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TOPIC REVIEW

Corticosteroid-use in primary and secondary brain tumour patients: a review

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Abstract Corticosteroids have been effective in the management of cerebral oedema, in the context of brain tumours, for many decades. Though their effectiveness is well-established, this needs to be balanced against their potential to cause significant side effects. There is currently little consensus in the literature about how this should be done. This article reviews the literature, specifically in relation to the role of corticosteroids in primary and secondary brain tumour patients. Areas reviewed include corticosteroid pharmacology, indications, mechanism of action, toxicity profile, prescribing practices, and corticosteroid-sparing agents.

Keywords Brain neoplasms · Corticosteroids · Quality of life

Introduction

Corticosteroids are used routinely in the medical care of patients diagnosed with brain tumours for the control of peritumoral cerebral oedema. While the benefit of corticosteroids for this indication is well-established [1, 2], they are not without burden and have the potential to cause significant adverse effects [3]. Though there have been significant advances in disease-modifying-therapies for both primary and secondary brain tumours in the past decade, overall prognosis remains poor for these patients and it follows, therefore, that the maintenance of an acceptable quality-of-life continues to be a priority of care. Careful corticosteroid prescribing, with a view to minimising toxicity, is one particular means of influencing quality of life in these patient groups. Despite their widespread use in neuro-oncology patients, there is very little guidance in the literature for the optimal and safe usage of corticosteroids in this specific setting. This article aims to review the literature in relation to corticosteroid-use in both primary and secondary brain tumour patients with a view to identifying gaps in knowledge and areas for further research.

Historical background

The discovery of the therapeutic role of corticosteroids in cerebral oedema has been described as 'arguably the greatest translational research contribution in the history of neurosurgery' [4]. A number of both laboratory-based and clinical observations preceded this discovery. In 1945, Prados et al. [5]. noted that spraying the brain with adrenal extract protected it from developing cerebral oedema in response to exposure to air. The first clinical observation of corticosteroid effectiveness in brain tumours was described in 1952 when cortisone-replacement therapy, used in craniopharyngioma patients post-operatively, was noted to reduce cerebral oedema [6]. In 1958, Dr. Galicich observed that the periodicity of fluorescein uptake at the blood brain barrier

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(BBB) in mice brains was the reciprocal of the adrenal corticosteroid rhythm, suggesting a regulatory function of corticosteroids on the normal BBB [4]. Eventually, this led to a large case-series of pre-operative dexamethasone-use in primary brain tumour patients, which demonstrated a marked decline in morbidity and mortality [1].

Corticosteroid pharmacology

Numerous types of synthetic corticosteroid have been developed. They differ in their anti-inflammatory (glucocorticoid) and their sodium-retaining (mineralocorticoid) potency. Table 1 summarises the relevant clinical properties of the most commonly used synthetic corticosteroids. They are all readily absorbed from the gastrointestinal tract [7]. They are metabolised primarily in the liver [8]. Hepatic metabolism occurs through cytochrome P450 oxidase enzymes, such as CYP3A4, and is, therefore, affected by a wide variety of drugs. Physiological corticosteroids bind primarily to corticosteroid-binding globulin (transcortin), with 90% binding to this and the remainder binding to albumin or circulating freely. Synthetic corticosteroids, by contrast, appear to bind less to corticosteroid-binding globulin and, therefore, may rely more heavily on other plasma proteins, such as albumin, for binding [8]. There is wide variability in the free fraction of synthetic steroids from patient to patient at comparable total plasma concentrations [7]. Corticosteroids exert their effects on cellular metabolism by crossing the cell membrane to bind to glucocorticoid (NR3C1) receptors within the cytoplasm; these receptors are located in all tissues. The ligand-receptor complex then binds to glucocorticoid-response elements on DNA, resulting in modulation of transcription.

