Atrial and ventricular arrhythmias with immune checkpoint inhibitor therapy in patients without evidence of myocarditis

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Background: Immune checkpoint inhibitor (ICI) therapy has improved the prognosis of many cancer types. Immune-related adverse events (irAEs) are common and recent studies suggest ICI therapy may be associated with an increased risk of arrhythmias. However, data on arrhythmias after ICI therapy has been limited by small sample sizes, the inclusion of patients with ICI myocarditis, or an incomplete characterization of the factors that drive arrhythmias with an ICI.

Purpose: This study aimed to characterize the association between ICIs and arrhythmias in patients without evidence of myocarditis.

Methods: We conducted a hospital network-wide retrospective cohort study on all patients treated with ICI who were free from arrhythmias at the start of ICI therapy, and had no evidence of immune-related myocarditis. We used a historical pre-ICI therapy era cohort of cancer patients of similar age and tumor types, diagnosed between 2008-2012. The main study outcome was the incidence of atrial fibrillation, atrial flutter, supraventricular tachycardia, and ventricular tachycardia after ICI therapy. International Classification of Diseases 9th and 10th edition codes were used to ascertain baseline characteristics and to detect the study outcomes. Myocarditis cases were identified through the application of natural language processing techniques to electronic health records. Patients on ICI therapy and controls were followed from the start of ICI therapy, and from the first visit after 2008, respectively, up to three years after the index date.

Results: The study population consisted of 7441 patients on ICI therapy and 2311 controls. Patients on ICI therapy were older (65 ± 13 vs. 63 ± 13 years, p<0.001) and more frequently had arterial hypertension (52% vs. 47%, p<0.001), but had lower rates of prior congestive heart failure (6% vs. 11%, p<0.001). Over a median follow-up period of 36 months, 9.8% on ICI therapy were diagnosed with any incident atrial or ventricular arrhythmia, compared to 7.1% in the control group (p<0.001) with corresponding incidence rates of 4.4 and 2.3 cases per 100 person-years, respectively (Fig. 1). When correcting for age, sex, cancer type, prior congestive heart failure, and cardiovascular risk factors, patients on ICI therapy had a higher risk of a composite outcome of any arrhythmia (hazard ratio [HR] 1.68, 95% confidence interval [CI]: 1.39-2.04, p<0.001), atrial fibrillation (HR 1.29, 95%CI: 1.02-1.63, p=0.034) and ventricular tachycardia (HR 2.01, 95%CI: 1.34-3.04, p<0.001). In a multivariable logistic regression model, the occurrence of a non-cardiovascular irAE was a predictor of an incident arrhythmia (odds ratio 1.81, 95%CI: 1.56-2.23, p<0.001).

Conclusion: This study, to the best of our knowledge, is the largest to report on ICI therapy-related arrhythmias and the first to show the occurrence of non-cardiovascular irAEs as a predictor of arrhythmia risk in patients on ICI therapy without evidence of myocarditis.

Fig. 1