

Incidence of Cancer Treatment Induced Arrhythmia Associated with Immune Checkpoint Inhibitors

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Introduction

- Immune checkpoint inhibitors (ICIs) have been associated with important forms of cardiotoxicity, including myocarditis
- The incidence of cancer treatment induced arrhythmias (CTIA) associated with ICI has not been well characterized

Methods

- We reviewed patients treated with ICIs at Emory from Jan. 2010 to Dec. 2015
- Electronic medical records, billing codes and manual chart review were used to identify cases of CTIA
- Arrhythmia diagnoses present prior to ICI therapy were not included as CTIA
- CTIA was defined as a new diagnosis of any of the following within 6 months of ICI therapy:
 - atrial fibrillation/atrial flutter
 - supraventricular tachycardia
 - sustained ventricular arrhythmias
 - symptomatic bradycardia
 - any arrhythmias requiring medical or procedural treatment
- Asymptomatic sinus brady- and tachycardia and premature beats not requiring treatment were not included

Results

- 268 patients were treated with either ICI monotherapy or ICI combination therapy and are presented in Table 1. From this cohort, 4 patients (1.5%) developed CTIA. Baseline characteristics, stratified by the presence of CTIA, are presented in Table 2.

Table 1: Distribution of ICI Treatment

Immune Checkpoint Inhibitor Monotherapy (N=190)	Immune Checkpoint Inhibitor Combination Therapy (N=78)
Ipilimumab (114)	Ipilimumab and Nivolumab (37)
Nivolumab (52)	Ipilimumab and Pembrolizumab (39)
Pembrolizumab (24)	Nivolumab and Pembrolizumab (2)

Table 2: Baseline Characteristics Stratified by the Presence of CTIA

Characteristics	Patients with CTIA (n= 4)	Patients without CTIA (n= 264)	P value
Age, y	76.8 +/- 6.5	66.8 +/- 12.6	0.113
Male Sex	4 (100.0)	172 (65.2)	0.302
Hypertension	3 (75.0)	157 (59.5)	0.65
Type II Diabetes Mellitus	2 (50.0)	54 (20.5)	0.194
Congestive Heart Failure	2 (50.0)	27 (10.2)	0.059
Coronary Artery Disease	2 (50.0)	90 (34.1)	0.609
Obstructive Sleep Apnea	0 (0.0)	24 (9.1)	> 0.999

- All 4 cases of CTIA involved ipilimumab, 2 of which also included concomitant nivolumab therapy
- 3 patients developed a new diagnosis of atrial fibrillation, one of whom required cardioversion
- 1 patient developed symptomatic sinus bradycardia which required dose reduction of a previously prescribed beta blocker for treatment of atrial arrhythmias
- Even among the cases of CTIA, in 2 instances there were additional factors which likely predisposed to the onset of arrhythmia, including significant metabolic abnormalities from DKA in one case and thyrotoxicosis in the other

Results

- 6 patients with a pre-existing diagnosis of paroxysmal atrial fibrillation experienced episodes of AF within 6 months of initiating ICI therapy
- These events were not included in the CTIA endpoint due to the pre-existing nature of the arrhythmia

Conclusions

- The incidence of arrhythmic complications associated with immune checkpoint inhibitors appears to be very low. Only 1.5% of patients treatment with ICIs experienced new onset arrhythmias
- Patients with preexisting paroxysmal AF may be at risk for experiencing episodes of AF during ICI treatment and should be monitored accordingly
- None of the arrhythmia events in this cohort were associated with known or suspected myocarditis
- These findings add to the data on the safety and cardiovascular toxicity profile of immune checkpoint inhibitors and suggest that from an arrhythmia perspective, ICIs appear to be very safe and well tolerated.