A Review of the Symptomatic Management of Malignant Gliomas in Adults

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Abstract
Malignant brain tumors are aggressive tumors with a very poor prognosis. Survival is on average 12 to 18 months. Patients with malignant gliomas are subject to multiple medical problems that can significantly impact their overall survival and quality of life, including seizures, cerebral edema, venous thromboembolism, cognitive and psychiatric disorders, and side effects of chemotherapy. This article examines the evidence for managing many of these issues to reduce symptoms and improve quality of life. (JNCCN 2013;11:424–429)

Approximately 66,300 new primary brain tumors were diagnosed in 2012, of which an estimated 24,300 were malignant and 13,700 resulted in death.1 Some of these diagnoses and deaths represent pediatric cases or lower-grade malignancies. However, gliomas represent approximately 30% of all primary brain tumors diagnosed, of which 60% are malignant. Malignant gliomas are relatively uncommon in childhood, especially when compared with other neuroepithelial and primitive tumors.1

Medical and neurologic problems are common in this patient population, and require frequent monitoring and treatment to maximize quality of life. The most common problems encountered by the treating physician are seizures, cerebral edema, venous thromboembolism (VTE), cognitive and psychiatric disorders, and side effects of chemotherapy. This article addresses the literature and current guidelines on many of these issues. Myelosuppression, constipation, and diarrhea are not unique problems to this patient population, and can generally be treated as they would in the non–central nervous system (CNS) population. For this reason, these issues are not addressed.

Seizures
Seizures are a major cause of morbidity associated with all brain tumors. The incidence of seizures among patients with brain tumors ranges from 30% to 70%. It is the presenting symptom of a brain tumor in up to 40% of patients.2 The risk of development of seizures in patients with brain tumors is related to tumor type. Low-grade gliomas are more frequently associated with seizures than high-grade gliomas.

The exact mechanism of seizures in patients with glioma is unknown but is probably multifactorial. Tumor type, changes in peritumoral tissue, expression of neurotransmitters, receptors, and the molecular genetics of the tumor likely participate in epileptogenesis.3 In addition, growing intracranial lesions can both structurally and functionally alter the surrounding brain tissue and participate in epileptogenesis.4 This is particularly true in malignant gliomas, in which tissue hypoxia, hemorrhage, and inflammation may be significant. Tumor-related seizures are usually “localization-related” and manifest as simple partial or complex partial seizures. Secondary generalization may occur but is not universal.

Prophylactic treatment of patients with glioma using antiepileptic drugs (AEDs) is somewhat controversial.
Based on a meta-analysis by Glantz et al5 and data from several additional trials, giving prophylactic AEDs routinely to patients with newly diagnosed primary brain tumors is not recommended, or the drug should be tapered off in the first postoperative weeks.2,5 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Central Nervous System Cancers currently recommend prophylactic AEDs only if the tumor is in a highly epileptogenic region, such as the temporal lobe (to view the most recent version of these guidelines, visit NCCN.org).6 Once a patient with a known tumor has a seizure, long-term treatment with AEDs is indicated because of the very high risk of seizure recurrence. The choice of anticonvulsant should take into consideration the possibility of drug–drug interactions with antineoplastic agents.

Several interactions between AEDs and chemotherapy are based on a shared cytochrome P450 enzyme metabolic pathway. Phenytoin, carbamazepine, oxcarbazepine, phenobarbital, and primidone are known enzyme-inducing AEDs. They are inducers CYP450, especially the 3A4 family.7 This may lead to significant reductions in the plasma levels of many antineoplastic drugs. They may decrease the efficacy of dexamethasone, which is also metabolized by CYP3A4.7 Valproic acid is a CYP450 inhibitor and can reduce the clearance of antineoplastic drugs.7 Retrospective analysis of the survival of patients in the RTOG 0525 trial based on AED use suggests improved survival in patients taking valproic acid versus those on other AEDs or no antiepileptic agents.8 Interestingly, a correlative analysis of patients in the North Central Cancer Treatment Group trial showed the opposite: superior outcomes in patients taking enzyme-inducing anticonvulsants.9 The effect of class of anticonvulsant on brain tumor survival remains unknown. Most newer agents, such as levetiracetam, lacosamide, gabapentin, and zonisamide, do not influence the CYP450 system and should be the preferred agents in patients with brain tumors. Extensive research on levetiracetam in patients with primary brain tumors has recently shown that it is well tolerated and produces effective seizure control.10–13

