A preliminary assessment of cardiotoxicities associated with immune-checkpoint inhibitor therapy

CIELITO REYES-GIBBY, DRPH

DEPARTMENT OF EMERGENCY MEDICINE

DEPARTMENT OF BIOSTATISTICS

THE UNIVERSITY OF TEXAS

M. D. ANDERSON CANCER CENTER

Background

The Emergency Department is a frequent site of care for millions of cancer patients.

Most recent data show almost 30 million ED visits in the US were made by patients with cancer for the period January 2006 to December 2012.

Of these visits, adult cancer-related ED visits resulted in inpatient admissions more frequently (59.7%) than non-cancer-related visits (16.3%) ($P < 0.001$).

Immune Checkpoint Inhibitors

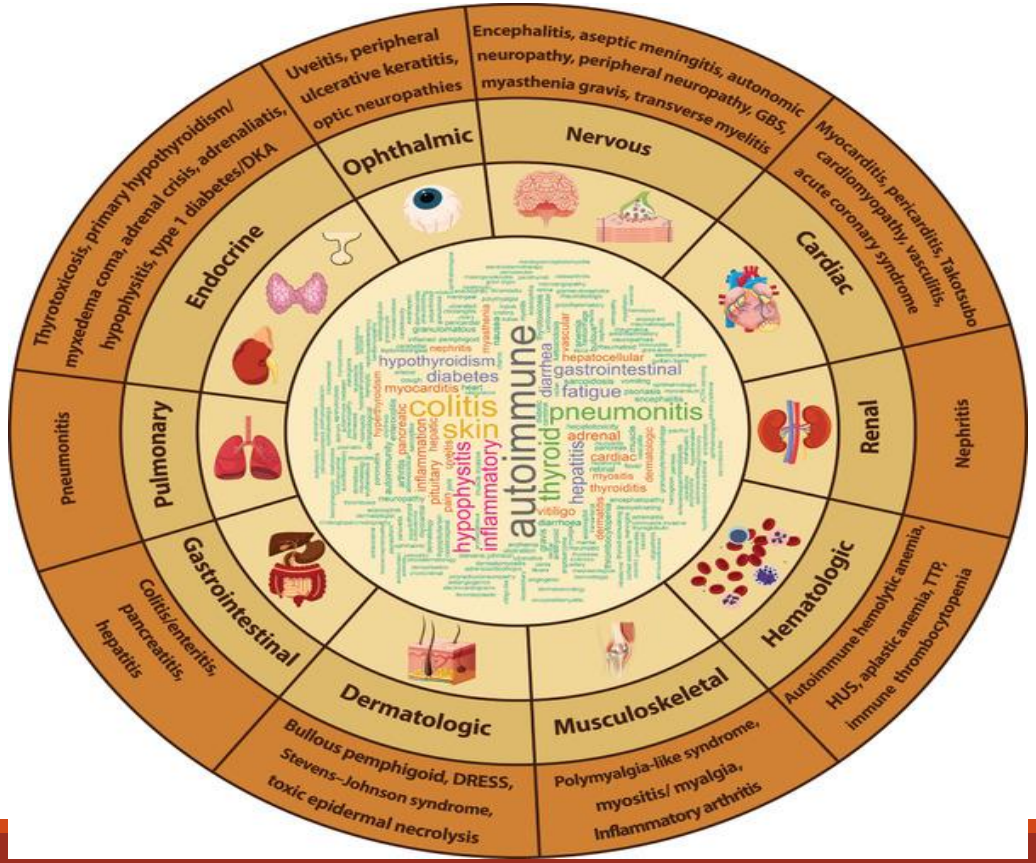
Immune checkpoint inhibitors (ICPIs) are a recent advance in cancer treatment.

A type of drug that blocks proteins called checkpoints that are made by some types of immune system cells, such as T cells, and some cancer cells. These checkpoints help keep immune responses from being too strong and sometimes can keep T cells from killing cancer cells. When these checkpoints are blocked, T cells can kill cancer cells better.

To date, there are 8 approved by the US Food and Drug Administration (FDA) – anti-CTLA-4: ipilimumab; anti-PD-1: nivolumab, pembrolizumab, cemiplimab; anti-PD-L1: atezolizumab, avelumab, durvalumab and most recently, dostarlimab.

Immune-related Adverse Events

While ICPIs have led to improved survival for many cancer patients, the immune-related adverse events (irAEs) from ICPI is a significant concern.



Cardiotoxicities

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.

Our preliminary animal data suggest delayed atherosclerosis associated with ICPIs (PD-1; PDL-1).

