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An Evidence-Based Summary of Recommendations for the use of Dexamethasone in the Management of Brain Metastases

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Abstract

Intracranial edema associated with brain metastases commonly contributes to symptoms of headache, nausea or emesis. Corticosteroids are the pharmacologic agent of choice for many patients, to temporize symptoms until definitive antineoplastic therapy can be initiated. However, careful management is required to minimize related side effects which may compromise a patient's quality of life. The literature on dosing, appropriate duration of therapy and tapering will be reviewed, along with practical guidelines on the initiation of dexamethasone, appropriate prophylaxis, and secondary screening for adverse events.

Keywords: Brain metastases; Dexamethasone; Steroid; Taper; Radiotherapy; Palliative

Abbreviations

AVN: Avascular Necrosis; BID: Twice Daily; BBB: Blood-Brain Barrier; CT: Computed Tomography; CVA: Cerebrovascular Accident; DM: Diabetes Mellitus; DXM: Dexamethasone; GERD: Gastroesophageal Reflux Disease; GI: Gastrointestinal; ICP: Intracranial Pressure; MRI: Magnetic Resonance Imaging; NR: Not Reported; nSAID: non-Steroidal Anti-Inflammatory; OD: Daily; PCP: Pneumocystis Carinii Pneumonia; PE: Pulmonary Embolus; PJP: Pneumocystis Jurovecii Pneumonia; QID: Four Times Daily; RCC: Renal Cell Carcinoma; RCT: Randomized Controlled Trial; RT: Radiotherapy; TB: Tuberculosis; VTE: Venous Thromboembolism; WBRT: Whole Brain Radiotherapy

Introduction

Almost 10% of all patients with cancer will develop brain metastases, which are most commonly diagnosed in lung, renal, breast, and colorectal cancers, and melanoma [1,2]. The edema commonly associated with brain metastases is typically due to increased vascular permeability. This is secondary to blood-brain barrier (BBB) disruption around the lesion(s), and is termed vasogenic edema. BBB disruption is caused by vascular endothelial growth factor overexpression and secretion by metastatic lesions. BBB disruption allows passage of plasma and proteins from the vascular compartment into brain parenchyma, resulting in edema and therefore increased interstitial pressure within and around the tumor. The resulting increase in intracranial pressure (ICP) leads to the classic symptoms of headache, nausea and vomiting [3].

Corticosteroids appear to have a mechanism of action specific to vasogenic edema, as they are relatively ineffective in cytotoxic or intracellular edema. Studies using gadolinium-enhanced magnetic resonance imaging (MRI) in primary and secondary brain tumours suggest that the anti-edema effect of corticosteroids is related to decreasing BBB permeability [4]. After seven days of treatment, a reduction in radiologically-apparent cerebral edema is seen which correlates with a reduction in blood-tumour-barrier transport [4].

Dexamethasone

Dexamethasone (DXM) is the corticosteroid of choice for treating edema associated with brain metastases because of its biological properties, including half-life and potency [3,5-6]. It has the least mineralocorticoid activity of the agents in this class, which results in a lower rate of peripheral fluid retention [7]. The biological half-life is 36-54 hours, such that frequent dosing is not necessary, and the potency is six times that of methylprednisolone, reducing tablet burden [7,8]. There are also multiple available routes of administration. However, the long half-life may increase the risk of adrenal suppression with long term use. It is also more difficult to taper slowly when sub-physiological dosing is required, due to lack of availability of very low strength formulations [9].

Side Effects

Side effects of DXM are common (Table 1), and they increase in frequency and severity with increased dose and duration of therapy [3].

In a review of the literature encompassing 93 cases (14 previously unpublished) and 29 clinical studies, the overall incidence of mild to moderate psychiatric symptoms such as anxiety, irritability, and insomnia was 27% (range 13-62%), while severe manifestations (mania, depression, psychosis) were limited to approximately 5% (range 1.6-50%) [10].

The relative risk of gastrointestinal toxicity while on corticosteroids has been reported by two meta-analyses: Messer et al evaluated 71 controlled clinical trials and described a 2.3 greater incidence of peptic ulcers during steroid therapy [11]. Conn et al 's meta-analysis included 93 double-blind randomized controlled trials (RCT) of more than 8700 patients, reporting an estimated annual peptic ulcer

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Table 1: Commonly reported dexamethasone adverse effects. Incidence varies based on total daily dose.

