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Managing Disease and Therapy-Related Complications in Patients with Central Nervous System Tumors

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Opinion Statement

Treating patients with brain tumors can be divided into tumor-directed therapies, the management of tumor-related symptoms and complications and the psychosocial aspect of patient care. In this review, we will discuss the management of disease and treatment-related complications, which can negatively impact patient quality of life and functional status. Brain edema is a common complication or brain tumors and often causes more symptoms than the tumor itself. Treatment options are limited to the use of corticosteroids, which although effective have a plethora of side effects, so the goal should be the lowest dose that maximizes symptoms. Seizures are more common in lower grade brain tumors and treatment should be limited to patients who have seizures using agents that do not affect the metabolism of other drugs, especially chemotherapies. Blood clots are also common in patients and although there is a "fear" of tumoral bleeding, this is not a frequent occurrence; hence, using anticoagulants should be routinely used in patients who experience this complication.

Introduction

Central nervous system (CNS) tumors are associated with many complications including peritumoral edema, seizures, and venous thromboembolism. Treatment of these issues is often associated with adverse effects, which can further exacerbate patients' symptoms. It is essential for physicians to recognize these medical issues and appropriately manage them to minimize morbidity and maximize quality of life. In this article, we will discuss the medical management of tumor-related complications and treatment-related side effects.

Edema

- Peritumoral vasogenic edema is a common complication of CNS tumors and often leads to greater neurologic dysfunction and morbidity than the tumor itself. Vasogenic edema results from the disruption of the blood-brain barrier which causes extravasation of fluid into the brain parenchyma. The pathophysiology of vasogenic edema is related to angiogenic factors secreted by primary and metastatic brain tumors. Vascular endothelial growth factor (VEGF), among others, promotes vascular proliferation of new vessels that are fenestrated and with few or no endothelial tight junctions that increases vascular permeability and "leakiness" [1].
- Edema occurs within the white matter tracts and, depending on tumor type and grade, can be disproportional to the size of the tumor [2]. Clinical findings depend upon the location and amount of edema with symptoms ranging from hemiparesis, hemianesthesia, and encephalopathy to signs of marked elevated intracranial pressure with severe headaches, nausea, vomiting, papilledema, lethargy, coma, and even death [2, 3].
- Radiographically, peritumoral vasogenic edema is visualized as a hypodensity on CT and as a hyperintensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MR conforming to the white matter tracts surrounding the tumor, which if severe enough can cause mass effect and shift of the brain contents. Contrast-enhanced studies help differentiate the causative tumor from its edema [1]. MR is superior to CT in evaluation of edema [4].

Treatment

- Corticosteroids are the mainstay treatment for peritumoral edema, with significant but transient improvements in neurologic function [5]. Seventy to 100 % of primary and secondary brain tumor patients are treated with corticosteroids at some point in their management [6]. Although the exact mechanism of action of corticosteroids is not fully understood, it is proposed that they modulate the endothelial cells of the blood-brain barrier cells thereby decreasing permeability and extravasation of fluid [7].

- Dexamethasone is the most commonly used agent due to its minimal mineralocorticoid effects which minimizes water and sodium retention, long half-life which allows daily or twice-daily dosing, and decreased risk of psychosis and cognitive impairment [8]. Symptomatic improvement can be seen in several hours but is maximal between 24 and 72 h [2]. Although dexamethasone has been used extensively for decades, there is no consensus on dosage, duration, or tapering schedule.
- The goal of steroid therapy should be to use the lowest effective dose that controls patients' symptoms for the shortest duration to minimize toxicity. In the acute setting, intravenous doses of 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 [8]. Total daily doses as high as 16 mg may not be necessary as a randomized control trial assessing the efficacy of 4 mg, 8 mg, and 16 mg of dexamethasone in metastatic brain tumor patients showed similar clinical improvement in Karnofsky performance scale (KPS) amongst all doses, if there was no risk of herniation; however, there was a dose-dependent increase in side effects [9]. Dexamethasone may not be needed in patients with asymptomatic edema and a lower total daily dose of 4–8 mg should be used in patients with moderate symptoms [10]. The length of treatment is dependent on clinical improvement; however, tapering should be attempted as soon as possible. Steroids may be tapered rapidly if treatment is less than 10–14 days but should be slower for any longer treatment course to avoid adrenal insufficiency, which may present as headache, nausea, myalgias, and symptomatic hypotension [5, 11].

