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Incidence of Cancer Treatment Induced Arrhythmia Associated with Immune Checkpoint Inhibitors

Luke Joseph[1], Andrew C. Nickel[2], Akshar Patel[3], Nabil F. Saba[1,4], Angel R. Leon[1,3], Mikhael F. El-Chami[1,3], Faisal M. Merchant[1,3]

[1]Emory University School of Medicine, Atlanta, GA
[2]University of Colorado School of Medicine, Aurora, CO
[3]Cardiology Division, Section of Cardiac Electrophysiology, Emory University School of Medicine, Atlanta, GA
[4]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA

Abstract

Background: Cancer treatment induced arrhythmia (CTIA) is a well-recognized form of cardiotoxicity associated with chemotherapy. Immune checkpoint inhibitors (ICI) have been associated with important forms of cardiotoxicity, including myocarditis. However, the incidence of CTIA associated with ICI has not been well characterized.

Methods: We reviewed all patients treated with ICIs at our institution from Jan. 2010 to Oct. 2015. CTIA was defined as a new diagnosis of clinically relevant arrhythmia within 6 months after ICI initiation.

Results: During the study period, 268 patients were treated with immune checkpoint inhibitors, of whom 190 received monotherapy with ipilimumab (n=114), nivolumab (n=52) or pembrolizumab (n=24) and 78 received combination therapy: ipilimumab & nivolumab (n=37), ipilimumab & pembrolizumab (n=39) and nivolumab & pembrolizumab (n=2). Four patients (1.5%) developed CTIA. Of these, 3 patients developed a new diagnosis of atrial fibrillation (AF), one of whom required cardioversion. In 2 cases of new-onset AF, significant provoking factors were present in addition to ICI therapy including thyrotoxicosis in one and metabolic disarray in another. Six patients (2.2%) with a pre-existing diagnosis of paroxysmal AF experienced episodes within 6 months of initiating ICI therapy. None of the arrhythmic events were associated with known or suspected myocarditis.

Conclusion: The incidence of arrhythmic complications associated with immune checkpoint inhibitors appears to be very low (~1.5%). Patients with a pre-existing diagnosis of AF may be at-risk of recurrence during ICI treatment and should be monitored accordingly. These data suggest that from an arrhythmia perspective, ICIs appear to be very safe and well-tolerated.

Introduction

Immune checkpoint in hibitors (ICI) are a relatively new class of anti-neoplastic systemic agents that have gained significant importance as a novel class of cancer therapy and have revolutionized the treatment of a large number of cancers[1-3]. In addition, the use of these agents has been advocated as safer than traditional cytotoxic chemotherapeutic drugs and has been advocated and approved for maintenance therapy,unlike other forms of chemotherapy, in a number of malignancies including lung cancer[4]. The use of ICIs is therefore expected to increase overtime and will be introduced in different regions of the world. Identifying ICI related toxicities regardless of their frequency, is therefore of high significance.

Key Words

Atrial Fibrillation; Chemotherapy; Immune Checkpoint Inhibitors; Cardiooncology

Corresponding Author
Faisal M. Merchant, MD
Emory University Hospital Midtown, 550 Peachtree Street, MOT 12th floor
Atlanta, GA 30308

Immune checkpoint inhibitors target a range of co-stimulatory signaling molecules on T lymphocytes and antigen presenting cells, including cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1/ligand-1 (PD-1/PD-L1)[5-7]. ICIs have been associated with the development of immune-related adverse events (irAEs), which can target various organ systems[6]. Cardiovascular manifestations of ICI-associated toxicity take several forms including myocarditis, pericardial disease and vasculitis[6,8,9]. Cancer treatment induced arrhythmia (CTIA) is a well-recognized form of toxicity occurring in the setting of chemotherapy [10,11] and several forms of CTIA have been reported in association with ICIs, including atrial and ventricular tachyarrhythmias and symptomatic bradycardia, including complete heart block [5,8]. Arrhythmic events associated with ICIs have mostly been reported to occur in the setting of myocarditis [5]; however, risk factors for the development of arrhythmias associated with ICIs have not been well-characterized. Therefore, we sought to describe the incidence of, risk factors for, and clinical outcomes associated with CTIA during ICI therapy.

	with CTIA (n= 4)	without CTIA (n= 264)	p
Age (years)	71.5 ± 6.5	66.8 ± 12.6	0.11
Male gender	4 (100)	172 (65)	0.30
Hypertension	3 (75)	157 (60)	0.65
Diabetes Mellitus	2 (50)	54 (21)	0.19
Congestive Heart Failure	2 (50)	27 (10)	0.06
Coronary Artery Disease	2 (50)	90 (34)	0.61
Obstructive Sleep Apnea	0	24 (9.1)	1.00

