Treatment of Medical Complications in Patients with Brain Tumors

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Opinion statement

Patients with primary brain tumors and those with cerebral metastases are at risk throughout their illness for several major medical problems, including vasogenic edema, seizures, and symptomatic venous thrombosis. In turn, the corticosteroids, anti-epileptic drugs, and anticoagulants used to treat these problems may produce significant adverse effects and result in important drug-drug interactions that may complicate chemotherapy. Although few Class I studies address any of these issues, guidelines can be offered to maximize quality of life and minimize hospital readmissions. Optimal management of brain edema involves minimizing corticosteroid use and tapering the steroid dose slowly to avoid steroid withdrawal symptoms. Prophylaxis of *Pneumocystis* pneumonia is necessary for patients requiring corticosteroids for more than 1 month. Anti-epileptic drugs (AEDs) should be avoided unless patients experience seizures. If possible, non-CTY (P450) enzyme-inducing drugs should be chosen. AED levels should be obtained frequently during corticosteroid taper. Multimodality venous thrombosis prophylaxis should begin at the time of the original surgery with external leg compression and unfractionated subcutaneous heparin or a low molecular weight heparin (LMWH). Brain tumor patients with symptomatic venous thrombosis or pulmonary embolism can be anticoagulated safely with warfarin or with LMWH, and LMWHs are preferable from the standpoints of efficacy, safety, and convenience for long-term outpatient treatment of venous thrombosis. Clinicians should be aware of potential drug-drug interactions between prescribed AEDs and chemotherapy and possible interactions with complementary and alternative therapies chosen by their patients. They also should be aware of interventions to minimize late sequelae of brain tumors and their treatment, including cognitive decline, depression, and increased stroke risk.

Introduction

Guiding brain tumor patients to appropriate surgical and chemotherapeutic options is an important function of neurologists making the initial diagnosis. For neurologists who continue to follow their brain tumor patients for supportive care, an additional responsibility is to minimize hospitalization and maximize quality of life by effective management of the most common medical complications. These include treatment of tumor-associated vasogenic edema, seizures and associated medication adverse effects, venous thromboembolism, and prophylaxis of predictable infections. In this article, appropriate management of these problems for all brain tumors types is outlined, but specific attention is given to special circumstances of patients with primary central nervous system lymphoma (PCNSL), meningiomas, and metastases when they differ from general recommendations for primary glial neoplasms.

EDEMA

Several types of edema are associated with brain tumors [1•, Class III]. Intracellular edema is the least likely type of edema in patients with brain tumors, although it may be present when herniation has resulted in circulatory interruption. Vasogenic edema associated with brain tumors is extracellular, resulting from increased brain capillary permeability. Microvessels in glioblastoma multiforme have low levels of proteins that maintain tight endothelial junctions such as the claudins and occluding [2, Class II]. Vascular endothelial growth factor (VEGF) expression, a potent permeability activator, is associated with malignancy grade. Vasogenic edema is most prominent in white matter. Osmotic edema results from altered osmotic gradient between plasma and interstitial fluid and is associated with hyponatremia or rapid reduction of hyperosmolarity. An edema mechanism that may be specific to meningiomas is an excretory-secretory mechanism, in which tumor-produced substances appear in peritumoral tissue. Hydrocephalic edema results from the obstruction of cerebrospinal fluid flow.

For most patients, corticosteroids will be the mainstay of treatment. However, for a subset of patients with leptomeningeal metastases in whom a combination of hydrocephalic and vasogenic edema combine to produce symptomatic pressure waves, acetazolamide 250 to 500 mg two or three times daily may be a useful option [3, Class III].

Corticosteroids reduce expression of VEGF and decrease capillary permeability. A direct antineoplastic effect of corticosteroids is applicable only to malignant B-cell lymphocytes in PCNSL. Dexamethasone, the most commonly prescribed corticosteroid, is nearly six times as potent as prednisone (10 mg of dexamethasone is equivalent to approximately 65 mg prednisone). Full efficacy of any corticosteroid is not apparent until 24 to 72 hours. Table 1 summarizes the dose equivalencies of available corticosteroids. Only one randomized trial has addressed the optimal therapeutic dosage and dose-related adverse effects of corticosteroids. Ninety-six patients with brain metastases were randomized to 4, 8, or 16 mg/day dexamethasone. In this study, side effects were dose-dependent, particularly proximal muscle weakness 4 weeks after the start of treatment, but all three groups of patients experienced the same degree of neurologic improvement [4, Class I].