Treatment complications

- Corticosteroid toxicity limits its chronic use. The incidence of side effects are related to both the cumulative dose and length of treatment; however, they can occur within days of initiating therapy [11, 12••]. Weissman et al. reported that in a cohort of 59 neuro-oncology patients who received dexamethasone, 51 % had at least one steroid side effect. In patients whose cumulative dexamethasone dose was greater than 400 mg or were treated for more than 3 weeks, there was a significant increase in the incidence of side effects [13]. Corticosteroid use is associated with numerous systemic side effects including weight gain, osteoporosis, insomnia, delirium and psychosis, glucose intolerance, acne, amongst many others; however, in this review, we will highlight two serious complications: steroid myopathy and pneumocystis jiroveci pneumonia [14].

Steroid-induced myopathy

- Steroid-induced myopathy has been reported in up to 10 % of primary brain tumors patients and 60 % of general oncology patients [15, 16]. Onset is typically subacute with most patients

becoming symptomatic between weeks 9 and 12 of treatment; however, some may develop weakness only after a few weeks of therapy (especially older patients) or even up to a year [8, 15]. Both treatment duration and cumulative doses have been implicated as contributing factors for steroid-induced myopathy [15, 16].

- The presenting symptom is typically painless or mildly painful bilateral proximal weakness affecting the pelvic girdle muscles more than the arms. Patients may describe difficulty arising from a seated position and climbing stairs. Less commonly distal muscles and even respiratory muscles can be affected [16, 17]. Serum muscle enzymes are typically normal and electromyography may demonstrate myopathic findings [17].
- Steroid myopathy has a significant impact on patients' quality of life [15]. Treatment requires discontinuation or tapering of steroids, which can be challenging due to worsening of edema causing neurologic deficits. Steroid myopathy can sometimes make it difficult to determine a steroid's side effect from a tumoral side effect. Physical therapy may also be beneficial [18].

Pneumocystis jiroveci pneumonia

- Corticosteroid therapy can lead to immunosuppression predisposing patients to opportunistic infections. Pneumocystis jiroveci pneumonia (PJP) is a rare, yet potentially fatal fungal infection with an increased incidence in brain tumor patients treated with dexamethasone. Based on two small series, the incidence rate has been estimated to be 2–6 % after a median steroid treatment course of 10–12 weeks [19, 20]. Increased susceptibility to PJP during steroid taper has been suggested but not always observed [21]. Concurrent therapy with temozolomide is also associated with increased PJP risk [22]. The mortality rate has been reported as high as 40 % [19].
- Presenting symptoms include fever, dyspnea, nonproductive cough, and chest pain for days to weeks; however, there should be a low threshold for further workup with any respiratory symptoms in patients receiving chronic steroid and/or chemoradiation therapy [21, 23]. Prophylaxis has been suggested for patients with a CD4+ count $<300/mm^3$, persistent absolute lymphocyte count <500 cells/mm^3, receiving dexamethasone therapy for longer than 1–2 months, and those receiving chemoradiation therapy with prolonged courses of temozolomide [3, 24].
- 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 pentamadine 300 mg every month or dapsone 100 mg daily may be used [23].

