Curr. Treat. Options in Oncol. (2020) 21:77
DOI 10.1007/s11864-020-00771-7

Neuro-oncology (GJ Lesser, Section Editor)

Optimal Management of Corticosteroids in Patients with Intracranial Malignancies

Karan S. Dixit, MD
Priya U. Kumthekar, MD[*]

Address
[*]Department of Neurology, Division of Neuro-Oncology, Northwestern University Feinberg School of Medicine, Chicago, USA
Email: Priya.Kumthekar@nm.org

This article is part of the Topical Collection on *Neuro-oncology*

Keywords Corticosteroids · Glioma · Brain metastases · Immunotherapy · Immunosuppression · Myopathy · Quality of life

Opinion statement

Corticosteroids have been essential in the management of brain tumor patients for decades, primarily for the treatment of peritumoral cerebral edema and its associated neurologic deficits. Dexamethasone is the drug of choice with standard practice being administration up to four times per day, however, because of its long biologic half-life and high potency, once or twice a day dosing is likely adequate in patients without elevated intracranial pressure. The length of corticosteroid treatment should be limited to the shortest period of time to minimize the risk of potential toxicities that can significantly affect quality of life, as well as to avoid a possible detrimental impact on survival in high-grade glioma patients and abrogation of the effect of immunotherapy. Agents such as bevacizumab should be considered in patients who are unable to wean completely off of steroids as well as those who have symptomatic edema and are on immunotherapy. Several other agents have been studied without much success. An increased understanding of the complex pathophysiology of peritumoral vasogenic edema is critically needed to discover new agents that are safer and more effective.

Introduction

Corticosteroids have widely been used for patients with brain cancer since the 1950s; when it was discovered, they alleviate vasogenic edema in patients with brain metastases. Corticosteroids, specifically dexamethasone, have since become the gold standard for management of peritumoral cerebral edema and its associated

Published online: 30 July 2020

neurologic symptoms [1, 2]. Although corticosteroids provide significant clinical benefit to patients, they are associated with numerous potential side effects, especially with prolonged use [3]. There is also mounting evidence suggesting a negative impact on survival in glioma patients treated with corticosteroids. Thus, judicious use of corticosteroids is needed to minimize undesirable effects. In this review, we will summarize the pharmacology, toxicity profile, and optimal use and dosing strategies for corticosteroids, with an emphasis on dexamethasone.

Pharmacology and mechanism of action

Corticosteroids, which consist of both glucocorticoids and mineralocorticoids, are hormones released by the adrenal cortex and mediate critical physiologic functions including stress response, inflammation, metabolism, and homeostasis [4]. They exert their effects by binding to intracellular glucocorticoid receptors after crossing the plasma cell membrane which then localize into the nucleus to bind to DNA to modulate transcription [5, 6].

Exogenous corticosteroids are readily absorbed through the gastrointestinal tract with an oral bioavailability ranging from 60 to 100% [7, 8]. A recent study in community-acquired pneumonia patients showed that the oral bioavailability of dexamethasone is 81% compared to intravenous delivery [9]. Corticosteroids are primarily bound to albumin and are metabolized in the liver through the cytochrome P450 oxidase system [7, 8]. Because of their metabolism through the CYP450 system, there are many potential drug-drug interactions to be aware of, especially with older anti-epileptic agents such as phenytoin and carbamazepine [10]. Metabolic disturbances from renal and hepatic dysfunction also impact the metabolism of dexamethasone; thus, organ function must be carefully monitored and managed. Renal dysfunction increases dexamethasone clearance thereby decreasing the biologic half-life while hepatic dysfunction does the opposite [11].

Although the exact mechanism of corticosteroids on peritumoral vasogenic edema is not fully understood, it has been postulated to occur through multiple pathways. One proposed mechanism is the modulation of claudin and occludin expression, which comprise the tight junctions between endothelial cells of the blood-brain barrier, and are downregulated in vasogenic edema to decrease capillary permeability and extravasation of fluid [12]. Blood-brain barrier breakdown is strongly mediated by the overexpression of vascular endothelial growth factor (VEGF) which increases vascular permeability thus another proposed mechanism for vasogenic edema control is suppression of tumor cell VEGF mRNA expression by glucocorticoids [13, 14]. Another possible mechanism is glucocorticoid-mediated suppression of pro-inflammatory transcription factor NF- B and proinflammatory cytokines to decrease extent of cytokine-driven blood-brain barrier breakdown [5].

Dosing

Dexamethasone is the most commonly used corticosteroid in neuro-oncology due to its low mineralocorticoid effects which minimize water and sodium retention, its high potency, as well as its extended biologic half-life of 36–54 h which allows daily or twice-daily dosing [15].