Corticosteroids in doses required for vasogenic edema have multiple adverse effects, most of which are dose-related with considerable interindividual variability. At least five major complications of corticosteroids are of particular relevance to brain tumor patients. 1) Glucose intolerance that may persist after steroid withdrawal develops in 50% of patients who are treated with corticosteroids for more than one month. In nearly half of these patients, disturbances persist despite reduction or withdrawal of the drug [5, Class II]. 2) Peptic ulceration with gastrointestinal hemorrhage has been a concern for patients on high-dose corticosteroids, but the association has been questioned as the result of a meta-analysis of randomized controlled trials of corticosteroids for various diseases. It seems that the risk of peptic ulceration is quite low unless the patient also is taking nonsteroidal anti-inflammatory drugs [6, Class II]. Therefore, consensus is emerging that the use of H2-blockers and proton pump inhibitors can be restricted to the postoperative period of high-dose corticosteroid use and to those patients with a prior history of peptic ulcer disease. 3) Steroid myopathy represents a source of significant morbidity in up to 20% patients taking in excess of 8 mg dexamethasone or its equivalent in other corticosteroid doses for more than 2 weeks. Steroid myopathy is subacute and painless with large thigh muscles most involved and there is marked inter-individual susceptibility. Serum creatine phosphokinase and aldolase usually are normal and electromyography is not helpful [7, Class II]. Steroid myopathy is less common in patients taking phenytoin and possibly other enzyme-inducing drugs as a result of induction of dexamethasone metabolism by the AED. 4) Neuropsychiatric disturbances range from sleep deprivation when steroids are given at regular intervals around the clock to frank psychosis necessitating reduction in dosage or administration of neuroleptic medication. It is the author's impression that no particular corticosteroid preparation is particularly less likely to cause this disturbing adverse effect. 5) *Pneumocystis* pneumonia, though most common in HIV-infected patients with low CD4+ counts and rather rare among patients with solid tumor is recognized as a particular hazard for brain tumor patients on corticosteroids, occurring in close to 2% of patients in one retrospective series [8, Class III]. The causative organism, recently renamed *P. jirovecii* ("cannot infect the rat," i.e. is host-specific) is a fungus. Features of *Pneumocystis* pneumonia in brain tumor patients make the disease both more difficult to diagnose and to treat than in AIDS patients. The smaller number of infecting organisms results in a lower diagnostic yield of induced sputum and bronchoalveolar lavage, the two preferred diagnostic methods, and the larger number of inflammatory cells in brain tumor patients correlates with poorer oxygenation and an overall high mortality rate of 30% to 60% [9•, Class II]. The median duration of corticosteroid therapy in affected patients was the equivalent of 16 mg prednisone (2.5 mg dexamethasone) for a period of 8 weeks. Prophylaxis of this infection in brain tumor patients is now recommended with one double-strength trimethoprim-sulfamethoxazole tablet daily or one double-strength strength tablet twice daily three times per week. Kovacs *et al.* [10, Class I] have provided a good review of the transmission, diagnosis, and therapy of *Pneumocystis* pneumonia.

Table 1. Dose equivalence of corticosteroid preparations [1•]

Drug	Dose equivalent to 20 mg cortisone, *mg*	Biological half-life, h*	Anti-inflammatory activity (cortisol=1)	Mineralocorticoid activity (cortisol=1)
Dexamethasone	0.75	36 to 54	25 to 30	<2
Hydrocortisone or cortisol	20	8 to 12	1	1
Prednisone	5	12 to 36	3.5	0.8
Methylprednisolone	4	12 to 36	5	0.5

*Half-life shortened in the presence of enzyme-inducing drugs
(*From* Kaal and Vecht [1•]; with permission)

EPILEPSY

Seizures are the presenting symptom of a brain tumor in up to 40% of patients, and occur during the course of the illness in more than 60% of patients with supratentorial tumors. Seizures are the presenting symptom in the most patients with low-grade tumors and may represent a medically intractable condition, diminishing quality of life in patients with an otherwise good prognosis based on tumor histology. This section considers prophylaxis of epilepsy in brain tumor patients, choice of drug in those requiring treatment, and alternatives including surgery and chemotherapy for medically intractable epilepsy in patients with brain tumors [11,12 Class II].

Prophylaxis In a meta-analysis of four randomized trials involving AEDs and including over 300 patients with a variety of brain tumors, prophylaxis with phenytoin, phenobarbital, or valproate was ineffective in preventing seizures. When additional patients from eight nonrandomized trials were added for a total of 1100 patients, nearly 25% had side effects, usually cognitive problems or rashes, leading to discontinuation of the first AED chosen. Based on this analysis, an American Academy of Neurology's Practice Parameter recommended that prophylactic AEDs not be routinely given to patients with newly diagnosed brain tumors, or that AEDs be tapered off in the first postoperative week [13••, Class I]. Since that practice parameter was issued, a study by Forsyth *et al*. [14, Class I] involving 40 primary tumors and 60 metastases suggested that overall slightly more than 25% of patients had seizures and there was no difference in the seizure rate between patients taking or not taking AEDS. A definitive prospective randomized study addressing the efficacy of prophylactic AEDs after craniotomy for brain tumor does not exist, but the currently available data do not suggest any benefit from the older AEDs. It is not yet clear if certain groups of brain tumor patients could benefit from the use of any of the new AEDs that may prevent epileptogenesis without causing significant cognitive effects or drug interactions.

