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EDITORIAL COMMENT

Inflammatory Biomarkers to Detect Immune Checkpoint Inhibitor-Associated Cardiotoxicity in Lung Cancer Patients

Ready for Prime Time?*

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Lung cancer is the leading cause of cancer-related death in the United States and worldwide. Non-small cell lung cancer (NSCLC) represents nearly 80% of all lung cancer cases, with most of these cases diagnosed at an advanced stage (1). Although targeted therapies have redefined treatment options for patients with molecularly defined NSCLC (e.g., epidermal growth factor receptor [EGFR] mutant and anaplastic lymphoma kinase [ALK]-rearranged NSCLC), these therapies are ineffective in those whose tumors lack such genetic alterations. Immune checkpoint inhibitors (ICI) harness the immune system and have emerged as novel treatment options for patients with locally advanced or metastatic lung cancer (2). This approach has resulted in improved survival and a more favorable toxicity profile than conventional chemotherapy.

ICI target immune "brakes," systematically activating of immune cells, particularly T lymphocytes, and providing antitumor responses. ICI include antibodies against programmed cell death receptor (PD-1), programmed cell death ligand (PD-L1), and cytotoxic T-cell lymphocyte antigen 4 (CTLA-4). However, ICI treatment can result in immune-related adverse events (irAEs) targeting any organ. Cardiovascular irAEs, particularly myocarditis, have received considerable attention due to their potentially fatal outcome (3,4). ICI were initially tested and approved as single therapy in patients with metastatic melanoma, a cancer type that historically had few treatment options and poor survival (5). Later, these therapies were tested in patients with lung cancer and renal cell carcinoma (6,7). In the latter studies, ICI were tested either in combination with or following exposure to classic chemotherapies or targeted therapies. As a result, there was a growing need to define the cardiovascular sequelae in lung cancer patients treated with ICI, where the cardiovascular risk was complicated by exposure to cardiotoxic non-immune-based cancer therapies and a high prevalence of conventional cardiovascular risk factors (8). There was also a need to identify biomarkers or imaging approaches that screened for early cardiotoxic effects from immunotherapy and to identify patients at risk who would benefit from closer monitoring (9).

Based on this rationale, in this issue of *JACC: CardioOncology*, Moey et al. (10) performed a retrospective analysis of lung cancer patients who received ICI therapy at a single medical center from 2015 to 2018. The authors defined major adverse

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cardiac events (MACE) following ICI therapy as: 1) non-ST-segment elevation myocardial infarction (NSTEMI); 2) new onset supraventricular tachycardia (SVT); 3) myocarditis; and 4) pericardial disorders. Among their overall cohort of 196 patients, 23 patients (11%) developed MACE, including 9 patients with "possible" myocarditis, 3 with NSTEMI, 7 with SVT, and 4 with pericardial disorders. The investigators hypothesized that baseline inflammatory state, as measured by a neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP), would be higher in patients with MACE than those without. Indeed, baseline NLR was elevated in patients who developed MACE compared to those without MACE, as well as those without other irAEs. There were no differences between baseline CRP concentrations among the groups. Both NLR and CRP at the time of MACE were significantly increased from baseline values. Based on those findings, the authors concluded that NLR and CRP may be useful in the screening and diagnosis of MACE in patients with lung cancer treated with ICI.

Cardiovascular toxicities after ICI therapy in lung cancer patients have not been well described, so the authors should be congratulated on completing this study. However, there are a number of limitations with phenotyping this cohort (11). First, the authors used a broad and nonstandard definition of MACE, which conventionally has been defined as cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure (12). In this case, the authors defined MACE as myocarditis, NSTEMI, pericardial disease, or SVT and assumed those endpoints all represented immune-related cardiotoxicities. Although myocarditis has an immune-related pathophysiology and an established and biologically plausible complication of ICI treatment, that may not be the case for isolated myocardial infarction or SVT. It was also unclear if the same underlying biomarkers would predict these inherently different disease processes. Also concerning was the lack of application of standard diagnostic modalities to diagnose myocarditis. Of the 9 patients who developed myocarditis, none underwent tissue characterization using cardiac magnetic resonance imaging or biopsy to confirm the presence of myocardial inflammation (13). Whether the patients truly had myocarditis remains unclear. It is worth noting that, although all 9 myocarditis cases in this study only met "possible" criteria, suspected cases could still meet "probable" or "definite" myocarditis criteria without advanced imaging through a robust standard cardiac workup (13). Similarly, pericardial diseases may represent pericarditis, which may be immune-related, or pericardial effusion, which is related to the cancer itself. Radiation therapy prior to immunotherapy has been postulated to prime an endogenous antigen-specific immune response; however, this "double hit" may make lung cancer patients more susceptible to pericardial disorders (14). Prior analysis of VigiBase (World Health Organization, Basel, Switzerland), the WHO's global Individual-Case-Safety-Report database, suggested that pericardial disorders were overrepresented in patients receiving anti-PD-1/PD-L1 therapy for lung cancer (15). In the present study, the incidence of pericardial disorders in an exclusive lung cancer cohort was lower than expected (2%). Whether the pericardial disorders reported were driven by immune toxicity or complications from malignancy needs further clarification. The lack of standardization in methods and quality assurance in evaluating cardiovascular irAEs represents a major need for the field of cardio-oncology.

The second issue is the lack of adjustments for confounders and the need for a multivariable analysis. The authors were interested in evaluating commonly obtained inflammatory markers as diagnostic tools for identifying and monitoring irAEs. In the present study, NLR and CRP levels were retrospectively evaluated at baseline and at the time of MACE. Although these assays are routinely available and inexpensive, elevations in NLR and CRP were not demonstrated to be specific to cardiovascular irAEs. Univariable analysis showed that baseline NLR was indeed statistically different among patients with MACE compared to patients without MACE. However, most baseline laboratory values, including hemoglobin, white blood cell counts, platelets, and creatinine levels were also significantly different between the 2 groups. By not adjusting for potential confounders, including any hematological markers, the specificity of baseline NLR in predicting ICI-associated irAE is unclear. Indeed, for NLR or CRP to emerge as important biomarkers, a multivariable analysis would be a more appropriate approach. This is especially relevant in this cohort where the use of higher doses of steroid in the MACE group (78% vs. 35%, respectively; $p < 0.001$) could be the primary driver of neutrophil demargination and elevated NLR. The authors admit that CRP has been previously shown to be elevated in their population presenting with ICI-related pneumonitis, and NLR was elevated in patients that developed noncardiac irAEs. Thus, the search for a specific biomarker indicative of cardiac irAEs continues and likely requires a prospective clinical trial.

In summary, the characterization of cardiovascular toxicity among lung cancer patients receiving

immunotherapy represents an important contribution to the field of cardio-oncology. As the indications for immunotherapy continue to expand, the need to understand the risk factors for the development of potentially life-threatening cardiovascular toxicities arising from immunotherapy is imperative. Although inflammatory biomarkers may be associated with the development of MACE, it remains to be determined whether these markers are specific enough to change life-prolonging immunotherapy treatment strategies.

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