Adverse Effect	Incidence Range	Example References
Hyperglycemia	5-72%	[3,14,18,21,25]
Cushing's syndrome	4-65%	[21,25]
Psychiatric disorder*^	10-62%	[3,14,21,25]
Insomnia^	22-62%	[3,14]
Hypertension	12-45%	[3,21]
Muscular weakness / proximal myopathy	4-38%	[3,14,21,25]
Peripheral edema	5-26%	[18,21,25]
GI symptoms**^	3-24%	[14,21,25]
Increased appetite^	22%	[14]
Infection including PCP, PJP	6-9%	[3,14,21]
Oropharyngeal +/- esophageal candida^	5-7%	[14,18,25]
PE / VTE	2%	[25]
Other (seizures, CVA, weight gain^, hiccups^, osteoporosis, acne^, AVN)	NR	[3,14]

*Anxiety, irritability, mania, psychosis, or depression. **Peptic ulcer, bowel perforation or GI bleed. ^Included in 13-item Dexamethasone Symptom Questionnaire along with weight loss, nausea, vomiting and anorexia. Abbreviations: AVN: Avascular Necrosis; CVA: Cerebrovascular Accident; GI: Gastrointestinal; NR: Not Reported; PCP: Pneumocystis Carinii Pneumonia; PE: Pulmonary Embolus; PJP: Pneumocystis Jurovecii Pneumonia; VTE: Venous Thromboembolism.

Table 2: Prophylaxis of and methods to minimize dexamethasone side effects.

Adverse Effect	Approach	Population	Intervention	Example References
Oropharyngeal candida	Prophylactic	All patients	Nystatin 500 000U (5mL) po swish & swallow QID x7 days*	[28,31]
Gastric irritation	Prophylactic	All patients but especially those with a history of gastric ulcer or hiatus hernia	Pantoprazole 40mg po OD - BID	[28]
Gastric irritation	Prophylactic	Discontinue nSAID use during dexamethasone	Consider replacing with a weak opioid	[13]
Pneumocystis jirovecii Pneumonia	Prophylaxis	Anticipated dose equivalent: prednisone 20mg daily for one month or more	Trimethoprim-sulfamethoxazole€ DS three times weekly until completion of taper^	[31-33]
Avascular necrosis	Secondary screening	Patients who develop groin, hip or femur pain	Perform plain x-rays of bilateral hips	[34]
Hyperglycemia	Secondary screening	Patients with DM; patients with or without DM who develop symptoms	Blood glucose monitoring BID - QID	[3]
Reactivation Hepatitis B	Secondary screening	Anticipated dose equivalent: prednisone 7.5mg daily for one month or more	Hepatitis B serology (surface antigen or core antibody)	[36]
Reactivation Tuberculosis	Secondary screening	Anticipated dose equivalent: prednisone 15mg daily for one month or more	TB screening especially in those who are at high risk of latent TB	[35,36]
Strongyloides Hyperinfection Syndrome**	Secondary screening	Any corticosteroid dose and duration in a patient who has lived in or travelled to an endemic area at any time	Strongyloides stercoralis screening	[36]
Proximal Myopathy	Treatment	Symptomatic proximal myopathy	Switch from DXM to prednisolone	[7]

*Or for 2 days after improvement. **Mortality approaches 100%. €Sulfamethaxazole 800mg + trimethoprim 160mg. ^Decreases the risk of infection by 91% in HIV-negative individuals. Abbreviation: BID: Twice Per Day; DM: Diabetes Mellitus; DXM: Dexamethasone; nSAID: non-Steroidal Anti-Inflammatory; OD: Daily; QID: Four Times Daily; TB: Tuberculosis.

incidence of 1.7% in the control group and 2.1% in the steroid group (RR 1.2) [12]. The relative risks of GI hemorrhage cited by the same papers were 1.5 and 1.2, respectively [11,12]. In a nested case-control study of 1415 patients hospitalized for gastric or duodenal ulcer or upper GI hemorrhage of unknown cause (versus 7063 controls), those receiving concurrent non-steroidal anti-inflammatory medication had a risk of peptic ulcer disease 15-foldhigher than non-users of either drug [13].

Comorbidities such as pre-existing gastro esophageal reflux disease (GERD) and diabetes mellitus (DM) are likely to increase the risk of clinically significant DXM-related toxicity [14]. Likewise, poor nutrition resulting in hypoalbuminemia (<25g/L) increases the risk of toxicity because the percentage of unbound steroid increases [15]. DXM is metabolized by the cytochrome p450 3A4 pathway shared by many other drugs, increasing the potential for interaction with other medications, including the risk of rapid catabolism of DXM [3].

Methods to minimize known DXM side effects should be instituted especially in patients at increased risk (Table 2). This may be in the form of adjustments in DXM dosing, addition of prophylactic agents, or proactive management of side effects. Patients

Table 3: Summary of factors to consider before starting corticosteroids in brain metastases.

