9 Management of Seizures in Brain Metastases

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Epidemiology, Incidence, and Etiology of Seizures in Patients with Brain Metastases

Managing seizures is an integral aspect of neuro-oncological care in patients with brain metastases. Seizure has been reported as the presenting symptom in brain metastases in up to 20% of patients [1, 2]. A recent systematic review reported the incidence of seizures at 14.8%, although this has been cited as high as 40% in the literature [1–18]. Regardless of the exact percentage, seizures are a common problem in this population. The incidence varies depending on tumor type: In a retrospective series of 470 patients with brain metastases, the likelihood of seizure was highest in melanoma (67%) and lowest in breast cancer (16%). Other common tumor types were lung (29%), gastrointestinal (21%), and unknown primary (25%). The high incidence of seizure with melanoma brain metastases is thought to be due to the tendency toward hemorrhagic conversion, which can be epileptogenic.

Tumor location is another important factor that can impact the frequency of seizures in patients with brain metastases. Seizures are almost exclusively due to supratentorial disease, most commonly cortical lesions in the frontal lobe, parietal lobe, and temporal lobe. This is undoubtedly due to the inherent epileptogenicity of the cortical gray matter [2]. Occipital lobe seizures are seen less frequently. Masses near the fissure of Rolando are more prone to seizures, but lesions in the pituitary or posterior fossa are rarely associated with seizures unless they invade supratentorially [19]. There is increased risk of seizures with a higher number of metastatic lesions.

Clinicians should carefully consider the etiology of seizures in a patient with brain metastases. In addition to the metastasis itself acting as a focus for seizure, other possibilities include leptomeningeal or dural metastases, metabolic conditions, cerebral infarction or hemorrhage, infections, and treatment-related causes. Table 9.1 identifies some of the potential etiologies of seizures in patients with metastatic brain tumors. Cancer patients are at higher risk for metabolic encephalopathies such as hyponatremia or hypoglycemia, opportunistic infections, or side effects of therapy. Paraneoplastic encephalitis is another potential cause of seizures in patients with systemic cancer.

Much research has attempted to clarify the various factors that contribute to seizure development in patients with brain metastases. While the mechanism of tumor-associated epilepsy remains poorly understood, theories focus on peritumoral amino acid disturbances, local metabolic imbalances, cerebral edema, pH abnormalities, and

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Table 9.1 Possible etiologies of seizures in the patient with brain metastases

Metastatic central nervous system neoplasms	Treatment-related causes
Parenchymal metastases	Radiation therapy
Dural-based metastases	Acute
Leptomeningeal metastases	Early-delayed
	Late-delayed
Toxic/metabolic conditions	Chemotherapy
Hyponatremia	Antimetabolites
Hypoglycemia	Methotrexate
Hypoxia	Cytarabine
Hypocalcemia	l-asparaginase
Hypomagnesemia	Vincaakaloids
	Topoisomerase inhibitors
Cerebral infarction	Alkylators
	Ifosfamide
Cerebral hemorrhage	Nitrosoureas
	Cisplatin
Infections	Bevacizumab
Bacterial	
Listeria monocytogenes	Opioids
Viral	Meperidine
Cytomegalovirus	Antiemetics
Herpes simplex	Phenothiazines
Fungal	Butyrophenones
Cryptococcus neoformans	Antibiotics
Aspergillus fumigatus	Penicillins
Candida species	Fluoroquinolones
Parasites	Imipenem-cilastatin
Toxoplasma gondii	Paraneoplastic disease

**Edited and updated from (Table 4–9, pg. 108, from DeAngelis/Posner book "Neurological Complications of Cancer" 2nd edition. Edited and updated with permission from Oxford University Press

altered immunologic activity (Fig. 9.1) [20, 21]. Further understanding of these mechanisms may elucidate why some patients with seizures become refractory to antiepileptic drugs even after removal of the metastatic lesion.

Clinical Manifestations

Seizures in patients with brain metastases are usually focal but can appear generalized if the focal discharge is asymptomatic. The presence of an aura (warning sign), or specific ictal and peri-ictal phenomena, typically reflects the tumor's location within the brain. The ictus can be caused by cortical irritation from invasion of cortical brain parenchyma, adjacent leptomeningeal deposits, or local edema. Tumor-related seizures are often repetitive or stereotyped, preceded by an aura and followed by a postictal phase. The International League Against Epilepsy (ILAE) recently proposed a new classification of seizure types that classifies focal seizures based on whether consciousness is altered during the episode [22].

