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Myocarditis Surveillance in Patients with Advanced Melanoma on Combination Immune Checkpoint Inhibitor Therapy: The Memorial Sloan Kettering Cancer Center Experience

The consensus document from the Checkpoint Inhibitor Safety Working Group identified monitoring strategies as a key information gap in the realm of immune checkpoint inhibitor (ICI)-associated myocarditis [1]. Given its potentially fulminant course, experts have proposed screening algorithms using serial troponin (Tn) and/or electrocardiogram (ECG) for early detection of subclinical disease and prompt initiation of therapy to potentially mitigate cardiac morbidity and mortality [2–4].

We evaluated screening troponin I (TnI) and ECG in 76 asymptomatic patients with advanced melanoma undergoing combination ICI therapy with ipilimumab and nivolumab. Baseline and weekly TnI/ECG were obtained until the second dose, corresponding to the typical timing of onset, for a maximum of four samples. Outcomes of interest were myocarditis, major adverse cardiac events (MACE), and all-cause mortality.

The median age was 65 years (interquartile range 57–70), with 45 (59.2%) male patients. The prevalence of coronary artery disease, hypertension, hypercholesterolemia, and diabetes mellitus was 10.5% (n = 8), 40.8% (n = 31), 34.2% (n = 26), and 13.2% (n = 10), respectively. Thirty-one (40.3%) patients had previously received ICI therapy, one (1.3%) with doxorubicin and three (3.9%) mediastinal radiation. Over half (n = 49, 64.5%) developed noncardiac immune-related adverse events, of which 37 received corticosteroids at some point during the course of combination ICI therapy.

Over a median of 198 days, none of the 76 patients developed clinical or subclinical myocarditis or MACE. All deaths (n = 17, 22.4%) were cancer related. Additionally, none had elevated TnI levels (>0.64 ng/mL) or ECG abnormalities. Minimally detectable nondiagnostic TnI levels (≥0.01 ng/mL and <0.06 ng/mL) were seen in 13 (17%) patients only after adoption of a higher sensitivity assay (Table 1). At the time of detectable TnI, all remained asymptomatic and hemodynamically

Table 1. Detectable troponin I case description

Case	TnI, ng/mL	Timing	Clinical history	Presentation during detectable TnI	Steroids during detectable TnI	ICI discontinuation (reason)	Melanoma outcome
1	0.02	Baseline	HTN, HL, CCa, former smoker	Asymptomatic	No	No[a]	Response
2	0.01	Day 9	CAD, HTN, HL, former smoker	Asymptomatic	No	Yes[a] (immune-related colitis)	Partial response
3	0.02 0.01	Baseline; Day 7	HTN, CCa, former smoker	Night sweats, cough, dyspnea, bronchial obstruction; Fevers, pneumonia	No	No[a]	Response
4	0.03	Day 21	HL, CCa	New dermatitis	No	Yes[a] (immune-related hepatitis)	Response
5	0.02	Day 21	None	Asymptomatic	No	No[a]	Response
6	0.01 0.02	Day 14; Day 21	HL	Asymptomatic; Transient PR segment prolongation on ECG (212 msec)	No	Yes[a] (immune-related hypophysitis and hepatitis)	Response
7	0.02[b]	Baseline, weekly	HTN, CCa, CKD, former smoker	Asymptomatic	No	No[a]	Response
8	0.02[c] 0.04	Baseline, weekly; Day 21	Former smoker, prior ICI	Asymptomatic; New dermatitis and disease progression	Yes, brain and spine metastases	Yes[a] (disease progression)	Progression, death
9	0.04	Day 21	HTN, prior combination ICI	Lower extremity weakness	Yes, orbital metastases	Yes (disease progression)	Progression
10	0.02	Baseline	None	Asymptomatic	No	Yes[a] (disease progression)	Progression
11	0.02	Day 21	HTN	Left hemiparesis, brain metastasis	Yes, brain metastasis	Yes[a] (response)	Response
12	0.01	Day 21	HTN, HL, postrenal transplant, prior ICI	Acute kidney injury, progression of liver metastases	Yes, post-transplant antirejection	Yes[a] (disease progression)	Progression
13	0.01	Day 21	HL	Asymptomatic transaminitis	Yes, transaminitis	Yes[a] (disease progression)	Progression

[a]Received additional ICI dose after detectable TnI.
[b]Weekly levels at 0.02 ng/mL.
[c]Weekly levels at 0.02 ng/mL until day 21 check.
Abbreviations: CAD, coronary artery disease; CCa, coronary calcium on chest computed tomography; CKD, chronic kidney disease; ECG, electrocardiogram; HL, hyperlipidemia; HTN, hypertension; ICI, immune checkpoint inhibitor; TnI, troponin I.

stable, and complementary testing not limited to serial TnI/ECGs did not identify any obvious acute cardiac and/or systemic pathology. At follow-up, 11 patients had undetectable TnI, and two had nontrending levels. There was no association between detectable TnI and all-cause mortality. Twelve of 13 received further ICIs without cardiac events, and one discontinued ICI therapy because of disease progression.

This is the first report on myocarditis screening among patients undergoing combination ICI therapy. Despite inclusion of a higher-risk cohort, none of our patients developed myocarditis. We also demonstrated that ICIs can be safely continued in asymptomatic, hemodynamically stable patients with minimally detectable TnI levels after careful consideration of the clinical context. Likewise, the study by Sarocchi et al. of 59 patients undergoing serial TnI checks during nivolumab monotherapy had one patient with presumed subclinical myocarditis who tolerated continued ICI therapy without cardiac events [5]. These minor non-diagnostic TnI levels could cloud diagnostic judgment, initiate unnecessary downstream testing and treatments, and interfere with the course of potentially life-saving cancer treatment. As more institutions adopt higher sensitivity assays, there is a trend toward increased Tn detection at a loss of discriminatory capacity, without improvement in short-term cardiovascular outcomes [6, 7].

Our study is reflective of the low prevalence of ICI-associated myocarditis and, therefore, low screening yield. However, it is possible that a larger study with improved risk stratification and patient selection could prove some utility for TnI/ECG screening.

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