Seizures

- Seizures are a major cause of morbidity in brain tumor patients. They occur in approximately 30 % of all brain tumor patients; however, the overall incidence is highly variable depending on the type of tumor [25]. Twenty to 40 % of patients will initially present with seizures while another 20–45 % will develop them later it the course of their illness [26]. Low-grade tumors are more epileptogenic than high-grade tumors and primary tumors are more epileptogenic than metastases [27]. The underlying epileptogenic mechanism of brain tumors is not fully understood and is likely multifactorial from a combination of change in inhibitory and excitatory neurotransmitters, electrolyte imbalance, inflammatory and morphological changes of the cortex, hypoxia, and metabolic derangements [28••].
- Brain tumor patients with first-time seizures should be treated with antiepileptic drugs (AEDs) on a long-term basis due to the high risk for recurrence. Brain tumor-related seizures are commonly resistant to pharmacotherapy [26]. There have been no studies comparing the relative efficacy of AEDs in brain tumor patients thus the choice of drug should be based on acuity (need for intravenous formulation to attain rapid therapeutic level), side effect profile, potential drug interactions, and cost [29].
- The role of prophylactic AEDs in brain tumor patients without a history of seizures has been investigated in several meta-analyses, including one performed by the American Academy of Neurology, with a general consensus recommending against their use [30–32, 33•]. In these studies, older generation AEDs were used thus it is unclear if newer medications would have a different effect on seizure prophylaxis, although they have less side effects and minimal drug interactions [3].

Pharmacologic treatment

- Older hepatic enzyme inducing AEDs (phenytoin, carbamazepine, phenobarbital) interact with many medications including corticosteroids, chemotherapy, and other AEDs which limits their use [29]. Enzyme-inducing AEDs can decrease the efficacy of several chemotherapy drugs, and conversely, these chemotherapies may also decrease the efficacy of AEDs thus increasing the risk of seizures [3].
- Newer non-enzyme inducers, namely levetiracetam, have thus gained favor in recent years. Levetiracetam has shown efficacy in brain tumor patients as monotherapy, adjunctive therapy, and in the post-craniotomy setting compared to phenytoin [34–36]. Levetiracetam also does not have any known drug interactions, is well tolerated, does not require level monitoring, is generic, and can be started at therapeutic dose in either oral or intravenous formulation [37]. Table 1 provides a

Table 1. Selected antiepileptic drugs for brain tumor patients

Generic name (brand name)	Dose	PO/IV	Notable and common side effects	Primary metabolism
Non-enzyme-inducing drugs				
Levetiracetam (Keppra)	1000–3000 mg/day divided BID	PO and IV	Sedation, fatigue, aggression, headaches	Hepatic
Valproic acid (Depakote)	10–60 mg/kg/day divided BID to QID Goal drug level, 50–100 μg/mL	PO and IV	Drowsiness, tremor, nausea and vomiting, hepatotoxicity, `weight gain, thrombocytopenia	Hepatic
Topiramate (Topamax)	100–400 mg/day divided BID	PO	Cognitive impairment, parasthesias, decreased appetite	Renal, minimal hepatic
Lamotrigine (Lamictal)	225–500 mg/day divided BID, 100–200 mg/day if adjunct with valproic acid	PO	Rash, Steven's Johnson's Syndrome (requires slow titration), headache, dizziness	Hepatic
Lacosamide (Vimpat)	100–400 mg/day divided BID	PO and IV	Dizziness, drowsiness, nausea, first degree AV block	Hepatic and renal
Zonisamide (Zonegran)	100–600 mg/day once daily or BID	PO	Drowsiness, dizziness, decreased appetite, impaired concentration	Hepatic
Pregabalin (Lyrica)	150–600 mg/day divided BID to QID	PO	Drowsiness, dizziness, peripheral edema, weight gain, incoordination	Renal
Enzyme-inducing drugs				
Phenytoin (Dilantin)	15–20 mg/kg IV load then 300–400 mg/day divided BID to TID Goal drug level, 10–20 μg/mL	PO and IV	Drowsiness, ataxia, nystagmus, gingival hyperplasia, hepatotoxicity, bone marrow suppression, cardiac arrhythmias and hypotension with rapid IV infusion	Hepatic
Phenobarbital	10–20 mg/kg load then 2–3 mg/kg/day daily or BID Goal drug level, 15–40 μg/mL	PO and IV	Somnolence, lethargy, hepatotoxicity, megaloblastic anemia, respiratory depression	Hepatic
Carbamazepine (Tegretol)	400–1600 mg/day divided BID Goal drug level, 4–12 μg/mL	PO	Dizziness, ataxia, lethargy nausea, hyponatremia, blurry vision, hepatotoxicity, arrhythmias	Hepatic
Oxcarbazepine (Trileptal)	1200–2400 mg/day divided BID	PO	Dizziness, ataxia, somnolence, lethargy, headache, nausea, diplopia, abdominal pain, hyponatremia, rash	Hepatic