Focal seizures with retained awareness (previously known as simple partial seizures) are further separated based on the semiology and epileptic region on the cortex. For example, a seizure in the occipital cortex may manifest as flashing lights in the opposite field of vision, whereas a seizure that begins in the motor cortex may cause rhythmic jerking movements of the contralateral face, arm, and leg. A parietal cortex seizure can disrupt spatial perception, while a mass in the dominant frontal cortex can disrupt language and cause aphasic seizures. Temporal lobe seizures may begin with auras such as an abnormal taste, smell, or gastrointestinal symptoms. Patients may experience only auras, which are focal seizures that can cause symptoms, but not impair consciousness. Auras can be present for months and eventually progress to a generalized seizure [23]. Patients may either return to normal immediately after the event or have a prolonged postictal period of worsened neurological function, corresponding to where the seizure originated in the brain. Notably, a patient with a focal motor seizure of the arm may suffer from postictal weakness that can last for minutes to hours, also known as Todd's paralysis.

Focal seizures with impaired consciousness, formerly known as complex partial seizures, occur in patients who have alteration of awareness during the event. During these seizures, patients may be alert but not respond to environmental stimuli; they may engage in repetitive behaviors like facial grimacing, chewing, or lip smacking, otherwise known as automatisms. Hostile or aggressive behavior can also occur in patients who have a focus in the deep frontal lobe. Similarly, patients may have an aura, ictal period, followed by a postictal period.

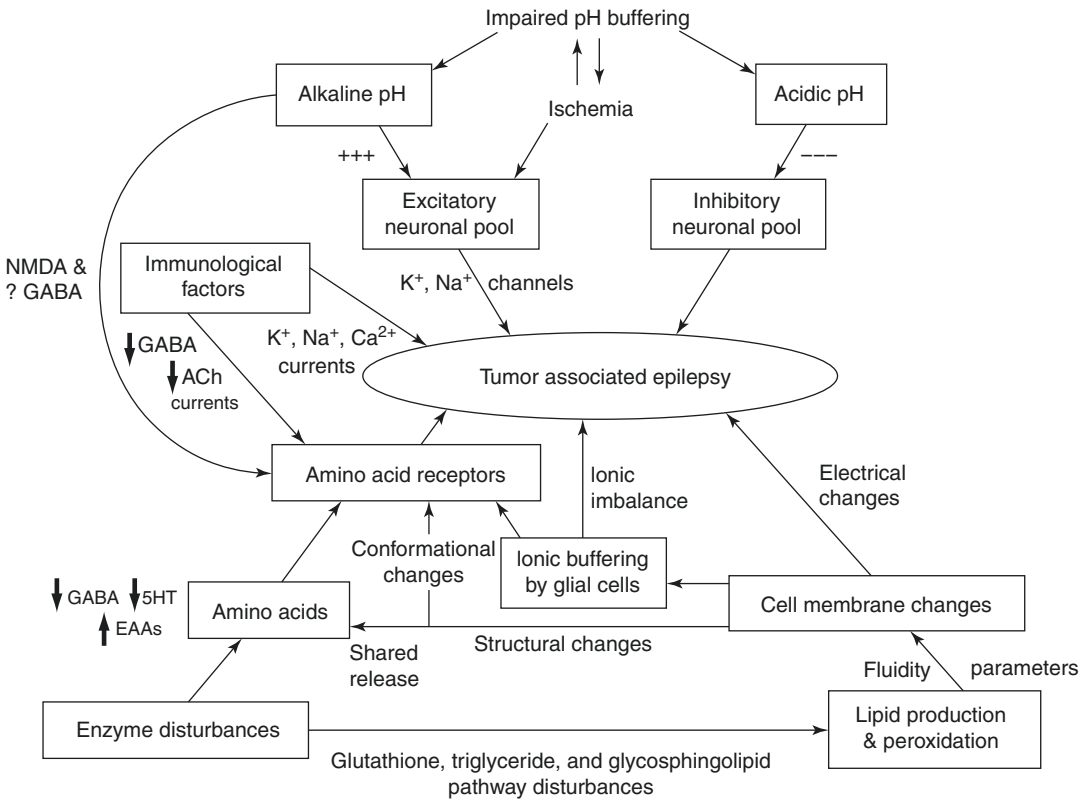

Fig. 9.1 Summary of possible causative and influencing mechanisms on tumor-associated epilepsy. The rich interplay of the varied factors and many plausible routes for seizure causation is highlighted. (From: Beaumont A, Whittle IR. The pathogenesis of tumour associated epilepsy. Acta Neurochir (Wien). 2000;142(1):1–15. Reprinted with permission from Springer)

Any type of focal seizure can progress to generalization, which often involve tonic-clonic movements. The tonic phase begins with a sudden loss of consciousness followed by stiffening of the arms, legs, chest, and back, which can then evolve into jerking of muscles for minutes. The clonic phase is characterized by tongue biting as well as frothy and bloody sputum. The postictal phase begins after movement has ceased; the patient usually enters a deep sleep that can last several minutes before the patient gradually wakens.