Treatment of seizures In addition to well-established and generally inexpensive older AEDs, clinicians now have available a large number of AEDs that do not induce hepatic enzymes and have relatively few drug interactions. Five sets of considerations influence drug choice. 1) Efficacy against partial seizures is a first requirement. 2) Rate of titration and route of administration may be important for brain tumor patients who present actively seizing and requiring rapid therapeutic levels. Late in the course of the illness, it may be advantageous to have AEDs available in liquid form. 3) Adverse effects, particularly on cognition in already vulnerable brain tumor patients, must be weighed. 4) Drug-drug interactions in patients on corticosteroids and chemotherapy will influence AED choice. 5) Route of metabolism may be relevant to patients with systemic cancer resulting in impaired hepatic or renal dysfunction. Table 2 summarizes older and newer AEDs and their particular effects of concern to patients with brain tumors.

Phenytoin remains the most widely prescribed AED for brain tumors, and has the advantage of a parenteral loading option and low cost. However, its most potent disadvantage is its enzyme-inducing capacity. This feature decreases the activity of many other concurrently used medicines, including corticosteroids and chemotherapeutic agents such as cisplatin, paclitaxel, irinotecan, topotecan, thiotepa, cyclophosphamide, methotrexate, doxorubicin, and nitrosoureas. Inhibition of the metabolism of nitrosoureas or etoposide by valproate can lead to chemotherapy toxicity. Increased toxicity of phenytoin is reported with 5-fluorouracil [15••, Class III]. The enzyme-inducing properties of AEDS are considered in the design of many clinical therapeutic trials that have separate arms or dosage adjustments for patients on these drugs.

Interactions of corticosteroids with drugs metabolized by the hepatic cytochrome p450 system can lead to clinically relevant problems of insufficient seizure control or, conversely, inadequate edema control for a given dose of corticosteroid. Even the longest acting corticosteroids should not be given just once daily in patients receiving enzyme-inducing AEDs. Patients on enzyme-inducing AEDs should have frequent AED level monitoring in the weeks after surgery. As steroids are tapered, phenytoin level, in theory, should go up, but the 5 to 7 days required to reach steady state and the practice of administering the drug intravenously in hospital and phenytoin self-induc-

Table 2. Antiepileptic drugs: special considerations in patients with brain tumors

Enzyme-inducing AEDs	Average dose and dosing intervals*†	Metabolism	Relevant adverse effects
Phenytoin	20 mg/kg load; then 3 to 5 mg/kg daily or twice daily† (10 to 20 µg/mL)	Hepatic	Rash, osteomalacia, Stevens-Johnson syndrome‡
Carbamazepine	800 to 2400 mg two to four times a day† (8 to 12 µg/mL)	Hepatic	Drowsiness, diplopia, rash, Stevens-Johnson syndrome‡, slow titration, leucopenia
Phenobarbital	10 mg/kg load then 1 to 3 mg/kg/d† (15 to 40 µg/mL)	75% hepatic; 25% renal	Drowsiness, Stevens-Johnson syndrome‡, frozen shoulder
Oxcarbazepine	900 to 2400 mg two to four times a day† (12 to 30 µg/mL)	80% hepatic	Hyponatremia, diplopia
Non-enzyme–inducing AEDs			
Valproic acid	10 to 60 mg/kg three to four times a day† (60 to100 µg/mL); Intravenous infusion rate is 20 mg/min, same dose as oral	Hepatic	Hair loss, weight gain, pancreatitis, thrombocytopenia, platelet dysfunction, tremor, parkinsonian extrapyramidal syndrome
Gabapentin	900 to 4800 mg three to four times a day	Renal	Drowsiness, rapid titration, ataxia, weight gain
Topiramate	100 to 400 mg twice a day	30% to 50% hepatic: 50% to 70% renal	Cognitive impairment, paresthesias, slow titration, weight loss, renal calculi
Levetiracetam	500 to 3000 mg twice a day†	Unclear	Agitation, psychosis, drowsiness, rapid titration
Lamotrigine	300 to 500 mg twice a day (3 to 20 µg/mL)	85% hepatic	Drowsiness, rash, particularly with concurrent valproate, slow titration
Tiagabine	24 to 56 mg two to four times a day	90% hepatic	Drowsiness, tremor, slow titration
Zonisamide	200 to 600 mg once or twice a day (10 to30 µg/mL)	> 90% hepatic	Drowsiness, headache, weight loss, renal calculi, slow titration