Current clinical indications

Corticosteroids: their adjunctive role

Though corticosteroids may be used alone where patients do not qualify for or want disease-modifying therapy, they are generally used as adjuncts to surgery, radiotherapy, and chemotherapy. In their adjunctive role, they contribute to the symptomatic and radiologic response achieved by disease-modifying therapies. The magnitude and duration of this contribution depends primarily on the response of the tumour to therapy and is therefore highly variable depending on the context. In the post-treatment period, when a complete response to disease-modifying therapy is obtained, the palliative role of steroids should not be necessary. Where only a partial or stable response to therapy has been obtained, continued use of steroids may be necessary for symptomatic control of persistent peritumoral oedema. The contribution of steroids to clinical response has been acknowledged in clinical trials of glioma therapies since 1990 through the use of the Macdonald response criteria [9] and more recently through the use of the response-assessment in neuro-oncology (RANO) criteria [10]. According to such criteria, a complete radiological response does not constitute a complete response to therapy unless a patient has stopped corticosteroids. For secondary brain tumours being treated with whole brain radiotherapy (WBRT), the contribution of corticosteroids to the overall clinical response has been poorly acknowledged in clinical trials. For example, in a systematic review of the impact and contribution of steroids to patients receiving WBRT for cerebral metastases, it was found that only 10 of 21 randomised-controlled trials (RCTs) acknowledged a contribution from steroids to the WBRT-response [11].

Corticosteroids: their role at the end of life

At the end of life, corticosteroids are the most effective agents for the control of symptoms relating to raised intracranial pressure. At this stage, however, dose-escalation may be limited by side-effects as duration of therapy increases.

Corticosteroid mechanisms of action in brain tumours

To understand how corticosteroids work, it is necessary to understand the physiological and pathological state of the structure which they modify.

Table 1 Commonly used corticosteroid preparations in clinical use (data from Ref [8, 66, 67])

Corticosteroid	Relative anti-inflammatory potency	Equivalent anti-inflammatory dose (mg)	Biological half-life (hrs)	Relative sodium-retaining potency
Hydrocortisone	1	20	8–12	1
Prednisolone	4	5	18–36	0.8
Methylprednisolone	5	4	18–36	0.5
Dexamethasone	30	0.75	36–54	0
Fludrocortisone	6	Not used clinically as an anti-inflammatory	18–36	400

Site of corticosteroid action

Corticosteroids appear to be relatively ineffective in cytotoxic or intracellular oedema [12], indicating that their mechanism of action is specific to vasogenic oedema. This would suggest that the anti-oedema effect of corticosteroids relates to mechanisms of BBB disruption. Blood-tumour-barrier analysis using gadolinium-DTPA (Gd DTPA) in primary and secondary brain tumour patients confirms this; for example, it has been shown that, after 7 days of dexamethasone, a radiologically-evident reduction in cerebral oedema correlates with a reduction in the blood-tumour-barrier transport rate constant [13], suggesting that dexamethasone reduces BBB permeability.

Normal BBB structure and function

The BBB is a highly selective interface separating the brain from the blood [14]. It mainly consists of microvascular endothelial cells and overlying astrocytic foot processes. The capillary endothelium which comprises the BBB differs significantly from the capillary endothelium in extracerebral vessels. Most importantly, it is non-fenestrated and cells are held together by junctional complexes which primarily consist of tight junctions and adherens junctions [15]. Para-cellular BBB permeability is largely determined by these junctional complexes. These consist of transmembrane and cytoplasmic proteins, several of which have been identified and characterised, including claudins, occludins, ZO-1, ZO-2, ZO-3, cingulin, 7H6, and JAM proteins [15]. The way in which these junctional proteins operate and interact appears to be regulated by signalling pathways which are currently under intensive investigation. Signal regulators which have been studied to date include protein kinase C, protein tyrosine kinases, and mitogen-activated protein (MAP) kinases [15, 16].

Mechanisms of disruption of the BBB in brain tumours

In general, pathological increases in permeability are mostly associated with increased paracellular permeability [15]. With regard to primary brain tumours and brain metastases, disturbance of the BBB and subsequent vasogenic brain oedema has been hypothesised to be caused by either, or a combination, of two mechanisms:

(1) Decreased expression of functioning tight junctions:

Several studies support the hypothesis that brain tumour microvessels express lower levels of functioning tight junction proteins. For example, high-grade gliomas do not express functional occludin [17] and only low-levels of claudin-1 are expressed in glioblastoma microvessels [18]. Alternatively, over-expression of aquaporin-4 in endothelial foot processes may be another mode of BBB disruption; this protein has been shown to be highly upregulated in high-grade gliomas [19].