Of note, plateau waves (or pressure waves) in a patient with elevated ICP, often due to leptomeningeal disease, can frequently mimic seizure; however, the two diagnoses should not be confused as treatment differs significantly. Plateau waves are events that can involve dizziness, lightheadedness, presyncope, or even frank syncope and are typically associated with positional changes (e.g., sitting to standing). These episodes occur in the setting of increased intracranial pressure (ICP) or venous obstruction, even in the absence of headache. Key physical exam findings that would suggest increased ICP include papilledema on funduscopic exam and hydrocephalus on imaging. Seizures have been reported in up to 25% of patients with leptomeningeal disease. Patients with seizures should be treated with antiseizure drugs, while patients with increased ICP should be treated with steroids and/or neurosurgical intervention.

Brain tumor patients can also develop status epilepticus, which may be either focal or generalized, convulsive or nonconvulsive. Management of status epilepticus is discussed later in this chapter.

Diagnostic Evaluation

The diagnostic evaluation of a brain metastasis patient with a seizure requires careful history taking, detailed neurological exam, electroencephalography (EEG), and neuroimaging [19, 24]. The history of present illness should include a reliable description of the event not only from the patient but also from an eyewitness, understanding that one is not always present. Questions should focus on possible triggers or precipitants of seizure that can lower the seizure threshold, such as strong emotions, exercise, and alcohol use [25]. An accurate description of the seizure involves descriptions of the events leading up to the seizure, the ictal phenomena, and the postictal state. The history summarizes the various seizure semiologies, past antiepileptic use with associated side effects, birth history, and any history of CNS infections. The neurological exam of a seizure patient is usually normal unless a structural CNS lesion causing localizing signs such as Todd's paralysis is present. Comprehensive laboratory testing including AED levels, complete blood count, electrolytes, glucose, calcium, magnesium, renal function, liver function, and urinalysis should all be completed in case there are any reversible metabolic abnormalities lowering the seizure threshold [26].

EEG is an important diagnostic tool for the evaluation of a seizure patient. EEG can help support the diagnosis of epilepsy, localize the origin of epileptic activity, and at times assist in determining the underlying epileptic syndrome. However, there are limitations of EEG. For example, intermittent EEG changes and interictal epileptiform discharges (IEDs) can be infrequent and not always present during the recording of a patient who has had a prior seizure. Additionally, epileptic activity from brain metastases that are small or deep in the brain may not have a concordant EEG finding as these microvolt signals may not be visible on scalp recordings. Clinicians must thus understand the strengths and weaknesses of EEG to diagnose a patient with epilepsy. An EEG may not be required in a patient who has had a clinically obvious seizure with full recovery. EEG is also not routinely needed for those without clinical evidence of a seizure. However, EEG is essential for diagnosing nonconvulsive seizures and nonconvulsive status epilepticus (NCSE) and should be considered in all patients with brain metastases who have altered mental status.

Monitoring patients during the diagnostic workup can be done with a routine EEG (ambulatory or inpatient) or with prolonged video EEG monitoring while inpatient. During a routine EEG, electrical activity is recorded from electrodes placed on the scalp in standard positions for a short amount of time—generally 30 min. The sensitivity of detecting IEDs is low in a routine EEG and can be increased with prolonged monitoring overnight with video EEG monitoring [27]. Sensitivity can also be increased when seizure frequency increases and timing of EEG is closer to last seizure or if seizures are provoked by hyperventilation, photic stimulation, sleep deprivation, or medication withdrawal. However, treatment should never be delayed if the clinician believes that seizure is the most likely diagnosis. Interpretation of EEG findings is best done by an experienced clinician with specific training in EEG. Lateralized periodic discharges (LPDs, previously known as PLEDs) are commonly seen in patients with rapidly growing cerebral malignancies, which cause acute cortical injury. LPDs are defined by lateralized, persistent spikes, sharp waves, or sharply contoured slow waves that occur repetitively [28]. Focal slowing or generalized slowing of the EEG rhythm is nonspecific and can be seen in patients with multiple systemic issues, a postictal period, or an underlying structural lesion that is not necessarily epileptogenic.