Table 1: **Baseline characteristics stratified by the presence of cancer treatment induced arrhythmia (CTIA)**

*Data are presented as mean ± standard deviation or n (%)

Methods

The protocol for this study was approved by the Emory University Institutional Review Board. We retrospectively reviewed all patients receiving de novo treatment with ICIs at Emory Healthcare/Winship Cancer Center from January 2010 to October 2015. Inpatient and outpatient electronic medical records (EMR) and pharmacy orders were queried to identify first-time orders for the following ICIs: ipilimumab, nivolumab and pembrolizumab. Four additional ICIs have been approved since the period of our study but were not included in this analysis. The end date for this analysis corresponds to the transition from International Classification of Diseases (ICD) 9 to ICD 10, which occurred in conjunction with changes to the EMR and pharmacy systems at our institution. Therefore, all analyses were performed using ICD-9 for consistency.

Electronic medical record databases were queried to identify cases of CTIA associated with ICIs. CTIA was defined as a new diagnosis (either billing code diagnosis or new inclusion of a diagnosis code in the medical problem list) for any of the following occurring up to 6 months after the initiation of immune checkpoint inhibitor therapy: atrial fibrillation/atrial flutter (AF), supraventricular tachycardia (SVT), sustained ventricular arrhythmias, sinus node dysfunction/sinoatrial node dysfunction, 2nd degree atrioventricular (AV) block, 3rd degree AV block, complete heart block and any symptomatic arrhythmia requiring treatment (i.e. change in medical therapy, cardioversion/defibrillation, need for catheter ablation or pacemaker/defibrillator implantation). Asymptomatic sinus bradycardia and sinus tachycardia and premature atrial and/or ventricular beats not requiring treatment were not included in the CTIA definition. A combination of billing codes and medical problem list queries, manual chart review and review of available electrocardiograms (ECGs) was used to identify cases of CTIA.

Only new arrhythmia diagnoses were included in the definition of CTIA. Patients with a pre-existing diagnosis of arrhythmia, present prior to the initiation of ICI therapy, were not included in the primary endpoint. However, data were collected on recurrences of arrhythmias among patients with pre-existing diagnoses to report separately from the primary endpoint. Baseline demographics and clinical covariates known to be associated with the development of arrhythmias (hypertension, diabetes mellitus, congestive heart failure, coronary artery disease and obstructive sleep apnea) were ascertained by EMR query, ICD-9 billing codes and manual chart review. Relevant clinic notes and results of cardiovascular testing were reviewed to identify known or suspect cases of my ocarditis.

Statistical Analysis

The primary endpoint for this analysis was the incidence of CTIA at 6 months after initiation of ICI therapy. Continuous variables are presented as mean ±standard deviation (SD) and categorical variables are presented as frequencies and percentages. Comparisons between groups were tested using the Fisher's exact test, Chi-squared test, or T-test, as appropriate. A two-tailed $p < 0.05$ was considered significant. All statistical analyses were performed using Statistica® (Statsoft, Tulsa, OK).

Results

During the period of interest,268 patients were treated with immune checkpoint inhibitors, of whom 190 received mono therapy with ipilimumab (n=114), nivolumab (n=52) or pembrolizumab (n=24). Seventy-eight patients received combination therapy with ipilimumab & nivolumab (n=37), ipilimumab & pembrolizumab (n=39) and nivolumab & pembrolizumab (n=2). Across the entire cohort, at the time of ICI initiation, mean age was 60.9 ± 12.5 years, 66% were male and comorbidities included hypertension (60%), diabetes (21%), coronary artery disease (34%), congestive heart failure (11%) and sleep apnea (9%).

By 6 months following initiation of ICI therapy, 4 patients (1.5%) met the primary endpoint definition for CTIA. The Table presents baseline characteristics, stratified by the presence of CTIA. Patients with CTIA tended to be older and were numerically more likely to be male and have a history of hypertension, although differences were not significant. All 4 cases of CTIA involved ipilimumab, two of which also included concomitant nivolumab therapy. No cases were identified with pembrolizumab.

A brief summary of the clinical features of the 4 CTIA cases follows:

1. 78-year-old male with history of hypertension developed symptomatic atrial fibrillation with rapid ventricular response (AF with RVR) approximately 5 months after initiating ipilimumab for metastatic melanoma. He was initially treated with transesophageal echocardiogram (TEE)-guided cardioversion and discharged home with anticoagulation and an increased dose of beta blockers, which he had previously been taking for hypertension. He presented again in AF with RVR 48 hours after the first discharge. During the second admission, he was loaded on amiodarone and again underwent cardioversion

2. 68-year-old male with hypertension and diabetes being treated with concomitant ipilimumab and nivolumab for metastatic melanoma was admitted for diabetic ketoacidosis (DKA) approximately 2 months after initiating combination ICI therapy. During hospitalization, while on an insulin drip, he developed self-limited AF which resolved spontaneously after about 48 hours as metabolic abnormalities and volume status were corrected. No additional therapy for AF was required.

