Cardiovascular Events as Oncologic Emergencies in Patients on Immune-Checkpoint Inhibitor Therapy

Aiham Qdaisat, MD, Cielito C. Reyes-Gibby, Dr. PH, Jun-ichi Abe, MD, PhD, Nicolas Palaskas, MD, Sanjay S. Shete, Ph.D. , Sai-ching Yeung, MD, PhD

The University of Texas MD Anderson Cancer Center

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Background

Cardiovascular diseases (CVD) and cancer are leading causes of death.[1] The incidence of CVD is higher in cancer patients than the general population.[2] In recent years, a dramatic breakthrough in cancer therapy emerged as a result of the introduction of immune-checkpoint inhibitor therapy (ICI). As new ICI agents and novel combinations of these agents came into use, the relative proportions of immune-related adverse effects (irAEs) seen in the emergency department (ED) have shifted. Oncocardiology and emergency medicine are closely collaborative, as many cardiac events in cancer patients can be immediately life-threatening and require emergency intervention and care. A well-known cardiotoxic irAE is immune myocarditis which may present as a life-threatening event, and yet there may be cardiotoxicities induced by ICPIs beyond myocarditis.[3] Here we describe emergent vs non-urgent presentation of cardiovascular events in cancer patients who received ICI in a comprehensive cancer center.

Methods

A retrospective cohort study of patients 18 years and older who received ICI at our comprehensive cancer center between April 1st, 2016, and March 31st, 2020. Demographics, clinical and cancer-related data were collected from the institution's data warehouse. The billing database was queried for all cardiovascular-related diagnoses before and after ICI initiation from the patient's initial presentation up to 01/01/2022. Descriptive statistics and competing risk analyses were used to analyze the data.

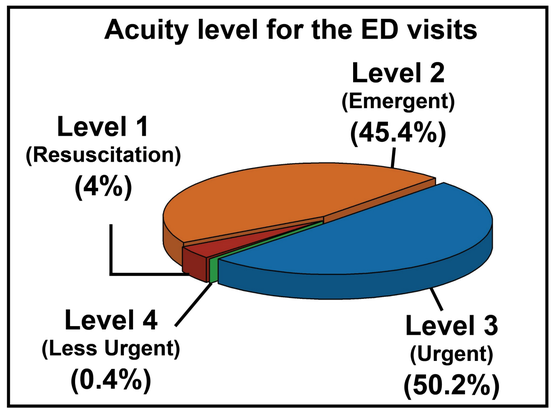
Results

A total of 9,412 patients were included, with a median age of 64 years (interquartile range= 55-72 years), who were mostly white (80.4%). Lung, kidney/urinary bladder, and melanoma were the top three cancer diagnoses Almost one-quarter of the patients had cardiovascular disease documented before ICI initiation (Table 1).

Characteristic	N (%)
Total	9412
Age, median (IQR), years	64 (55, 72)
Gender	
Female	3780 (40.2)
Male	5632 (59.8)
Race	
White	7568 (80.4)
Black or African American	655 (7.0)
Asian	467 (5.0)
American Indian or Alaska Native	31 (0.3)
Native Hawaiian or Other Pacific Islander	13 (0.1)
Others or unknown	678 (7.2)
Charlson comorbidity index, median (IQR)	6 (6, 7)
Cancer type	
Lung	2004 (21.3)
Melanoma	1386 (14.7)
Kidney	795 (8.4)
Head and Neck	743 (7.9)
Urinary bladder and ureters	385 (4.1)
More than one cancer type	721 (7.7)
Others	2833 (30.1)
Number of immune checkpoint inhibitors	
1	7381 (78.4)
2 or more	2031 (21.6)
Number of existing baseline heart diseases	
0	7131 (75.8)
1	1591 (16.9)
2	465 (4.9)
3 or more	225 (2.4)

Table 1. Demographics and clinical characteristics for patients treated with immune checkpoint inhibitor initiation

Around 19.5%(1832/9412) of the patients had ED visits with a diagnosis of heart disease. The median number of ED visits with a diagnosis of heart disease is 1 (IQR:1-2). Most of these ED visits had an acuity level of urgent or emergent. Furthermore, the majority of the patients were admitted either to the hospital or the observation unit (Figure 1).



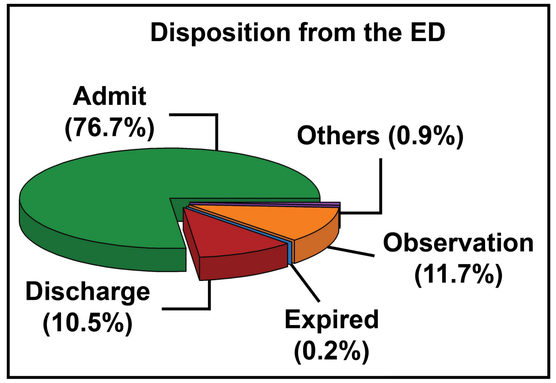


Figure 1. Acuity level and disposition of patients who received ICI and had an ED visit with a diagnosis of heart disease.

Of the patients with no previous documented cardiovascular disease (7131), 1877 (26.3%) had a new diagnosis of cardiovascular diseases documented after ICI therapy, with tachyarrhythmias (19.0%), diseases of the pericardium (5.6%), and heart failure (4.6%) being among the topmost frequent diagnosis. For most cardiovascular events, the risk was significantly higher in patients who were treated with combination ICI therapy, with hazard ratios ranging from 1.26 to 1.65 (Table 2).

Heart disease	Subdistribution Hazard Model	
	Hazard Ratios (95% CI)	P
Pericardium diseases including pericarditis	1.55 (1.27–1.89)	<0.001
Tachyarrhythmias	1.37 (1.23–1.53)	<0.001
Valvular heart disease	1.43 (1.11–1.85)	0.006
Heart failure	1.31 (1.05–1.64)	0.016
Conduction disorder	1.63 (1.28–2.07)	<0.001
Cardiomyopathy	1.57 (1.2–2.05)	0.001
Cardiac arrest	1.26 (0.8–1.97)	0.310
Myocardial infarction	1.65 (1.22–2.23)	0.001
Endocarditis	1.28 (0.85–1.93)	0.240
Myocarditis	1.57 (0.94–2.62)	0.086
Other heart diseases	1.58 (1.29–1.93)	<0.001
Other ischemic heart diseases	1.41 (1.18–1.69)	<0.001

Table 2. Competing risks analysis for heart disease in ICI patients estimating the sub-distribution of failure from cardiac event for combination ICI therapy and mono ICI therapy (reference).

Conclusions

The clinical use of ICI is still expanding, and early versus delayed manifestation of ICI-induced toxicities is yet to be defined in cancer patients. Understanding the timing and the acuity level of the presentation of cardiovascular events associated with ICI therapy will allow the provision of better care for this population.

References

1) Heron M, Anderson RN. Changes in the Leading Cause of Death: Recent Patterns in Heart Disease and Cancer Mortality. NCHS Data Brief. 2016;(254):1-8.
2) Sturgeon KM, Deng L, Bluethmann SM, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J. 2019;40(48):3889-3897. doi:10.1093/eurheartj/ehz766
3) Patel RP, Parikh R, Gunturu KS, et al. Cardiotoxicity of Immune Checkpoint Inhibitors. Curr Oncol Rep. 2021;23(7):79. Published 2021 May 3. doi:10.1007/s11912-021-01070-6