summary of commonly prescribed AEDs in brain tumor patients.

- AEDs are associated with many side effects, most commonly sedation, cognitive impairment, dizziness, nausea, and rashes. There is data to suggest a higher incidence of side effects in brain tumor patients compared to a general population on AEDs, which may be due to additive effects from the underlying tumor or chemoradiation therapy. Up to 24 % of patients experienced side effects severe enough to necessitate either a change or discontinuation of AEDs [31].

Venous thromboembolism

- Venous thromboembolisms (VTE) are very common in CNS tumor patients and contribute significantly to their morbidity and mortality. The estimated incidence in patients with high-grade gliomas is 30 % and is 20 % in patients with metastases or primary CNS lymphoma [38]. The underlying pathogenesis of VTE in CNS tumor patients is not fully understood and may be multifactorial from a combination of increased levels of procoagulant proteins, such as tissue factor, and fibrinolytic proteins, such as plasminogen activator inhibitor, from tumor cells [39].
- Risk factors for VTE in glioma patients include older age (>75), prior VTE, prolonged immobility, obesity, higher-grade tumor, larger tumor (>5 cm), recurrent disease, subtotal tumor resection, chemotherapy, and poorer Karnofsky performance status [40••, 41]. The risk for VTE is highest within the first few months following surgery; however, an increased risk persists throughout the course of the disease [42]. Patients who develop VTE have a 30 % increased risk of mortality at 2-year follow-up [43].
- Perioperative VTE prophylaxis with combination of mechanical (compression stockings and pneumatic compression) and pharmacologic therapy with either subcutaneous heparin or low-molecular-weight heparin (LMWH) has demonstrated benefit in reducing risk of VTE without increasing the risk of hemorrhage and may be started 24 h after surgery and continued until the patient is ambulatory [44–46]. A randomized control trial, which was halted early due poor accrual, assessing primary VTE prevention with LMWH in patients with newly diagnosed malignant glioma demonstrated a trend of decreased risk of VTE but an increased incidence of intracranial hemorrhage thus the role of primary prevention is unclear and not recommended [47].
- In patients with CNS tumors, the management of VTE is challenging given the risk of intracranial hemorrhage (ICH); however, studies have demonstrated safety in both primary and

metastatic tumors [48, 49]. Anticoagulation is generally contraindicated in patients with metastases from melanoma, clear cell renal carcinoma, thyroid carcinoma, and choriocarcinoma, given their predisposition for spontaneous ICH; however, a recent small retrospective study did not demonstrate any significant risk with anticoagulation in patients with melanoma metastases [50, 51•]. Other contraindications to anticoagulation include prior history of ICH, major systemic bleeding, thrombocytopenia (<50,000–75,000 platelets/μL), and recent or planned neurosurgery within 2 weeks [46].

