The risk of sudden cardiac death or ventricular arrhythmias on Immune checkpoint Inhibitors

M. Mirabel, P. Karapetiantz, E. Marijon, C. Le Beller, Z. Reda Al-Sayed, J.S. Hulot, A. Lillo-Lelouet

European Hospital Georges Pompidou, Paris, France
Funding Acknowledgement: Type of funding source: None

Background: Immune checkpoint inhibitors (ICI) have significantly improved the prognosis of many advanced cancers, and may be given in non-metastatic cancer in the near future. ICI have recently been reported to induce fulminant cardiotoxic effects such as myocarditis, responsible for ~50% mortality rates.
Objective: To estimate the risk of sudden death (SD) and ventricular arrhythmias in patients receiving ICI using the World Health Organization individual case safety report (ICSR) database, Vigibase (WHO international pharmacovigilance database).
Methods: The system organ class MEDRA was used to identify cases as ICSR with the terms sudden death, sudden cardiac death, cardiac arrest, ventricular fibrillation, ventricular tachycardia, ventricular arrhythmia and torsades de pointes (named as SD events) from Nov 1967 to Nov 2019. We used the ATC code L01 which regroups 219 antineoplastic agents including ICI avelumab (anti-PDL1), ipilimumab (anti CTLA4), nivolumab (anti-PD1) and pembrolizumab (anti-PD1). A disproportionality analysis was performed to estimate of relative Odds Ratio (ROR). Signals were considered significant when the lower boundary of the 99.97% confidence interval (ROR0.25) was $\geq$1.
Results: We found that avelumab was significantly associated with SD events (ROR0.25=1.7). This overreporting was not observed for other ICIs. Avelumab was associated with 12 cases of cardiac arrest (n=11) or sudden death (n=1), which were reported since 2017 as the drug became available. There were however no signals regarding other terms including ventricular arrhythmias.
Conclusions: In spite of the potential severity of ICI-myocarditis, ICI do not appear as associated with the occurrence of sudden death or life-threatening arrhythmias, with the exception of avelumab (anti-PDL1), one of the latest developed ICI, indicated in metastatic Merkel cell carcinoma and advanced renal cell carcinoma. Further attention is warranted to confirm this signal that may vary among ICI therapies.