Dexamethasone has also been shown to be highly effective at decreasing symptoms associated with vasogenic edema in over 70% of treated patients with primary and metastatic brain tumors [16]. Symptomatic improvement can be seen in several hours but is maximal between 24 and 72 h [16]. Although dexamethasone has been used extensively for decades, there is little consensus on dosage, duration, or appropriate tapering schedule.

The goal of corticosteroid therapy should be to use the lowest effective dose that controls patients' symptoms for the shortest duration to minimize toxicity. In the acute hospital-based setting when patients present with progressive neurologic deterioration, intravenous doses of dexamethasone 10–20 mg are given with a maintenance dose of 16 mg per day divided as either 4 mg four times daily or 8 mg twice daily [15]. An every 6-h dosing schedule is commonly prescribed which dates back to the landmark study from 1961 by Dr. Joseph Galicich et al. which demonstrated significant improvement in neurologic symptoms related to vasogenic edema by using a bolus of dexamethasone 10–40 mg followed by 4 mg every 6 h [17]. This dosing schedule may expose patients to more corticosteroids than needed and often disrupts sleep leading to poorer quality of life. Based on the biologic half-life of dexamethasone, twice a day or even once a day administration is likely adequate in most cases. A recent Letter to the Editor in *Neurosurgery* authored by a leading group of neuro-oncologists was published with a goal to update dexamethasone prescribing patterns to a more contemporary and pharmacobiologically based dosing regimen [18].

Total daily doses of dexamethasone 16 mg may also not be necessary. A randomized control trial assessing the efficacy of 4 mg, 8 mg, and 16 mg of dexamethasone in metastatic brain tumor patients showed similar improvement in the Karnofsky Performance Scale (KPS) between all doses if patients were not at risk of elevated intracranial pressure and there was no risk of herniation. There was, however, a dose-dependent increase in side effects with patients receiving more than 8 mg/day of dexamethasone being more likely to develop Cushingoid facies and fluid retention while those who received more than 4 mg/day were at higher risk of developing corticosteroid-related myopathy compared to patients who received lower than 4 mg/day (38 vs 14%) [19]. Thus, for patients with symptomatic vasogenic edema and without signs of elevated intracranial pressure and mass effect, starting dexamethasone 4 or 8 mg once per day is a reasonable dose. Asymptomatic patients with radiographic findings of peritumoral vasogenic edema should not routinely be prescribed corticosteroids [20–22].

The length of corticosteroid treatment is highly dependent on rate and extent of clinical improvement; however, tapering should be attempted as soon as clinically possible. Corticosteroids can be tapered rapidly, over the course of a week, if treatment has been less than 10–14 days. However, patients treated with longer courses should be tapered more slowly over the course of 2 weeks or longer to avoid adrenal insufficiency which may present as headache, nausea, myalgias, and symptomatic hypotension [23]. To treat secondary adrenal insufficiency, hydrocortisone 15 mg total per day in two or three divided doses can be given [24].

Side effects

Corticosteroid toxicity limits its chronic use. The incidence of side effects is related both to the cumulative dose as well as the length of treatment, however,

they may occur early into the treatment course [23, 25]. In a cohort of 59 patients with brain tumors who received dexamethasone, 51% had at least one steroid side effect, with nearly 20% of patients ultimately requiring hospitalization [3]. Corticosteroid use is associated with numerous systemic side effects including myopathy, immunosuppression, fluid retention, weight gain, glucose intolerance, acne, osteoporosis, insomnia, behavioral disturbances including delirium and psychosis, cerebral atrophy, among many others; however, in this review, we will highlight myopathy, *Pneumocystis jiroveci* pneumonia, and behavioral disturbance as they have significant morbidity and implications for brain tumors patients [26].

Corticosteroid-induced myopathy

Corticosteroid-induced myopathy has been reported in up to 10% of primary brain tumors patients and 60% of general oncology patients [27, 28]. Both treatment duration and cumulative doses have been implicated as contributing factors for corticosteroid-induced myopathy [27, 28]. It typically develops as subacute onset with most patients becoming symptomatic after 9 weeks of therapy, however, older patients may develop symptoms only after a few weeks of therapy [15, 27].

Painless or mildly painful bilateral proximal weakness is the hallmark of steroid-induced myopathy with the pelvic girdle muscles being affected more often than the shoulders. Patients often describe difficulty arising from a seated position and with climbing stairs. Rarely, distal muscles and respiratory muscles can be affected [28, 29]. Serum creatine kinase muscle enzymes are typically normal and electromyography may demonstrate myopathic findings [29].

Treatment requires discontinuation or tapering of corticosteroids, which may pose a challenge due to balancing other worsening neurologic deficits. Corticosteroid myopathy symptoms, such as gait difficulty, may be confused with symptoms related to peritumoral edema. Physical therapy can also be beneficial and should be considered for all patients [30].

