EDITORIAL COMMENT

Immune Checkpoint Inhibitor–Related Cardiovascular Toxicity in Lung Cancer

Is Routine Screening Indicated?*

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With widespread use of immune checkpoint inhibitors (ICI), a variety of immune-mediated cardiac toxicities are increasingly recognized and reported. ICI-associated myocarditis generally occurs within 3 months of treatment initiation, with a median time of 17 to 65 days after initial dose of ICI (1); delayed cardiac toxicities have also been reported (2). In addition to immune-related myocarditis, cardiovascular toxicities linked with ICI include pericardial disease, vasculitis, arrhythmias and heart failure (3). In this issue of *JACC: CardioOncology*, Chitturi et al. (4) report results from a cohort study of 252 patients with lung cancer. Patients treated with ICI had a small, but nonsignificant, increase (13.3% vs. 10.3%) in the incidence of major adverse cardiac events (MACE), defined as a composite endpoint composed of cardiovascular death, nonfatal myocardial infarction or stroke, or heart failure hospitalization compared with patients treated with non-ICI regimens. The groups were reasonably well balanced; there were more patients with prior myocardial infarction in the group treated with ICI and more patients with diabetes, chronic kidney disease, and small cell lung cancer in the non-ICI group. Elevated troponin and B-type natriuretic peptide (BNP) levels at baseline or during ICI therapy correlated with the risk for MACE (hazard ratio: 7.27; 95% confidence interval: 2.72 to 19.43) with elevated troponin; hazard

ratio: 2.65; 95% confidence interval: 1.01 to 6.92 with elevated BNP). A dose-dependent relationship with ICI and differences in MACE incidence based on baseline patient characteristics or type of ICI-containing regimens were not found, although these types of analyses were limited by small sample size. As the investigators suggest, a dose-response relationship is not expected, on the basis of the mechanism of ICI effect, which is largely independent of drug dosing. The investigators conclude correctly that further studies are needed to determine whether cardiac biomarkers such as troponin and BNP are useful as part of a monitoring strategy with ICI therapy. Can the results of this study provide insights into the next steps in prevention, monitoring, and management of cardiac immune-related adverse events? With a relatively small sample size and a heterogeneous population consisting of lung cancer patients with multiple histology types, the risks of multiple comparisons and opportunities for type I error must be considered in interpreting their conclusions.

Even though Chitturi et al. (4) found no statistically significant association of ICI with MACE, this small study is not evidence for an absence of an association of ICI with cardiac toxicity. Indeed, a number of other recent large retrospective studies do suggest quite convincingly that cardiac toxicity from ICI does occur (1,5-8). Large trials of ICI monotherapy in non-small cell lung cancer, which did not routinely check cardiac biomarkers before or during treatment, reported rates of cardiac immune-related adverse events of <1% for pembrolizumab (9), nivolumab (10), and atezolizumab (11). By contrast, a large retrospective meta-analysis including >20,000 ICI-treated patients reported that 9.8% of treatment-related deaths were

from cardiovascular events, including heart failure, myocardial infarction, and cardiomyopathy, suggesting the possibility of a much higher incidence of cardiac side effects (8). Although under-reporting and under-recognition likely played a role in the low reported numbers of cardiac toxicities in the prospective clinical trials, cardiovascular immune-related adverse events are still considered rare events, with myocarditis rates ranging from <0.1% in pharmaceutical safety databases (6) to 1.14% in multi-institutional experiences (7). Slightly higher rates are seen in patients treated with dual checkpoint blockade (e.g., ipilimumab and nivolumab), but further investigations are needed to assess cardiac risks associated with combination therapies. In the current study, fewer than 10 patients received dual checkpoint blockade, limiting any conclusions that can be drawn for this group of patients. Many patients with advanced lung cancer now receive combination chemotherapy with ICI therapy; registration trials for ICI chemotherapy combinations did not report an increased rate of cardiac toxicities (12,13). However, in a trial of durvalumab after chemoradiotherapy in patients with stage III non-small cell lung cancer, adverse cardiac events were reported in 21 patients (4.4%) (14).

Growing concerns about serious cardiac complications, such as immune-related myocarditis, with mortality rates reported from 36% to 67% (5), have led to proposals for routine patient screening with the goal of early detection in an asymptomatic phase. Very few institutions use standardized pathways for screening and managing immune-related cardiac toxicities, however, and guidelines from the American Society of Clinical Oncology do not recommend serial cardiac biomarker testing (15). Current guidelines from the Society of Immunotherapy in Cancer recommend baseline electrocardiograms and consideration of troponin testing, especially for patients initiating combination immune therapies, which may confer higher risk for cardiac toxicities, but do not recommend additional cardiac examinations such as echocardiogram, BNP, and stress tests unless indicated by signs and symptoms (15).