In this preliminary analyses, we assessed the extent of CVD-associated diagnosis among patients who received ICPI at a major cancer center in the U.S.

Methods

A retrospective analyses of patients who received ICPI for the period 4/01/2017-11/15/2020.

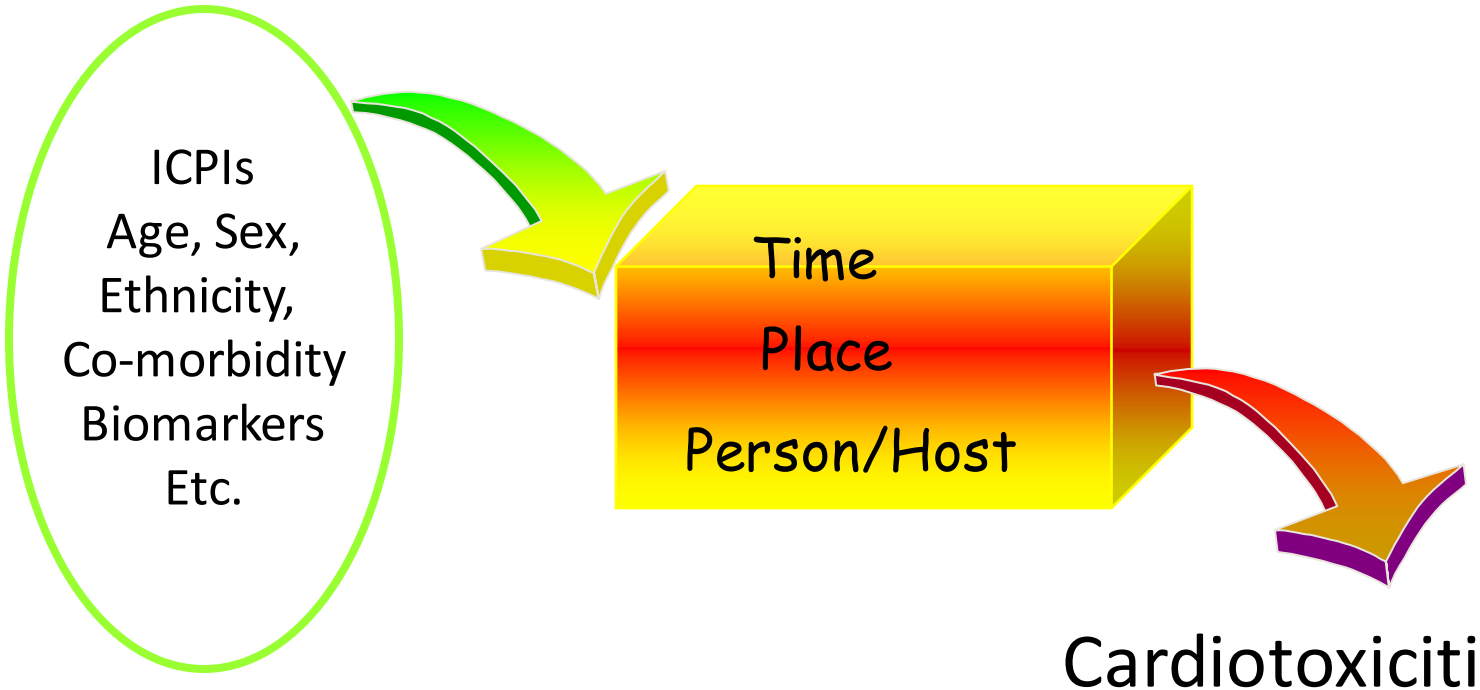
Demographics, clinical and cancer-related data were abstracted from the institution data warehouse.

The billing database was queried for CVD-related diagnosis (International Classification of Disease-version10) before and after ICPI treatment. Timeframe was from first presentation to MD Anderson to present (thus, patients have variable follow-time, a limitation of the study).

We used descriptive statistics to summarize the clinical characteristics of the patients.

Epidemiology—underlying premise is that disease (or disease condition) does not occur at random but rather in patterns that reflect the operation of underlying factors