Pneumocystis jiroveci pneumonia

Corticosteroid therapy can lead to immunosuppression which predisposes patients to opportunistic infections. *Pneumocystis jiroveci* pneumonia (PJP) is a rare, yet potentially fatal fungal infection, with a mortality rate reported as high as 40% [31]. Brain tumor patients are uniquely at higher risk of developing PJP, especially those on prolonged courses of corticosteroids with an incidence rate estimated to be 2–6% after a median dexamethasone treatment course of 10–12 weeks [31, 32]. Radiation and concurrent therapy with temozolomide are also associated with increased risk of PJP [33–35]. As such, there is a black-box warning for temozolomide which recommends PJP prophylaxis in newly diagnosed patients undergoing chemoradiation. Despite this warning, there are varied practice patterns with a minority of practitioners at US-based cancer centers deferring PJP prophylaxis [36]. Prophylaxis has also been recommended for patients with a CD4+ count < $300/mm^3$, persistent absolute lymphocyte count < 500 cells/mm^3, and those receiving dexamethasone therapy greater than 3 mg (or prednisone 20 mg equivalent) for longer than 1–2 months [34, 37–39].

Presenting symptoms include fever, dyspnea, nonproductive cough, and chest pain for days to weeks. There should be a low threshold to workup patients with any respiratory symptoms in patients receiving chronic corticosteroid and/or chemoradiation therapy [40, 41].

First-line prophylactic therapy is double-strength trimethoprim-sulfamethoxazole (TMP/SMX 160 mg/800 mg) three times weekly, which is both effective and inexpensive. Alternatively, aerosolized pentamidine 300 mg every month or dapsone 100 mg daily may be used in cases of allergy or intolerance to trimethoprim-sulfamethoxazole [41].

Behavioral disturbances

Neuropsychiatric symptoms are common with corticosteroid use and may affect up to 60% of patients [42]. Patients can present with a variety of symptoms including anxiety, irritability, delirium, hypomania, euphoria, insomnia, memory impairment, attentional and concentration deficits, depression, and even frank psychosis [42–44]. Symptom onset typically occurs within 3–14 days of starting corticosteroids but can occur up to a month later [45, 46]. The incidence is likely dose-related as well. Patients who received more than 80 mg/day of prednisone (dexamethasone 12 mg) had a nearly 20% chance of developing psychiatric symptoms compared to 1% in individuals receiving less than 40 mg/day (dexamethasone 6 mg) [47].

Management of corticosteroid-induced psychiatric symptoms begins with tapering, and ultimately, discontinuing the drug. Delirium symptoms often improve a few days after discontinuing corticosteroids, while psychotic and depressive symptoms can take up to several weeks [48]. For patients who are unable to completely wean off of corticosteroids due to neurologic symptoms, neuroleptics such as olanzapine or lithium can be considered [49, 50].

Lymphoma

The classical teaching for potential cases of central nervous system lymphoma is to avoid the administration of corticosteroids as they are lymphotoxic leading to a radiographic response and ultimately reduce the diagnostic yield of a biopsy [51]. This notion has been challenged by two studies which demonstrated no significant detriment on obtaining a diagnosis of CNS lymphoma after administration of corticosteroids.

In a Mayo series, only 8 of 109 (7%) patients who received pre-biopsy corticosteroids required a second biopsy to obtain a diagnosis. Another observation noted in the study was that only 18% of patients showed a radiographic tumor regression after receiving corticosteroids prior to biopsy [52]. A more recent study also demonstrated that an accurate diagnosis of primary central nervous system lymphoma was made in 15 of 16 patients who received corticosteroids prior to biopsy [53]. However, these studies are limited by their retrospective nature; thus, as a general practice, it is still prudent to defer the use of corticosteroids in suspected cases of central nervous system lymphoma. Furthermore, publishing on "false negatives" of true lymphoma cases that are masked by corticosteroid use is more difficult to ascertain and may likely add to this publication bias. The early administration of corticosteroids prior to beginning chemotherapy in cases

of newly diagnosed central nervous system lymphoma did not have a negative impact on treatment response or survival [54].

Impact on survival in glioma

There is a mounting body of evidence suggesting corticosteroid dependence, especially when given during chemoradiation, as an independent risk factor for poorer outcome in glioma patients who are dependent on corticosteroids [55–57]. One study reported an overall survival of 12.7 months compared to 22.6 months for those who received dexamethasone during radiation and chemotherapy [55]. A pivotal study by Pitter et al. confirmed the use of corticosteroids as an independent negative prognostic predictor, adjusting for performance status, age, and extent of resection, in three large independent cohorts totaling over 2000 patients [56]. The mechanism is not fully elucidated; however, it is proposed that corticosteroids may have a cytoprotective effect on glioma cells which ultimately render the tumor less radiosensitive. Nineteen genes associated with the mitotic cycle were identified as being downregulated when exposed to dexamethasone ultimately leading to decreased tumor proliferation by causing glioma cells to spend more time in the G1 phase (more radioresistant phase), rather than G2/M cell cycle [56].