*Route of administration is oral unless otherwise indicated
†Available in liquid form
‡Stevens-Johnson syndrome is particularly likely in a setting of radiation therapy and corticosteroid taper
AED—antiepileptic drug

tion of metabolism in practice often result in a subtherapeutic phenytoin level in the immediate postoperative period. Carbamazepine levels, conversely, may go up after hospital discharge. Phenytoin, carbamazepine, and phenobarbital have been reported to produce a high incidence of rashes evolving in the setting of corticosteroid taper and concurrent radiation therapy. In the extreme form, life-threatening Stevens-Johnson syndrome may develop necessitating continuation of higher doses of corticosteroids. Some authors have invoked a complex interaction among phenytoin, corticosteroids and H2-blockers [16, Class III].

Drugs that may lower seizure threshold are a concern for patients who frequently are on various different medicines. Fortunately, most drugs that theoretically lower the seizure threshold are rarely a practical problem. In the author's opinion this statement includes tricyclic antidepressants and selective serotonin reuptake inhibitors. Depression is a significant quality of life problem in this patient group, and therapy should not be denied because of the risk of seizures. One exception to this rule is the antidepressant bupropion, which carries the highest risk of seizures and should be avoided [17, Class III].

VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE) is a common cause of morbidity and mortality among patients with brain tumors of all types, particularly in the postoperative period [18•, Class III]. Patients with PCNSL may have the highest risk. In one study, 59.5% of 42 patients with PCNSL developed VTE for 7% of whom the VTEs was fatal. Almost all VTE in patients with PCNSL were within the early period of intensive therapy [19, Class III]. Sev-

eral risk factors have been identified in patients with high-grade gliomas. These include age younger than 60 years, larger tumor size, and a paretic leg. In one study, when patients were stratified by ABO blood group, those with AB and A types were at greater risk than patients with blood type O [20, Class III]. A recent review has called attention to the persistently high risk of VTE in patients with malignant glioma. Marras *et al.* [21, Class I] surveyed prospective studies of deep venous thrombosis (DVT) and concluded that the best study reported a 24% rate of symptomatic DVT over the 17 months of follow-up beyond the first 6 postoperative weeks. A randomized, controlled trial is needed to clarify whether the risks and costs of long term anticoagulant prophylaxis in this population outweigh the benefits.

The practical consequence for this high risk population is that clinicians must have a high index of suspicion for DVT at all times. Patients with brain tumors should be considered to have high clinical probability of VTE. Therefore, although many medical studies have validated expedited diagnostic strategies to exclude DVT based on normal D-dimer levels and low clinical probability [22–24, Class I], these patients must have additional workup, including compression ultrasonography of the legs, preferably comprehensive duplex ultrasonography, repeated if necessary to detect proximally extending DVT [25, Class I]. Cost-effective, evidence-based prophylaxis of this potentially fatal complication must be instituted from the beginning of the patient's initial hospitalization (See Table 3). Neurosurgical series have established the safety of perioperative subcutaneous heparin for prophylaxis of VTE in patients having craniotomy [26]. In another recent study, multimodality prophylaxis including graduated compression stockings and intermittent pneumatic compression and enoxaparin 40 mg/day or heparin 5000 units twice a day eliminated symptomatic DVT and pulmonary embolism in 150 patients having craniotomy for brain tumor. The overall rate of asymptomatic VTE was 9.3% and did not differ between the groups [27, Class I]. Another study showed the superiority of enoxaparin plus compressive stockings compared with compressive stockings alone in VTE prophylaxis in elective neurosurgical patients [28•, Class I]. A third showed the equivalence in safety and efficacy of LMWHs and unfractionated heparins (UFHs) in the prevention of VTE in neurosurgical patients [29••, Class I]. Gerlach *et al.* [30] additionally showed the safety of LMWHs in patients having intracranial surgery in the largest prospective study involving 2823 patients who received compression stockings and nadroparin in the first 24 hours after surgery. There were 1.5% major postoperative hemorrhages, a result comparable to previous studies with unfractionated heparin [30, Class I]. The hemorrhage rate among glioblastoma multiforme patients was 6.2%. Other LMWHs, such as dalteparin, seem to show similar efficacy in immobilized patients, although a large scale clinical trial in brain tumor patients has not been done [31, Class I]. Despite these encouraging results, a survey of American neurosurgeons published 1 year later suggested that more than 75% reported using solely mechanical methods of prophylaxis, there by underestimating the risk of DVT and under-utilizing effective and safe pharmacologic antithrombotics [32, Class III].