Treatment

- Given the increased risk of VTE and its associated morbidity and mortality, clinicians must keep a low threshold for urgent workup for any patient who experiences lower extremity edema or pain, dyspnea, tachycardia, or any other respiratory complaints. Venous ultrasound and CT angiogram are highly sensitive for diagnosis of DVT and PE, respectively [40••]. Once VTE is diagnosed, pharmacologic therapy should be started on patients to prevent PE and to alleviate symptoms [14]. Therapeutic options include unfractionated heparin and warfarin, LMWH followed by warfarin, and LMWH as monotherapy.
- LMWH is the preferred agent in all cancer patients for initial and long-term treatment; however, there are no studies specific to patients with CNS tumors [52]. Benefits of LMWH include simplicity of dosing, minimal drug interactions, or need for regular monitoring of PT/INR [3]. Table 2 summarizes the pharmacologic options for VTE treatment in patients with CNS tumors. Treatment should be continued for at least 6 months for initial VTE and indefinitely for recurrent VTE, if no significant contraindications such as those discussed previously [46]. Newer anticoagulants might be of value but there is no real data on safety and if a patient had an intracranial hemorrhage, the anticoagulant effects of these agents cannot be rapidly reversed.
- Inferior vena cava (IVC) filters have been used in the past due to concerns for ICH with anticoagulation; however, they are associated with several complications including recurrent PE and DVT, filter thrombosis, pneumothorax, infection, and postphlebitis syndrome [49, 53]. Complications are more frequent in glioma patients and reported to be as high as 62 % [53]. IVC filters should only be reserved for patients with strict contraindications to anticoagulation [37]. While IVC filters may prevent a PE, they do not treat the thrombus, which often occurs in the weak limb that is further impaired by edema. For some patients, an IVC filter can be placed and low dose anticoagulation used, i.e., those who might be a fall risk.

Table 2. Selected anticoagulation agents for venous thromboembolism treatment in brain tumor patients

Generic name (brand name)	Dose	Half-life	Monitoring	Reversal
Unfractionated heparin	Treatment: 40 units/kg bolus, followed by 18 mg/kg/h intravenously Prophylaxis: 5000 units subcutaneously every 8–12 h	1 h	aPTT goal 1.5–2.5 times baseline, check four times daily until stable then daily	Protamine 1 mg/100 units slow intravenous infusion
Dalteparin (Fragmin)	Treatment: 200 units/kg daily or 100 units/kg subcutaneously every 12 h	3–5 h	None	Protamine 1 mg/100 units slow intravenous infusion; recombinant factor VIIa 90 μg/kg
Enoxaparin (Lovenox)	Treatment: 1 mg/kg subcutaneously every 12 h Prophylaxis: 40 mg subcutaneously daily	4.5 h	Anti-Xa levels	Protamine 1 mg/100 units slow intravenous infusion; recombinant factor VIIa 90 μg/kg intravenously
Fondaparinux (Arixtra)	Treatment: 5–10 mg/day subcutaneously, weight based (5 mg/day for <50 kg; 7.5 mg/day for 50–100 kg; 10 mg/day for >100 kg) Prophylaxis: 2.5 mg subcutaneously daily	17–21 h	Anti-Xa levels	Recombinant factor VIIa 90 μg/kg intravenously
Argatroban	Treatment: 2 μg/kg/min intravenously with normal hepatic function, 0.5 μg/kg/min with impaired hepatic function	30–50 min	aPTT goal 1.5–2.5 times upper limit of normal; check 2–4 h after initiation and dose changes then daily	Recombinant factor VIIa 90 μg/kg intravenously
Warfarin (Coumadin)	Treatment: start 2.5–5 mg daily, adjust to goal INR	20–60 h	INR, goal level 2–3	Vitamin K 1–5 mg orally for INR correction, 10 mg IV for serious bleeding. For rapid reversal: fresh frozen plasma 10–15 mL/kg IV or recombinant factor VIIa 90 μg/kg IV

Compliance with Ethics Guidelines

Conflict of Interest

Jeffrey J. Raizer has received compensation from Genentech, Novocure, Midatech, Proximagen, Foundation Medicine and AbbVie for service on advisory boards, and from Genentech for service on speakers' bureaus. Karan S. Dixit declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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