Another proposed mechanism for corticosteroids impairing survival is based on their effect on raising blood glucose level. Several studies have demonstrated poorer prognosis in glioma patients with hyperglycemia [58–61]. Proposed mechanisms for hyperglycemia contributing to poor outcome include promoting proliferation of hypoxic cells, which are more radioresistant; providing an energy source for tumor cell glycolysis leading to tumor proliferation; and producing pyruvate and lactate which have anti-oxidative properties that would impact the efficacy of ionizing radiation [62].

Immunotherapy

There have been significant advances in the use of immunotherapy in cancer and there is a growing interest in neuro-oncology. Despite numerous clinical trials, there has unfortunately been little success in glioblastoma, however, patients with brain metastases, especially those with melanoma, non-small cell lung cancer, and renal cell carcinoma, have shown response to checkpoint inhibitors [63–65]. Corticosteroid use in immunotherapy has been associated with poorer disease response. A retrospective study in non-small cell lung cancer patients treated with immunotherapy revealed a greater than 10% decrease in response rate in patients with baseline corticosteroids use prior to starting treatment [66]. In a trial of melanoma patients with brain metastases treated with ipilimumab, those not on corticosteroids showed a 24% intracranial response, while those treated with corticosteroids had an intracranial disease control rate of only 10% [63]. The immunosuppressive nature of corticosteroids has been implicated as one of the potential contributors to the lack of response with immunotherapy in recurrent glioblastoma [67, 68]. Although there is a lack of concrete data regarding the full effect of corticosteroids and their relationship to glioblastoma, due to the potential immunosuppression and negative effects, the use of

dexamethasone should be limited to the smallest effective dose and the shortest duration to control neurologic symptoms

Future directions

Alternatives to corticosteroids for vasogenic edema management are critically needed due to aid in symptomatic cerebral edema while decreasing the numerous potential side effects, their negative impact on survival, and because of their interaction with immunotherapy which will likely have an increasingly important role. As previously discussed, vascular endothelial growth factor (VEGF) is upregulated in brain tumors and plays a significant role in the development of vasogenic edema. Bevacizumab, a VEGF inhibitor, is currently the most widely used corticosteroid-sparing agent for vasogenic edema management and can allow patients to wean off of corticosteroids [69, 70]. Cediranib, another VEGF inhibitor, also demonstrated a radiographic and clinical response, as well as allowed patients to reduce their corticosteroid usage [71].

Corticotropic-releasing factor (CRF) is a neuropeptide that has also been shown to reduce vasogenic edema by decreasing tumor vascular permeability [72, 73]. Corticorelin acetate, a synthetic analog of CRF, was studied in a prospective, randomized, double-blinded study in patients with both primary and secondary brain tumors with vasogenic edema. The primary endpoint of dexamethasone dose reduction of 50% was not met but the maximum percent reduction of dexamethasone was higher in the treatment group (62.7%) compared to the control group (51.4%). Those receiving corticorelin acetate were also less likely to have a Cushingoid appearance or myopathy [74].

Cyclooxygense-2 (COX-2) inhibitors have also been studied as elevated COX-2 expression has been discovered in microglial cells within brain tumors [75]. In pre-clinical studies and case reports, COX-2 inhibition has demonstrated decreased vascular permeability and possible anti-vasogenic edema activity [76–78]. There are not yet been any large studies to assess the validity of these drugs yet.

Boswellic acids have also been studied for their anti-inflammatory properties with several studies in brain tumor patients demonstrating some activity in vasogenic edema management [79–81]. The proposed mechanisms for boswellic acid activity in vasogenic edema may be a combination of suppression of pro-inflammatory prostaglandins and VEGF-mediated angiogenesis [82, 83]. A randomized, double-blinded study demonstrated a reduction of vasogenic edema by 75% in 60% of the experimental arm compared to 26% of the placebo arm [81]. Curcumin, or turmeric, is a spice isolated from the *Curcuma longa* plant which has been used for centuries as an anti-inflammatory agent in alternative medicine and also has shown evidence for improvement in brain edema after hemorrhage in mouse model [84]. A purported mechanism is through inhibition of the NF-κB pathway and subsequent decrease of gene and protein expression of aquaporin-4 and aquaporin-9 [85–87].

Conclusion

Corticosteroids play a critical role in the management of patients with brain tumors by improving symptoms related to peritumoral vasogenic edema.

