IMMUNE-RELATED ADVERSE DRUG REACTIONS ASSOCIATED TO IMMUNE CHECKPOINT INHIBITORS: DATA FROM THE ITALIAN SPONTANEOUS REPORTING SYSTEM

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Introduction: The introduction of immune checkpoint inhibitors (ICIs) in clinical practice has brought significant benefits for patients, leading to long-lasting tumor responses. Currently, 6ICIs are available on the European pharmaceutical market: PD-1inhibitors, nivolumab and pembrolizumab; PD-L1inhibitors like atezolizumab, avelumab and durvalumab; the CTLA-4inhibithor, ipilimumab. Despite their proved clinical efficacy, among the most dangerous adverse drug reactions (ADRs) related to these innovative drugs, immune-related ADRs (irADRs) are worthy of note. Since ICIs act on the immune system, irADRs can involve any tissue and organ. Indeed, althought irADRs can occur at anytime, different chronological trends for CTLA-4and PD-1/PD-L1therapies have been described. If not promptly recognized and properly managed, irADRs can be seriously debilitating and life-threatening. So, considering the clinical relevance of ICIs-induced irADRs, we analyzed the individual case safety reports (ICSRs) related to ICIs, collected in National Pharmacovigilance Network (NPN), focusing on ICSRs reporting irADRs.

Material and methods: In order to conduct our analysis, we retrieved from the Italian Reazioni Avverse dei Medicinali (RAM) system (for national safety data) and the NPN (for Campania safety data) all ICSRs reported from January 1st 2002to February 28th 2019related to ICIs. We carried out a descriptive analysis for such ICSRs, in terms of number, seriousness degree, gender, mean age, System organ Class (SOC) and irADRs p-term. Indeed, using more precise NPN data, we also performed a descriptive analysis of ICIs-related ICSRs reported in the Campania region, focusing on irADR's reports.

Results: We found overall 2088ICSRs related to ICIs listed in the RAM system. About 70% of ICSRs involved nivolumab, followed by ipilimumab, pembrolizumab, atezolizumab, and avelumab. Only 1ICSR was durvalumab-related. Majority of ICSRs reported ADRs occurred in male patients whose age relapsed in range >66years. SOCs more involved were "General disorders and administration site conditions", "Respiratory, thoracic and mediastinal disorders" and "Gastrointestinal disorders". Among all 2088ICSRs listed in RAM system, 801out of 3988reported ADRs were irADRs (20%). Majority of reported irADRs showed gastrointestinal and skin toxicity. Moreover, majority of reported irADRs was related to nivolumab, followed by ipilimumab and pembrolizumab. In the same study period, 253out of 2088ICI-related ICSRs were sent to the Campania Pharmacovigilance Regional Centre. 121out of 253ICSRs reported ICIs-induced irADRs (47.8%). More than 50% those ADRs occurred in male patients with a median age of 66years old. Reported irADRs were serious in 37.2% of cases and had an unfavorable outcome in 32.2% of cases. Overall we found 7fatal cases. Drug most commonly involved in the occurrence of irADRs was nivolumab, but the most serious cases were ipilimumab-induced involving gut. Rare irADRs like renal, cardiac and ocular ADRs have been reported. No statistical significance emerged in terms of gender-difference. Instead, statistically significant differences between cases of irADR and no-irADR emerged for both nivolumab and ipilimumab. Median time to event of all ICI class was 51days and ipilimumab-induced events occurred early compared to nivolumab. Finally, differences emerged in timing of onset of different toxicity type induced by nivolumab and ipilimumab.

Discussion and conclusion: Our results showed that several serious cases irADRs have been reported, some of which with fatal outcome. Oncologists as well as general practitioners must be ready to detect and manage irADRs knowing these adverse reactions and how to prevent and anticipate them. Patients should also be educated to report immediately any new symptoms or worsening of pre-existed ones, in order to prevent the progression of adverse event severity and avoid interruption of the immunotherapeutic treatment.