

# Use of corticosteroids in patients with brain metastasis

## In search of evidence to guide therapy

Rashmi Koul, MD; Arbind Dubey, MD; Kalyani Vijay, MD; David D. Eisenstat, MD, FRCPC

**M**etastasis to the brain, a potentially life-threatening complication of systemic malignancy, is the most commonly reported intracranial tumour in adults, and accounts for approximately 40% of intracranial neoplasms. The incidence of brain metastasis is rising with the increase in survival of cancer patients. Multiple, large autopsy series suggest that, in order of decreasing frequency, cancers of the lung, breast, skin (melanoma), kidney and colon are the

most common primary tumours to metastasize to the brain.<sup>1</sup> In addition, primary cancers of unknown origin sometimes present with brain metastases.

Brain metastases are responsible for varied neurologic symptoms and produce severe morbidity, decreasing quality of life and reducing survival.<sup>2</sup> Patients are often brought to hospital by family members or friends who have noticed lethargy, emotional lability or personality changes.<sup>3</sup> Physical examination may demonstrate objective neurologic signs, but sometimes only minor cognitive signs are present. Vasogenic edema resulting from disruption of the blood-brain barrier allows protein-rich fluid to accumulate in the extracellular space, contributing significantly to morbidity.<sup>4-6</sup> Computed tomography (CT) or magnetic resonance imaging (MRI) are the most sensitive and specific diagnostic tests currently available in most hospitals.

Most patients with brain metastasis and peritumoural edema are adequately managed with corticosteroids followed by external cranial radiation; however, the optimal management of brain metastasis is unknown.<sup>7</sup> The mechanism of action of corticosteroids is not fully understood, but dexamethasone has recently been shown to upregulate Ang-1, a stabilizer of the blood-brain barrier, whereas it downregulates vascular endothelial growth factor (VEGF), which promotes permeability of astrocytes and pericytes.<sup>8</sup> Dexamethasone is the corticosteroid of choice to reduce peritumoural edema because its lower mineralocorticoid activity compared to prednisone reduces the potential for fluid retention. Reduction of intracranial pressure and improvement in neurologic symptoms usually begins within hours. A decrease in capillary permeability can be identified within six hours, and changes in diffusion-weighted MRI indicating decreased edema are identifiable within 48 to 72 hours. However, adequate reduction in elevated intracranial pressure resulting from peritumoural edema may take several days with corticosteroid therapy alone — and additional treatment such as intravenous mannitol, calcium channel blockers, analgesia and sedation may be required in the initial management of these patients.<sup>9</sup>

Unfortunately, in addition to their potent anti-inflammatory action, corticosteroids have potentially serious adverse effects that worsen with longer administration. Common effects from long-term use include weight gain, muscle weakness (myopathy), insomnia, moodiness, acne, osteoporosis, hypertension, swelling of the face, cataracts, osteonecrosis (death of bone cells), impaired wound healing, susceptibility



CT image showing a metastatic lesion in brain with associated vasogenic edema.

**Rashmi Koul, MD, Arbind Dubey, MD and Kalyani Vijay, MD** are Radiation Oncologists in the Department of Radiation Oncology, CancerCare Manitoba. **David D. Eisenstat, MD, FRCPC** is a Neuro-Oncologist in the Department of Pediatric Oncology and Chair of the Brain Tumour Disease Site Group, CancerCare Manitoba. Address for correspondence: Dr Rashmi Koul, Dept of Radiation Oncology, Allan Blair Cancer Centre, 4101 Dewdney Ave, Regina, SK, Canada S4T 7T1; Tel: (306) 766-2288; Email: rashmi.koul@saskcancer.ca

# FEATURE

to infections, pneumonia, and elevated blood sugar that sometimes results in diabetes. A common short-term complication is steroid myopathy, which can be mistaken for progression of brain metastases. This may trigger the use of more steroids, worsening the myopathy. Physical therapy can be helpful for patients with myopathy. Some patients with brain metastases detected by imaging who are otherwise asymptomatic do not require corticosteroids.<sup>10</sup>

The usual starting dose is 4 to 16 mg per day. The most common dose is 4 mg four times per day (QID; 16 mg per day),<sup>11</sup> but can vary with physician comfort level, and is continued for a few weeks or longer.