Although the benefit to patients' neurologic symptoms can be significant, their use is associated with side effects which can affect nearly every organ system, can impact on quality of life, and may even potentially be fatal. Moreover, there is mounting evidence that the use of corticosteroids is an independent risk factor for poorer outcome in patients with high-grade glioma. In addition, corticosteroids may abrogate the effect of immunotherapy which is being used more often in primary and metastatic brain cancer management. Due to these reasons, as clinicians, we must always be mindful about our usage of corticosteroids by ensuring they are used for the proper indication and when used, they are at the smallest effective dosage for the shortest possible duration. Currently, bevacizumab is the only readily available non-corticosteroid agent for vasogenic edema management and should be used in cases where patients are unable to wean off corticosteroids. A better understanding of the molecular basis of vasogenic edema will hopefully lead to new and more effective agents with fewer side effects.

References and Recommended Reading

1. Kofman S, Garvin JS, Nagamani D, Taylor SG 3rd. Treatment of cerebral metastases from breast carcinoma with prednisolone. J Am Med Assoc. 1957;163(16):1473–6.
2. Walsh D, Doona M, Molnar M, Lipnickey V. Symptom control in advanced cancer: important drugs and routes of administration. Semin Oncol. 2000;27(1):69–83.
3. Weissman DE, Dufer D, Vogel V, Abeloff MD. Corticosteroid toxicity in neuro-oncology patients. J Neuro-Oncol. 1987;5(2):125–8.
4. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev. 2000;21(1):55–89.
5. Barnes PJ. Molecular mechanisms and cellular effects of glucocorticosteroids. Immunol Allergy Clin N Am. 2005;25(3):451–68.
6. McEwen BS. Non-genomic and genomic effects of steroids on neural activity. Trends Pharmacol Sci. 1991;12(4):141–7.
7. Czock D, Keller F, Rasche FM, Haussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. Clin Pharmacokinet. 2005;44(1):61–98.
8. Cummings DM, Larijani GE, Conner DP, Ferguson RK, Rocci ML Jr. Characterization of dexamethasone binding in normal and uremic human serum. DICP. 1990;24(3):229–31.
9. Spoorenberg SM, Deneer VH, Grutters JC, Pulles AE, Voorn GP, Rijkers GT, et al. Pharmacokinetics of oral vs. intravenous dexamethasone in patients hospitalized with community-acquired pneumonia. Br J Clin Pharmacol. 2014;78(1):78–83.
10. Benit CP, Vecht CJ. Seizures and cancer: drug interactions of anticonvulsants with chemotherapeutic agents, tyrosine kinase inhibitors and glucocorticoids. Neurooncol Pract. 2016;3(4):245–60.
11. Kawai S, Ichikawa Y, Homma M. Differences in metabolic properties among cortisol, prednisolone, and dexamethasone in liver and renal diseases: accelerated metabolism of dexamethasone in renal failure. J Clin Endocrinol Metab. 1985;60(5):848–54.
12. Salvador E, Shityakov S, Forster C. Glucocorticoids and endothelial cell barrier function. Cell Tissue Res. 2014;355(3):597–605.
13. Heiss JD, Papavassiliou E, Merrill MJ, Nieman L, Knightly JJ, Walbridge S, et al. Mechanism of dexamethasone suppression of brain tumor-associated vascular permeability in rats. Involvement of the glucocorticoid receptor and vascular permeability factor. J Clin Invest. 1996;98(6):1400–8.
14. Kim H, Lee JM, Park JS, Jo SA, Kim YO, Kim CW, et al. Dexamethasone coordinately regulates angiopoietin-1 and VEGF: a mechanism of glucocorticoid-induced stabilization of blood-brain barrier. Biochem Biophys Res Commun. 2008;372(1):243–8.
15. Dietrich J, Rao K, Pastorino S, Kesari S. Corticosteroids in brain cancer patients: benefits and pitfalls. Expert Rev Clin Pharmacol. 2011;4(2):233–42.
16. Kaal EC, Vecht CJ. The management of brain edema in brain tumors. Curr Opin Oncol. 2004;16(6):593–600. https://doi.org/10.1097/01.cco.0000142076.52721.b3.