Factor	If Yes…	If No…	Example References
Mild to moderate baseline neurologic signs +/- symptoms or symptoms of increased ICP?	Start DXM 4-8mg daily	Do not start steroids	[6,25,27-29]
Severe baseline neurologic signs +/- symptoms or symptoms of increased ICP?	Start DXM 16mg daily Consider mannitol	Do not start steroids	[23,25,29]
Asymptomatic but undergoing brain RT	Consider starting DXM 4mg daily	^Do not start steroids	[21,27]
Asymptomatic but undergoing brain RT with vasogenic edema apparent on baseline imaging	Consider starting DXM 4mg daily	Do not start steroids	[21]
Patient currently receiving targeted biological agent or small molecule therapy	Discuss with Medical Oncologist prior to starting steroids		[27]
Has the patient had all age-appropriate vaccines/ boosters?	Start steroids	Immunize, then start steroids	[36]

^If no immediate radiotherapy planned. Abbreviations: DXM: Dexamethasone; ICP: Intracranial Pressure; RT: Radiotherapy.

Table 4: Example of gentle tapering schedule. Overall average prednisone equivalent dose of this regimen is 44.4mg/day (including week 5).

Time	Dose	Duration
Baseline	8mg po BID	14 days
Week 1	4mg po BID	7 days
Week 2	2mg po BID	7 days
Week 3	1mg po BID	7 days
Week 4	1mg po OD	7 days
Week 5*	1mg po q alternate day	4 doses

*Optional.

and caregivers should be informed of pertinent signs and symptoms to report.

The Dexamethasone Symptom Questionnaire [16] is an example of a validated instrument used to systematically measure DXM toxicity. It includes 13 symptoms reflective of DXM toxicity (Table 1), and has been recently used in a RCT assessing relative risks and benefits of DXM in radiation treatment of bone metastases [17]. Each item is scored independently (not at all/a little/quite a bit/ very much), with a higher total score indicative of worse symptom severity [16].

Literature Summary: Initial Dose

The optimal DXM starting dose that confers maximal benefit at minimal toxicity for patients with brain metastases is not known [7]. In a survey of 34 oncologists and palliative care specialists involved in managing patients with lung, breast, renal cell, gastrointestinal cancers and melanoma, 45% prescribed DXM at a fixed dose of 16mg daily. The presence or absence of symptoms, types of symptoms, neurologic deficits, and the degree of edema on imaging were factors cited by respondents as impacting the choice of starting dose [14] (Table 3). This dose schedule of 4mg QID has been reported in small prospective trials [18-19]. In a systematic review of twenty one RCTs of whole brain radiotherapy (WBRT) used in the setting of multiple brain metastases, 18 studies documented steroid use, but only five provided details on the specific agent and dose [20]. DXM was the most commonly used at total daily doses ranging from 8mg to 16mg [20]. In a pooled analysis of two sequential RCTs involving 89 evaluable patients with brain metastases, Vecht et al compared quality of life, Karnofsky performance status (100 point scale) and side effects of 4mg or 8mg versus 16mg daily doses of DXM. More side effects were reported at 28 days by the patients treated with 16mg ($p<0.03$), with no significant improvement in performance status (PS) in comparison to those receiving lower doses [21]. At 7 days, the 4-mg group had improved by 6.7 points (SD 11.3) versus 9.1 (SD 12.4) in the 16-mg group. In the 8-mg group, at the same time point, PS had improved by a mean of 8 points (SD 10.1) compared to 7.3 (SD 14.2) in the 16-mg group [21]. On balance, the literature favors treating mildly or moderately symptomatic patients with a starting daily dose of 4-8 mg, and those with severe symptoms with 16mg, divided into two doses [6,21-23] (Table 3). Anecdotally, patients may experience less insomnia if their two daily doses are delivered with breakfast and lunch, rather than on a strictly BID schedule.

Literature Summary: Duration

Patients should remain on DXM for the minimum necessary duration [7]. The first 10 days of corticosteroid therapy should be looked upon as a 'dose-finding' period, in which the DXM schedule is adjusted according to degree of symptomatic benefit, antineoplastic treatment modality instituted, and side effects [7]. There are presently many options for the definitive treatment of brain metastases, depending on the number of lesions, their size and location, the patient's PS, extracranial disease and preferences [24]. Many receive radiotherapy (RT), either stereotactic or WBRT. Some patients experience progressive neurological symptoms during RT as a result of the treatment itself, due to transient increases in edema. If that occurs, DXM dose should be increased for a short period of time, such as from 4mg to 8-16mg daily for three days, then decreased back to the baseline schedule [18]. A retrospective single-institution review of 91 patients with brain metastases (1992-1997), all of whom received whole brain RT and DXM initiated at diagnosis, demonstrated a mean duration of DXM treatment of 6.9 weeks (range 1-50.5 weeks), with 17.6% requiring DXM until death [25].

