Systemic Anti-PD-1 Immunotherapy Results in PD-1 Blockade on T Cells in the Cerebrospinal Fluid.

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Public Summary: Importance: Little is known about the penetration and bioactivity of systemically administered programmed cell death 1 (PD-1) antibodies in the central nervous system. Such information is critical for advancing checkpoint antibody therapies for treatment of brain tumors. Objective: To evaluate pembrolizumab concentrations and PD-1 blockade on T cells in the cerebrospinal fluid (CSF) after intravenous administration. Design, Setting, and Participants: Cerebrospinal fluid and blood samples were collected from 10 adult patients with high-grade gliomas who were participating in clinical trials of intracranially administered chimeric antigen receptor (CAR) T cells and intravenous pembrolizumab at City of Hope in Duarte, California, from 2017 through 2019. Neuropharmacokinetic and immunologic correlative studies were performed on CSF and serum samples. Interventions or Exposures: Pembrolizumab, 200 mg, was given intravenously every 3 weeks with a median of 2 cycles (range, 1-8). CAR T cells were administered intracranially every 1 to 4 weeks. Cerebrospinal fluid and blood samples were collected on the day of CAR T-cell administration and then 24 hours later for a total of 100 paired samples. Main Outcomes and Measures: Pembrolizumab concentrations were measured by enzyme-linked immunosorbent assay, PD-1 blocking on T cells by flow cytometry, and results of PD-1 blockade on CAR T-cell function by in vitro tumor rechallenge assays. Results: Of the 10 patients included in this study, the mean (SD) age was 45.7 (11.0) years, and 6 (60%) were women. Steady-state pembrolizumab concentrations in the CSF were achieved by 24 hours after initial intravenous administration, with a mean CSF:serum ratio of 0.009 (95% CI, 0.004-0.014). The CSF concentrations of pembrolizumab effectively blocked PD-1 on both endogenous T cells and intracranially administered CAR T cells in the CSF, with flow cytometric detection of surface PD-1 on the T cells decreasing from a mean (SD) of 39.3% (20.2%) before pembrolizumab to a mean (SD) of 3.8% (5.8%) 24 hours after pembrolizumab infusion. Steady-state concentrations in the CSF were maintained throughout the 21-day cycle of pembrolizumab, as was the PD-1 blocking effect, evidenced by no increase in detectable surface PD-1 on T cells in the CSF during that time period. Incubation of PD-1–expressing T cells with CSF samples from patients treated with pembrolizumab also resulted in PD-1 blockade. Conclusions and Relevance: Results of this study demonstrate steady-state concentrations of pembrolizumab in CSF after intravenous administration as well as CSF concentrations that are sufficient for blocking PD-1 on endogenous and adoptively transferred T cells. This provides mechanistic insight regarding the ability of systemically administered PD-1 blocking antibodies to modulate T-cell activity in the brain.

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