Ethics Approval The study was approved by the University of California San Diego’s Institutional Review Board, approval number 150348.

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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 chemotheraphy, 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 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).
Conclusions To the best of our knowledge, this is the largest and comprehensive real-world longitudinal study for stroke events in advanced cancer patients treated with ICI. Cumulative incidence of stroke was significantly higher in patients on anti-CTLA-4 monotherapy and anti-CTLA-4 plus anti-PD-1 combination therapy in comparison to anti-PD-1/PD-L1 monotherapy. Malignant melanoma and anti CTLA-4 therapy were independent risk factors for stroke.

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Ethics Approval The IBM MarketScan national database contains de-identified linked inpatient, outpatient, and pharmacy claims data. University Hospitals’ Institutional Review Board determined this study to be exempt from review and requirement of an informed consent.

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642 RETROSPECTIVE REVIEW OF PULMONARY PATHOLOGY ASSOCIATED WITH CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY

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Background Chimeric antigen receptor (CAR) T-cell therapy is an immunotherapy which uses genetically modified T cells engineered to express CARs to recognize and kill cells that harbor specific antigens. CAR T-cell products designed to target the tumor specific antigens have been used for the treatment of relapse and/or refractory of acute lymphoblastic leukemia, non-Hodgkin lymphomas, myeloma, and solid tumor in clinical trials at our institution. Several side effects have been reported including increased risk of infection.

Methods Retrospective review of morphologic, microbiologic and flow cytometric evaluations done on bronchioalveolar lavages (BAL), pleural effusions, and tissue biopsy specimens from post CAR T-cell adult patients with respiratory complications at our institution from March 2013 to January 2020.

Results Thirteen cases with BAL, 8 cases with biopsy (including lymph node and lung tissue) and 5 cases with pleural effusion are reviewed. All infectious diseases were detected on BAL specimens; while primary disease involvement post-CAR-T cell therapy was mostly observed in pleural effusions and tissue biopsies (figure 1). Interestingly, we found a case of a patient with refractory diffuse large B cell lymphoma that had developed mediastinal lymphadenopathy 9 months after CD19 CAR T-cell infusion (defined composition CD4 and CD8 CAR T-cells). Subsequent biopsies showed granulomatous inflammation with minimal evidence of necrosis (figure 2). Special stains with AFB, Gram, Warthin Starry, and Wright Giemsa showed no evidence of infectious organisms. Special stains were negative for acid fast, fungal, bacterial, or spirochetal organisms. Polymerase chain reaction for Mycobacterium tuberculosis complex DNA by hsp65 amplified probe, and nontuberculous mycobacteria (including Mycobacterium avium complex) by 16s rDNA, hsp65, and rpoB primer sets were both negative. No abnormal B or T cell population was found by concurrent flow cytometry; however, CAR T-cells were detected at low levels.

Conclusions Granulomatous inflammation is a chronic, histiocytic response to various chemical mediators of cell injury caused by broad etiologies. 8yT cells and T helper cells play roles on recruiting circulating monocytes and maturing of macrophages and ultimately the formation of granulomas. In our case, the patient has no documented autoimmune disease. Extensive infectious disease work-ups failed to identified infectious etiology. The presence of CAR T-cells in mediastinal lymph node 9 months after infusion is not unexpected given CAR T-cells can be detected in the blood for years in some patients. The granulomatous inflammation can be part of exaggerated tissue repair process after lymphoma cells killed by CAR T-cells. However, it may complicate or even mislead