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RESEARCH LETTER

Myocarditis Surveillance With High-Sensitivity Troponin I During Cancer Treatment With Immune Checkpoint Inhibitors

Myocarditis is a serious adverse event from immune checkpoint inhibitors (ICIs) (1,2). We implemented surveillance for ICI-associated myocarditis at Stanford Cancer Institute. Myocarditis surveillance was performed in 214 patients on ICI monotherapy or combination therapy over 9 months. High-sensitivity troponin I (hsTnI) was measured in plasma at baseline and every 2 to 4 weeks with each ICI cycle up to 10 cycles using the Siemens Dimension-EXL (Siemens, Newark, Delaware) (3). A positive hsTnI was defined as ≥55 ng/l and negative as <55 ng/l (99th percentile concentration for general population). Patients with positive hsTnI were evaluated by a multidisciplinary cardio-oncology team (**Figure 1**). Per consensus-based definitions, myocarditis was diagnosed by clinical syndrome, biomarkers, magnetic resonance imaging (MRI), and coronary angiography (4). Clinical outcomes were assessed. Number needed to test (NNT) was determined by dividing the study cohort by the number of myocarditis cases. Negative predictive value (NPV) was calculated as the proportion of patients without myocarditis among all patients with negative hsTnI, and positive predictive value (PPV) as the proportion of myocarditis cases among all patients with positive hsTnI, according to various hsTnI thresholds. Stanford Institutional Review Board approval was obtained.

Two-hundred fourteen patients were monitored from September 2019 to June 2020. Before ICI therapy, 101 (47.2%) had a baseline hsTnI; 113 patients had started ICI before our cardiotoxicity surveillance algorithm. Malignancies included non-small cell lung cancer (33.6%), renal cell carcinoma (17.8%), and melanoma (16.4%). ICIs included programmed death 1 (78.5%), programmed death ligand 1 (16.8%), and programmed death 1/cytotoxic T lymphocyte-associated protein 4 (9.8%) inhibitors. Median ICI doses/patient was 6 (range, 1 to 10 doses). In total, 1,274 hsTnI measures were obtained over a median follow-up of 5.2 months (range 0.2 to 13.6 months).

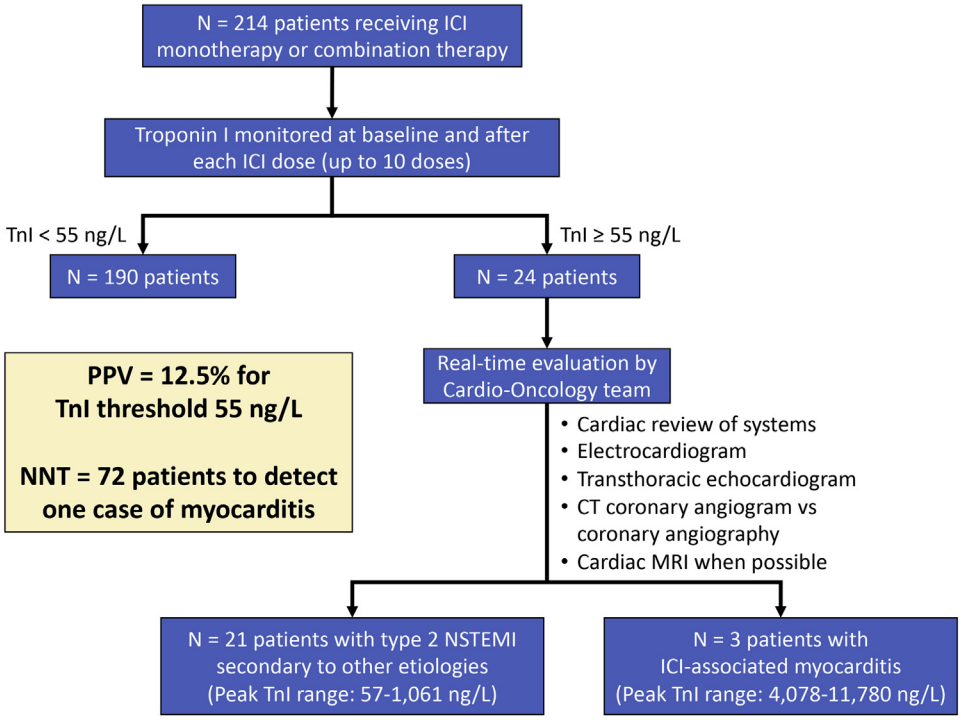
Of 24 (11.2%) patients with a positive hsTnI, 3 had myocarditis (incidence: 1.4%) by consensus-based definitions (4). In the other 21 patients, positive hsTnI was attributed to cardiovascular causes other than myocarditis (e.g., type II myocardial infarction). Using hsTnI thresholds 55, 1,000, or 2,000 ng/l, the PPV for myocarditis was 12.5% (95% confidence interval [CI]: 0% to 26%), 75.0% (95% CI: 33% to 100%), and 100% (95% CI: not available [N/A]), respectively; NPV was 100% (95% CI: N/A) at each threshold. NNT to detect one case was 72 patients.