## CANCERCARE MANITOBA CASE SERIES

To evaluate the practice pattern of seven different radiation oncologists regarding use of corticosteroids in patients with brain metastasis, our group conducted a retrospective review

### Key points

- Brain metastases are a common development in patients with cancer, and cause severe symptoms that reduce quality of life and survival.
- The main treatments for brain metastases are radiation and the corticosteroid dexamethasone, but clinical practice for both treatments varies widely.
- The variation and lack of standardization in protocols both for radiation and steroids impedes efforts to obtain evidence on efficacy and side effects of both treatments.
- A case series conducted at CancerCare Manitoba showed variation in dosage of dexamethasone used in patients with brain metastases and incomplete documentation of dosages, tapering schedules and side effects.
- Previous studies support the possibility that lower doses and shorter duration of dexamethasone may provide equivalent efficacy in ameliorating symptoms of brain metastases while decreasing the toxic side effects, which increase with longer duration of therapy.
- A Phase II Canadian study now underway is evaluating efficacy and side effects of lower doses of dexamethasone than used by the majority of oncologists, in combination with whole-brain radiation therapy (WBRT).

of data collected from the computerized oncology information system of 51 patients (30 male, 21 female, median age 60 years) diagnosed radiologically with brain metastasis at CancerCare Manitoba between 2004 and 2007. Most patients (72%) had multiple metastases, located mainly in the cerebrum (76%) (Table 1). Presenting with a broad variety of symptoms and neurologic complaints, the majority experienced headaches, seizures, weakness of extremities, difficulty walking and vomiting (Table 2). All patients received palliative treatment which included corticosteroids and radiation therapy (n = 42), or best supportive care without radiation but including corticosteroids (n = 9). Radiation protocols varied, and evolved over the course of the study.

The majority (90%) were prescribed oral dexamethasone on the day imaging confirmed brain metastasis. Reasons for prescribing corticosteroids were presence of symptoms (especially neurologic deficit and worsening of neurologic symptoms over time) and edema seen on CT scan. During external radiation, oncologists adjusted the corticosteroid dose, especially on the last day of radiation, and prescribed tapering dosages of dexamethasone. Although corticosteroids are known to cause heartburn and indigestion, only 50% of oncologists regularly gave ranitidine or proton pump inhibitors.

Dosages of dexamethasone varied: 60% of patients were prescribed 4 mg QID (16 mg per day), 20% were on 4 mg BID (8 mg per day) and 20% had another dosing schedule. A tapering dose was mentioned in 20% of case notes but the

**TABLE 1. Baseline demographic and clinical characteristics**

variable	number of patients	percent
male	30	58.82%
female	21	41.17%
median age (years)	60	
single metastasis	09	17.65%
multiple metastases	42	82.35%
leptomeningeal spread	01	1.96%
necrotic appearance	6	11.76%
edema seen on CT scan	46	90.19%
diabetes mellitus	08	15.69%
hypertension	12	23.52%
palliative brain radiation	42	82.35%
best supportive care	09	17.64%
<b>brain involvement</b>		
cerebrum	39	76.47%
corpus callosum	03	5.88%
cerebellum	04	7.84%
basal ganglia	01	1.96%
orbit and brain	02	3.92%
brain stem	01	1.96%
periventricular area	01	1.96%

actual schedule was not available; in 70% of cases the tapering dose was evident from a duplicate of the prescription attached to the chart.

Tapering schedules varied according to the oncologist: 60% tapered for 1–2 weeks, 20% for 2–3 weeks and 20% had no fixed schedule. Tapering usually started once brain radiation was completed, and lasted 3–4 weeks in 70% of patients and 4–5 weeks in 20%. Patients with disease progression or deterioration in neurologic function returned to high-dose corticosteroids under supervision of an oncologist or family physician.

Followup also varied: 30% of patients were seen in radiation clinic approximately six to eight weeks after completion of brain radiation, 18% had repeat brain imaging after radiation to assess response, and those who had residual disease were offered a stereotactic boost (especially if the physician was trained in stereotactic radiation). The tapering of corticosteroids was cancelled in 20% of patients due to worsening neurologic symptoms; these patients had prolonged use of corticosteroids.

The most common side effects of corticosteroids, documented mainly in the radiation prescription sheets, were upset stomach, insomnia, muscle weakness, restlessness and irritability. Eight patients had hyperglycemia before starting corticosteroids, of whom four were on insulin and had to increase insulin intake under supervision by family physicians; one was admitted to the intensive care unit for management of acute hyperglycemia. Two patients had increased blood pressure. Two were treated for oral candidiasis with systemic fluconazole antifungal medication. Thirty percent received prescriptions for a sedative (either during radiation or in followup appointments). Information on quality of life and cognitive function was not available.

**QUESTIONING DOSAGE AND TAPERING SCHEDULES**

Few trials in the English literature have evaluated lower doses of dexamethasone for treatment of edema associated with brain metastases. Table 3 (page 10) summarizes findings from a number of recent studies, showing that prescribing practices vary among physicians, even in the same institution, and that documentation is often incomplete.

