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EDITORIAL COMMENT

Cardiac Surveillance in Immune Checkpoint Inhibitor Therapy

Biomarkers Versus Imaging*

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Immune check point inhibitors (ICIs) have been major breakthrough therapies for various types of cancer with durable and lasting tumor responses, particularly for those that were difficult to treat previously.[1] ICIs up-regulate host antitumor immunity targeting cytotoxic T lymphocyte-antigen-4 (CTLA-4), programmed cell death receptor-1 (PD-1), and its ligand (PD-L1). The toxicity profile of ICIs is generally favorable. However, as result of nonspecific immune stimulation induced by ICIs, specific immune-related adverse events (irAEs), potentially affecting any organ system, have been described. Some of these irAEs may be life threatening.[2]

Cardiovascular toxicities related to the use of ICIs include myocarditis, stress cardiomyopathy, vasculitis, pericardial disease, arrhythmia, and increased atherosclerosis.[3] For some irAEs, such as pericardial and vascular disorders, the true incidence remains unknown. Myocarditis is the most frequently reported cardiovascular irAE associated with ICI therapy. The reporting of ICI-associated myocarditis is probably increasing because of enhanced awareness of this adverse consequence and because of the potential for fatality in 25% to 50% of cases.[4,5] Early diagnosis of myocarditis is key in order to start glucocorticoid treatment and withdraw ICI therapy.

In a registry of ICI-related myocarditis, the clinical presentation consisted of troponin elevation (94% of cases) and abnormal electrocardiographic (ECG) findings in almost all patients (84% of cases), whereas reduction of left ventricular (LV) ejection fraction (LVEF) was present in 50% of cases.[4] The time course of these alterations has not been evaluated, but based on previous series, it could be speculated that monitoring of troponin levels and ECG would be a strategy to detect earlier ICI-related myocarditis rather than monitoring changes in LVEF. Furthermore, measurement of troponin levels and evaluation of ECG changes are widely available, whereas imaging techniques for the measurement of LVEF with may not be readily accessible. In addition, LVEF is less sensitive than LV global longitudinal strain to detect early structural changes of the myocardium such as the inflammatory response induced by the ICIs. Tissue characterization with cardiac magnetic resonance (CMR) is considered the noninvasive reference standard to diagnose myocarditis. However, CMR is a less affordable and accessible screening tool as compared with troponin levels, ECG, or echocardiography and requires specific expertise for the interpretation of the images. The ideal screening tool to identify the patients at risk of developing ICI-related myocarditis as well as other cardiovascular irAEs remains to be defined.

In this issue of *JACC: CardioOncology*, Tamura et al[6] provide additional insights into the time course of cardiac irAEs by systematically evaluating changes in global and regional LV longitudinal strain and their association with the occurrence of myocarditis and increase in troponin levels. Of 129 patients receiving ICIs, 6 were diagnosed with myocarditis, 18 patients presented with troponin I elevation, and 26 died. The median time elapsed between the onset of ICI therapy and the elevation of troponin levels was 62 days

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whereas the median time to the diagnosis of myocarditis was 98 days. All patients presenting with myocarditis were treated with pembrolizumab (a PD-1 monoclonal antibody), and all but 1 of them had elevated levels of troponin. In terms of echocardiographic parameters, patients who had increased troponin levels showed a reduction in LV global longitudinal strain (from 17.3% [IQR: 16.7%-18.5%] to 15.7% [IQR: 14.8%-17.4%]) at 8 to 14 days after ICIs, whereas LVEF did not change significantly (from 65.2% [IQR: 62.2%-66.7%] to 64.9% [IQR: 62.1%-67.3%]). By contrast, patients without increased levels of troponins did not have changes in LV global longitudinal strain or LVEF. The proportion of patients showing a relative reduction in LV global longitudinal strain by ≥15% was significantly higher among patients with increased troponin levels as compared with their counterparts (22.2% vs 4.5%; $P = 0.022$). Interestingly, changes in LV longitudinal strain were more pronounced in the basal and mid-ventricular segments, whereas the apical segments showed preserved longitudinal strain.

These findings are important because they highlight the potential role of echocardiographic surveillance with measurement of LV longitudinal strain for the identification of patients at early stages of myocardial damage. In addition, the relative reduction of longitudinal strain associated with increased troponin levels or with myocarditis was lower in the basal or mid-ventricular segments as compared with global longitudinal strain (10% vs 15%), suggesting that the inflammatory response concentrates in these segments rather than the apex. This hypothesis is further corroborated by another publication describing structural changes in these segments as detected with tissue characterization CMR techniques.[7,8] Furthermore, given that the changes in LV longitudinal strain appear to precede the increase in troponin levels or development of myocarditis, this raises the question as to whether these events are associated with the cumulative exposure to ICIs. Previous series have reported more frequent myocarditis or pericardial diseases when ICIs agents are combined or when adjuvant radiotherapy is used. However, in this present series, the majority of the patients received ICIs in monotherapy, and in the context of limited numbers, there was no discernible association between exposure to radiotherapy or anthracyclines and elevated troponin. Moreover, the retrospective design of the study does not allow several questions to be answered. 1) Considering the poor outcomes of the underlying cancer, would withdrawal of ICIs prevent further myocardial damage and be justified when LV global or regional (basal and mid-ventricular) longitudinal strain reduce ≥15%? 2) Would corticosteroid treatment be effective in preventing myocardial damage when LV longitudinal strain starts to be impaired? 3) Would cardioprotective therapies (such as beta-blockers and angiotensin-converting enzyme inhibitors) help in preventing further LV dysfunction?

Current European Society of Cardiology Practice Guidelines on Cardio-Oncology recommend an ECG and measurement of troponin levels at baseline in all patients treated with ICIs and an echocardiogram only in high-risk patients (patients receiving combined ICI treatments, or combination of ICI with other cardiotoxic agents, patients with history of cardiotoxicity, noncardiovascular irAEs, and patients with cardiovascular diseases).[9] In addition, surveillance of ICI therapy with echocardiography to measure LVEF and global longitudinal strain is recommended if there are new-onset symptoms or when cardiac biomarkers increase, whereas CMR is only indicated when myocarditis is suspected.[9] The guidelines do not have specific recommendations for cardioprotective therapy in primary or secondary prevention of cardiotoxicity associated with ICIs. The findings of the study by Tamura et al[6] provide new evidence that may help in the design of prospective studies aiming to answer the questions that may help to inform future guidelines.

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