Dexamethasone May Make Immune Checkpoint Inhibitors Less Effective for Glioblastoma

Study finds that patients with gliobllastoma who received corticsteriod dexamethasone had significantly worse overall survival.

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Among patients with glioblastoma receiving an immune checkpoint inhibitor, those who received the corticosteroid dexamethasone at baseline for cerebral edema had significantly worse overall survival, according to results of a study published in Clinical Cancer Research, a journal of the American Association for Cancer Research.

“Dexamethasone is a potent corticosteroid that is often prescribed to patients with glioblastoma to treat symptoms related to cerebral edema, or swelling in the brain,” said David A. Reardon, MD, clinical director of the Center for Neuro-Oncology at Dana-Farber Cancer Institute in Boston. “Cerebral edema is a common yet potentially life-threatening complication for patients with glioblastoma, and treatment with corticosteroids can help to suppress the inflammation in the brain,” he added.

“Historically, patients with glioblastoma have been empirically treated with dexamethasone, even without symptoms, with many clinicians prescribing steroids for prolonged periods of time, out of a concern that patients may start to develop edema,” Reardon continued. “Our study was designed to look at that paradigm of clinical practice, particularly in the immunotherapy era, and determine if there could be negative consequences associated with dexamethasone use among patients with glioblastoma treated with immune checkpoint inhibitors.”

Reardon and colleagues evaluated the effect of concurrent dexamethasone administration with an immune checkpoint inhibitor (anti-PD-1 therapy) in syngeneic murine glioblastoma models. In an immunosensitive mouse model, which is inherently responsive to immune checkpoint blockade, the researchers found that the addition of dexamethasone to anti-PD-1 therapy resulted in reduced survival in a dose-dependent manner. Additionally, in an immunoresistant mouse model, which Reardon noted is more representative of human glioblastoma, the addition of dexamethasone to anti-PD-1 therapy or anti-PD-1 therapy plus radiotherapy also resulted in reduced survival.

“In our preclinical studies, we found that steroids had a significant detrimental effect on the efficacy of anti-PD-1 therapy, even in an immunosensitive model, which over-predicts the benefit of immune checkpoint blockade in glioblastoma patients,” said Reardon.

The researchers next analyzed overall survival data from 181 patients with glioblastoma treated with either anti-PD-1 or anti-PD-L1 therapy at Dana-Farber Cancer Institute who were diagnosed before April 1, 2019. This patient population was heterogeneous, with patients receiving treatment through a clinical trial or on a compassionate use basis; roughly 76 percent were treated for recurrence, and roughly 24 percent were treated for a new diagnosis. Of these 181 patients, around 35 percent were taking dexamethasone at baseline.

Reardon and colleagues evaluated the potential detrimental effect of dexamethasone using multivariable analysis, where they adjusted for a variety of factors, including disease setting (newly diagnosed versus recurrent), tumor volume at treatment initiation, age, and extent of resection, among the 163 patients that had complete annotated data for relevant prognostic factors. Compared with patients who were not taking dexamethasone at baseline, patients treated with dexamethasone had roughly twice the risk of death. Further, baseline use of dexamethasone was the strongest identified negative risk factor for overall survival.

“Our results suggest that we should try to avoid dexamethasone among patients with glioblastoma who are treated with immunotherapy, and if corticosteroids are clinically required, we should use these drugs judiciously,” Reardon said. “Further, our results highlight that other strategies for the treatment of cerebral edema that do not have such a broad anti-inflammatory effect critically need to be investigated.”

Limitations of the study include the retrospective nature of the clinical analyses. Further, in their preclinical studies, the researchers solely evaluated the effect of dexamethasone on the efficacy of anti-PD-1 treatment. “Whether the same observations would occur with other immunomodulatory checkpoint targeting agents, or even other immunotherapy treatments—such as vaccines, adoptive cellular therapies, or genetically engineered oncolytic viruses—remains to be evaluated,” Reardon said.

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