Of 21 patients with positive hsTnI not attributed to myocarditis, 3 (14.3%) had a subsequent ICI delay due to abnormal hsTnI. Three (14.3%) were referred to the emergency department. Abnormal hsTnI prompted 11 (52.4%) cardiology referrals and 5 (23.8%) cardiovascular risk-reducing medications. Supraventricular tachycardia occurred in 5 patients, including 1 with myocarditis. No patients developed a decreased left ventricular ejection fraction (LVEF) <55% or absolute decrease ≥10%.

The first myocarditis case was an asymptomatic 76-year-old male with stage III lung adenocarcinoma with hsTnI 1,232 ng/l (peak: 10,394 ng/l) 8 weeks after durvalumab initiation. His transthoracic echocardiogram (TTE) showed an LVEF of 59% and new inferior/posterior hypokinesis; his electrocardiogram was without ischemic changes; his MRI showed basal anterolateral wall delayed gadolinium enhancement; and his computed tomography angiogram was without coronary disease. Based on MRI and hsTnI, he was diagnosed with probable myocarditis (4). He received prednisone 1 mg/kg per day (5-week taper). ICI therapy was discontinued. His cardiac MRI at 3 months was stable. One year after ICI discontinuation, he is without cardiovascular complications or cancer recurrence.

The second case was a 67-year-old female with metastatic renal cell carcinoma with hsTnI 5,890 ng/l (peak: 11,780 ng/l) 2 weeks after nivolumab/ipilimumab initiation. She reported dyspnea without chest pain. The diagnostic workup included an electrocardiogram without ischemic changes; a creatine kinase level of 1,242 U/l (7.4 times above the upper limit of normal [ULN]); a TTE with LVEF at 65% with normal

FIGURE 1 Myocarditis Surveillance Algorithm



HsTnI-based myocarditis surveillance with a multidisciplinary cardio-oncology team and outcomes, CT = computed tomography; HsTnI = high-sensitivity troponin I; ICI = immune checkpoint inhibitor; MRI = magnetic resonance image; NNT = number needed to test; PPV = positive predictive value; TnI = troponin I.

wall motion; and coronary angiography without obstructive disease. A cardiac MRI was not performed due to altered mental status. Based on symptoms, hsTnI, and negative coronary angiogram, she was diagnosed with possible myocarditis (4). ICI therapy was discontinued. She received a prolonged dexamethasone taper with mental status recovery after 4 months. Eight months after ICI discontinuation, she is without cardiovascular complications or cancer recurrence.

The third case was an 82-year-old male with chronic kidney disease and locally advanced urothelial carcinoma with hsTnI 4,078 ng/l 15 weeks after pembrolizumab initiation. He reported chest pain and dyspnea. Inpatient diagnostic workup included an electrocardiogram showing an incomplete right bundle branch block (baseline); TTE with LVEF 66% with normal wall motion; coronary angiography with non-obstructive coronary disease; and cardiac MRI with delayed gadolinium enhancement in nonvascular distribution. Based on the MRI, hsTnI, and symptoms, he was diagnosed with definite myocarditis (4). He received 2 days of methylprednisolone 1 mg/kg/day followed by prednisone 1 mg/kg/day with a 5-week taper. Five months after ICI discontinuation, he remained without cardiovascular complications or cancer recurrence but died from ischemic stroke.

To our knowledge, this is the largest published prospective study of ICI-associated myocarditis surveillance. Surveillance prompted myocarditis evaluation in 3 patients, leading to timely diagnosis/treatment. No adverse cardiovascular outcomes occurred after management. Cardiology expertise was essential in adjudicating myocarditis. A cardio-oncology team facilitated timely response to each positive hsTnI case, enabling a low rate of ICI delays.

HsTnI levels in the 3 cases of myocarditis were >20-times above ULN at diagnosis. Peak hsTnI ranged from 4,078 to 11,780 ng/l (74 to 214 times above ULN) with myocarditis and 57 to 1,061 ng/l (1.04 to 19.3 times above ULN) without myocarditis. Using 55 ng/l as a cutoff, the PPV of positive hsTnI for myocarditis was 12.5%. Using 1,000 or 2,000 ng/l, hsTnI had PPVs of 75.0% and 100%, respectively, suggesting utility of a higher hsTnI threshold for ICI-associated myocarditis. Although three-quarters of myocarditis cases

are identified by dose 2 to 3 (2), cases occurred up to dose 5. Two cases occurred with single-agent ICI therapy.

Our cohort remains small; only half had baseline hsTnI because we included patients who had already started ICI therapy. Calculating NPV was limited by lack of imaging in patients with negative hsTnI and low suspicion for myocarditis. We favored cardiac MRI (with or without negative coronary angiography and clinical correlation) over endomyocardial biopsy in the setting of clinical response to steroids without cardiogenic shock (4).

As ICI use increases, cardio-oncology teams may serve to facilitate myocarditis surveillance. Given the high case fatality rate of ICI-associated myocarditis, data are needed to evaluate benefits of earlier identification and intervention. Our findings show feasibility of monitoring hsTnI to detect myocarditis, potentially diminishing subsequent cardiovascular events. Additional studies are needed before recommending biomarker surveillance as standard of care.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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