Exposure/Variables



Study Population

VARIABLE	N (%)
Total	1225
Age, median (IQR), years	64 (55, 71)
Gender	
Female	567 (46.3)
Male	658 (53.7)
Race	
White or Caucasian	924 (75.4)
Black or African American	110 (9.0)
Asian	73 (6.0)
Others or unknown	118 (9.6)
Ethnicity	
Not Hispanic or Latino	1037 (84.7)
Hispanic or Latino	162 (13.2)
Others or unknown	26 (2.1)
CCI, median (IQR)	7 (6, 9)
Cancer type	
Lung	299 (24.4)
Kidney and urinary bladder	169 (13.8)
Melanoma	167 (13.6)
Head and Neck	90 (7.4)
Lymphoma	58 (4.7)
Gastroesophageal	56 (4.6)
Colorectal	44 (3.6)
Breast	34 (2.8)
Hepatobilliary	33 (2.7)
Cutaneous Squamous Cell Carcinoma	33 (2.7)
Cervix	18 (1.5)
Merkel Cell Carcinoma	22 (1.8)
Others	201 (16.4)
Number of immune checkpoint inhibitors	
1	1005 (82.0)
2 or more	220 (18.0)

VARIABLE	N (%)
Number of existing heart diseases at baseline	
0	801 (65.4)
1	265 (21.6)
2	95 (7.8)
3	37 (3.0)
4 or more	27 (2.2)
Heart diseases at baseline	
Tachyarrhythmias	245 (20.0)
Pericardium diseases including pericarditis	58 (4.7)
Valvular heart disease	52 (4.2)
Conduction disorder	43 (3.5)
Heart failure	42 (3.4)
Myocardial infarction	26 (2.1)
Cardiomyopathy	26 (2.1)
Myocarditis	1 (0.1)
Endocarditis	11 (0.9)
Baseline related comorbidities	
Dyslipidemia and disorders of lipoprotein metabolism	205 (39.7)
Hypertension	427 (34.9)
Peripheral vascular diseases	53 (4.3)
Diabetes mellitus	181 (14.8)

Cardiovascular diseases (ICD-10) after immune checkpoint inhibitor initiation

Disease	N (%)
Tachyarrhythmias	502 (41.0)
Heart failure	132 (10.8)
Pericardium diseases including pericarditis	125 (10.2)
Valvular heart disease	84 (6.9)
Conduction disorder	77 (6.3)
Cardiomyopathy	71 (5.8)
Myocardial infarction	57 (4.7)
Endocarditis	37 (3.0)
Myocarditis	25 (2.0)
Cardiac arrest	17 (1.4)

Limitations: Need to assess other cancer treatment that may also be cardiotoxic (chemotherapy, etc.); Need to conduct multivariable analyses to adjust for other factors including clinical and demographic factors.

Time to first event for patients with new cardiovascular diseases

Disease	Months to first event, median (IQR)
Valvular heart disease	6.2 (1.8-15.1)
Myocardial infarction	4.2 (1.2-11.2)
Cardiac arrest	4 (2-6.5)
Conduction disorder	3.9 (1.6-8.6)
Other heart diseases	3.7 (1.4-9.3)
Endocarditis	3.5 (1.8-7.6)
Other ischemic heart diseases	3.5 (1-8.4)
Cardiomyopathy	2.8 (1.5-6.9)
Tachyarrhythmias	2.8 (0.9-7)
Pericardium including pericarditis	2.3 (0.7-5.6)
Myocarditis	1.7 (0.9-2.3)

Limitations: Need to assess other factors that may influence these findings including other cancer treatment; type of cancer, etc.

First Presentation: ED versus Clinic

Disease	N (%)	
	ED	Non-ED
Myocarditis	14 (56.0)	11 (44.0)
Tachyarrhythmias	229 (45.6)	273 (54.4)
Pericardium diseases including pericarditis	53 (42.4)	72 (57.6)
Cardiomyopathy	28 (39.4)	43 (60.6)
Heart failure	51 (38.6)	81 (61.4)
Other heart diseases	55 (36.4)	96 (63.6)
Myocardial infarction	20 (35.1)	37 (64.9)
Other ischemic heart diseases	72 (33.3)	144 (66.7)
Conduction disorder	23 (29.9)	54 (70.1)
Cardiac arrest	4 (23.5)	13 (76.5)
Endocarditis	8 (21.6)	29 (78.4)
Valvular heart disease	17 (20.2)	67 (79.8)

Limitations: Patients may have presented to EDs in the community or clinics in the community, etc. which is not captured in this dataset.

Discussion

Our preliminary findings suggest ICPIs may have cardiotoxic effects other than myocarditis.

Active surveillance for cardiotoxic effects is important in the care of these patients.

These preliminary findings require additional assessment of other potential factors. There are several limitations including using extant data and single center.

Future studies for a better understanding of biological mechanisms for delayed atherosclerosis in order to develop potential treatment strategies.

Team science

Cielito Reyes-Gibby

Sai-Ching Jim Yeung

Jun-Ichi Abe

Aiham Qdaisat

Demis Lipe

Mary Flores

Patients, Faculty and Staff at MD Anderson