Refractory epilepsy is not uncommon in patients with structural lesions of the CNS; the frequency varies from 12% to 50%,14 particularly in lower-grade tumors. The basis of the resistance to drug treatment is unknown; however, growing evidence suggests that several multidrug-resistance genes may play a role.14 Even if complete seizure control cannot be achieved, AEDs can help decrease seizure severity and frequency. Surgical treatment of brain tumor–related epilepsy is generally indicated only in patients with slow-growing tumors with a good prognosis. This is a separate consideration from the potential impact of surgery on progression-free or overall survival. The best results are obtained when the pathologic lesion and adjacent epileptogenic cortex are resected. Radiation may improve seizure control in some patients.15

Cerebral Edema

By definition, brain edema represents increased brain volume from a local excess of water and/or sodium.16,17 There are 3 general categories of brain edema: vasogenic, cytotoxic, and hydrocephalic. The edema associated with brain tumors is mainly vasogenic in origin and contributes significantly to mortality. Vasogenic edema in tumors is caused by disruption of the blood–brain barrier, which allows protein-rich fluid to accumulate in the extracellular space. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor damage the endothelial cell junctions of blood vessels. Increased interstitial fluid pressure has an important role in treatment resistance through contributing to tumor hypoxia and preventing adequate tumor penetration by chemotherapy agents.18 In addition, edema may also exacerbate seizures.2 Cerebral edema is easily visible on both CT and MRI. On CT, it causes an area of low signal, whereas on MRI it increases T2 and fluid-attenuated inversion recovery (FLAIR) signal.

Since their introduction in 1957 as a treatment for cerebral edema caused by brain metastases, corticosteroids have remained the mainstay of therapy for vasogenic edema of any source, although identification of new agents is a priority. Patients with glioma with vasogenic edema can usually be adequately managed with corticosteroids. Steroids are indicated in all symptomatic patients.2 Dexamethasone is usually the preferred steroid because of its relative lack of mineralocorticoid activity. Few randomized trials have addressed the optimum dosage of dexamethasone. A commonly
used, reasonable dexamethasone regimen consists of a 10-mg loading dose followed by 4 mg 4 times per day. However, because of the long half-life of dexamethasone, 4-times-daily dosing is not always necessary, and it can be used twice daily.

Because an adequate decrease in elevated intracranial pressure caused by vasogenic edema may take up to several days with steroid treatment alone, other interventions, such as elevating the head of the bed, fluid restriction, hyperventilation, and administration of mannitol or hypertonic saline, may be needed to emergently decrease intracranial pressure.

Despite the beneficial effect of steroids, they are well-known to have a large number of potential side effects, including insomnia, tremor, hiccups, impaired glucose tolerance, gastritis, and peptic ulcer disease. Long-term use is frequently associated with myopathy and osteopenia. Even short-term use of corticosteroids may result in myopathy. To reduce the risk of these potential side effects, they should be used in divided doses in the minimum amount required to control symptoms and should be tapered as quickly as possible. Many physicians coprescribe H₂-blockers along with dexamethasone to reduce the risk of gastritis or peptic ulcer disease. Glucocorticoids have a direct catabolic effect on muscle through decreasing protein synthesis and increasing the rate of protein catabolism. This can lead to significant muscle atrophy. Patients with brain tumors who are receiving chemotherapy and corticosteroids are at particular risk for Pneumocystis carinii pneumonia. For this reason, appropriate antibiotic prophylaxis is usually recommended in this population. The most commonly used prophylactic agent is trimethoprim-sulfamethoxazole on a 3-times-weekly schedule. Other agents that can be used include dapson and inhaled pentamidine. Atovaquone has been studied in oncology settings and can also be prescribed, although its use has been limited in the brain tumor population.

Surgery can be considered in the presence of edema-related obstructive hydrocephalus that can be treated with shunting, ventriculostomy, or emergent resection of a strategically located mass to reduce intracranial pressure and prevent herniation.

VEGF plays an important role in the pathogenesis of peritumoral edema. Antiangiogenic agents that block the VEGF pathway, such as bevacizumab, are able to decrease vascular permeability by restoring the abnormal tumor vasculature to a more normal state. These agents may minimize adverse effects by decreasing corticosteroid use, and can theoretically improve clinical outcome by decreasing cerebral edema. The use of antiangiogenic agents remains experimental, and the known toxic effects of these agents and the high cost associated with their use may render them impractical for routine cerebral edema therapy.