(2) Disruption of normally expressed tight-junction proteins through tumour-mediated changes in the microenvironment:

There is also much evidence to support this mechanism. Vascular endothelial growth factor (VEGF)-mediated BBB-disruption is the most widely described mechanism to date. This protein has very strong permeability activity, being 1,000 times more potent than histamine [20]. In gliomas, VEGF mRNA is up to 50-fold over-expressed when compared to normal brain tissue [20]. This upregulation has been correlated with capillary permeability measures in human gliomas [21]. Further evidence for the role of VEGF in brain oedema comes from clinical trials of VEGF inhibitors [22]. The mechanism by which VEGF actually mediates vascular leakage is speculative. Fenestrated endothelium has been shown to be associated with VEGF expression [23] suggesting that VEGF may induce this morphological change in normal BBB endothelium or lead to the formation of capillaries with this morphology. Pro-inflammatory cytokines and other mediators are also thought to trigger BBB disruption. For example, leukotrienne C4 (produced via the arachidonic-acid lipoxygenase pathway) has been found in high concentrations in glioblastoma and concentrations have been shown to correlate with the amount of peri-tumoral oedema [24, 25].

Mechanism of corticosteroid action in brain tumours

Although we know that corticosteroids affect the BBB, their exact mechanism of action is still not fully clear. The strongest evidence exists for the role of corticosteroids in inhibiting VEGF-triggered processes, but other mechanisms have also been postulated. Postulated mechanisms are enumerated below:

(1) VEGF-modulation:

Several studies have shown that corticosteroids reduce the expression of VEGR in brain tumour or BBB cells [26–30]. The corticosteroid-sparing role of VEGF inhibitors in glioblastoma provides further evidence for the possibility that corticosteroids act via the VEGF pathway. For example, one of the trials leading to the FDA approval of Bevacizumab (a humanised monoclonal antibody against VEGF) as monotherapy for recurrent glioblastoma demonstrated that 58% of patients on steroids at the start of the trial were able to achieve an average steroid reduction of 59% in response to Bevacizumab [31].

(2) Anti-inflammatory mechanism:

Some studies suggest that corticosteroids work at the BBB through their anti-inflammatory effects. One study analysed the inflammatory cell infiltrate in rat glioma models. This demonstrated a 50% reduction in lymphocytic

and microglial infiltration in the tumours that had been treated with dexamethasone in comparison with non-treated controls [32].

(3) Arachidonic-acid pathway-modulation:

Some studies suggest that dexamethasone may operate by inhibiting phospholipase A2 of the arachidonic-acid cascade [14]. There is evidence in human brain tumour studies that dexamethasone causes a decrease in regional cerebral perfusion (rCBF) in both tumour and contralateral cortex [33, 34] and this may be mediated through antagonism of the vasodilator effects of prostaglandins.

Corticosteroid toxicity

Frequency

Despite the long-term use of steroids in the neuro-oncology population, there is very little data available on the severity and frequency of steroid side-effects within this patient group. One retrospective study of neuro-oncology patients found that 51% (30/59) of patients had at least one steroid toxicity and that 19% (11/59) required hospital admission due to steroid-related complications [3]. Another retrospective study of 88 patients with brain metastases reported that dexamethasone toxicity was especially present in those who received 16 mg dexamethasone per day at the time of commencement of radiotherapy. In this group ($n = 46$), 91% (40/46) reported at least one dexamethasone-related side effect at some point. By contrast, patients who commenced radiotherapy at a lower dose of dexamethasone (<16 mg/day) had a lower toxicity profile, with 65% (24/37) reporting at least one dexamethasone-related side effect at some point [35].

Type of side effects

Corticosteroid side-effects have been variously measured and reported in the neuro-oncology literature and it is, therefore, difficult to estimate the true frequency of each type of side effect. A commonly reported problem in the palliative care literature has been the difficulty in distinguishing between corticosteroid toxicity and disease progression [36, 37] and this may also apply to the neuro-oncology population. Table 2 outlines the frequencies of some of the side effects that have been most frequently measured and highlighted in the neuro-oncology literature. Prospective studies appear to report higher frequencies, in general, than retrospective studies, presumably due to limited documentation of toxicity in retrospective studies. Hyperglycaemia is a particularly important side effect in the context of primary brain tumours as persistent outpatient hyperglycaemia at 3 months post surgical resection has been shown to be independently significantly correlated with a worse survival outcome [38]. Psychiatric side effects appear to be under-measured or reported in neuro-oncology patients, presumably because of difficulties in measuring and defining such side effects in a population where cognitive deficits and neuropsychiatric dysfunction may be present at baseline. In the general medical literature, a study by the Boston Collaborative Drug Surveillance Programme ($n = 676$) showed that severe psychiatric illness was uncommon (1.3%) at doses of less than 40 mg per day of prednisolone but that it increased to 18.4% at doses of greater than 80 mg per day (equivalent to 12 mg/day of dexamethasone) [39]. Corticosteroid-induced osteoporosis has not been specifically studied in the brain tumour population but is likely to be of increasing importance as survival from primary and secondary brain tumours increases with new chemotherapeutic regimens. In the general medical population, it is estimated that the risk of fracture increases by 50 to 100% in recipients of oral corticosteroids [40].