Dr Andrea Bezjak of the Princess Margaret Hospital was the principal investigator of a Phase II prospective study<sup>20</sup> that aimed to provide adequate statistical evaluation of


**Other approaches to peritumoural edema**

Because of the adverse effects of corticosteroid therapy, there is interest in alternative treatments for peritumoural edema. One candidate is corticotrophin-releasing factor, which has a direct effect on blood vessels. A preliminary study suggested that cyclooxygenase-2 (COX-2) inhibitors may be effective in treating cerebral edema.<sup>21</sup> Another approach is anti-VEGF antibodies (e.g. bevacizumab), or VEGF receptor inhibitors (e.g. pazopanib, sorafenib, sunitinib), as VEGF plays an important role in the pathogenesis of peritumoural edema<sup>8,9</sup>.

**TABLE 2. Symptoms at presentation**

symptoms	number of patients	percent
confusion	23	45.09%
headaches	19	37.25%
limb weakness	11	21.56%
nausea	10	19.60%
vision problems	06	11.76%
vomiting	03	5.88%
seizures	05	9.80%
urinary incontinence	02	3.92%
rectal incontinence	01	1.96%
hemiparesis	02	3.92%
cognitive dysfunction	01	1.96%
behavioural dysfunction	01	1.96%
personality changes	02	3.92%
depression	02	3.92%
panic attacks	01	1.96%
severe earache	01	1.96%
speech problems	02	3.92%
fainting episode	01	1.96%
tinnitus	01	1.96%
forgetfulness	02	3.92%

patients regarding the role of corticosteroid therapy in managing cerebral metastases. Patients with single or multiple brain metastases receive dexamethasone 8 mg once per day if symptomatic, and dexamethasone 4 mg if asymptomatic, in addition to whole-brain radiation therapy (WBRT). Results suggested that most patients require an increased dose or are unable to adhere to a preset tapering schedule when they start WBRT.

While we await results of future trials designed to find the optimum dose of corticosteroid that alleviates symptoms of brain metastases with minimal toxicity, the literature supports lower dosages and tapering immediately after finishing radiation, to reduce side effects and maintain quality of life. More standardization in the use of corticosteroids would help in evaluating the effectiveness of radiation protocols. Dosages and toxicities need to be well documented. 

**Disclosure**

The authors report no conflicts of interest pertaining to this article.

**References**

- Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. *CA Cancer J Clin* 2001;51(1):15-36.
- Wen PY, Loeffler JS. Management of brain metastases. *Oncology* 1999; 13(7):941-54, 957-61.
- Wolfson AH, Snodgrass SM, Schwade JG et al. The role of steroids in the management of metastatic carcinoma to the brain. A pilot prospective trial. *Am J Clin Oncol* 1994;17(3):234-8.
- Santarelli JG, Sarkissian V, Hou LC et al. Molecular events of brain metastasis. *Neurosurg Focus* 2007;22(3):E1.

**TABLE 3. Summary of main studies of corticosteroids given for cerebral edema associated with brain metastases**

Reference	study type	patients	study treatment	conclusions
Vecht 1994 <sup>12</sup>	double-blind randomized controlled trial	n = 96 Karnofsky ≤ 80	- Study 1: dexamethasone 8 mg vs 16 mg/day - Study 2: dexamethasone 4 mg vs 16 mg/day - Both for 4 weeks, taper not specified - no radiation	- 4 mg/day dexamethasone results in the same improvement as 16 mg/day after one week of treatment, in patients who have no signs of impending herniation. - Toxicities greater in those receiving 16 mg/day for 4 weeks.
Weissman 1991 <sup>13</sup>	prospective, single-arm	n = 20	- Dexamethasone 8 mg (16 mg) BID for 4 days, then 4 mg BID for 4 days, then 2 mg BID until the last day of radiation; median duration 19.5 days (range 8–42 days). - WBRT* 2000 cGray/5 fractions to 5800 cGray/29 fractions, starting within 5 days	- Short duration of corticosteroids with twice-daily dosing and effective tapering, with discontinuation at completion of brain radiation, is safe and effective.
Hempen 2002 <sup>14</sup>	retrospective	n = 138 (91 with brain metastases and 47 with primary brain tumours)	- Dexamethasone 7–12 mg at diagnosis and during radiation; 13 received no dexamethasone; average duration 7 weeks for patients with metastatic brain tumours and 23 weeks for those with primary brain tumours - radiation not specified	- Dexamethasone is effective in reducing neurologic symptoms and side effects of radiation. - Corticosteroid therapy-induced toxicity increases over time. - Dosing should be individualized.
Sturdza 2008 <sup>15</sup>	retrospective	n = 88 patients, 34 oncologists	- Over a 6-month course of WBRT, 52% of patients received dexamethasone 4 mg QID and 66% were instructed to taper dexamethasone after WBRT	- Prescribing practices vary considerably, even within a single institution. - Many patients receive high doses of steroids for considerable periods of time and develop related side effects.
Millar 2004 <sup>16</sup>	review of 21 RCTs of patients receiving WBRT for multiple cerebral metastases	n = not known	- 18 of 21 studies mentioned corticosteroid therapy	- Reporting of use of corticosteroids is inconsistent and insufficiently detailed to allow assessment of the additional benefit of WBRT.
Horton & Olson 1971 <sup>17</sup>	open label prospective study	n = 48	- Group 1: no radiation, prednisone 40 mg for 4 weeks, then 30 mg until disease progression - Group 2: brain external radiation + prednisone 30 mg vs placebo	- Little difference was seen between groups in rate of disease progression (however time intervals were not given).
Borgelt 1981 <sup>18</sup>	prospective	n = 64	- Group 1: radiation 12 Gray in 2 fractions with or without corticosteroids. - Group 2: radiation 20 Gray in 5 fractions with or without corticosteroids	- Patients who received corticosteroid had faster improvement in neurologic signs and symptoms compared to those not receiving corticosteroid.
Kurtz 1981 <sup>19</sup>	Randomized controlled trial	n = 255	- Group 1: radiation 30 Gray in 10 fractions with or without corticosteroid - Group 2: radiation 50 Gray in 20 fractions with or without corticosteroids.	- Patients had the same rate of improvement with or without corticosteroids. - No significant effect of corticosteroids was seen on relief of neurologic symptoms.