17. Galicich JH, French LA, Melby JC. Use of dexamethasone in treatment of cerebral edema associated with brain tumors. J Lancet. 1961;81:46–53.
18. Lim-Fat MJ, Bi WL, Lo J, Lee EQ, Ahluwalia MS, Batchelor TT, et al. Letter: when less is more: dexamethasone dosing for brain tumors. Neurosurgery. 2019;85(3):E607–E8.
19. Vecht CJ, Hovestadt A, Verbiest HB, van Vliet JJ, van Putten WL. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized study of doses of 4, 8, and 16 mg per day. Neurology. 1994;44(4):675–80.
20. Ryken TC, McDermott M, Robinson PD, Ammirati M, Andrews DW, Asher AL, et al. The role of steroids in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. J Neuro-Oncol. 2010;96(1):103–14.
21. Kostaras X, Cusano F, Kline GA, Roa W, Easaw J. Use of dexamethasone in patients with high-grade glioma: a clinical practice guideline. Curr Oncol. 2014;21(3):e493–503.
22. Expert Panel on Radiation Oncology-Brain M, Lo SS, Gore EM, Bradley JD, Buatti JM, Germano I, et al. ACR Appropriateness Criteria(R) pre-irradiation evaluation and management of brain metastases. J Palliat Med. 2014;17(8):880–6.
23. Roth P, Happold C, Weller M. Corticosteroid use in neuro-oncology: an update. Neuro-Oncology Practice. 2014;2(1):6–12.
24. Crown A, Lightman S. Why is the management of glucocorticoid deficiency still controversial: a review of the literature. Clin Endocrinol. 2005;63(5):483–92.
25. Ryan R, Booth S, Price S. Corticosteroid-use in primary and secondary brain tumour patients: a review. J Neuro-Oncol. 2012;106(3):449–59.
26. Drappatz J. Medical care of patients with brain tumors. Continuum Lifelong Learning Neurol. 2012;18(2):275–94.
27. Dropcho EJ, S-j S. Steroid-induced weakness in patients with primary brain tumors. Neurology. 1991;41(8):1235–9.
28. Batchelor TT, Taylor LP, Thaler HT, Posner JB, DeAngelis LM. Steroid myopathy in cancer patients. Neurology. 1997;48(5):1234–8.
29. Gupta A, Gupta Y. Glucocorticoid-induced myopathy: pathophysiology, diagnosis, and treatment. Indian J Endocrinol Metab. 2013;17(5):913–6.
30. LaPier TK. Glucocorticoid-induced muscle atrophy. The role of exercise in treatment and prevention. J Cardpulm Rehabil. 1997;17(2):76–84.
31. Henson JW, Jalaj JK, Walker RW, Stover DE, Fels AO. Pneumocystis carinii pneumonia in patients with primary brain tumors. Arch Neurol. 1991;48(4):406–9.
32. Slivka A, Wen PY, Shea WM, Loeffler JS. Pneumocystis carinii pneumonia during steroid taper in patients with primary brain tumors. Am J Med. 1993;94(2):216–9.
33. Yu SK, Chalmers AJ. Patients receiving standard-dose temozolomide therapy are at risk of Pneumocystis carinii pneumonia. Clin Oncol. 2007;19(8):631–2.
34. De Vos FY, Gijtenbeek JM, Bleeker-Rovers CP, van Herpen CM. Pneumocystis jirovecii pneumonia prophylaxis during temozolomide treatment for high-grade gliomas. Crit Rev Oncol Hematol. 2013;85(3):373–82.
35. Cooley L, Dendle C, Wolf J, Teh BW, Chen SC, Boutlis C, et al. Consensus guidelines for diagnosis, prophylaxis and management of Pneumocystis jirovecii pneumonia in patients with haematological and solid malignancies, 2014. Intern Med J. 2014;44(12b):1350–63.
36. Skorupan N, Ranjan S, Mehta S, Yankulina O, Nenortas N, Grossman S, et al. Pneumocystis jirovecii prophylaxis in patients treated for high-grade gliomas: a survey among neuro-oncologists. Neurooncol Pract. 2019;6(4):321–6.
37. Lacy J, Saadati H, Yu JB. Complications of brain tumors and their treatment. Hematol Oncol Clin North Am. 2012;26(4):779–96.
38. Hughes MA, Parisi M, Grossman S, Kleinberg L. Primary brain tumors treated with steroids and radiotherapy: low CD4 counts and risk of infection. Int J Radiat Oncol Biol Phys. 2005;62(5):1423–6.
39. Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(30):3043–54.
40. Schiff D. Pneumocystis pneumonia in brain tumor patients: risk factors and clinical features. J Neuro-Oncol. 1996;27(3):235–40.
41. Wen PY, Schiff D, Kesari S, Drappatz J, Gigas DC, Doherty L. Medical management of patients with brain tumors. J Neuro-Oncol. 2006;80(3):313–32.
42. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes. A report of 14 cases and a review of the literature. J Affect Disord. 1983;5(4):319–32.
43. Stiefel FC, Breitbart WS, Holland JC. Corticosteroids in cancer: neuropsychiatric complications. Cancer Investig. 1989;7(5):479–91.
44. Sacks O, Shulman M. Steroid dementia: an overlooked diagnosis? Neurology. 2005;64(4):707–9.
45. Naber D, Sand P, Heigl B. Psychopathological and neuropsychological effects of 8-days' corticosteroid treatment. A prospective study. Psychoneuroendocrinology. 1996;21(1):25–31.
46. Nishimura K, Harigai M, Omori M, Sato E, Hara M. Blood-brain barrier damage as a risk factor for corticosteroid-induced psychiatric disorders in systemic lupus erythematosus. Psychoneuroendocrinology. 2008;33(3):395–403.
47. Acute adverse reactions to prednisone in relation to dosage. Clin Pharmacol Ther. 1972;13(5):694-8.
48. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. Mayo Clin Proc. 2006;81(10):1361–7.

