Thirty to 50 percent of patients with brain tumor present initially with a seizure; as many as 30 percent more will develop seizures throughout their disease course.¹ There is significant variability based on tumor type, but slow growing tumors are the most epileptogenic.² More specifically, dysembryoplastic neuroepithelial tumor and GG have a seizure incidence of 80-100 percent, low grade gliomas have a seizure incidence of 60-85 percent, and glioblastoma has a seizure incidence of 30-60 percent.³ Seizure type is most commonly localization related with or without alteration of consciousness and secondary generalization.³,⁴ Epilepsy in patients with tumor appears to be more pharmacoresistant than many other etiologies, particularly low grade tumors.²

Several theories exist as to why tumoral epilepsy is so pharmacoresistant. These theories invoke changes in cellular function, AED metabolism, and disease severity. The target theory proposes that the normal cellular targets of anti-epileptic drugs (AEDs) are absent or altered in the tumor and the tissue surrounding the tumor.²,⁵ Some examples include alteration of glutamate and GABA receptor function, ion level changes, and synaptic vesicle protein function.²,⁵ Alternatively, the transporter hypothesis suggests that alterations in the function of the blood brain barrier via upregulation of multi-drug transporters results in accelerated removal from the brain or decreased transport into the brain.²,⁵ Lastly, the intrinsic severity hypothesis proposes that high frequency of seizures in the early disease course is due to the severity of the underlying disease process and will influence the treatment response.²,⁵

WHEN AND WHY TO INITIATE TREATMENT

Given the severity and frequency of tumoral epilepsy, it is not uncommon for physicians to initiate seizure prophylaxis with AEDs in patients with brain tumors. However, there is no clear evidence that AEDs are effective in preventing first seizures in these patients.¹,⁶ Furthermore, the unfavorable side effect profile of AEDs, including possible negative effects on cognition, bone marrow, and the liver, confers unnecessary risk to brain tumor patients.¹,⁶ Lastly, interactions with chemotherapeutic agents, corticosteroids, and AEDs are common and should be avoided if possible.¹,⁶ The formal recommendation of the American Academy of Neurology states: “because of their lack of efficacy and their potential side effects, prophylactic anticonvulsants should not be used routinely in patients with newly diagnosed brain tumors.”⁶

However, once a patient presents with a seizure, treatment with an AED is commonly warranted. The risk of recurrent seizure will vary based on specific tumor type, location, size, growth rate, cellular composition and neurochemical profile.³,⁴ However, there is a lack of randomized controlled data to aid physicians in their selection of an AED. Several factors should be taken into consideration, such as possible efficacy, side effects, anticipated course, potential bidirectional interactions between chemotherapy and AEDs, and anticipated course.¹,⁴
There are unfortunately no large randomized controlled studies available to provide evidence in favor of a particular AED for the management of focal seizures secondary to brain tumor.\(^1,2,5\) Recently, research on levetiracetam monotherapy has found >50 percent seizure reduction in 65-90 percent of patients in small populations.\(^2\) Topiramate, pregabalin, gabapentin, and zonisamide have all been studied as monotherapy and/or add-on therapy in small cohorts of patients with brain tumor. Topiramate resulted in seizure freedom of 55.6 percent, and an additional 20 percent of patients had >50 percent seizure reduction. Treatment with pregabalin resulted in seizure freedom in 50 percent of patients, and 50 percent of patients had a >50 percent seizure reduction. Gabapentin therapy resulted in seizure reduction of >50 percent in all patients in a small study.\(^2\) Zonisamide adjunctive therapy resulted in a responder rate of 83.3 percent. Lacosamide therapy had a responder rate of 78.6 percent in a small cohort.\(^2\) Comparisons of newer and older AEDs have resulted in similar rates of seizure control; however, newer AEDs have been noted to have a more favorable side effect profile.\(^2\) In the future, knowledge of alterations in expression of molecular targets for a given tumor type may help guide AED selection.\(^2\) For example, the amount of SV2A expression has been correlated with response to levetiracetam.\(^2\)

**CONSIDERING SIDE EFFECTS**

Patients with brain tumors may be particularly susceptible to side effects from AEDs.\(^3\) Increased risk of Stevens-Johnson Syndrome and other skin rashes has been noted to be associated with radiotherapy, and administration of oxcarbamazepine, phenytoin, and phenobarbital.\(^1,2\) Summative effects of AEDs, epilepsy, and tumor on cognition are also of significant concern in brain tumor patients.\(^1,2\) Interactions between AEDs and cancer therapy, such as chemotherapeutics and steroids, should also be considered when selecting an AED for a patient with a brain tumor.\(^1,2,5\) Inducers such as phenytoin and carbamazepine enhance metabolism of many drugs, including steroids and several anti-cancer medications.\(^1\) Temodar does not seem to be among the medications affected, but irinotecan, etoposide, erlotinib, and imatinib can be significantly affected by p450 interactions.\(^1\) In general, the selection of enzyme inducing or enzyme inhibiting drugs is considered less favorable than the selection of newer drugs with little or no enzyme inducing properties, renal excretion, lower protein binding, and fewer interactions, such as levetiracetam.\(^2\)

Valproic acid, a p450 inhibitor, has been retrospectively noted to be associated with longer survival (13.8 v 10.8 months) in glioblastoma patients.\(^2\) This has been postulated to occur due to increasing serum concentrations of chemotherapeutic agents compared to patients treated with p450 inducers or agents that are p450 neutral.\(^2\) Additionally, valproic acid may also have anti tumor properties. Valproic acid inhibits tumor growth via histone deacetylase inhibitor activity, induces autophagy in glioma cells, and may also enhance cellular redox effects if used in combination with some types of chemo including temodar.\(^1,2,3\) Valproic acid may also sensitize malignant cells to radiotherapy and chemotherapy.\(^1\) While this is interesting, further prospective work is needed to clarify these findings and determine their clinical utility. On a similar note, studies of levetiracetam have determined that it sensitizes glioblastoma cells to temozolomide by restoring O6-methylguanine DNA-methyltransferase inhibitory activity.\(^2\) This is another finding worthy of future study.

**CO-MANAGEMENT AND COORDINATION OF CARE**

Knowledge of the anticipated course of treatment and collaboration with neuro-oncology and neurosurgery are key components in management of epilepsy in brain tumor patients. For example: surgical planning may influence selection in favor of an agent with an available IV formulation, selection of chemotherapy may influence AED selection, increases in seizure frequency or recurrence of seizures may be the result of tumor progression or recurrence and should be rapidly re-evaluated by oncology.\(^1-3\) For patients with low grade tumors, multi-disciplinary case discussion may be required for consideration of extended lesionectomy, requiring more lengthy epilepsy surgery evaluation in order to provide improved seizure control.\(^2\)

Specific knowledge of tumor type reviewed with neuro-oncology may also assist in providing patients with a more accurate seizure prognosis. For example, WHO grade II oligodendrogial tumors with a deletion of only 19q have better seizure control than those without. Expression of ki-67 in patients with low grade gliomas has been negatively associated with seizure control. And isocitrate-dehydrogenase 1 and 2: if 2 is more prevalent, it may be epileptogenic because structurally similar to glutamate and may activate NMDA receptors.\(^3\)

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