Impact on quality of life

Whilst drug toxicity is generally considered to impair quality of life, no research studies have been done to assess the exact impact that corticosteroid toxicity has on the quality of life of brain tumour patients. Vecht et al. [41] did use the Karnofsky performance scale (KPS) to assess the benefit of various starting doses of dexamethasone, which gives some indication of quality of life. In this study, the mean improvement in Karnofsky performance status at day 28 of the study was smaller in those patients who developed cushingoid facies, ankle oedema or proximal myopathy, suggesting that the net benefit of radiotherapy may be reduced in those who experience corticosteroid side effects.

Known predictors of toxicity

There is consensus in the general medical literature that the development of corticosteroid toxicity is related to both the cumulative dose of corticosteroid and the duration of use [42–44]. This association has also been reported in the neuro-oncology literature. In relation to cumulative dosing, for example, Weissman et al. [3] demonstrated that patients who received a total dose of dexamethasone of >400 mg had an incidence of toxicity of 75% (27/36) compared to 13% (3/23) for those with a total dose of <400 mg. Another potential predictor which has been investigated in the general medical literature is serum albumin. The Boston Collaborative Drug Surveillance Programme reviewed prednisolone use in 240 patients and demonstrated that the development of complications was both related to corticosteroid dose and albumin, with the highest incidence of

Table 2 Corticosteroid side effects in neuro-oncology patients

Side effect	Frequency (%)	Study population	Study design:	Dexamethasone start-dose (range in mg)	References
Hyperglycaemia	18–25 (depending on start-dose)	89 secondary brain tumour patients	Prospective	4–16	[41]
	6.7	89 secondary brain tumour patients	Retrospective	0–24	[68]
	19	32 primary/secondary brain tumour patients and 27 spinal cord compression patients	Retrospective	Not specified	[3]
	9	88 secondary brain tumour patients	Retrospective	0–16	[35]
	47 in secondary brain tumour patients and 72 in primary brain tumour patients	99 secondary brain tumour patients and 47 secondary brain tumour patients	Retrospective	0–24	[56]
Proximal myopathy	60	4 secondary brain tumour patients amd 9 spinal cord compression patients	Prospective	Up to 100 mg per day. Lower point of range not provided.	[69]
	4.4	89 secondary brain tumour patients	Retrospective	0–24	[68]
	21.6	88 secondary brain tumour patients	Retrospective	0–16	[35]
	14–38 (depending on start-dose)	89 secondary brain tumour patients	Prospective	4–16	[41]
	19	32 primary/secondary brain tumour patients and 27 spinal cord compression patients	Retrospective	Not specified	[3]
	4.4 in secondary brain tumour patients and 8.5 in primary brain tumour patients	99 secondary brain tumour patients and 47 primary brain tumour patients	Retrospective	0–24	[56]
Cushingoid appearance	32–65 (depending on start-dose)	89 secondary brain tumour patients	Prospective	4–16	[41]
	<10	88 secondary brain tumour patients	Retrospective	0–16	[35]
	4.4 in secondary brain tumour patients and 14.9 in primary brain tumour patients	99 secondary brain tumour patients and 47 primary brain tumour patients	Retrospective	0–24	[56]
Peptic Ulcer disease/GI complaints	10	88 secondary brain tumour patients	Retrospective	0–16	[35]
	18–24 (depending on start-dose)	89 secondary brain tumour patients	Prospective	4–16	[41]
	14	32 primary/secondary brain tumour patients and 27 spinal cord compression patients	Retrospective	Not specified	[3]
	5.6 (Ulcer only)	89 secondary brain tumour patients	Retrospective	0–24	[68]
Insomnia	21.6	88 secondary brain tumour patients	88 secondary brain tumour patients	0–16	[35]
Psychiatric complaints	10	88 secondary brain tumour patients	Retrospective	0–16	[35]
	3	32 primary/secondary brain tumour patients and 27 spinal cord compression patients	Retrospective	Not specified	[3]
	10	99 secondary brain tumour patients and 47 primary brain tumour patients	Retrospective	0–24	[56]

toxicity being seen in the patient group with a serum albumin <2.5 g/dl [39]. Weissman et al. [3] demonstrated that, for neuro-oncology patients who experienced toxicity, there was a significant drop in their serum albumin from the time of commencement of therapy, which may relate to the finding of the larger study.