49. Goldman LS, Goveas J. Olanzapine treatment of corticosteroid-induced mood disorders. Psychosomatics. 2002;43(6):495–7.
50. Terao T, Yoshimura R, Shiratuchi T, Abe K. Effects of lithium on steroid-induced depression. Biol Psychiatry. 1997;41(12):1225–6.
51. Cartmill M, Allibone R, Bessell EM, Byrne PO. Primary cerebral non-Hodgkin's lymphoma: problems with diagnosis and development of a protocol for management. Br J Neurosurg. 2000;14(4):313–5 discussion 6.
52. Porter AB, Giannini C, Kaufmann T, Lucchinetti CF, Wu W, Decker PA, et al. Primary central nervous system lymphoma can be histologically diagnosed after previous corticosteroid use: a pilot study to determine whether corticosteroids prevent the diagnosis of primary central nervous system lymphoma. Ann Neurol. 2008;63(5):662–7.
53. Binnahil M, Au K, Lu JQ, Wheatley BM, Sankar T. The influence of corticosteroids on diagnostic accuracy of biopsy for primary central nervous system lymphoma. Can J Neurol Sci. 2016;43(5):721–5.
54. Gessler F, Bernstock JD, Behmanesh B, Brunnberg U, Harter P, Ye D, et al. The impact of early corticosteroid pretreatment before initiation of chemotherapy in patients with primary central nervous system lymphoma. Neurosurgery. 2019;85(2):264–72.
55. Shields LB, Shelton BJ, Shearer AJ, Chen L, Sun DA, Parsons S, et al. Dexamethasone administration during definitive radiation and temozolomide renders a poor prognosis in a retrospective analysis of newly diagnosed glioblastoma patients. Radiat Oncol. 2015;10:222.
56. Pitter KL, Tamagno I, Alikhanyan K, Hosni-Ahmed A, Pattwell SS, Donnola S, et al. Corticosteroids compromise survival in glioblastoma. Brain J Neurol. 2016;139(Pt 5):1458–71.
57. Hui CY, Rudra S, Ma S, Campian JL, Huang J. Impact of overall corticosteroid exposure during chemoradiotherapy on lymphopenia and survival of glioblastoma patients. J Neuro-Oncol. 2019;143(1):129–36.
58. McGirt MJ, Chaichana KL, Gathinji M, Attenello F, Than K, Ruiz AJ, et al. Persistent outpatient hyperglycemia is independently associated with decreased survival after primary resection of malignant brain astrocytomas. Neurosurgery. 2008;63(2):286–91 discussion 91.
59. Hagan K, Bhavsar S, Arunkumar R, Grasu R, Dang A, Carlson R, et al. Association between perioperative hyperglycemia and survival in patients with glioblastoma. J Neurosurg Anesthesiol. 2017;29(1):21–9.
60. Derr RL, Ye X, Islas MU, Desideri S, Saudek CD, Grossman SA. Association between hyperglycemia and survival in patients with newly diagnosed glioblastoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(7):1082–6.
61. Mayer A, Vaupel P, Struss HG, Giese A, Stockinger M, Schmidberger H. Strong adverse prognostic impact of hyperglycemic episodes during adjuvant chemoradiotherapy of glioblastoma multiforme. Strahlenther Onkol. 2014;190(10):933–8.
62. Klement RJ, Champ CE. Corticosteroids compromise survival in glioblastoma in part through their elevation of blood glucose levels. Brain J Neurol. 2017;140(3):e16.
63. Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol. 2012;13(5):459–65.
64. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. Lancet Oncol. 2016;17(7):976–83.
65. De Giorgi U, Carteni G, Giannarelli D, Basso U, Galli L, Cortesi E, et al. Safety and efficacy of nivolumab for metastatic renal cell carcinoma: real-world results from an expanded access programme. BJU Int. 2019;123(1):98–105.
66. Arbour KC, Mezquita L, Long N, Rizvi H, Auclin E, Ni A, et al. Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(28):2872–8.
67. Filley AC, Henriquez M, Dey M. Recurrent glioma clinical trial, CheckMate-143: the game is not over yet. Oncotarget. 2017;8(53):91779–94.
68. Wong ET, Lok E, Gautam S, Swanson KD. Dexamethasone exerts profound immunologic interference on treatment efficacy for recurrent glioblastoma. Br J Cancer. 2015;113(2):232–41.
69. Gerstner ER, Duda DG, di Tomaso E, Ryg PA, Loeffler JS, Sorensen AG, et al. VEGF inhibitors in the treatment of cerebral edema in patients with brain cancer. Nat Rev Clin Oncol. 2009;6(4):229–36.
70. Vredenburgh JJ, Cloughesy T, Samant M, Prados M, Wen PY, Mikkelsen T, et al. Corticosteroid use in patients with glioblastoma at first or second relapse treated with bevacizumab in the BRAIN study. Oncologist. 2010;15(12):1329–34.
71. Batchelor TT, Sorensen AG, di Tomaso E, Zhang WT, Duda DG, Cohen KS, et al. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. Cancer Cell. 2007;11(1):83–95.
72. Wei ET, Gao GC. Corticotropin-releasing factor: an inhibitor of vascular leakage in rat skeletal muscle and brain cortex after injury. Regul Pept. 1991;33(2):93–104.
73. Tjuvajev J, Uehara H, Desai R, Beattie B, Matei C, Zhou Y, et al. Corticotropin-releasing factor decreases vasogenic brain edema. Cancer Res. 1996;56(6):1352–60.
74. Recht L, Mechtler LL, Wong ET, O'Connor PC, Rodda BE. Steroid-sparing effect of corticorelin acetate in

