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EDITORIAL COMMENT

Cardiovascular and Oncological Outcomes in Immune Checkpoint Inhibitor–Induced Myocarditis

Balancing Perspectives*

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Immune checkpoint inhibitors (ICIs) have revolutionized the therapeutic landscape for various malignancies.[1] However, potential immune-related adverse events (irAEs) raise concern. The incidence of ICI-induced myocarditis is approximately 1% but with a fatality rate among the highest of any reported irAEs.[2] Because of the exponential increases in indications for and prescription of ICIs, an increasing number of patients with cancer are at risk for ICI-induced myocarditis.[3,4]

The research by Itzhaki Ben Zadok et al[5] presented in this issue of *JACC: CardioOncology* addresses a critical knowledge gap regarding long-term contemporary outcomes in patients with ICI-induced myocarditis across the spectrum of clinical severity. In this retrospective cohort study, including 160 patients seen at Mass General Brigham with suspected ICI-induced myocarditis between 2015 and 2022, the authors examined the characteristics of patients with severe and nonsevere ICI-induced myocarditis and evaluated cardiovascular mortality, all-cause mortality, and cardiovascular readmissions. In addition, resumption of ICI therapy and left ventricular ejection fraction over a median follow-up period of 18 weeks (Q1-Q3: 8-67 weeks) were also assessed.

The investigators classified the spectrum of clinical severity for ICI-induced myocarditis into severe, nonsevere, and negative categories according to the International Cardio-Oncology Society criteria, which involve hemodynamic instability, heart failure necessitating noninvasive or invasive ventilation, complete or high-degree heart block, and/or significant ventricular arrhythmias. However, the lack of consensus and universal definitions of the clinical classification of ICI-induced cardiotoxicity is notable. For example, we believe that ICI-induced myocarditis might also be categorized as mild, severe, and critical on the basis of the results of clinical, biological, and imaging investigations. This classification of ICI myocarditis varies slightly across European Society of Cardiology, American Society of Clinical Oncology, and other oncologic guidelines.[6-8] The impact of the severity of myocarditis treatment and cancer therapy discontinuation are also factors to be considered in defining and understanding the significance of myocarditis.

In this study by Itzhaki Ben Zadok et al,[5] patients with severe myocarditis had an increased risk for cardiovascular mortality compared with their counterparts with nonsevere disease, yet this effect was limited to the early postmyocarditis period (29% vs 5%; HR: 6.52; 95% CI: 2.2-19.6; $P < 0.001$). Meanwhile, 1-year all-cause mortality did not differ among severe, nonsevere, and negative cases ($P = 0.74$). As shown in the investigators' Figure 2, the majority of cardiovascular deaths occurred within 60 days following the diagnosis of myocarditis, regardless of the patient group. Because of the high mortality rate during the acute phase of myocarditis,[9] we speculate

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that this contributes significantly to the comparable all-cause mortality observed across the patient subgroups. However, as information regarding details of cancer-specific survival and the specific causes associated with noncardiovascular deaths is not available in the present study, the contributions of other factors, including cancer disease progression, to the increased all-cause mortality among patients with nonsevere myocarditis is not clear.

Currently, permanent discontinuation of ICI therapy is generally recommended for grade 4 irAEs. The decision to resume ICI treatment after grade ≥2 irAEs often remains challenging. In this study, ICI resumption was low (7% in patients with severe myocarditis and 13% in those with nonsevere myocarditis), even among negative cases. To rechallenge or not is a dilemma every clinician and patient faces after severe irAEs have resolved. As detailed by the guidelines, patients who experience ICI-induced myocarditis are not typically rechallenged, because of its life-threatening nature. However, ICI discontinuation may be detrimental to cancer control.[10] This is an important consideration, as ICI-based therapy may be potentially lifesaving from an oncologic perspective.

Previous research shows that patients with irAEs tend to have a better overall treatment response and survival.[11] This contradiction arises from the "long-tail effect" associated with ICIs and is perhaps related to a greater therapeutic response.[11,12] Similarly, Itzhaki Ben Zadok et al[5] demonstrated that the majority of patients without ICI resumption succumbed to disease progression, especially among those with nonsevere myocarditis. Watson et al[13] demonstrated that among carefully selected patients who have recovered from significant irAEs, ICI resumption is not only safe but may improve survival outcomes. A prospective assessment of the potential safety of resuming ICI therapy, with close monitoring of any recurrent myocarditis, is an area of important future research. Moreover, the field calls for a meticulous evaluation in each individual patient by the multidisciplinary care team. This collaborative effort will help further define optimal strategies for care.

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