Inter-individual variation in toxicity

While corticosteroid toxicity may be explained to a significant degree by cumulative dose and duration, some patient population subsets appear to experience toxicity much earlier and more intensely than others. Weissman et al. [3], in their retrospective study of corticosteroid toxicity in neuro-oncology patients, noted that one-third of patients developed their first toxic event within the first 3 weeks of treatment, suggesting that dose and duration cannot be used alone to predict which patients will develop toxicity. These observations suggest that certain patient characteristics, possibly genomic differences, may influence the experience of toxicity. Inter-individual variation in response to glucocorticoids has been demonstrated in the literature through the demonstration of a variable inter-individual suppressive response to 0.25 mg dexamethasone ('dexamethasone suppression test') [45]. A number of polymorphisms of the glucocorticoid receptor (*GR*) gene have been shown to be associated with both increased and decreased sensitivity to this test. For example, the *N363S* polymorphism has been shown to be associated with increased glucocorticoid sensitivity [46] but studies show conflicting data on possible associations with certain metabolic phenotypes, such as increased BMI [47]. The *Bcl-1* polymorphism has also been shown to be associated with increased glucocorticoid sensitivity and a dose-allele response has been demonstrated [48]. Again, however, there have been conflicting results in the literature with regard to its association with certain metabolic phenotypes such as BMI and obesity [47]. Clearly, more pharmacogenomic studies are needed, specifically focusing on the phenotype of corticosteroid toxicity, in order to establish whether foreknowledge of genotype could be useful for determining an appropriate corticosteroid starting dose.

Prescribing practices in neuro-oncology settings

There appears to be much variability in corticosteroid prescribing practices in the neuro-oncology setting, with little consensus and guidance in the literature [35]. The evidence relating to the various parameters of corticosteroid-prescribing is described below. In addition, Fig. 1 provides guidance, within each prescribing parameter, which may help to minimise corticosteroid toxicity in clinical practice.

Choice of corticosteroid

Dexamethasone is the most commonly prescribed corticosteroid for the management of cerebral oedema. This was the corticosteroid used in the first report of corticosteroid efficacy in pre-operative primary brain tumour patients, and since then, has been the corticosteroid of choice [2]. It was chosen at that time due its low mineralocorticoid activity. There has been very limited study of other types of synthetic corticosteroids in relation to cerebral oedema, such that conclusions cannot be drawn about the effectiveness of other corticosteroids in this context. Importantly, no prospective direct comparative studies have been done to show that dexamethasone is more effective relative to other corticosteroids in the context of malignancy-related cerebral oedema. The haematology literature suggests that dexamethasone may have better penetration of the central nervous system than prednisolone; for example, in an RCT comparing dexamethasone and prednisolone efficacy in children with acute lymphoblastic leukaemia (ALL), children who received dexamethasone, as opposed to prednisolone, had half the risk of isolated CNS relapse, in comparison to those receiving prednisolone [49].

There are both advantages and disadvantages to the use of dexamethasone over other corticosteroids. Advantageously, it has the least amount of mineralocorticoid activity of all the corticosteroids and this has been shown to be associated with a lower rate of fluid retention in comparison with prednisolone [50]. It also has a long biological half-life, such that frequent dosing is not necessary, and a high potency, resulting in reduced tablet burden for patients. Disadvantageously, however, its long biological half-life may lead to a higher risk of adrenal suppression with long-term use [51]. It is also more difficult to taper slowly when sub-physiological dosing is required, due to lack of availability of very low-strength formulations. Apart from its lack of mineralocorticoid activity, it has a similar side effect profile to other corticosteroids, though it is thought to cause proximal myopathy more frequently than non-flourinated corticosteroids, such as prednisolone [52].