3. 66-year-old male with hypertension being treated with concomitant ipilimumab and nivolumab for metastatic melanoma presented with AF with RVR approximately 6 weeks after initiating combination ICI therapy. Evaluation was notable for hyperthyroidism,

felt to possibly be drug-induced toxicity from the ICIs. Thyroid stimulating hormone level was markedly suppressed at 0.01 mU/L, with elevated levels of T3 and free T4. Hyperthyroidism was treated with methimazole and steroids and AF with RVR controlled with beta blockers. Anticoagulation was not started due to recurrent gastrointestinal bleeding from metastatic duodenal melanoma.

4. 74-year-old male with diabetes and extensive cardiac history including 3 prior ablations for atrial fibrillation was being treated with ipilimumab for metastatic melanoma. Approximately 3 months after initiating ICI therapy, he presented with increased fatigue and dizziness with sinus bradycardia (heart rates in the high 40s to low 50s at rest). He had been maintained on beta blockers for many years given the history of AF and previously, sinus rates had been adequate despite beta blocker therapy. Given concern that sinus bradycardia may be contributing to his symptoms, the dose of beta blocker was halved. Despite the history of atrial fibrillation, because sinus node dysfunction had not been documented prior to ICI therapy, and the dose of beta blocker was reduced, this event was included in the definition of CTIA.

None of the CTIA cases required stopping treatment with the ICIs. In addition to the 4 cases meeting the primary endpoint definition of CTIA, 6 additional patients with a history of paroxysmal atrial fibrillation developed episodes of AF within 6 months after beginning ICI therapy. These cases were not included in the CTIA definition given the pre-existing arrhythmia diagnosis. None of the cases of CTIA, or cases of recurrent AF in those with a pre-existing diagnosis of atrial fibrillation, were associated with known or suspected myocarditis.

Discussion

Our data demonstrate that the incidence of arrhythmic complications associated with immune checkpoint inhibitors appears to be very low. Only 4 cases (1.5%) in the cohort met the primary endpoint definition of CTIA occurring within 6 months of ICI treatment and in most instances, the arrhythmias could be managed in a relatively straightforward manner. None of the cases required stopping ICI therapy. Patients with a pre-existing diagnosis of atrial fibrillation may be at-risk of recurrence during ICI treatment and should be monitored accordingly. Importantly, none of the arrhythmia events in this cohort were associated with suspected myocarditis. These data add to the available literature on the cardiovascular safety profile of ICIs and suggest that from an arrhythmia perspective, ICIs appear to be very safe and well-tolerated.

Even among the CTIA cases in this cohort, in two instances there were significant additional factors which likely predisposed to the onset of arrhythmia, including significant metabolic abnormalities from DKA in one case and thyrotoxicosis in the other. In the case of sinus node dysfunction, although the need to reduce the dose of beta blocker therapy, strictly speaking, met our definition for CTIA, the clinical importance of this event is likely minimal.

Although much has been written about cardiovascular toxicities associated with ICIs, relatively little is known specifically about arrhythmic events. Although it has been suggested that most arrhythmic events associated with ICIs occur in the setting of myocarditis [5], this association has not been well-characterized and none of the arrhythmic events in our cohort occurred in the setting of suspected myocarditis. Atrial fibrillation is the arrhythmia most commonly associated with ICIs. In an analysis of the World Health Organization Vigi Base, a global database of individual case safety reports, arrhythmic adverse events due to atrial arrhythmias were significantly more common in association with ICIs compared to non-ICIs (0.71 vs. 0.42%) [8]. In contrast, adverse events related to other arrhythmic complications (ventricular arrhythmias, prolonged QT interval/Torsade de pointes and conduction system disorders) were not significantly different between ICIs and non-ICIs. Among recent clinical trials of newer ICIs, in the PACIFIC trialwith durvalumab for non-small-cell lung cancer (n=473 patients in the ICI arm), atrial arrhythmias occurred in 4 patients in the ICI arm and none in the placebo arm [5,12]. In the DETERMINE study of tremelimumab for mesothelioma (n=382 patients in the ICI arm), atrial arrhythmias occurred in 13 patients in the ICI arm and 7 in the placebo arm[5,13]. In aggregate, our data are consistent with prior reports which show that although atrial arrhythmias can occur during ICI therapy, the incidence appears to be quite low (~1-3% across studies).

The incidence of atrial arrhythmias associated with ICIs appears comparable to the incidence associated with others forms of chemotherapy. Atrial arrhythmias have been reported to occur within the first 6 months of treatment in about 3% of patients treated with other forms of chemotherapy including anthracyclines, monoclonal antibodies and tyrosine kinase inhibitors [11].

