally, a longer time between recognition of CRS and the administration of tocilizumab was associated with an increase in CV events.

The close relationships among CRS development, troponin release, and the occurrence of CV events represent a red flag that must be considered with greater attention in this clinical setting. As observed by Alvi et al. (4), the increase in troponin occurred in patients with a CRS grade of at least ≥2, that is, in patients with a higher degree of inflammation. Troponin level is a reliable indicator of myocyte injury in oncology patients with cardiotoxic effects of anticancer drugs. In the case of CAR-T cell therapy, the increase in troponin appeared to be primarily related to the hypotension and tachycardia induced by CRS. Treatment with CAR-T cells is associated with a marked increase in interleukin (IL)-6. IL-6 exerts its detrimental effect on several tissues, including myocardium in CRS (5). This finding is entirely consistent with the information obtained using tocilizumab for the treatment of these patients. Tocilizumab is a recombinant humanized anti-IL-6 monoclonal antibody that has been used primarily in the treatment of rheumatoid arthritis. More recently, it has demonstrated great use in successfully contrasting CRS and blunting its progression from subclinical to clinical stages (6). It should be noted that if the main anti-inflammatory properties of corticosteroids are used to counteract the detrimental CV effects of immune checkpoint inhibitors (2), then the cardiotoxicity of CAR-T cells may be specifically counterbalanced by tocilizumab. In the study by Alvi et al. (4), early administration of tocilizumab was associated with a significantly lower rate of CV events, without preventing the antitumor effects of CAR-T cells.

Together, these results point to major practical implications that should be considered when using CAR-T cells. First, results confirm the need for close cooperation between oncologists/hematologists and cardiologists in order to maximize the benefits of innovative therapies for malignant tumors while reducing and controlling the burden of CV complications, the characteristics and mechanisms of which are often not yet well understood (7). Practically, the combination of old age and evidence of multiple pre-existing CV risk factors implies the need for a preliminary, comprehensive cardiological

work-up before the beginning of CAR-T cell therapy. This work-up (**Figure 1**) should include biomarker assessment (troponin and B-type natriuretic peptide), a resting 12-lead electrocardiogram (ECG), and a complete echocardiography-Doppler examination (including global longitudinal strain) to identify cardiac conditions representing the background of subsequent CV complications. Values of LVEF should be determined with good accuracy at baseline in patients who had previously experienced potentially cardiotoxic drugs, such as anthracyclines and radiotherapy, and repeated periodically during CAR-T cell therapy. In this respect, the use of 3D echocardiography, which allows a more accurate and reproducible assessment of LVEF and, therefore, is more suitable for serial cardiac imaging evaluation, should not be underestimated. In addition, the preliminary assessment could include 24-h Holter ECG monitoring and the search for inducible ischemia (stress imaging) in patients with known or suspected coronary artery disease and a high risk of developing episodes of arrhythmia. During treatment, beyond clinical assessment (i.e., fever), both troponin and LVEF should be monitored. Any increase in troponin associated with a CRS grade of ≥2 at day 5 after CAR-T cell administration should prompt the initiation of cardioprotective therapy with tocilizumab. The same can be done in case of a drop in LVEF. Conversely, an isolated increase in troponin (a CRS grade of <2) should not be treated, although caution is warranted in the absence of additional data. Therefore, even if there is a reason for concern, further studies including more patients are needed to better understand the relationship between CAR-T cells and cardiovascular toxicity.

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