Neuroimaging is vital to the evaluation of seizure in a patient with suspected or known brain metastases [29]. Computed tomography (CT) is usually the first imaging modality obtained in a patient with a new-onset seizure because it is available quickly and can exclude certain neurological emergencies such as hemorrhage [29, 30]. Contrast-enhanced magnetic resonance imaging (MRI) is a more sensitive imaging modality for the detection of brain metastases

than CT and is the neuroimaging modality of choice [31]. Better spatial resolution and soft-tissue contrast allows for visualization of smaller brain metastases and leptomeningeal disease. Positron-emission tomography (PET) and functional MRI are additional neuroimaging modalities that can be used for presurgical evaluation of patients with brain metastases [32].

Lumbar puncture should be performed if there is suspicion for a CNS infection or leptomeningeal metastasis. Appropriate neuroimaging with CT or MRI should be performed before lumbar puncture to rule out any space-occupying lesion that may render the procedure unsafe.

Treatment

Seizures in patients with brain metastases contribute to morbidity and mortality and should be aggressively treated when they occur [33]. The two mainstays of treatment include antiepileptic drug therapy and tumor-directed therapy. Anti-seizure drug therapy is usually first to be administered while plans are made for tumor-directed therapy.

Anti-seizure Drug Therapy

Every patient who has a seizure due to a brain metastasis should be treated with anti-seizure medications due to the high risk of recurrent seizure. There are no randomized trials that have established superiority of one agent over another agent in this population. AEDs should be chosen with the goal of controlling seizure at the lowest effective dose while minimizing toxicity. Certain AEDs require monitoring serum levels at recommended intervals. AED interactions with chemotherapy regimens should also be considered before prescribing.

AEDs with no or minimal hepatic enzyme-inducing or enzyme-inhibiting properties, such as levetiracetam, brivaracetam, pregabalin, lamotrigine, lacosamide, and topiramate, are generally preferred in initial treatment due to a favorable side effect profile and minimal drug-drug interactions (Table 9.2) [34–37]. Levetiracetam is often prescribed in the general population because it is well-tolerated; however some patients can have neuropsychiatric side effects such as irritability, agitation, anxiety, and depression [37]. Clinicians should remain vigilant as patients with frontal lobe brain metastases are at higher risk for these neuropsychiatric side effects.

Multidrug regimens should be avoided if possible since monotherapy will increase the likelihood of compliance, provide a wider therapeutic window, and be more cost-effective over time. Single-drug therapy also minimizes potential interactions with chemotherapy and other drug-drug interactions. Data from patients with primary brain tumors suggest approximately 50% of patients with tumor-related epilepsy will respond adequately to a single AED [38]. If a patient experiences recurrent seizures, the initial AED dose should be maximized, and appropriate serum levels should be checked before switching or adding a second anti-seizure drug. Lacosamide has been shown to be efficacious as an adjunctive agent in patients with medically refractory epilepsy and primary brain tumors [39, 40].

Levetiracetam

One retrospective study examined the role of levetiracetam in patients with metastatic brain tumors—of the 13 patients treated with levetiracetam as monotherapy (6 patients) or adjunctive therapy (7 patients) with a median dose of 1000 mg/day, the median seizure frequency decreased to 0 per week, suggesting complete seizure control. Only 3 of 13 patients reported somnolence or headache as the most common adverse event [41]. There does not appear to be any significant interaction with other drugs or chemotherapy, which is why levetiracetam is often the first drug used for neuro-oncologic patients. It is also conveniently available in both oral and intravenous forms. Brivaracetam is a newer formulation that is advertised to have similar efficacy without the psychiatric side effects of levetiracetam; however, there have been no studies of this drug in brain metastases.

