VIEWPOINT

Dexamethasone—Friend or Foe for Patients With Glioblastoma?

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Dexamethasone is a synthetic corticosteroid with a broad range of biologic effects, including strong anti-inflammatory activity. It has been used to treat cerebral edema in patients with glioblastoma since its introduction by Drs Lyle French and Joseph Galicich in the early 1960s. At that time, the dosage was empirically determined and set at a 10-mg bolus followed by a maintenance dose of 4 mg every 6 hours, with a physician's choice of tapering. This has become a standard of care for patients found to have a brain tumor. However, recent laboratory and clinical data have revealed that dexamethasone can be both helpful and detrimental, depending on the clinical context.

After its introduction in the clinic, early investigations revealed that dexamethasone induces considerable ultrastructural changes in cerebral vasculature.[1] Electron microscopy analysis of tissue from patients with intracranial neoplasms has shown swollen astrocyte vascular foot processes and dilated extracellular space in the adjacent brain tissue, but these changes were absent under the influence of dexamethasone. Furthermore, mouse experiments using horseradish peroxidase as an agent to measure blood-brain barrier permeability showed a dexamethasone-induced reduction in endothelial vesicles and capillaries with little effect on larger vessels. The kinetics of this decrease in permeability is also rapid and can be observed on magnetic resonance imaging 1, 3, and 7 days after treatment, with a progressive attenuation of 13%, 33%, and 57% in T1 relaxation, respectively.[2] These histologic and radiologic data collectively support the notion that dexamethasone's rapid and potent effects in attenuating cerebral edema caused by brain tumors result in clinical benefit and thus represent the principal indications for its use in patients with glioblastoma.

Dexamethasone is most often used as an efficacious anti-inflammatory and immunosuppressant agent. Generally, glucocorticoids have a potent effect on nuclear factor κ light-chain–enhancer of activated B-cell (NFκB) signaling in lymphocytes, which is necessary for effector function associated with tumor surveillance and antitumor immunity. Early studies[3] showed that a single 12-mg dose of dexamethasone results in the persistent suppression of T-cell clonal expansion in healthy human volunteers. This raises the issue of dexamethasone's ability to potentiate opportunistic infections in the population with glioblastoma. Indeed, infectious complications occurred in patients who used dexamethasone for 3 weeks or longer, and life-threatening *Pneumocystis carinii* pneumonia can develop during a taper.[4] This is similarly to the opportunistic pneumonia often observed among solid organ–transplant recipients who are treated with rapamycin and tacrolimus immunosuppressants.

Prolonged dexamethasone exposure may also suppress immune effector response against the glioblastoma by weakening the innate and adaptive immune systems. In cell-culture experiments, dexamethasone has been shown to induce immature dendritic cells' production of the immunosuppressive cytokine interleukin-10, and bias naive T cells toward a Th2 phenotype while inhibiting their production of interferon-γ. Coadministration of dexamethasone in patients with cancer during treatment also depletes their $CD4^+$ and $CD8^+$ lymphocytes. Therefore, dexamethasone induces both quantitative and qualitative changes in the adaptive immune system. It is important to recognize that these patients with glioblastoma already have impaired immune function, characterized by a reduced number and/or impaired function of naive T cells, γδ T cells, and natural killer cells, as well as by a large number of circulating granulocytic myeloid–derived immunosuppressive cells.[5] Concurrent dexamethasone use has been shown to have a larger effect on the γδ T cells and natural killer cells, resulting in a significant interference of potentially efficacious therapy for the glioblastoma itself.[5] Our post hoc analysis on the dexamethasone effect in the Effect of NovoTTF-100A in Recurrent Glioblastoma Multiforme (EF-11) trial population, in which participants with recurrent glioblastoma were randomized to Tumor-Treating Fields or the physician's choice of the best chemotherapy option, supports this notion.[6] Using an unbiased approach, we demonstrated that a dexamethasone dosage of 4.1 mg per day or more appears to shorten the survival of enrolled participants, and this outcome was not associated with tumor size and was seen in both groups. Therefore, a cutoff dosage near 4 mg per day appears to be important for patient survival. Others also observed that using a dexamethasone dosage of 4 mg or more at the end of treatment with radiation and temozolomide was associated with a worse outcome. This survival disadvantage may be mediated by dexamethasone's ability to weaken the already marginal antitumor immunity among these patients. Similarly, Pitter et al[7] analyzed the effect of dexamethasone from 3 major databases of patients with glioblastoma and found that dexamethasone use was negatively correlated with survival of those who had a gross total resection of the tumor. Collectively, these data point to dexamethasone's interference with glioblastoma treatments, but the retrospective nature of these analyses precludes our ability to draw a definitive conclusion.