Diagnosis and treatment of venous thromboembolism

The American College of Chest Physicians and the American Heart Association have published authoritative guidelines for the diagnosis of VTE and for acute and long-term care of patients receiving anticoagulant therapy, and their approaches are consistent with the recommendations outlined in this article [33–37, Class I]. Modifications are necessary for special conditions relevant to patients with brain tumors such as neurosurgery within the past 2 weeks, likely need for urgent neurosurgery in the near future, thrombocytopenia-producing chemotherapy, and inability to follow through with laboratory monitoring or to administer subcutaneous medications. For many years the majority of brain tumor patients with VTE were treated with a vena cava filter. However, reports of very high complication rates in brain tumor and other cancer patients, including post-phlebitic syndrome and pulmonary embolism, has led to a reconsideration of first-line therapy [38, Class III]. Most experienced neuro-oncologists would now consider medical therapy with unfractionated heparin intravenously followed by oral warfarin, or initial therapy with LMWHs the superior therapy for VTE [39, Class III]. Long-term medical maintenance therapy probably is appropriate for all patients with brain tumors except those with a completely resected meningioma or low-grade glial tumor and a DVT perioperatively for whom 3 to 6 months of therapy will suffice. Lee *et al.* [40••, Class II] have provided the most recent Class II information about VTE in cancer patients. In their multicenter, randomized, open-label study, the risk of recurrence of VTE at 6 months was twice as high in the group receiving warfarin as those receiving subcutaneous dalteparin. No significant difference in the rate of major bleeding was noted. Five per cent of the 336 patients in both groups had brain tumors with cancer, and their complication rate did not differ from that of other cancer patients. This study differs from that of Meyer *et al.* [41, Class I] who found in general a higher rate of bleeding complications, but neither study found any significant difference in major hemorrhage risk between LMWH and oral warfarin. Knovich and Lesser [42 ••, Class I] provide a comprehensive summary of these issues in their recent review.

Treatment

Diet and lifestyle for treatment of vasogenic edema

- Because corticosteroids are the mainstay of therapy and prolonged usage may be necessary, patients should be encouraged to maintain current body weight and avoid high salt, and high carbohydrate diets to minimize risk of electrolyte abnormalities and hypoglycemia. They should continue or institute an exercise regimen designed to minimize the degree of symptomatic steroid-associated proximal myopathy.

Pharmacologic treatment

- The aim of drug therapy is to reduce tumor-associated vasogenic edema and improve neurologic function.
- Begin corticosteroids. See Table 1 for dose equivalences.
- Dexamethasone is the most commonly prescribed corticosteroid.

Dexamethasone

Standard dosage A loading dose of 10 to 20 mg intravenously followed by 16 mg daily in divided doses. Dosing should be adjusted to the minimal needed to control edema.

Contraindications Prior sensitivity to corticosteroids. Actively bleeding peptic ulcer may require special prophylaxis.

Main drug interactions See introduction to this article. Major interactions are with enzyme-inducing AEDs. Risk of gastrointestinal bleeding increases with concomitant use of nonsteroidal anti-inflammatory drugs and this category of drug should be avoided in corticosteroid-dependent patients. Degree of contrast enhancement on magnetic resonace imaging or computed tomography scan will also change in a somewhat dose-dependent fashion while patients are on steroids.

Main side effects Acute: rise in blood pressure, intraocular pressure, and serum glucose, variable degree of hyponatremia and hypokalemia, oral candidiasis, potential psychosis and/or sleep disturbance, gastrointestinal upset and/or exacerbation of ulcer disease. Chronic: steroid myopathy, osteoporosis, immunosuppression with risk of opportunistic infections, including *Pneumocystis*.

Special points Even with the longer-acting corticosteroid preparations, sleep disturbance can be reduced by giving the bulk of the steroid dose in the morning dose and offering no dose later than dinnertime. Prophylaxis for *Pneumocystis* pneumonia should begin as indicated in Table 2 if the patient is likely to remain on corticosteroids for more than 1 month. Corticosteroids should be avoided if possible prior to diagnosis of a suspected case of primary CNS lymphoma as the tumor may "disappear" on MRI, delaying definitive diagnosis.

