Clinical, Diagnostic and Pathologic Features of Immune Checkpoint Inhibitor-Induced Cardiotoxicity

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BACKGROUND

- Immune checkpoint inhibitors (ICI) have revolutionized outcomes of cancers with traditionally poor survival.
- With growing use of ICIs in clinical practice, evidence of cardiac immune-related adverse events (CV-irAEs) has surfaced.
- However, little is known about the clinicopathologic characteristics of CV-irAEs.

METHODS

- A systematic review of the literature was conducted to identify case studies of CV-irAEs associated with ICI use.
- Individual case reports and case series were summarized, and descriptive statistics were employed to report clinicopathologic outcomes.

RESULTS

- Screening 15,092 studies yielded 44 cases, 52.2% of whom were males, with a mean age of 63.4.
- The median time to irAE onset was 47.5 days (8-365 days; ≤180 days in 93.2%) from initiation of ICI therapy, after a mean of 3.3 (SD 2.2) ICI cycles.
- The most common CV-irAEs reported were myocarditis (68.2%), followed by pericarditis (9.1%), and cardiac tamponade (4.6%).
- Myocarditis had an earlier onset from ICI initiation, compared to pericarditis (median 30 days vs 129 days; Figure 1 & Table 1).
- The most common presenting symptoms were dyspnea (45.5%) and chest pain (27.3%).
- Myocardial biopsy was performed in 15 patients with myocarditis; 93.3% had a lymphocytic infiltrate, whereas 26% of these biopsies revealed myocyte necrosis.

Figure 1. Time to Onset of Myocarditis and Pericarditis From First Immune-Checkpoint Inhibitor Infusion

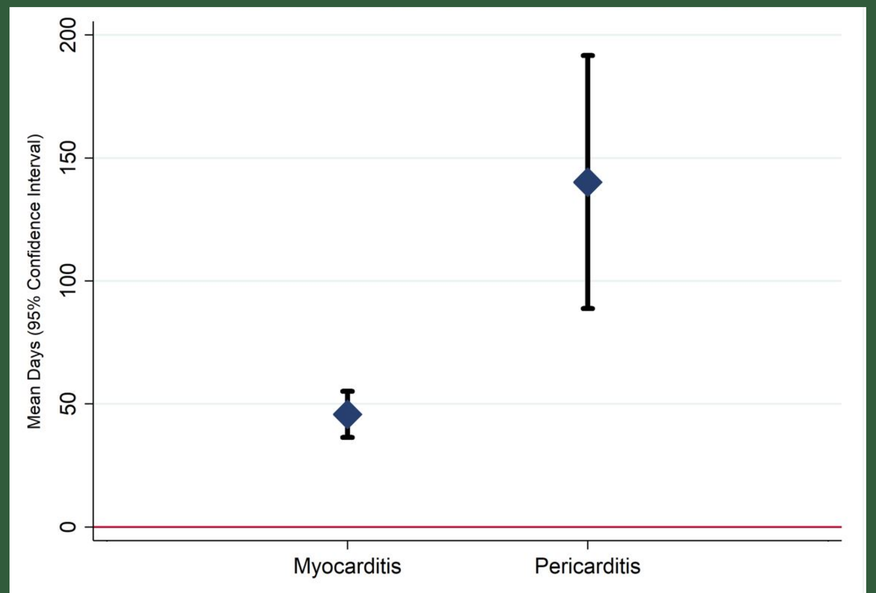

Table 1. Characteristics of Patients with Myocardial and Pericardial irAEs

	Myocarditis	Pericarditis
Patients, n (%)	30 (68.2)	4 (9.1)
Age, mean (SD)	61.7 (SD=10.3)	60.4 (SD=3)
Duration from ICI to irAE, Median (Range)	30 (8 - 113)	129 (42 - 252)
Chest pain, n (%)	6 (20)	3 (75)
Dyspnea, n (%)	14 (46.7)	2 (50)
Tamponade	0	0
ICI used, n	Nivolumab = 12 Ipilimumab =2 Pembrolizumab = 3 Pemb+Ipi+Nivo =1 Ipi+Nivo =11 Atezolizumab =1	Ipilimumab =3 Nivolumab =1
Treatment	Steroids=26 Infliximab=4 IVIG=1 IVIG +plasmapheresis=3	Steroids =4
Death, n (%)	Death=10 (33.3) Hospice=4 (13.3)	0

Pemb=pembrolizumab, Ipi=ipilimumab, Nivo=nivolumab, IVIG =Intravenous immunoglobulins

RESULTS CONTINUED…

- Most (84.6%) patients received corticosteroids with or without add-on immunosuppressive therapy.
- Overall, 10 deaths were reported, all in patients with myocarditis; most commonly due to ventricular arrhythmia (30%), followed by multi-organ failure (20%).
- Patients with myonecrosis on biopsy had a 60% case fatality rate, compared to 33% in patient with lymphocytic infiltration without myocardial necrosis.

CONCLUSION

- Of the CV-irAEs reported, myocarditis is the most common.
- ICI-induced myocarditis manifests earlier than pericarditis, and commonly has lymphocytic infiltration of myocytes on biopsy.
- Mortality so far has been reported only with ICI-induced myocarditis, whereas no mortalities from ICI-induced pericarditis have been reported to date.
- Myocyte necrosis may be an indicator of poor prognosis; this may highlight the potential utility of myocardial biopsy.
- Corticosteroids remain the mainstay of therapy utilized for CV-irAEs
- Further studies are needed to better guide clinicians in the management of and prevention of morality from CV-irAEs.
- The arrhythmogenic potential of ICI-induced myocarditis needs to be probed further.

DISCLOSURE INFORMATION

The authors have no potential conflicts of interest to disclose.