The presumed benefits of early detection of cardiac complications through active screening with serial electrocardiograms, troponins, and BNPs must be weighed against the cost of testing as well as the risk of false positives and misinterpretation of abnormal laboratory testing. For instance, elevated troponin levels in patients with advanced cancer are far more likely to represent myocardial ischemia, chemotherapy or radiation-induced cardiotoxicity, or even noncardiac disorders rather than immune-related myocarditis (16). Similarly, BNP can be elevated in patients with cancer just by virtue of underlying cancer-related inflammation (17). Collaboration between oncologists and cardiologists or cardio-oncologists is essential to evaluate the likelihood of true immune-related cardiac toxicity in a given patient. Isolated elevated biomarker test results, unless found in a suggestive clinical context, should not prompt discontinuation of ICI therapy (16). The decision to discontinue ICI is not a trivial one, given that ICI represents many patients' best therapeutic option, with highly meaningful long-term survival benefit in a minority of patients. In cases of Grade 1 or higher ICI-related cardiac toxicity, American Society of Clinical Oncology guidelines recommend permanent discontinuation of ICI and initiation of high-dose corticosteroids (15).

At this time, there are insufficient data to support any recommendations for *routine* testing of troponin and BNP in patients undergoing or about to undergo ICI therapy. One potential use of an elevated baseline biomarker such as troponin might be to inform a closer monitoring strategy that incorporates additional laboratory and imaging modalities, but not to disqualify a patient from receiving immune therapy. Even this use of baseline troponin and BNP data is speculative and will require prospective data collection for validation.

Although it is neither feasible nor advisable at this time to conduct baseline cardiac screening on every patient starting ICI therapy, efforts are certainly needed to determine which patients may be at highest risk for developing immune-related cardiac toxicities, and to consider focusing screening and management efforts on this group with the higher pretest probability of toxicity. Are patients with a history of chest radiation therapy, established cardiovascular disease, poorly controlled cardiovascular risk factors, or other (to be determined) immune-related biomarkers at higher risk for toxicity? In the Chitturi et al. (4) study, troponin and BNP levels at baseline or during initial ICI therapy were associated with increased MACE risk. Further study is needed to address these markers as a useful screening tool for cardiac toxicity risk. Ultimately, larger patient cohorts will be needed to estimate the true incidence of immune-related cardiac events, evaluate potential predictors to define higher-risk subgroups, and refine screening and management strategies. Although improved detection and management of

immune-related cardiovascular events are important, additional prospective evidence is needed before we can adopt routine cardiac screening in unselected patients starting ICI therapy. We also strongly recommend the involvement of cardiologists or cardio-oncologists in the interpretation of elevated markers of cardiac injury in patients being treated with ICI.

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REFERENCES

1. Ganatra S, Neilan TG. Immune checkpoint inhibitor-associated myocarditis. Oncologist 2018; 23:879-86.

2. Kanjanapan Y, Day D, Butler MO, et al. Delayed immune-related adverse events in assessment for dose-limiting toxicity in early phase immunotherapy trials. Eur J Cancer 2019;107:1-7.

3. Hu JR, Florido R, Lipson EJ, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors. Cardiovasc Res 2019;115:854-68.

4. Chitturi KR, Xu J, Araujo-Gutierrez R, et al. Immune checkpoint inhibitor-related adverse cardiovascular events in patients with lung cancer. J Am Coll Cardiol CardioOnc 2019;1:182-92.

5. Brumbaugh AD, Narurkar R, Parikh K, Fanucchi M, Frishman WH. Cardiac immune-related adverse events in immune checkpoint inhibition therapy. Cardiol Rev 2019;27:97-107.

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

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

8. Wang Y, Zhou S, Yang F, et al. Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: a systematic review and meta-analysis. JAMA Oncol 2019;5:1008-19.

9. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019;393:1819-30.

10. Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 2017;376:2415-26.

11. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255-65.

12. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018; 378:2078-92.

13. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 2018;379: 2040-51.

14. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 2017;377: 1919-29.

15. 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.

16. Spallarossa P, Tini G, Sarocchi M, et al. Identification and management of immune checkpoint inhibitor–related myocarditis: use troponin wisely. J Clin Oncol 2019;37:2201-5.

17. Bando S, Soeki T, Matsuura T, et al. Plasma brain natriuretic peptide levels are elevated in patients with cancer. PLoS One 2017;12:e0178607.