The result of Radiation Therapy Oncology Group (RTOG) 0913, a randomized phase II study using the mechanistic target of rapamycin (mTOR) inhibitor

everolimus has shed important light on the negative consequences of immunosuppression in the population with glioblastoma.[8] Preclinical work has shown that mTOR functions to transduce signals in glioma cells that are necessary for their survival and proliferation. It is approved by the US Food and Drug Administration for use and marketed as Afinitor (https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022334s016lbl.pdf) to oncologists for patients with advanced hormone receptor–positive, Her2-negative breast cancer, pancreatic neuroendocrine tumors, renal cell carcinoma, and subependymal giant-cell astrocytoma, with a recommended prescription dosage of 10 to 20 mg daily. Therefore, everolimus might be expected to halt glioblastoma progression and prolong the survival of patients with recurrent disease. However, the results of RTOG 0913 study clearly contradicted these expectations, and patients taking this medication died sooner by a median of 4.7 months. They also experienced more frequent infections of grade 4 and 5 severity.

It is noteworthy that everolimus is also a potent immunosuppressant, as are rapamycin and sirolimus, and it is FDA-approved and marketed as Zortress (https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021560s006lbl.pdf) to transplant surgeons for the prevention of kidney and liver rejection, with a recommended dosage of 0.75 to 1.0 mg twice daily. This is substantially lower than the dose prescribed for patients with cancer. Therefore, the everolimus dosage used in the RTOG 0913 study population with glioblastoma was at least 5 times higher than the dosage routinely used to prevent immune rejection of transplanted organs. Importantly, these results provide a cautionary note for translating cell-autonomous preclinical experimental data produced from drug effects observed in tumor cells to clinical efficacy in patients with glioblastoma.

The cytotoxic chemotherapy temozolomide has been shown to length the survival of patients with glioblastoma, but it can also cause immunosuppression. After initial therapy with radiation and temozolomide, 40% of patients had a nadir of less than 200 $CD4^+$ lymphocytes per mm^3 and a shortened overall length of survival, and this severe state of $CD4^+$ lymphopenia persisted for at least a year.[9] Surprisingly, $CD4^+$ lymphopenia was found in 15% of the population at initial diagnosis, before any therapeutic or nontherapeutic interventions were even initiated.[10] Therefore, any medications that may worsen immunosuppression during treatment, such as dexamethasone, should be reduced once the patient with glioblastoma is stabilized.

Together, the clinical experience with dexamethasone and everolimus offers compelling evidence to indicate that agents that interfere with immune effector function reduce the ability of patients with glioblastoma to mount an effective antitumor immune response. These patients are also likely to be at a greater risk of infection. In light of the large number of trials showing no efficacy from various chemotherapies, small molecule inhibitors, vaccines, and checkpoint inhibitors, a first and important step is for the neurooncology community to reexamine the possible association of dexamethasone with outcomes in trials that were nonspecific about corticosteroid use to determine if their initial analyses may have been compromised and quickly find potential replacements.

ARTICLE INFORMATION

Published Online: January 22, 2019. doi:10.1001/jamaneurol.2018.4530

Conflict of Interest Disclosures: Dr Wong reports receiving sponsored research agreements from Novocure and Novartis. Dr Swanson reports receiving a sponsored research agreement from Novocure. No other disclosures were reported.

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