Corticosteroids should be tapered as soon as possible after definitive tumor resection or successful chemotherapy. Decreasing the dose by 25% every 4 to 5 days is a rational approach. In patients who have required corticosteroids for more than 2 weeks, the "steroid withdrawal syndrome" may occur. This entity is characterized by arthralgias, myalgias, and joint pain. It usually follows a rapid taper, but also can present more insidiously in patients who have had a slow taper. A screening 8 am cortisol level is a good first step in diagnosis. The biggest risk of corticosteroid withdrawal is iatrogenic adrenal insufficiency that can persist for months and can be anticipated in a patient who has received more than 0.75 mg dexamethasone per day for more than 3 weeks. Acute adrenal insufficiency may present as hypotension refractory to volume repletion and requiring vasopressors. A small percentage of patients with brain tumor treated with corticosteroids will have tertiary adrenal insufficiency, that is, adrenal atrophy and a requirement for chronic steroid supplementation. Mild intercurrent illnesses may not require supplementary steroids, but moderate infections, surgery, or major illness may. The following recommendations are derived from guidelines appearing in several recent review articles in the medical literature [43-45, Class III].

	Treatment of long-term hypothalamic-pituitary-adrenal axis suppression: hydrocortisone 15 to 25 mg per day with 10 to 15 mg in the morning and a smaller dose in the evening to mimic normal diurnal steroid secretion. Steroid supplementation: 1) moderate illness (fever, minor trauma or surgery): increase daily steroid dose to equivalent of 15 mg prednisolone (50 to 75 mg hydrocortisone); return to normal dose after 24 hours; 2) severe illness (major surgery, critical illness): Increase steroids to 50 mg hydrocortisone (16 mg prednisolone) every 6 hours given intravenously or intramuscularly; taper dose to baseline by decreasing by 50% per day; 3) septic shock: 50 to 100 mg hydrocortisone intravenously every 6 hours with or without 50 µg fludrocortisone daily; treat for 7 days and taper corticosteroids as under 2).
Cost/cost-effectiveness	All expensive except prednisone.

Osmotic therapy

	Mannitol is used in patients with severe brain edema who cannot tolerate the 24-72 hours required for maximal corticosteroid effect, though corticosteroids are usually started simultaneously with the osmotic therapy agent.
Standard Dosage	1g/kg (250 mL of 20% solution).
Contraindications	Hyperosmolar nonketotic hyperglycemia or hyperosmolar state from diabetes insipidus.
Main drug interactions	No major considerations
Main side effects	The major concern is fluid and electrolyte imbalance. There may be negative effects of a disrupted blood-brain barrier with entrance of chemotherapeutic agents that normally cannot enter brain parenchyma.
Special points	Mannitol reduces intracranial pressure for only a few hours and there may be a "rebound phenomenon" with rapid rise in intracranial pressure after the drug is stopped. Mannitol is not recommended for more than 24 hours while other methods of intracranial pressure reduction are instituted.

Interventional procedures

- Surgery for the purpose of edema treatment is considered when there is edema-related obstructive hydrocephalus that can be treated with shunting, ventriculostomy, or emergent resection of a strategically-located, often posterior fossa mass.

Other treatments

- Patients who have received corticosteroids, radiation, and other treatments for brain tumors remain at increased risk for other medical conditions. Medical monitoring includes periodic fasting blood sugar and cholesterol measurement and annual dual-energy x-ray absorptiometry scan for osteoporosis. In one study of stroke incidence in cancer patients, brain tumor ranked second only to lung cancer in risk for ischemic stroke [44, Class III]. Minimizing risk factors, including appropriate use of statin therapy and antiplatelet agents, may reduce stroke risk in long-term brain tumor survivors [46].

Emerging therapies for vasogenic edema

- Corticotropin-releasing factor (CRF) has been studied in animal models and patients with brain tumor. CRF has a direct action on tumor microvasculature with repair of blood-brain barrier disruption [1, Class I]. In a phase II randomized, dose-ranging trial of CRF in brain tumor patients with symptomatic edema intravenously administered CRF resulted in improved neurologic function in 10 of 17 patients with brain metastases. Hypotension was the dose-limiting toxicity [47, Class II].