Starting-dose

In relation to starting-dose, a dexamethasone dose of 16 mg/day has been almost universally accepted as a starting dose for primary and secondary brain tumour patients. This starting dose dates back to 1961 when a dose–response curve was constructed in the first case-series of pre-operative dexamethasone-use in primary brain

- **Choice of corticosteroid:** Dexamethasone is the corticosteroid of choice for the control of cerebral oedema. A switch to prednisolone may be indicated if severe dexamethasone-related proximal myopathy emerges or in order to facilitate slow withdrawal of corticosteroid in the physiological dose-range.
- **Dexamethasone start-dose:** The optimal dexamethasone start-dose that confers maximum benefit at minimum toxicity is not known. If a starting dose of dexamethasone of 16mg per day is used, this should be tapered as soon as symptomatic benefit is established in order to find the lowest effective dose quickly. The first 10 days of corticosteroid therapy should be looked upon as a narrow 'dose-finding' window period, after which, rate of tapering will be limited by the need to allow adrenal recovery and by the patient's tolerance of and response to disease-modifying therapy.
- **Duration:** Patients should be left on corticosteroids for the minimum duration that is necessary. Early tapering is the only known means of identifying need and minimising unnecessary prolongation of therapy.
- **Tapering rate:** An attempt at tapering should be made in all patients. Anticipation of the re-emergence of symptoms should not deter attempts. The attempted rate of tapering should be fast in the first 10 days of corticosteroid therapy (e.g. every 1-3 days) but slower after this (e.g. every 4-7 days, and even slower once physiological doses are reached). Patients should be given a written schedule for corticosteroid tapering with information as to what to do and who to call should symptoms re-emerge. It is not justifiable to prescribe a fixed corticosteroid dose, with clinic reviews at 1-2 monthly intervals, unless an attempt at tapering has already been unsuccessful.
- **Terminal Phase:** The ratio of benefit to burden of corticosteroids during the terminal phase will differ between individual cases and may vary over time. It is necessary to review this ratio regularly and to approach decisions on an individual basis, in parallel with sensitive and open communication, within a multidisciplinary context.

Fig. 1 Prescribing practices which may help to minimise corticosteroid side effects—*Key points*

tumour patients [2, 53]. More recent studies and clinical experience suggest that a lower starting-dose may suffice in many cases, however. One randomised controlled trial of dexamethasone starting doses in metastatic brain tumour patients pre-radiotherapy provides compelling evidence for this [41]. In this study, 89 secondary brain tumour patients were randomised to a starting dose of 4, 8, or 16 mg/day. The results demonstrated that each group achieved the same improvement in Karnofsky performance status after 1 week of corticosteroid therapy, prior to commencement of radiotherapy. This is an important observation as the frequency and severity of steroid side effects relates to both cumulative dose and duration. A high starting dose may contribute to both of these determinants [54].

Duration

The actual duration of corticosteroid-use in primary and secondary brain tumour patients has not been clearly evaluated. Although glioma clinical trials take steroid-dosing into account when interpreting treatment-response, the reporting of actual doses used and of their duration is very limited within the published literature pertaining to these trials. In clinical practice, the duration of corticosteroid-use may reflect an individual patient's treatment-response and/or the physician's own corticosteroid-prescribing practice and/or the institution's prescribing protocol. One prospective cohort study of corticosteroid-use, following radiotherapy in glioma patients, found that 71% of malignant glioma patients were still on steroids at 3 months post radiotherapy [55]. A retrospective study of 138 patients showed that primary brain tumour patients required steroids for an average of 23 weeks post radiotherapy whereas secondary brain tumour patients required steroids for an average of 7 weeks [56].

Tapering-schedule

The optimal tapering schedule for steroids during and after radiotherapy is not known. Weissman et al. (1991) [57] demonstrated that twice daily tapering of dexamethasone during radiotherapy for brain metastases was possible for 14 out of 20 patients, with 13 out of the 14 patients remaining symptom-free off steroids at 30 days post completion of therapy; this does not appear to mirror trends in routine practice, however. A recent systematic review

(2010) of the role of steroids in metastatic brain tumour patients recommended that corticosteroids 'should be tapered slowly over a 2 week time period, or longer in symptomatic patients, based upon an individualised treatment regimen and a full understanding of the long-term sequelae of corticosteroid therapy'[58]. There are clear barriers to corticosteroid tapering. The first barrier is the risk of the re-emergence of symptoms and the second barrier is the need to slow tapering rate in order to promote adrenal recovery. The general consensus in the literature is that significant adrenal suppression may occur after 2 weeks of corticosteroid treatment [51] and, therefore, tapering needs to be more cautious after 10 days of therapy in order to promote adrenal recovery, particularly when physiological doses are approached. It is more difficult to influence duration and cumulative dosing, therefore, once a patient has received 10–14 days of corticosteroid therapy.