Table 9.2 Antiepileptic drugs

	Average dose (serum therapeutic range)	Metabolism	Mechanism of action	Common adverse effects
Enzyme-inducing AEDs				
Phenytoin	20 mg/kg load, then 3–5 mg/kg daily or twice daily (10–20 ug/mL)	Hepatic	Sodium channel	Rash, osteomalacia, Stevens-Johnson syndrome, gum hyperplasia, hirsutism
Carbamazepine	800–2400 mg, two to four times a day (8–12 ug/mL)	Hepatic	Sodium channel	Drowsiness, diplopia, rash, Stevens-Johnson syndrome, leukopenia, hyponatremia
Phenobarbital	10 mg/kg load, then 1–3 mg/kg/d (15–40 ug/mL)	75% hepatic; 25% renal	GABA	Drowsiness, Stevens-Johnson syndrome, frozen shoulder, rash, ataxia, mood change
Oxcarbazepine	900–2400 mg two to four times a day	80% hepatic	Sodium channel	Hyponatremia, diplopia, headache, drowsiness
Nonenzyme-inducing AEDs				
Valproic acid	10–60 mg/kg three to four times a day (60–100 ug/mL); intravenous infusion rate is 20 mg/min, same dose as oral	Hepatic	GABA, sodium channel	Hair loss, weight gain, pancreatitis, thrombocytopenia, platelet dysfunction, tremor, parkinsonism, extrapyramidal syndrome
Gabapentin	900–4800 mg daily in three to four doses	Renal	GABA	Drowsiness, rapid titration, ataxia, weight gain
Pregabalin	150–600 mg/day	Unknown	Calcium channel	Drowsiness, dizziness, ataxia
Topiramate	100–400 mg twice a day	30–50% hepatic; 50–70% renal	Sodium channel, GABA, AMPA/kainate	Cognitive impairment, paresthesias, slow titration, weight loss, renal calculi
Levetiracetam	500–2000 mg twice a day	Enzymatic hydrolysis	Synaptic vesicle protein binding	Agitation, psychosis, drowsiness, glaucoma
Brevitaracetam	50–100 mg twice a day	Hepatic and extrahepatic amidase mediated hydrolysis	Synaptic vesicle protein binding	Drowsiness, ataxia, nystagmus, hypersomnia
Lamotrigine	300–500 mg twice a day	85% hepatic	Sodium channel	Drowsiness, rash, particularly with concurrent valproate, slow titration
Zonisamide	200–600 mg once or twice a day (10–30 ug/mL)	>90% hepatic	Calcium, sodium channel	Drowsiness, headache, weight loss, renal calculi, slow titration
Lacosamide	200–400 mg/day	Hepatic demethylation	Sodium channel	Dizziness, headache, diplopia, blurred vision
Clobazam	5–40 mg/day	Hepatic N-demethylation	GABA agonist	Sedation, cognitive effects, drowsiness

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Phenytoin

Phenytoin is very effective in controlling seizures in brain metastases and is often preferred in the setting of status epilepticus as it can be conveniently loaded intravenously or given orally. It is often not preferred in routine management of seizures in patients with cancer, however, due to its activity as a CYP3A4 inducer and potential interaction with chemotherapy. It also has several side effects including elevated liver function tests, osteomalacia, ataxia, nystagmus, myopathy, and myelotoxicity.

Zonisamide

Zonisamide has not been specifically studied in brain metastases, but it has been investigated in other brain tumors. A study of six patients with glial brain tumors showed an 83% response rate and 69% reduction in seizure frequency [42]. Limiting side effects include renal calculi, sexual dysfunction, and drowsiness. The drug does not appear to interfere with the metabolism of other drugs that utilize the cytochrome P-450 enzyme system.

Oxcarbazepine and Carbamazepine

A retrospective study analyzed oxcarbazepine (mean dosage, 1162.5 mg/day) to assess efficacy and tolerability compared to phenobarbital and carbamazepine in patients with brain metastases. The results showed significantly fewer side effects with oxcarbazepine compared to these other drugs with equivalent efficacy [43]. Patients on therapeutic doses of carbamazepine may complain of intermittent diplopia as well as drowsiness. Carbamazepine can also cause leukopenia, which can be especially concerning in patients who are receiving myelosuppressive chemotherapy. The drug has also been reported to be associated with SIADH, aseptic meningitis, and rash. While oxcarbazepine can rarely cause rash and sedation, it is thought to have a more favorable side effect profile than carbamazepine.

Gabapentin and Pregabalin

Gabapentin was studied as an adjunctive antiepileptic in four patients with metastatic brain tumors, and there was reported seizure resolution in half of patients [44]. Similarly, another study showed that pregabalin (median dose, 300 mg) had a greater than 50% reduction in seizure frequency in patients with primary brain tumors [45]. Gabapentin and pregabalin appear to be quite safe, and these drugs are widely used in cancer patients to treat chemotherapy-induced peripheral neuropathy. There is little to no interaction with other agents; however, side effects include somnolence, dizziness, ataxia, fatigue, and weight gain.

Topiramate

Topiramate has been studied in primary brain tumors (n = 47) as an adjunctive therapy or monotherapy (mean dose, 240 mg/day). It has been reported to result in a 76% seizure reduction of greater than 50% with only 8% of patients experiencing side effects that led to discontinuation in 6% [46]. Notable side effects include somnolence, fatigue, psychomotor slowing, confusion, weight loss, glaucoma, and kidney stones. Little is known regarding its interaction with anticancer agents.