Pharmacologic treatment for seizures

- The American Academy of Neurology does not recommend prophylactic administration of AEDs to patients with brain tumors [13, Class I]. Some authors call attention to particular high-risk groups, such as those with melanoma or leptomeningeal disease, but there are no studies singling out these groups [39, Class III].
- Table 2 describes the drugs available for the treatment of partial epilepsy, doses, available preparations, and specific considerations. For acute treatment of seizures requiring parenteral administration of a long-acting AED, phenytoin or valproate are the only options. For acute seizure exacerbation in a setting that can be anticipated to be of brief duration such as radiation therapy transient increase in corticosteroid dose may be more beneficial than adding another AED.
- The enzyme-inducing drugs interfere with the efficacy of steroids, oral contraceptives, and with many chemotherapeutic agents (see text). Theoretically, a nonenzyme-inducing drug such as gabapentin, gabatril, or levetiracetam would be a better choice, and the author has had excellent experiences treating brain tumor-related seizures with all of these agents. However, there are no Class I or Class II studies on which to base this recommendation.
- Monotherapy should be the goal for brain tumor patients with brain tumors. The American Academy of Neurology has issued excellent parameters on initiation of treatment and treatment of refractory epilepsy with the newer antiepileptic drugs [48•, Class I].
- Adverse effects severe enough to necessitate a change in therapy occur in up to 25% of brain tumor patients [48•]. Morbilliform rashes, sometimes progressing to Stevens-Johnson syndrome, appear in over 20% of patients treated with phenytoin or carbamazepine [49, Class III]. Cognitive side effects are particularly important in this patient population and may mimic tumor effects. Aspects of cognitive and psychological adverse effects of AEDs are well-summarized in a review by Mattson [50•, Class III].

Interventional procedures

- Radiation therapy may be indicated in stable or slowly progressive low-grade primary brain tumors that produce refractory epilepsy.
- For some patients with oligodendroglioma, temozolomide can improve seizure control even with little or no reduction in MRI abnormalities [12, Class II].

Seizure surgery

- Patients with low-grade glial tumors, particularly oligodendroglial tumors, can expect long-term survival and refractory epilepsy becomes a major quality-of-life detractor. Patients with resected low-grade tumors should be referred for epilepsy monitoring for possible seizure surgery.

Assistive devices

- For selected patients with a good prognosis from their brain tumors who continue to require multiple AEDs, vagal nerve stimulation can improve seizure control.

- With the exception of patients who have an isolated seizure preoperatively and complete resection of a tumor with good prognostic histology (meningioma), it can be anticipated that most brain tumor patients will remain chronically on AEDs. Another exception would be the frequent occipital seizures as a manifestation of the reversible posterior leukoencephalopathy syndrome attributable to immunosuppressives or chemotherapeutic drugs, in which case treatment consists of withdrawal of the offending agent.

Other treatments

- Many patients with cancer will wish to take complementary or alternative medicines (CAM). They should be warned to inform their physician of all such preparations as several of the popular herbal remedies available on the market interact adversely with AEDs, antidepressants, and corticosteroids. Two prime examples of adverse reactions include decreased phenytoin levels when combined with the Ayurvedic syrup shankhapushpi and prolonged bleeding when warfarin is combined with Ginkgo biloba or garlic. Mamon *et al.* and Fugh-Berman [49, Class III; 51] provide a good discussion of these and other potentially hazardous interactions. Weiger *et al.* [52•, Class I] summarize references from many databases and Web sites regarding current evidence-based use of many complementary or alternative therapies.
- Long-term brain tumor survivors, particularly those who have been treated with radiation therapy and those who require continuous AEDs may experience persistent or progressive cognitive impairment. Although there are no Class I studies addressing cognitive enhancement for this patient cohort, in the author's experience, modafinil 200 mg each morning may improve concentration and alertness. Beneficial effects usually are apparent within a few days, and adverse effects, such as agitation and sleeplessness, also appear early so that treatment efficacy can be established rapidly.

Diet and lifestyle for treatment of venous thromboembolism

- Patients with all types of primary and secondary brain tumors are at risk for VTE. They should be encouraged to be up as soon as possible after surgery and to maintain an active exercise program. Prolonged air travel is a known risk for VTE [53, Class I].

Pharmacologic treatment

- The main purpose of VTE prophylaxis is to avoid the dangers of proximal vein thrombosis with pulmonary embolism. A second concern is prevention of postphlebitic syndrome and prolonged hospitalization in patients with limited life expectancy.

Prophylaxis of venous thromboembolism

- Unfractionated subcutaneous heparin (UFH) or low molecular weight heparin (LMWH) are the two main pharmacologic choices for VTE prophylaxis. See Table 3 for standard doses. Increasingly, consensus among oncologists is that it is both easier and more effective to treat patients with LMWHs that do not require monitoring and can be given once daily during hospitalization without increasing the risk of hemorrhage in neurosurgical patients.