\* WBRT = whole-brain radiation therapy

- Hwang TL, Close TP, Grego JM et al. Predilection of brain metastasis in gray and white matter junction and vascular border zones. *Cancer* 1996;77(8):1551-5.
- Raslan A, Bhardwaj A. Medical management of cerebral edema. *Neurosurg Focus* 2007;22(5):E12.
- Tsao MN, Sultanem K, Chiu D et al. Supportive care management of brain metastases: what is known and what we need to know. Conference proceedings of the National Cancer Institute of Canada (NCIC) Workshop on Symptom Control in Radiation Oncology. *Clin Oncol (R Coll Radiol)* 2003;15(7):429-34.
- Betz AL, Keep RF, Beer ME, Ren XD. Blood-brain barrier permeability and brain concentration of sodium, potassium, and chloride during focal ischemia. *J Cereb Blood Flow Metab* 1994;14(1):29-37.
- Eccher M, Suarez JI. Cerebral edema and intracranial pressure: monitoring and intracranial dynamics. In *Critical Care Neurology and Neurosurgery* (Suarez JI ed). Totowa, NJ: Humana Press, 2004;47–100.
- Soffietti R, Ruda R, Mutani R. Management of brain metastases. *J Neurol* 2002; 249(10):1357-69.
- Sinha S, Bastin ME, Wardlaw JM et al. Effects of dexamethasone on peritumoural oedematous brain: a DT-MRI study. *J Neurol Neurosurg Psychiatry* 2004;75(11):1632-5.
- Vecht CJ, Hovestadt A, Verbiest HB et al. 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.
- Weissman DE, Janjan NA, Erickson B et al. Twice-daily tapering dexamethasone treatment during cranial radiation for newly diagnosed brain metastases. *J Neurooncol* 1991;11(3):235-9.
- Hempen C, Weiss E, Hess CF. Dexamethasone treatment in patients with brain metastases and primary brain tumors: do the benefits outweigh the side-effects? *Support Care Cancer* 2002;10(4):322-8.
- Sturdza A, Millar BA, Bana N et al. The use and toxicity of steroids in the management of patients with brain metastases. *Support Care Cancer* 2008;16(9):1041-8.
- Portnow J, Suleman S, Grossman SA. A cyclooxygenase-2 (COX-2) inhibitor compared with dexamethasone in a survival study of rats with intracerebral 9L gliosarcomas. *Neuro Oncol* 2002;4(1):22-5.
- Millar BM, Bezjak A, Tsao M et al. Defining the impact and contribution of steroids in patients receiving whole-brain irradiation for cerebral metastases. *Clin Oncol (R Coll Radiol)* 2004;16(5):339-44.
- Horton J, Baxter DH, Olson KB. The management of metastases to the brain by irradiation and corticosteroids. *Am J Roentgenol Radium Ther Nucl Med* 1971; 111(2):334-6.
- Borgelt B, Gelber R, Larson M et al. Ultra-rapid high dose irradiation schedules for the palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1981; 7(12):1633-8.
- Sturdza AE, Bezjak A, Pond GR et al. A phase II prospective study of standardized steroid dosing for patients with brain metastases undergoing whole brain radiotherapy. ASCO 2008, Abstract 2050.
- Kurtz JM, Gelber R, Brady LW et al. The palliation of brain metastases in a favorable patient population: a randomized clinical trial by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1981;7(7):891-5.