Tumor-Directed Therapy

Treatment of brain metastases with surgery, radiation therapy, and/or chemotherapy may also improve seizure activity. Lesionectomy of the suspected epileptogenic zone has been shown to be efficacious in non-brain tumor patients, which has been extrapolated to brain tumor patients. But while several studies have examined the role of surgery in control of epilepsy, few of these studies were specifically focused on brain metastases; there are no standardized surgical approaches for seizure control in brain tumor patients. Additionally, it is difficult to compare studies focused on seizure surgery and brain tumors due to variable histology, pathology, and tumor locations. It is hypothesized that seizures in tumor-associated epilepsy do not necessarily originate from the mass lesion but rather from the adjacent brain tissue, and therefore tumor-associated epilepsy may differ from idiopathic epilepsy [47].

Three operative strategies exist for brain tumor resection for patients with seizures: (1) focal tumor resection, (2) radical tumor resection without electrocorticography, and (3) radical tumor removal with electrocorticography. Despite these options, resection without electrocorticography may not eliminate the epileptogenic focus. Likewise, many patients require antiepileptic drugs before, during, and after tumor resection. Several studies have demonstrated seizure frequency reduction after treatment

of primary brain tumors with chemotherapy, although none of these studies specifically included brain metastases [48–53].

Prophylaxis

The data for prophylactic anticonvulsants in patients with brain metastases are limited. A recent meta-analysis found only one study which met their inclusion criteria, the most strenuous of which was baseline information on study participants, including subgroups of those with brain metastasis [54]. The recommendation was level 3 for adults with brain metastasis who do not experience a seizure due to their metastatic brain disease; routine AED prophylaxis was not recommended. The recommendation was based on a study included in the meta-analysis, which used phenytoin or phenobarbital as a prophylactic AED [55]. Since seizure incidence was not significantly different in the treatment versus nontreatment group, the authors cited adverse effects of AEDs as a reason against their use.

However, newer AEDs such as levetiracetam and lacosamide have gained popularity in the brain tumor population and are thought to be useful and safe. In a retrospective study of patients with frequent, weekly seizures, levetiracetam use in metastatic lesions was tolerated well [41]. Seizure frequency was reduced in all patients with metastatic lesions to less than 50% of pre-levetiracetam baseline. There may be some subgroups of brain metastasis patients who benefit from prophylactic AED use. A group of patients with metastatic melanoma brain metastasis were evaluated for prophylactic AED use over a 2-year period [9]. Seizure risk was studied relative to brain metastasis characteristics—hemorrhage and multiple supratentorial metastases were associated with increased seizure risk. Univariate analysis revealed AED prophylaxis was significantly associated with a decreased seizure risk. Limitations of the study included its retrospective nature and small patient cohort. However, it suggests that AED prophylaxis may be beneficial in some subgroups of patients with brain metastasis.

Untoward Effects of Anticonvulsants

Drug Interactions

Interactions between antiepileptic drugs and chemotherapy are complex and mainly revolve around the cytochrome P-450 (CYP) system (Table 9.3). Phenobarbital, phenytoin, and carbamazepine, for example, are three antiepileptic drugs known to be strong CYP3A4 inducers and can significantly decrease the levels of vincristine, paclitaxel, irinotecan, teniposide, methotrexate, and busulfan. Valproic acid has several complex interactions with certain chemotherapies, as it is one of the few cytochrome enzyme-inhibiting AEDs with highly protein-bound properties, in addition to potential CYP2A6 induction. Highly protein-bound AEDs or chemotherapy agents—including phenytoin, phenobarbital, valproic acid, cisplatin, etoposide, and teniposide—can interact with each other, affecting free and bound levels of both drugs. It should be noted that some patients who take oral AEDs may have difficulty tolerating them while on highly emetogenic chemotherapy regimens. Clinicians should be cautious of heightened toxicity from the increased amount of unbound drug, especially in patients who are cachectic or malnourished. Chemotherapeutic agents such as methotrexate, doxorubicin, and cisplatin can decrease AED levels of valproic acid, carbamazepine, and phenytoin.

In the last decade, we have seen a substantial increase in the effectiveness of tyrosine kinase inhibitors (TKI) for the treatment of brain metastases from various systemic malignancies. It is necessary to pay close attention to drug interactions between antiepileptic drugs and TKIs moving forward. CYP3A4-inducing AEDs can significantly increase the clearance and reduce the AUC of TKIs, specifically crizotinib, dasatinib, imatinib, and lapatinib [56]. There are other TKIs that are 3A4 inhibitors; however, there is very little data reported on the metabolism of AEDs in this context.