Table 3. Drugs for prophylaxis and treatment of venous thrombosis [26,27,28•,29••,30,31,36•,40••,41]

Prophylaxis

Drug	Route of administration	Dose	Risks/major hemorrhage	Study
Unfractionated heparin	Subcutaneous	500 IU every 8 or 12 hours	Thrombocytopenia	[26,27]
Enoxaparin*	Subcutaneous	40 mg daily		[28•]
Dalteparin	Subcutaneous	500 units daily		[29••,31]
Nadroparin	Subcutaneous		None/1.5%	[30]
Treatment				
Unfractionated heparin,* warfarin*	Intravenous, oral	Loading: 5000 U or 80 U/kg adjust infusion to therapeutic PTT range.‡ Begin warfarin immediately. Target INR 2.5	Thrombocytopenia/1.5% to 7% in glioblastoma multiforme	[36•,40••,41]
Dalteparin*	Subcutaneous	100 units/kg every 12 hours or 200 units/kg daily; maximum dose is 18,000 units/d§; after 1 month can be reduced to 150 units/kg	No risk difference between warfarin and dalteparin	[40]
Enoxaparin*	Subcutaneous	1 mg/kg every 12 hours or 1.5 mg/kg daily; maximum dose is 180 mg daily	No difference between warfarin and enoxaparin groups	[36•]
Tinzaparin	Subcutaneous	175 units/kg daily; maximum dose is 18,000 units/d		[36•]
Nadroparin	Subcutaneous	86 units/kg every 12 hours or 171 units/kg daily; maximum dose is 17,100 units/d		[36•]

*Class I or II evidence for neurosurgical patients
†Major hemorrage intracranial or requiring surgical procedure or transfusion. A platelet count should be obtained in patients taking these drugs at day 3 to 5. Many Hemorrhagic events have little clinical impact.
‡PTT corresponds to heparin levels determined by antifactor X assay of 0.3 to 0.7 units/mL.
§Recommendations on dose for patients less than 100 kg not yet finalized

Unfractionated subcutaneous heparin or low molecular weight heparin

Contraindications Active systemic or intracranial bleeding or prior thrombocytopenia on any heparin preparation.

Main side effects All patients on any of the UFH or LMWH should have platelet counts checked at 3 to 5 days. UFH carry a higher risk of thrombocytopenia and osteoporosis.

Treatment of VTE

- The goal of treatment is relief of symptoms and prevention of embolization and recurrence. For most patients with systemic cancer and for those with PCNSL or glioblastoma multiforme this usually means life-long treatment.
- There are 3 options for pharmacologic management of VTE. Consensus is emerging that option 3 provides the best efficacy for long-term prevention of recurrent VTE in cancer patients:
  - Unfractionated intravenous heparin followed by oral warfarin or
  - Low molecular weight heparin followed by oral warfarin or
  - Low molecular weight heparin adjusted by weight as sole treatment.

Heparin

Standard dosage	See Table 3.
Contraindications	Neurosurgery performed or planned within two weeks of VTE. Prior thrombocytopenia on any heparin preparation. Active systemic bleeding, platelet count less than 40,000, endocarditis, uncontrolled systemic hypertension (>180mmHg systolic). Primary histology of tumor consistent with high risk of spontaneous hemorrhage (metastatic melanoma, choriocarcinoma and, probably, renal metastases).
Cost/cost effectiveness	Outpatient therapy with LMWHs is safe and effective. Outpatient treatment is unsuitable for patients with massive thrombosis or high risk of hemorrhage. LMWH is more expensive than UFH it reduces but overall costs by reducing hospital admission and laboratory monitoring.

Interventional procedures

- Thrombolysis with catheter-directed antithrombotic infusion is associated with a higher risk of bleeding than intravenous therapy and is reserved for patients with life-threatening pulmonary embolism or limb-threatening thrombosis present for less than 1 week.

Assistive devices

- Standard of care on neurosurgical services is compressive stockings with external pneumatic intermittent compression. These mechanical interventions should not replace subcutaneous UFH or LMWH because they are not sufficient to reduce VTE incidence [54, Class II].

Emerging Therapies for Venous Thromboembolism

- A new class of antithrombotic agents that specifically inhibit factor Xa and lack activity against thrombin is represented by fondaparinux. Fondaparinux has a long half-life allowing once daily administration and does not bind to platelet factor 4, making immune thromobocytopenia extremely unlikely. It was approved for prophylaxis of VTE after major orthopedic surgery. The Matisse Investigators study reports Class I evidence on almost 4500 patients with clinically symptomatic DVT or pulmonary embolism that once daily fondaparinux is as safe and effective as twice daily enoxaparin for 5 days followed by oral vitamin K antagonists [55, Class I].
- The orally administered direct thrombin inhibitor ximelagatran has been compared to 6 months of therapy with enoxaparin followed by warfarin. In this large Class 1 study of 2489 patients, rates of symptomatic recurrent VTE with or without pulmonary embolism and major bleeding complications were statistically the same [56, Class I]. Of possible relevance to cancer patients who require life-long anticoagulation, another placebo-controlled trial showed that ximelagatran reduced the rate of recurrent VTE without increasing major hemorrhage in patients who had already finished 6 months of standard treatment. A possible concern was liver enzyme elevations in 5% to 10% of patients on chronic therapy [57, Class I].

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