**VTE**

In general, patients with cancer are at significantly higher risk of developing VTE than those without cancer, and on average 15% of patients with cancer, will develop a deep vein thrombosis (DVT) or pulmonary embolism (PE) during their clinical course. VTE is the second leading cause of death in patients with cancer, and is an especially common cause of morbidity and mortality among patients with malignant glioma, particularly in the perioperative and postoperative periods. Other factors increasing the risk of VTE in these patients are age older than 60 years, large tumor volume, ongoing active therapy (particularly with antiangiogenic agents or agents such as thalidomide or its derivatives), use of hormonal therapy, or presence of hemiplegia. Timely diagnosis and initiation of therapy for VTE is important, because if left untreated, nearly 50% of all patients with symptomatic proximal DVTs will develop PE, which can increase mortality significantly.

The cause of VTE in patients with brain tumors is not yet completely understood. Normal brain tissue is a rich source of tissue factor, which plays a central role in the initiation of the coagulation cascade. Expression of tissue factor in gliomas is proportional to grade, with extremely high levels in glioblastoma. In addition, other indicators of activated coagulation, such as D-dimer, are elevated, and the fibrinolytic system may be abnormal.

Although clinical examination is a useful tool, classic clinical symptoms are not always present in patients with acute DVT. Duplex ultrasonography is the preferred venous imaging modality for initial diagnosis. On some occasions, repeat duplex may be required for patients who have suspected DVT and a negative or limited first duplex study. Diagnosis of PE involves a combination of clinical assessment and imaging studies with CT angiogram.
Chest radiograph and electrocardiogram alone are insufficient for diagnosis. Because the high risk of developing VTE, patients with brain tumors undergoing craniotomy (or being hospitalized for other reasons) should be treated with adequate prophylaxis. Unfractionated subcutaneous heparin (UFH) or low-molecular-weight heparins (LMWHs) are the 2 main pharmacologic choices for VTE prophylaxis. The LMWHs are easier to use and do not require monitoring. The duration of prophylaxis remains unclear, but studies suggest that prolonging prophylaxis for up to 4 weeks may be more effective than short-course prophylaxis in reducing postoperative VTE. Mechanical methods include early ambulation, compression stockings, electrical calf muscle stimulation, and intermittent external pneumatic compression devices, all of which also help limit venous stasis and enhance systemic fibrinolysis. Both LMWH and UFH have been shown to be effective prophylaxis for VTE in elective neurosurgery without introducing an excessive bleeding risk. Multiple societies have created guidelines for VTE prophylaxis in patients with cancer, including ASCO and NCCN. Although these do not address patients with brain tumors in particular, all concur that patients with cancer undergoing surgery should receive VTE prophylaxis, with the length of postoperative treatment dependent on the procedure. In addition, in the absence of contraindications, medically hospitalized patients with cancer should receive VTE prophylaxis.

Three trials of primary prophylaxis for VTE have been performed in ambulatory patients with glioma using LMWH. In 2002, the ECOG initiated a phase II trial of dalteparin in patients with newly diagnosed glioblastoma. The trial was stopped early because of the change in standard of care from radiation alone to combined chemoradiation with temozolomide. No VTE events occurred in 42 patients available for analysis, and no grade 3 or greater bleeding events. No change in median survival was apparent compared with historical controls. A similar trial of tinzaparin in patients with newly diagnosed malignant glioma showed a reduction in incidence of VTE while on versus off LMWH, and 2 patients experienced CNS hemorrhages (none greater than grade 2). A randomized, placebo-controlled trial of dalteparin in patients with newly diagnosed malignant glioma did not meet its accrual goals; however, a trend was seen toward a reduced rate of VTE, with a suggestion of increased intracranial bleeding. Further trials of LMWH or newer agents for primary prophylaxis in patients with malignant glioma are needed to answer these questions.

The main goals in the treatment of VTE are to prevent PE, improve limb circulation, and resolve leg edema and pain. UFH, and particularly LMWH, are widely used for the treatment of VTE. Fondaparinux, a synthetic indirect factor Xa inhibitor, is also a possibility for these patients. In the initial treatment, no significant difference in benefit or increased risk of hemorrhage apparent with UFH versus LMWH, and the choice depends on the individual physician preference and the patient’s medical condition. A meta-analysis comparing UFH and LMWH for the long-term treatment of DVT has shown better outcomes and reduction of major bleeding complications in patients treated with LMWH for 6 months. Warfarin is indicated primarily when anticoagulation is required to last longer than 6 months, or when financial considerations apply to the use of LMWH. The optimum duration of anticoagulation has yet to be determined. Thrombolysis and vena cava filters should be reserved for patients in whom anticoagulation is insufficient or contraindicated.