Alternative patterns of corticosteroid prescribing

Alternative patterns of corticosteroid prescribing, such as the use of high-dose pulse corticosteroids or of alternate daily dosing, have not been studied in brain tumour patients. Such patterns of prescribing may have an impact on reducing side effect rate [59]. Efficacy may be lost, through the use of such regimens, however, and therefore, formal study of such patterns, in a comparative fashion, is necessary to assess their suitability in the brain tumour population.

Prescribing in the terminal phase

In the last few weeks of life, corticosteroid dosages are often increased substantially to counteract the cerebral oedema associated with active and progressive tumour. By this time, patients may have been on steroids for several months and will have accrued a number of steroid side effects. Troublesome physical steroid side effects, of particular significance for the end of life period, include skin breakdown and fluid retention. These side effects complicate nursing care and may contribute to discomfort. High-dose corticosteroids may also cause psychiatric side effects and exacerbate 'terminal agitation' which is a multi-factorial, irreversible delirium-state which may occur at the end of life. This syndrome may be particularly distressing for family members if it is not adequately managed. Though each patient will have a different disease-experience, for the purpose of discussion and clarity, in general, clear decisions about corticosteroid-prescribing may need to be taken at two main time points during this period, assuming a gradual, rather than sudden trajectory. These time points are enumerated below:

(1) The beginning of the end-of-life period:

A substantial increase in dexamethasone (e.g., to 8–16 mg per day) may be justifiable at this point, in order to assess whether there is any reversibility to the deterioration and in order to aggressively palliate neurological symptoms, for which few alternative symptom-control agents exist. It is important that this increment is done as a 'timed-trial', however, and that this is communicated to the patient (if cognitively able to participate in discussions) and the carer beforehand. If the patient does not respond symptomatically to the increment in dexamethasone after 48 hours, it would be reasonable to reduce the dexamethasone back to the last effective dose as, theoretically, it is not reasonable to use dexamethasone for fixed neurological deficits. If, however, symptoms have responded to the increase in dexamethasone, it is reasonable to continue this dose for 4 days and then taper the dose, as tolerated, until a new lowest beneficial dose is found for the control of cerebral oedema. If it is not possible to taper the dose, it may be necessary to continue the patient on the maximum dose of dexamethasone as long as benefit is achieved. In this situation, benefit over burden needs to be reviewed regularly and patients should not be left on high-dose dexamethasone indefinitely without review. Burden may begin to outweigh benefit when intolerable side effects emerge or when benefit is no longer apparent and deterioration in symptom-control is not observed when a trial of dose-reduction is attempted. Continued gradual withdrawal may then be justified on the grounds of the principle of non-maleficence. At all times, discussion with patient or carer is essential, as correct assessment of benefit and burden can only be done when the patient's perception is taken into account.

(2) The last days of life:

This period may be recognised when the patient enters a comatose state and loses the ability to swallow, and hence, the oral route. The ethical dilemma that arises at this point is whether or not to continue dexamethasone parenterally, via the subcutaneous route, when the oral route is lost, in those patients who have been continued on corticosteroids throughout the end-of-life period. One retrospective study of corticosteroid-use in a specialist palliative care unit, which included brain tumour patients, focused specifically on the last few days of life and showed that only 2% ($n = 90$) of patients receiving long-term corticosteroids in the terminal phase of life were switched to parenteral corticosteroids when the oral route was lost [60]. This indicates that corticosteroids are withdrawn abruptly in the last few days of life in the majority of cases. There are a number of clinical and ethical arguments both for and against this practice in the last few days of life. Arguments in support of this practice are primarily based on the principle of non-maleficence. It may be argued that the