Side Effects

All antiepileptic drugs have potential side effects, summarized in Table 9.2. The most common side effects across all AEDs are lethargy and cognitive

Table 9.3 Pharmacological aspects of antiepileptic drugs and interactions with chemotherapy agents

AED	IV?	CYP inducer	PB (%)	AED effect on chemo	Chemo effect on AED
PHB	Yes	**1A2, 2A6, 2B6, 2C9, 3A4,** 2C19	50	Thi↓ Nit↓ Vbl↓ Vnc↓ Mtx↓ Pac↓ 9AC↓ Ten↓ Pro↑ Prd↓ Dox↓ Tam↓ Ifo↓	Tmz
PHT	Yes	**2B6, 2C9, 2C19, 3A4,** 1A2	**90**	Pro↑ Pac↓ Bus↓ Top↓Vbl↓ Vnc↓ Mtx↓ Iri↓ 9AC↓ Ten↓ Dex↓ SrI↓	Mtx↓ Pro↑ Cis↓ Nit↓ Eto↓ Dox ↓ Dac↓ Vbl↓ Ble↓ Dex ↓↑ Car↓ 5FU↑ Cpc↑ Tam↑ Tmz
CBZ	No	**1A2, 2B6, 2C9, 2C19, 3A4**	**75**	MTX↓ Pac↓ Vbl↓ Vnc↓ Ten↓ 9AC↓ Srl↓ Pro↑	Cis↓ Dox↓ Tmz
OXC	No	3A4	40	–	Tmz
VPA	Yes	2A6 (inhib. 2C9, 2C19, 3A4)	**90**	–	Mtx↓ Dox↓ Cis↓
TPX	No	3A4	30	–	Tmz
ZNS	No	(Inhib. 2E1)	50	–	–
LTG	No	No	50	Mtx	–
GBP	No	No	< 5	–	–
PGB	No	No	< 5	–	–
LVT	Yes	No	<5	–	–
LCS	Yes	No	<5	–	–

5FU 5-fluorouracil, *9AC* 9-aminocampothecin, *AED* antiepileptic drug, *Ble* bleomycin, *Bus* busulfan, *Ca* calcium channel, *Car* carboplatin, *CBZ* carbamazepine, *chemo* chemotherapy, *Cis* cisplatin, *cog* cognitive/behavioral, *Cpc* capecitabine, *CYP* cytochrome P-450, *Dac* dacarbazine, *Dex* dexamethasone, *Dox* doxorubicin, *Eto* etoposide, *GABA* ϒ-aminobutyric acid, *GBP* gabapentin, *Ifo* ifosfamide, *inhib.* enzyme inhibition, *Iri* irinotecan, *IV* intravenous, *K* kidney, *L* liver, *LCS* lacosamide, *LTG* lamotrigine, *LVT* Levetiracetam, *MAOI* monoamine oxidase inhibitor, *Mech* mechanism, *Met* metabolism, *Mtx* methotrexate, *Na* sodium channel, *Nit* nitrosourea, *NMDA* N-methyl-D-aspartate, *n/v* nausea and vomiting, *OXC* oxcarbazepine, *Pac* paclitaxel, *PB* protein binding, *PGB* pregabalin, *PHB* phenobarbital (and primidone), *PHT* phenytoin, *Prd* prednisone, *Pro* procarbazine, *Srl* sirolimus (and temsirolimus), *SV* synaptic vesicle, *Tam* tamoxifen, *Ten* teniposide, *Thi* thiotepa, *Tmz* temozolomide, *Top* topotecan, *TPX* topiramate, *Vbl* vinblastine, *Vnc* vincristine, *VPA* valproic acid, *ZNS* zonisamide

Boldface in table body denotes strong enzyme activity

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dysfunction, even if levels are within therapeutic range. These side effects are often enhanced when patients have several brain metastases. Side effects of specific antiepileptic drugs among individual patients can vary, and their use often requires an individualized approach. See Table 9.2 for a more detailed list of side effects of various antiepileptics.

Convulsive and Nonconvulsive Status Epilepticus

Status epilepticus is defined as either continuous or intermittent seizures without recovery of consciousness between seizures [57]. Status epilepticus can be either convulsive or nonconvulsive [58, 59]. Convulsive status epilepticus is a medical emergency and often requires aggressive intensive care with intubation and general anesthesia [57]; one approach is illustrated in Table 9.4.