peritumoral cerebral edema is associated with improvement in steroid-induced myopathy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(9):1182–7.
75. Badie B, Schartner JM, Hagar AR, Prabakaran S, Peebles TR, Bartley B, et al. Microglia cyclooxygenase-2 activity in experimental gliomas: possible role in cerebral edema formation. Clinical cancer research : an official journal of the American Association for Cancer Research. 2003;9(2):872–7.
76. Wei D, Wang L, He Y, Xiong HQ, Abbruzzese JL, Xie K. Celecoxib inhibits vascular endothelial growth factor expression in and reduces angiogenesis and metastasis of human pancreatic cancer via suppression of Sp1 transcription factor activity. Cancer Res. 2004;64(6):2030–8.
77. Portnow J, Suleman S, Grossman SA, Eller S, Carson K. A cyclooxygenase-2 (COX-2) inhibitor compared with dexamethasone in a survival study of rats with intracerebral 9 L gliosarcomas. Neuro-oncology. 2002;4(1):22–5.
78. Khan RB, Krasin MJ, Kasow K, Leung W. Cyclooxygenase-2 inhibition to treat radiation-induced brain necrosis and edema. J Pediatr Hematol Oncol. 2004;26(4):253–5.
79. Janssen G, Bode U, Breu H, Dohrn B, Engelbrecht V, Gobel U. Boswellic acids in the palliative therapy of children with progressive or relapsed brain tumors. Klin Padiatr. 2000;212(4):189–95.
80. Streffer JR, Bitzer M, Schabet M, Dichgans J, Weller M. Response of radiochemotherapy-associated cerebral edema to a phytotherapeutic agent, H15. Neurology. 2001;56(9):1219–21.
81. Kirste S, Treier M, Wehrle SJ, Becker G, Abdel-Tawab M, Gerbeth K, et al. Boswellia serrata acts on cerebral edema in patients irradiated for brain tumors: a prospective, randomized, placebo-controlled, double-blind pilot trial. Cancer. 2011;117(16):3788–95.
82. Pang X, Yi Z, Zhang X, Sung B, Qu W, Lian X, et al. Acetyl-11-keto-beta-boswellic acid inhibits prostate tumor growth by suppressing vascular endothelial growth factor receptor 2-mediated angiogenesis. Cancer Res. 2009;69(14):5893–900.
83. Siemoneit U, Koeberle A, Rossi A, Dehm F, Verhoff M, Reckel S, et al. Inhibition of microsomal prostaglandin E2 synthase-1 as a molecular basis for the anti-inflammatory actions of boswellic acids from frankincense. Br J Pharmacol. 2011;162(1):147–62.
84. Esatbeyoglu T, Huebbe P, Ernst IM, Chin D, Wagner AE, Rimbach G. Curcumin–from molecule to biological function. Angew Chem Int Ed Eng. 2012;51(22):5308–32.
85. Sun Y, Dai M, Wang Y, Wang W, Sun Q, Yang GY, et al. Neuroprotection and sensorimotor functional improvement by curcumin after intracerebral hemorrhage in mice. J Neurotrauma. 2011;28(12):2513–21.
86. Wang BF, Cui ZW, Zhong ZH, Sun YH, Sun QF, Yang GY, et al. Curcumin attenuates brain edema in mice with intracerebral hemorrhage through inhibition of AQP4 and AQP9 expression. Acta Pharmacol Sin. 2015;36(8):939–48.
87. Laird MD, Sukumari-Ramesh S, Swift AE, Meiler SE, Vender JR, Dhandapani KM. Curcumin attenuates cerebral edema following traumatic brain injury in mice: a possible role for aquaporin-4? J Neurochem. 2010;113(3):637–48.

Publisher's note