The most dangerous complication of anticoagulation in patients with a brain tumor is intracranial hemorrhage. Any sudden changes in neurologic symptoms or new onset of headache should prompt immediate evaluation with brain imaging. Antiangiogenic agents, such as bevacizumab, have significant procoagulant properties. Bevacizumab was approved for use in glioblastoma in 2009, and its use is increasing. A high index of suspicion of VTE should be maintained for patients on bevacizumab treatment who complain of lower extremity pain, color change, or swelling.

**Neurocognitive Symptoms**

At diagnosis, cognitive impairment is already present in many patients with brain tumors, and most will experience distressing neurocognitive symptoms during their illness. Surgery, radiation therapy, and chemotherapy will also influence patients’ cognitive status. Because cognitive impairment can
both affect quality of life (QOL) and interfere with the patient’s ability to function at premorbid levels both professionally and socially, understanding the potential neurocognitive sequelae associated with the tumor itself and the delayed effects of treatment can help physicians and patients make informed choices bearing on survival and QOL.

Several studies in patients with malignant gliomas showed that fatigue is the most frequently reported and troublesome of all symptoms. It is more common in patients with high-grade versus lower-grade tumors. Radiation therapy, anemia, AEDs, chemotherapy, depression, weight gain, and other issues related to steroid use or steroid withdrawal frequently contribute to fatigue. As stated earlier, tapering corticosteroids to the minimum necessary dose, reducing AEDs when possible, antidepressant therapy, and correction of metabolic abnormalities may help some patients. Psychostimulants, such as methylphenidate, dextroamphetamine, modafinil, pemoline, and armodafinil, may play a role in the treatment of brain tumor–related fatigue.

Depression is a common symptom in patients with brain tumors. It may be related to the tumor itself or to medications used for therapy. Unfortunately, too few physicians report or address these symptoms. In a report from the Glioma Outcome Project, 93% of patients reported these symptoms of depression in the immediate postoperative period, whereas physicians reported these symptoms in only 15% of patients. Reporting by physicians increased by 6 months after surgery; however, it remained less than 25%, whereas patient-reported depression remained greater than 90%. Pharmacologic treatment of depression lags even further behind physician reporting. Patients who are depressed should be considered for antidepressant therapy to improve QOL.

Cognitive deficits are also extremely common in patients with brain tumors. Problems such as poor short-term memory, distractibility, personality changes, loss of executive function, emotional liability, and decreased psychomotor speed can be seen. Radiation therapies, AEDs, chemotherapy, and steroid use can exacerbate these symptoms. Studies have shown that whole-brain radiation alone or in combination with high-dose chemotherapy results in greater cognitive decline than partial radiation or high-dose chemotherapy alone. MRIs in these patients may show periventricular white matter changes. A recent open-label study of donepezil in postradiation patients suggested improvement in attention, mood, and verbal memory. Psychostimulants and cognitive rehabilitation may be helpful in improving motivation and attention. Although no studies have yet been performed in patients with glioma, a recent abstract in patients with brain metastasis undergoing whole-brain radiation suggests possible benefit from the use of memantine.

Nausea and Vomiting

Chemotherapy-induced nausea and vomiting (CINV) is a frequent problem in oncology patients. The primary chemotherapy used in patients with newly diagnosed malignant gliomas is the alkylating agent temozolomide. This is listed as a moderate to highly emetogenic antineoplastic agent in the NCCN Guidelines for Antiemesis (to view the most recent version of these guidelines, visit NCCN.org). Prevention of nausea and vomiting is the goal, and the NCCN Guidelines are a useful tool to help oncologists select appropriate therapy. A unique issue in the glioma population is the potential for increased intracranial pressure, as outlined earlier. Nausea and vomiting are frequent symptoms of this issue. For this reason, dexamethasone is frequently useful in reducing nausea.

One concern that must be addressed is the potential for drug–drug interactions. Antidepressants are frequently necessary in patients with glioma, and these are potentially subject to severe interactions with many antiemetics. Metoclopramide is contraindicated in combination with most antidepressants. Prochlorperazine may increase the QT interval, and as a result may interact with most antidepressants. The serotonin antagonists are generally safe in combination with antidepressants. The commonly used medications, granisetron and palonosetron, have minimal to no reported interactions; however, the risk of serotonin syndrome remains, at least in theory. Ondansetron has the potential for causing QTc prolongation and serotonin syndrome in combination with most antidepressants, and caution should be used when prescribing them at the same time. Dolasetron should be avoided in patients taking antidepressants, because of potentially serious interactions.
Symptomatic Management of Gliomas

Summary
As with all patients with cancer, those with malignant gliomas have a variety of medical and neurologic issues that require management to maximize patient QOL. Attention to these details can do much to improve the daily functioning of patients with brain tumors.

References

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