The total dose and duration of DXM must be anticipated in order to institute appropriate prophylaxis and secondary screening measures (Table 2). Recommendations for prophylaxis in relation to the expected immunosuppressive effect of DXM are often described in terms of prednisone equivalent dose per day; 5mg of prednisone is equivalent to 0.75mg of DXM [7]. As an example of the importance of preventative measures, in a retrospective review of 10 729 patients receiving chemotherapy at a comprehensive cancer centre (2004-2007), 151 had either a positive hepatitis B surface antigen or core antibody; of those, patients who received hepatitis B prophylaxis had a significantly lower all-cause mortality compared to those who either did not receive antiretroviral therapy, or who were treated after reactivation, respectively (22% vs. 71% vs. 72%; $p<0.05$) [26].

Literature Summary: Tapering

Published evidence and specific recommendations about the

optimal tapering schedule vary [14]. Some authors report a taper to be unnecessary if a patient is asymptomatic at baseline and received 4mg per day or less, over 28 days or fewer [21]. However, the general consensus in the literature, as reflected by the review of Aulakh et al, is that significant adrenal suppression may occur after as little as two weeks of corticosteroids [9]. Early tapering is the only means of identifying need, and is critical to the minimization of side effects [7]. Anticipation of the re-emergence of symptoms should not deter attempts at tapering, which should be made in all patients [7]. DXM tapering should be instituted as soon as symptomatic benefit is seen, especially if on 16mg per day or if minimally symptomatic initially, in order to find the lowest effective dose quickly [7,27-28].

In general, tapering schedules most commonly reported involve a gradual decrease in dose and/or interval over a period of 2-4 weeks, with longer periods for patients who were symptomatic at baseline [14,20-22,29] (Table 4). Patients who were minimally symptomatic at baseline may tolerate a faster taper, over a few days [27]. Patients should be given a written schedule for tapering, preferably on a calendar, with information as to who to call should rebound symptoms of increased ICP emerge. Patients should be monitored regularly during a taper for this reason. Steroid withdrawal syndrome is seen in approximately 5% [18]. If such symptoms occur, DXM should be increased back to the previous dose on which the patient felt well. Some patients may require a switch from DXM to prednisolone to facilitate a slow withdrawal in the physiological dose range [7]. Additionally, it is good practice to warn patients and their caregivers that the 'beneficial' side effects of increased appetite and energy will also wane with the dose taper, and not to consider these constitutional signs of progressive disease.

The rate of tapering will be dictated in part by the patient's tolerance and response to disease-modifying therapy, such as radiotherapy [7]. Some clinicians institute a taper within one week of starting RT (before it has finished) [6,18,29], while some wait until the course of treatment has been completed to start decreasing the dose [14]. In a pilot study of 20 patients evaluating a novel schedule of DXM administration during palliative RT, DXM was tapered during radiation and discontinued on the last day of RT as planned, in 70% (14/20), with 93% (13/14) of those symptom-free off steroids at 30 days post-RT [18]. DXM taper should be safe to institute once any RT-related edema has resolved, although it is often difficult in practice to pinpoint that time in the treatment trajectory, since short follow-up CT scans of the brain are not usually performed [14].

After previous unsuccessful attempts at tapering, and in the terminal phase, the ratio of benefit to burden of continuing DXM differs than at baseline [7]. It is necessary to regularly review the pros and cons of continuing corticosteroids, and to ensure any appropriate prophylaxis and secondary screening have been instituted [7].

Special Patient Populations

If there are no symptoms to indicate the presence of cerebral edema, DXM is not routinely indicated [27] (Table 3). This often applies to patients who are incidentally diagnosed with brain metastases during a screening CT or MRI [30]. There is at present no compelling evidence that steroids should be started simply because an asymptomatic patient is about to begin RT [27]. This situation requires clinical assessment of the potential risks versus benefits, usually in conjunction with the treating radiation oncologist [30]. Technical factors such as the RT dose, target area, volume and fractionation may be relevant to decision-making in this setting.

Patients with melanoma and renal cell carcinoma (RCC) are frequently treated with targeted biologic agents or small molecules such a sipilimumab (melanoma), sunitinib (RCC) or interleukin-2 (both), whose antineoplastic efficacy may be compromised by concurrent corticosteroids. It is crucial that a multidisciplinary case conference occur prior to initiation of DXM to discuss the pros and cons, especially when the patient is only mildly symptomatic [27] (Table 3).

Conclusions

Dexamethasone is the corticosteroid of choice in addressing symptoms due to edema associated with brain metastases. Careful consideration of the patient's baseline symptom status and comorbidities, in relation to the planned antineoplastic therapy, guides whether to initiate steroids and at what dose. Regular monitoring, early tapering and appropriate prophylaxis can minimize the negative impact on quality of life from steroid-related side effects.

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