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Corticosteroids for peritumoral edema: time to overcome our addiction?

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The use of corticosteroids to treat cerebral edema in brain tumor patients dates back to case reports by Ingraham and Matson in 1952.[1] A few years later, a then new corticosteroid with comparatively low mineralocorticoid properties and high glucocorticoid potency named dexamethasone was first synthesized.[2] In the early 1960s, Galichich and colleagues published their experience with dexamethasone in brain tumor patients.[3] Ever since, dexamethasone has been the standard corticosteroid used to treat vasogenic cerebral edema in brain tumor patients. Despite its widespread use, there are few prospective studies available to guide the optimal dosing and use of dexamethasone.[2]

The long-term side effects of dexamethasone are well known, including Cushingnoid appearance, truncal obesity, lymphopenia, immunosuppression, hyperglycemia, steroid myopathy, fluid retention, visual blurring, tremor, mood/behavioral changes (including psychosis), osteoporosis, and cerebral atrophy.[2] Dexamethasone may decrease blood–tumor barrier permeability and thus alter the appearance of postcontrast imaging.[4] While some studies suggest that dexamethasone may also restrict penetration of chemotherapy across the blood–tumor barrier, the data are conflicting.[5]

A recent study published in the May 2016 issue of *Brain* by Pitter and colleagues provides additional evidence on the negative impact of dexamethasone on survival in glioblastoma multiforme (GBM) patients.[6] Using 3 separate GBM patient cohorts (622 patients treated at Memorial Sloan-Kettering Cancer Center, 513 patients treated on the pivotal European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada study establishing radiation and temozolomide as standard of care, and 832 patients treated in the German Glioma Network), dexamethasone use during radiation was shown to be an independent marker of shorter survival, even after adjusting for established prognostic factors such as age, performance status, and extent of surgery. Studies in a mouse model with platelet derived growth factor–driven gliomas showed that pretreatment with dexamethasone can adversely impact the survival benefit of irradiation. Comparing untreated and dexamethasone treated mouse glioma samples, they identified 19 genes, many of which were involved in proliferation, that were downregulated in the dexamethasone-treated mice. Analyzing the database of The Cancer Genome Atlas, patients with the dexamethasone-associated gene expression signature were shown to have a shorter survival. These data suggest that dexamethasone-induced antiproliferative effects may confer protection from radiotherapy and chemotherapy and provides additional rationale for minimizing the use of corticosteroids. In particular, the widespread practice of maintaining patients on corticosteroids during radiation therapy in case they develop peritumoral edema should be discontinued in asymptomatic patients, and corticosteroids administered only if patients develop symptomatic edema.

For asymptomatic patients with brain metastases[7,8] or high-grade glioma,[9] clinical practice guidelines are clear; steroids are not required. For symptomatic patients, clinical guidelines suggest starting doses of 4–8 mg/day of dexamethasone, although patients with impaired consciousness or other signs of increased intracranial pressure may benefit from higher doses. [7,8] Two consecutive randomized studies on dexamethasone dosing in patients with brain metastases found no statistically significant improvement in KPS comparing high-dose dexamethasone (16 mg/day) and low-moderate dose dexamethasone (4 or 8 mg/day) after one week of treatment.[10] However, there was greater toxicity seen in the 16 mg cohort.

The most commonly used dexamethasone dosing schedule is 4 mg every 6 hours, which is an onerous dosing schedule. However, dexamethasone need not be dosed so frequently. Although the plasma half-life of oral dexamethasone is 3–4 hours, the biologic half-life is 34–54 hours.[11] Therefore, dexamethasone administered once or twice daily can achieve a similar effect as dexamethasone divided 4 times daily.[10,12]

As clinicians, we are often too liberal with dexamethasone dosing in many brain tumor patients. Sometimes, patients are treated based on edema seen on imaging studies, even if they are asymptomatic. Frequently, dexamethasone is started at much higher and more frequent doses than necessary, not based on data but based on our 4 mg q6h habit. Sometimes, dexamethasone is started prophylactically to guard against symptoms from cerebral edema that may never occur in the absence of dexamethasone.[8] Ideally, patients would not

receive dexamethasone, but if necessary, we should always aim for the lowest dose that can achieve the desired effect. We must always be aware that our decision to treat a patient about to start radiation with dexamethasone brings with it side effects that impact a patient's quality of life and possibly even survival in light of data from Pitter et al.

Our patients need more effective and less toxic alternatives to corticosteroids for treatment of peritumoral edema. Bevacizumab and other agents targeting vascular endothelial growth factor and its receptors are effective in reducing peritumoral edema but are associated with significant cost and some toxicity.[13] The Response Assessment in Neuro-Oncology working group has established a committee to evaluate steroid use as an endpoint in clinical trials. Hopefully, this will lead to the development of more effective therapies for peritumoral edema and help reduce our addiction to corticosteroids.

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