Characterizing Severe Acute Kidney Injury in Patients Treated with Immune Checkpoint Inhibitors

Background Renal immune-related adverse events (irAEs), are relatively rare in patients treated with immune checkpoint inhibitors (ICIs). This retrospective analysis characterizes the etiology of severe acute kidney injury (AKI) in patients treated with ICIs at the University of California, San Diego.

Methods The electronic medical record was used to identify all patients with an estimated glomerular filtration rate (eGFR) <15 mL/hr who received ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, cerinlimab between 1/2000 and 1/2019. Patients with baseline eGFR < 15 mL/hr or who experienced an eGFR decline to <15 mL/hr prior to ICI initiation were excluded. Extracted data included serum creatinine, eGFR, ICI dose, urinalysis, renal ultrasound, clinical documentation of both ICI-related nephritis and other suspected causes of AKI. These data were analyzed to determine cause of AKI and possible relation to ICI.

Results 46 patients who received ICI therapy and subsequently developed an AKI with eGFR < 15 mL/hr were identified. Three of these 46 patients (6.5%) had AKIs partially or predominately attributed by the clinician to ICI therapy (table 1). Characteristics of ICI-related AKI for these patients are summarized in (table 2). AKI onset occurred 32–110 days after ICI initiation. All three patients exhibited proteinuria, pyuria, and hematuria on urinalysis with negative urine cultures, but none underwent confirmatory renal biopsy. Only one patient had urine eosinophils checked, which was negative. Two (66%) of these patients received high-dose corticosteroids with subsequent complete eGFR recovery. Neither of these two patients required renal replacement therapy. One patient (33%) declined corticosteroid treatment due to concomitant multiorgan failure. An additional four (8.5%) patients developed multifactorial AKIs with other concurrent irAEs that were treated with corticosteroids, but were not formally diagnosed with ICI-related AKI.

Conclusions In our cohort, 6.5% of patients who develop AKI after receiving ICI therapy experienced immune-related nephritis. A further 8.7% of patients experienced other irAEs with AKI, suggesting that the true prevalence of immune-related nephritis is likely underdiagnosed. Notably, 84.8% of patients who develop AKI after ICI therapy have a non-ICI-related etiology, and no patient in our cohort of 46 patients underwent renal biopsy, highlighting the need for blood-based biomarker development for immune-related nephritis.
INCIDENCE AND RISK FACTORS FOR STROKE ASSOCIATED WITH IMMUNE CHECKPOINT INHIBITOR THERAPY IN CANCER PATIENTS USING REAL-WORLD CLINICAL DATA

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Background Immune checkpoint inhibitors (ICIs) can cause unique, high-grade immune-related adverse events. Although rare, ICI related stroke events can have high morbidity and mortality. Neurological monitoring is not routinely performed in patients on ICI treatment, thus risk factors remain unknown. Characterisation of such rare, but fatal adverse events requires integration of real-world data.

Methods U.S claims data (IBM MarketScan) of over 30 million commercially insured individuals was leveraged to identify 2,687,301 cancer patients between 2011–2018. Patients ≥18 years of age, treated with ICIs (targeting CTLA4 (ipilimumab) and/or the PD1 (nivolumab, pembrolizumab)/PDL1 (atezolizumab, avelumab, durvalumab) alone or in combination with ICI and/or chemotherapy were identified and followed until disenrollment. All strokes (ischemic or haemorrhagic), comorbidities, and treatment details were identified using diagnosis and billing codes. Patients from the ICI cohort were matched 1:1 to those in the chemotherapy cohort according to age, gender, NCI comorbidity score, and primary cancer as presented in the study design (figure 1). The matched cohorts were split by the specific type of chemotherapy (targeted or cytotoxic) used in the control patients. This yielded a total of 2,177 pairs of matched patients where the control arm received targeted chemotherapy, and 3,550 pairs of matched patients where the control arm received cytotoxic chemotherapy. Analyses included descriptive statistics and Cox proportional hazards regression.

Results A total of 16,574 patients received at least one dose of ICI therapy for any advanced cancer. Overall 9,496 patients who were treated with ICI met the study eligibility criteria. Stroke was identified in 489 (5.14%) patients. Mean age (±standard deviation, SD) was 60 (±12), male 62%, mean (±SD) NCI comorbidity index 2.3 (±2.12), median time to stroke was 168 days. 51.3% patients received anti-PD1 monotherapy, 37.6% received anti-CTLA4, 3.3% anti-PD-L1 and 7.8% received combination therapy (anti-PD1 plus anti-CTLA4). One-year cumulative incidence (CI) in the matched ICI vs. targeted and ICI vs. cytotoxic chemotherapy were 6.3% vs. 5.7% (p=0.07) and 4.95% vs. 4.08% (p=0.90) respectively (table 1). Within the ICI cohort, CI of stroke events with anti-CTLA4 monotherapy, 37.6% received anti-CTLA4, 3.3% anti-PD-L1 and 7.8% received combination therapy (anti-PD1 plus anti-CTLA4). One-year cumulative incidence (CI) in the matched ICI vs. targeted and ICI vs. cytotoxic chemotherapy were 6.3% vs. 5.7% (p=0.07) and 4.95% vs. 4.08% (p=0.90) respectively (table 1). Within the ICI cohort, CI of stroke events with anti-CTLA4 monotherapy vs. anti-PD1/PD-L1 and anti-CTLA4 plus anti-PD-1 combination vs. PD1/PD-L1 monotherapy were 9.89% vs. 4.54% and 6.69% vs. 3.73%, respectively (table 2). On multivariable regression analyses, patients with malignant melanoma, and those receiving anti-CTLA4 monotherapy were associated with higher risk of stroke events, while the risk was lower in patients with head and neck cancer and those who received anti-PD-1 monotherapy (table 3 and 4).