Control Number: 74

Abstract Category: Clinical Science in Cardio-Oncology

Title: Taking It To Heart- Clinical, Diagnostic and Pathologic Features of Immune-Checkpoint Inhibitor Induced Cardiotoxicity.

ABSTRACT BODY

Background

Immune checkpoint inhibitors (ICI) have revolutionized outcomes of cancers with traditionally poor outcomes. With the growing use of ICIs in clinical practice, evidence of cardiac immune-related adverse events (CV-irAEs) have 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 findings.

Results

Overall, screening of 15,092 studies yielded 44 cases, 52.2% of whom were males, with a mean age of 63.4 (table 1). 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%), pericarditis (9.1%), and cardiac tamponade (4.6%); Myocarditis had earlier onset from ICI initiation, compared to pericarditis (median 30 days vs 129 days; image 1 & image 2). 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. Most (84.6%) patients received corticosteroids with or without add-on immunosuppressive therapy. Cardiac arrest occurred in 2.3% of patients. 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% mortality rate, compare to 33% in patient with lymphocytic infiltration without myocardial necrosis.

Conclusion

Myocarditis manifests earlier than pericarditis, and commonly has lymphocytic infiltration of myocytes on biopsy, and may lead to mortality more commonly than pericarditis. Myocyte necrosis may be an indicator of poor prognosis. Future studies should verify these findings and identify effective diagnostic and therapeutic strategies to prevent mortality from ICI-induced cardiotoxicity.

Clinical Implications

CV-irAEs are an uncommon adverse event of ICI therapy. Prompt recognition and early treatment of CV-irAEs should be pursued to improve outcomes.

Table

Table 1. Reported Cases of Cardiotoxicity with Immune-Checkpoint Inhibitor Use							
	Nivolumab	Ipilimumab	Pembrolizumab	Atezolizumab	Ipilimumab + Nivolumab	Ipilimumab + Pembrolizumab	Ipilimumab + Nivolumab + Pembrolizumab
No.	17	8	3	1	11	3	1
Mean age	63.6 (SD 10.3)	62.9 (SD 11.3)	73.3 (SD 0.58)	55	56.3 (SD 11.8)	58.8 (SD 14.9)	73
Male	9 (52.9)	4 (50)	1 (33.3)	0	6 (54.5)	2 (66.7)	1 (100)
Duration from ICI to irAE in days- Mean(SD)	43.6 (SD 35.0)	99.0 (SD 71.2)	70.7 (SD 33.1)	63	24.4 (SD 109.6)	36.3 (SD 28.3)	14
Reported Symptomatology, n (%)							
Dyspnea	7 (41.1)	5 (62.5)	3 (100)	0	5 (45.5)	0	0
Chest Pain	4 (23.5)	5 (62.5)	0	0	3 (27.3)	0	0
Fatigue/ lethargy	4 (23.5)	0	0	1 (100)	6 (54.5)	0	0
Palpitation	2 (11.8)	1 (12.5)	0	0	0	0	0
Cardiac Immune-Related Adverse Event (irAE), n(%)							
Myocarditis, n(%)	12 (70.6)	2 (25)	3 (100)	1 (100)	11 (100)	0	1 (100)
Pericarditis and / or pericardial effusion	4 (23.5)	3 (37.5)	0	0	0	0	0
Takotsubo Cardiomyopathy	0	2 (25)	0	0	0	0	0
Conduction Abnormalities, n (%)							
AV block	3 (5.9)	1 (12.5)	0	0	2 (18.2)	0	0
Atrial fib	0	1 (12.5)	0	0	0	0	0
Ventricular fib or v tach	4 (23.5)	1 (12.5)	1 (33.3)	1 (100)	1*(9.0)	0	0
Therapy used for irAE, n (%)							
Steroids, n (%) / not mentioned	14/16	4 /5	3 (100)	1 (100)	10 (90.9)	0	1 (100)
Infliximab	3[#] (18.8)	0	0	0	0	0	0
Mycophenolate Mofetil	2 (0.6)	0	0	0	0	0	0
Plasmapheresis	2*(0.6)	0	0	0	1* (9.0)	0	0
IVIG	2 (0.6)	0	0	0	2 (18.2)	0	0
Cardio-pulmonary Support, n (%)							
Circulatory support	IABP=1* (5.9)	0	0	IABP=1	IABP=1* (9.0)	0	0
Respiratory support	IMV = 4 (23.5) ECMO=1 (5.9)	0	0	0	ECMO=2 (18.2)	0	0
Index Troponin and Ejection Fraction at presentation							
Index trop >0.03 ng/ml or elevated, n/total n measured.	11/12	2 / 4	1/1	1/1	8/9	0	0
Index EF <50%, n/total n measured.	8/9	1 / 4	3/3	1/1	2/8	0	0
Myocardial Histology on Biopsy n=15							
Myonecrosis, n (% of total biopsies per ICI treatment class)	4 (57.1)	1 (33.3)	0	0	1 (14.3)	0	0
CD3 infiltration n (% of total biopsies per ICI treatment class)	2 (28.6)	1 (33.3)	0	0	3 (42.9)	0	0
CD8 infiltration n (% of total biopsies per ICI treatment class)	4 (57.1)	0	2 (100)	0	2 (28.6)	0	0
Myocardial fibrosis n (% of total biopsies per ICI treatment class)	0	1 (33.3)	0	0	1 (14.3)	0	0
Outcomes, n (%)							
Hospice, n (%)	2 (11.8)	0	1 (33.3)	0	1 (9.0)	0	0
Death, n (%)	4 (23.5)	2 (25)	0	0	4 (36.4)	0	0