continuation of dexamethasone at this point may merely 'prolong dying' rather than promote comfort. This would only be an effective argument, however, if steroids were felt to be futile, in terms of palliation, at this point. It may also be argued that the use of a separate subcutaneous device to administer dexamethasone may be overly burdensome on the patient. Arguments against the practice of abrupt withdrawal are based both on the principles of beneficence and non-maleficence. In terms of beneficence, in a patient whose symptoms have previously been heavily dependent on corticosteroids for control, it would appear illogical to deem such agents as 'non-essential' and lacking in benefit in the last few days of life. In terms of non-maleficence, it may be argued that the abrupt withdrawal of corticosteroids could induce a harmful acute withdrawal syndrome which could easily be prevented by parenteral use. Symptoms of acute withdrawal include myalgia, arthralgia, nausea, abdominal pain, conjunctivitis, fever, and Addisonian crisis [61]. Psychosis, associated with acute corticosteroid withdrawal, has also been reported [62]. Another important reason for continuation of steroids parenterally, also based on the principle of non-maleficence, would be to remove any doubts that steroid-withdrawal was implicated in the mechanism of death; this may be a particularly relevant argument if there is any uncertainty amongst staff or family members about the nature of the patient's decline.

Clearly, more research is necessary, both quantitative and qualitative, on the views of clinicians and family members on the use of corticosteroids in the last weeks and days of life. As a working rule, as in all palliative care situations, it is necessary to approach decisions on an individual basis, in parallel with sensitive and open communication, within a multidisciplinary context.

Corticosteroid-sparing agents—a role in the future?

The necessity of sparing corticosteroids until they are absolutely essential has led to the development of numerous corticosteroid-sparing agents in autoimmune and inflammatory diseases. These agents are generally immunosuppressant in their action and may also be associated with significant, though qualitatively different, side effects. Malignancy-related cerebral oedema differs significantly in mechanism and context, however, to other medical conditions where corticosteroids are used, and such agents, therefore, have not been considered in the management of cerebral oedema. To date, candidate corticosteroid-sparing agents in peritumoral cerebral oedema, which have progressed to human studies, include Bevacizumab and Corticorelin Acetate. Not unexpectedly, given its anti-VEGF activity, Bevacizumab was shown to have corticosteroid-sparing effects in phase 2 trials involving recurrent glioblastoma patients [63]. These studies do not provide sufficient evidence for the use of Bevacizumab in place of corticosteroids where the primary goal is to avoid corticosteroid side effects, however. Though the risk of Bevacizumab-related intra-cerebral haemorrhage and thromboembolism was considered be acceptably low when weighed against the survival benefit conferred in the setting of recurrent glioblastoma [64], this risk is unlikely to be acceptable where the primary goal of therapy is to avoid non-life-threatening corticosteroid side effects. Studies have not been conducted which directly compare Bevacizumab and dexamethasone before, during or after standard chemo-radiotherapy, to investigate this particular risk–benefit. In addition to the risks associated with Bevacizumab, given the cost of Bevacizumab relative to the cost of dexamethasone, use of Bevacizumab solely as a corticosteroid-sparing agent, is unlikely to be a cost-effective strategy. Corticorelin acetate, a synthetic targeted human corticotrophin-releasing factor analogue, is another candidate corticosteroid sparing agent under investigation. A randomised controlled double-blind study suggested that this agent, administered as a twice daily subcutaneous injection, may have similar efficacy to dexamethasone for control of symptom exacerbations in primary malignant glioma, with acceptable tolerability [65]. However, due to the small sample size in this study ($n = 37$), no statistical analysis was performed and it is, therefore, not possible to draw definite conclusions about the role of this agent at present. Clearly, further more robust studies are needed to accurately assess the potential of these agents as corticosteroid-sparers and further candidates need to be developed in the laboratory setting.

Conclusion

Corticosteroids remain the most efficacious agents for the treatment of peritumoral cerebral oedema. Corticosteroid side effects reduce the net benefit associated with these agents, however, by impacting on quality of life. The true frequency of corticosteroid toxicity is not known in this population as uniform definitions of 'corticosteroid-related toxic events' have not been developed. Further study needs to be done on the mechanism of action of corticosteroids on the BBB so that corticosteroid-sparing agents or synergistic agents may be developed. In the absence of alternatives to corticosteroids, better knowledge of factors that may predict corticosteroid response may allow better individualisation of dosing. Without knowledge of predictive factors, it is necessary to use corticosteroids at the lowest effective dose for the shortest duration of time necessary. Overall, greater attention to the role of corticosteroids in brain

tumour patients may open doors to drug discovery, may provide opportunity for the practice of personalised medicine and may ultimately lead to a reduction in distressing and disabling corticosteroid side effects.

Conflict of interest The authors declare that they have no conflict of interest.

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