Less is known about the incidence of arrhythmic complications other than atrial arrhythmias associated with ICIs. Other than the one case of mild sinus node dysfunction which necessitated a reduction in beta blocker dose, we did not identify any other cases of symptomatic brady-arrhythmias in this study. Case reports have identified complete heart block associated with ICI therapy, typically in the setting of myocarditis [14,15], which may be reversible with cessation of ICI treatment [16]. However, beyond individual case reports, our study is among the limited datasets to systematically look for cases of heart block and brady-arrhythmias in the setting of ICI therapy and suggests that the incidence of this complication is very low.

Limitations

Several important limitations of our work should be noted. First, due to the transition from ICD-9 to 10 and associated changes in medical diagnosis and billing codes, our cohort includes only the 3 original immune checkpoint inhibitors approved for use and not any of the agents approved subsequently. Second, because we used billing codes and medical problem lists in our EMR to identify cases of CTIA, arrhythmic events that were managed outside our health system during ICI treatment may have been missed. Third, data on left ventricle ejection fraction were only available for a small number of patients in the cohort (n=30) and were not systematically obtained. Therefore, we cannot comment on the association between ejection fraction and risk for CTIA with ICIs. Finally, some arrhythmic events are asymptomatic and do not come to clinical attention but may have important prognostic and treatment implications, such as anticoagulation for subclinical atrial fibrillation. Our study only looked at clinically apparent arrhythmias and did not use any form of continuous rhythm monitoring to look for subclinical events.

Conclusions

The incidence of new-onset arrhythmias during the first 6 months after immune checkpoint inhibitor therapy appears to be very low (~1.5%) and most of the arrhythmias were relatively easily managed from a clinical perspective. Patients with a pre-existing diagnosis of atrial fibrillation may be at-risk of developing recurrences during ICI treatment and should be monitored accordingly. Importantly, none of the arrhythmias noted in this cohort occurred in the setting of suspected myocarditis. These data suggest that ICIs have an excellent safety profile from an arrhythmia perspective.

References

1. Ferris RL, Blumenschein G, Jr., Fayette J et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 2016;375:1856-1867.
2. Larkin J, Chiarion-Sileni V, Gonzalez R et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med 2019;381:1535-1546.
3. Reck M, Rodriguez-Abreu D, Robinson AG et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-1833.
4. Saba NF, Mody MD, Tan ES et al. Toxicities of systemic agents in squamous cell carcinoma of the head and neck (SCCHN); A new perspective in the era of immunotherapy. Crit Rev Oncol Hematol 2017;115:50-58.
5. Ball S, Ghosh RK, Wongsaengsak S et al. Cardiovascular Toxicities of Immune Checkpoint Inhibitors: JACC Review Topic of the Week. J Am Coll Cardiol 2019;74:1714-1727.
6. Mahmood SS, Fradley MG, Cohen JV et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. J Am Coll Cardiol 2018;71:1755-1764.
7. Moslehi JJ. Cardiovascular Toxic Effects of Targeted Cancer Therapies. N Engl J Med 2016;375:1457-1467.
8. Salem JE, Manouchehri A, Moey M et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. Lancet Oncol 2018;19:1579-1589.
9. Johnson DB, Balko JM, Compton ML et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. N Engl J Med 2016;375:1749-1755.
10. Buza V, Rajagopalan B, Curtis AB. Cancer Treatment-Induced Arrhythmias: Focus on Chemotherapy and Targeted Therapies. Circ Arrhythm Electrophysiol 2017;10.
11. Nickel AC, Patel A, Saba NF, Leon AR, El-Chami MF, Merchant FM. Incidence of Cancer Treatment-Induced Arrhythmia Associated With Novel Targeted Chemotherapeutic Agents. J Am Heart Assoc 2018;7:e010101.
12. Antonia SJ, Villegas A, Daniel D et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med 2018;379:2342-2350.
13. Maio M, Scherpereel A, Calabro L et al. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. Lancet Oncol 2017;18:1261-1273.
14. Behling J, Kaes J, Munzel T, Grabbe S, Loquai C. New-onset third-degree atrioventricular block because of autoimmune-induced myositis under treatment with anti-programmed cell death-1 (nivolumab) for metastatic melanoma. Melanoma Res 2017;27:155-158.
15. Katsume Y, Isawa T, Toi Y et al. Complete Atrioventricular Block Associated with Pembrolizumab-induced Acute Myocarditis: The Need for Close Cardiac Monitoring. Intern Med 2018;57:3157-3162.
16. Reddy N, Moudgil R, Lopez-Mattei JC et al. Progressive and Reversible Conduction Disease With Checkpoint Inhibitors. Can J Cardiol 2017;33:1335 e13-1335 e15.