Nonconvulsive status epilepticus (NCSE) in patients with brain metastases may be underdiagnosed as patients are often altered or comatose with no overt signs of seizure activity. One study suggests an increased risk of mortality within 2 months in patients with metastatic disease and progressing brain lesions [60]. In another series, 8% of comatose patients were found to be in electrographic status epilepticus [59]. In any comatose patient with risk factors for seizures and subtle motor or oculomotor movements, electroencephalogram is recommended to definitively rule out electrographic seizures.

Table 9.4 Protocol for the treatment of convulsive status epilepticus at Memorial Sloan Kettering Cancer Center

First 5 min
ABCs
Diagnose status epilepticus
Obtain IV access
Begin ECG monitoring
Fingerstick for glucose—correct if necessary
Draw blood for BMP, Mg, Ca, Ph, CBC, LFT, AED levels (PHB, PHT, VPA, CBZ), toxicology screen
Call Neurology consult
6–10 min
Thiamine 100 mg IV; 50 ml of D50 IV in appropriate clinical setting
Lorazepam 4 mg IV over 2 min; if necessary, repeat once every 5 min. If no IV access, give diazepam 20 mg rectally or midazolam 10 mg intranasally or intramuscularly
10–20 min
Add fosphenytoin 20 mg/kg IV at 50 mg/min with BP and ECG monitoring. Can re-bolus fosphenytoin 10 mg/kg if seizures persist. Maintain level 15–20 μg/mL
20–60 min
If seizures persist, *intubate* and start phenobarbital IV 20 mg/kg at 50–100 mg/min
If still seizing, can add or switch (PHB) to midazolam: load 0.0.2 mg/kg; repeat 0.2–0.4 mg/kg boluses every 5 min until seizures stop, up to a maximum total loading dose of 2 mg/kg. Initial rate 0.1 mg/kg/h. Continuous IV range 0.05–2 mg/kg/h
Or
Propofol: Load 1 mg/kg; repeat 1–2 mg/kg boluses every 3–5 min until seizures stop, up to a maximum total loading dose of 10 mg/kg. Initial rate 2 mg/kg/hour. Dose range 1–15 mg/kg/hour
After 60 min
If seizures persist, use anesthetics
Continuous IV propofol: Load 1 mg/kg; initial 2 mg/kg/hr. Titrate until burst suppression
Will need to arrange continuous EEG monitoring (preferably as soon as the patient does not awaken rapidly)
Another possible consideration for fourth line treatment is valproate 40 mg/kg over 10 min. Can re-bolus 20 mg/kg over 5 min
If bacterial meningitis is suspected, start ceftriaxone, vancomycin, and ampicillin (can start along with treatment for SE). Start acyclovir if HSV encephalitis is suspected. Perform LP when stable

∗∗Edited and updated from Table 4–11, pg. 111, DeAngelis/Posner, Neurological complications of Cancer, with permission from Oxford University Press

Driving

Placing driving restrictions on patients with seizures from brain metastases is a highly controversial topic. The development of efficacious seizure medications over the last several decades has reversed historical conviction that no patient with seizures—controlled or uncontrolled—should be allowed to drive. There is consensus, however, that patients with uncontrolled seizures should not drive given their increased risk of motor vehicle accidents and subsequent property damage, as well as potential for injury to self or others. For those patients with controlled seizures, clinicians must balance the risk of public safety with patient autonomy and preservation of quality of life. Driving restrictions can significantly impact a patient's ability to maintain employment, attend social activities, and/or participate in school. Data are limited in determining which patients with seizures can safely drive, and therefore regulations vary considerably in the USA from state to state. Clinicians should consult the regulations of their respective state or country in which they practice before advising patients. It should be emphasized, however, that clinician judgment supersedes any state regulation.

While no studies have specifically looked at patients with brain metastases, data extrapolated from other epilepsy studies suggest that the most reliable predictor of risk of seizure while driving

is the seizure-free interval. Limited data have advocated for a seizure-free interval ranging anywhere from 3 to 12 months [61–65].

Seizures at the End of Life

Seizures are common at the end of life in patients with brain metastases. For those who are able to swallow medications and have a previous history of seizures, patients should continue their antiepileptic drugs. However, clinicians should be aware of the often inevitable depressed mental status and the need to convert oral antiepileptics to non-oral routes. In patients who cannot safely swallow, seizure management will depend on the location of care support. If the patient requires inpatient care, intravenous access can be maintained and parenteral antiepileptics can be continued. For those at home, subcutaneous/sublingual lorazepam or buccal clonazepam can be used to control seizures. Rectal diazepam and rectal/subcutaneous phenobarbital are another option in the home setting. Initiation of dexamethasone should be considered for patients with seizures caused by increased intracranial pressure from mass effect.

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