Table 1: ICI – Immune checkpoint inhibitors, irAE – Immune related adverse event, SD – Standard deviation, Fib – Fibrillation, V tach – ventricular tachycardia, EF – Ejection fraction, ECMO – Extracorporeal membrane oxygenation, IVIG – Intravenous immunoglobulin, IABP – Intra-aortic balloon pump, IMV – Invasive mechanical ventilation, Trop – Troponin, CD – Cluster of differentiation

Image 1

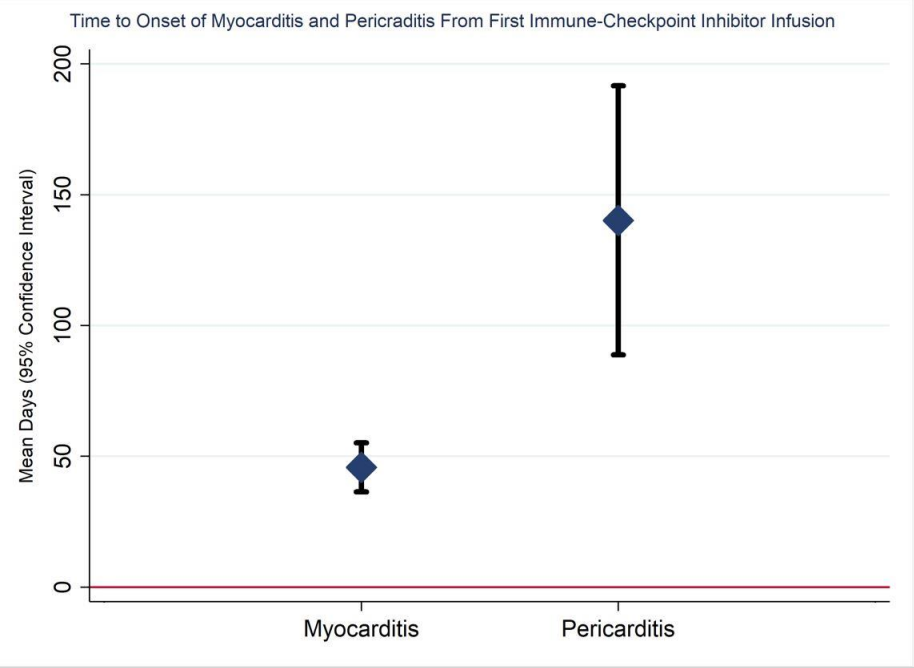

Image 2

Table 2: Comparison of Myocardial to Pericardial irAE's		
	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		