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EDITORIAL COMMENT

Cardiac Adverse Events Related to Immune Checkpoint Inhibitors*

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Immune checkpoint inhibitors (ICIs) have revolutionized the care for patients with metastatic cancer, with significant improvement in overall survival across several tumor types and different toxicity profiles than standard chemotherapeutic agents. ICIs are monoclonal antibodies that inhibit either cytotoxic T-lymphocyte-associated antigen 4 or programmed death (PD)-1/programmed death ligand (PD-L)-1, which prevents T-cell deactivation and promotes antitumor activity (1). These therapies are now standard treatment options across several cancer types including lung, melanoma, head and neck, and urological cancers. It is estimated that 20% to 30% of cancer patients respond very well to checkpoint inhibitor therapy (2). However, side effects can be unpredictable. They involve mainly the skin, lungs, gastrointestinal, and endocrine systems. Cardiovascular toxicities of ICIs include a wide spectrum of cardiovascular syndromes from atrial fibrillation, pericarditis/pericardial effusion, and subclinical or smoldering myocarditis to full-blown fulminant myocarditis.

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In this issue of *JACC: Case Reports*, Chahine et al. (3) report their experience of cardiac immune-related adverse effects (IRAE) in patients treated with ICIs at a large tertiary oncology and cardiovascular center. They identified 9 patients with myocardial or pericardial toxicity from a total of 2,830 patients who received ICIs. The first striking observation is the low observed frequency of cardiac adverse effects/complications (0.3% of the cohort). This is in keeping with data from a recent multicenter registry, where 1.1% of patients receiving ICIs developed myocarditis (4). The true incidence of cardiovascular side effects is unknown and likely underestimated because most cancer clinical trials did not systemically evaluate cardiovascular side effects. Most of the available published information is based on case reports and case series. Severe and fatal myocarditis is expected to occur in <1% of these patients; however, this may be an underestimation of the true incidence of milder forms of cardiotoxicity (5).

The second observation the authors identified was the varied and often nonspecific, atypical presentations of patients. Three major cardiac toxicities were identified by the authors: myocarditis, pericarditis, and cardiomyopathy. In addition, they found 5 of the 9 patients presented with other IRAEs, including myositis, myasthenia gravis, hepatitis, pancreatitis, hypothyroidism, and pneumonitis. Therefore, a low index of suspicion for cardiac IRAEs is required in patients receiving ICIs, particularly where other immune-related toxicities occur. The median time to clinical manifestation of cardiac IRAE is about 2 months, but it can occur as early as 2 days and as late as 15 months after initiation of therapy (6). The electrocardiogram (ECG) in these patients can show sinus tachycardia or atrial arrhythmia but also can be associated with advanced atrioventricular block. Cardiac biomarkers including troponins and brain natriuretic peptides are almost always elevated. Left ventricular systolic dysfunction is seen in many symptomatic patients, and cardiac magnetic resonance may show myocardial edema (6). Myocardial biopsy, considered to be the gold standard for the diagnosis of myocarditis in general, is a valuable

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diagnostic tool when available but is often avoided due to its invasive nature. More data are needed regarding the role of cardiac magnetic resonance imaging and myocardial biopsies as standard diagnostic tools in this setting. It is worth noting that accurate diagnosis of ICI-related myocarditis is critical in managing these patients. Stress/takotsubo cardiomyopathy is not uncommon in patients undergoing cancer therapy. Several of the patients in this case series could have been experiencing transient noninflammatory/takotsubo left ventricular systolic dysfunction and not necessarily myocarditis. Differentiating ICI toxicity from other forms of acute cardiomyopathy has a major impact in the acute and long-term management of these patients.

It is important to recognize cardiac IRAE promptly. In this series, 3 of the 6 patients with myocardial disease died. Patients may present or seek advice from a range of different health care providers, ranging from their general practitioner, oncologist, cardiologist, or a general internal medicine specialist. Increased awareness of possible cardiac IRAEs within these specialties is required for prompt recognition of these events. It is still unknown if there is any potential role for cardiac imaging or cardiac biomarkers in early detection of myocarditis. Limited clinical observations have led the Society for Immunotherapy of Cancer (7) and more recently the American Society of Clinical Oncology (8) to add ECG and troponin to their consensus recommendations on how to monitor these patients. The Society for Immunotherapy of Cancer recommendations can be summarized by obtaining ECG and troponin at baseline and then weekly for 6 weeks, especially in patients with known structural heart disease. They acknowledge this may not be a cost-effective approach but strongly encourage testing if cardiopulmonary symptoms develop (7).

Once recognized, cessation of ICI with initiation of high-dose steroids (prednisolone 1 to 2 mg/kg) is recommended (8). Guideline-directed therapy for patients with left ventricular impairment is also recommended. Response to steroids manifests as improvement in symptoms together with improvement in relevant cardiac structural abnormalities (left ventricular function/pericardial effusion/myocardial inflammation). In patients who do not respond to high-dose steroids, alternative immunosuppressants may be tried, although efficacy data in this setting are lacking.

ICI therapy has improved the survival and quality of life of patients with cancer. Ongoing phase III clinical trials in a range of cancer types is likely to mean an expanding range of indications. Therefore, although relatively rare, we can expect a greater number of patients to be at risk of cardiac IRAEs. The case series from Cleveland Clinic provides several clinical pearls that will be of use to all physicians who may be involved in the care of these patients. Despite being a rare event, catastrophic cardiovascular toxicity in the form of fulminant myocarditis related to checkpoint inhibitors is associated with high mortality. There are still many questions that need to be answered. At present, our understanding of risk factors, the most accurate diagnostic tools in confirming diagnosis and optimal management of cardiac IRAEs, is limited. In addition, identifying if a contributing effect of an antibody-mediated mechanism is present or if differences in T-cell subsets activated by different ICI molecules has any role in defining the severity of cardiovascular toxicity is important (9). Complications of ICI can affect almost any organ and often manifest as multiorgan involvement; consequently, collaboration among specialists is key to improving outcomes.

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REFERENCES

1. Lyon AR, Yousaf N, Battisti NML, Moslehi J, Larkin J. Immune checkpoint inhibitors and cardiovascular toxicity. Lancet Oncol 2018;19:e447–58.

2. Fernandes M, Brábek J. Cancer, checkpoint inhibitors, and confusion. Lancet Oncol 2017;18:e632.

3. Chahine J, Collier P, Maroo A, Wilson Tang WH, Klein AL. Myocardial and pericardial toxicity associated with immune checkpoint inhibitors in cancer patients. J Am Coll Cardiol Case Rep 2020;2:191–9.

4. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. J Am Coll Cardiol 2018;71:1755–64.

5. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med 2016;375:1749–55.

6. Escudier M, Cautela J, Malissen N, et al. Clinical features, management, and outcomes of immune checkpoint inhibitor-related cardiotoxicity. Circulation 2017;136:2085–7.

7. Puzanov I, Diab A, Abdallah K, et al., for the Society for Immunotherapy of Cancer Toxicity Management Working Group. Managing toxicities

associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer 2017;5:95.

8. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2018;36:1714–68.

9. Wei SC, Levine JH, Cogdill AP, et al. Distinct cellular mechanisms underlie anti-CTLA-4 and anti-PD-1 checkpoint blockade. Cell 2017;170:1120–33.e17.

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