

Evaluation and Management of Seizures in the Patient With Cancer

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Seizures are a common neurologic complication in patients with primary central nervous system (CNS) malignancies or metastases from systemic cancers. They may also result from metabolic derangements, infections, hematologic abnormalities, or the treatment of systemic cancer. Although most seizures are easily controlled and managed, they may, as in the case of status epilepticus, be life threatening. This article will define the classification, common etiologies, evaluation, and treatment of seizures, including status epilepticus, in the patient with cancer.

Classification

A standard classification of seizures facilitates communication among physicians caring for patients with seizures and provides insights into their prognosis and therapy. Initial classification schemes divided seizures into grand mal, petit mal, and hysteroid. In 1969, The International League Against Epilepsy proposed a classification scheme that distinguished between seizures that are generalized at onset and those that are focal initially and later become generalized.¹ In this system, seizures were classified according to clinical type, electroencephalographic type, interictal electroencephalographic expression, anatomic substrate, and patient age.

In 1981, the ILAE proposed a re-

vised classification. According to this proposal, seizures were classified, on the basis of both clinical type and ictal and interictal electroencephalographic expression, into one of the following categories: partial, generalized, or unclassified (Table 1).²

• **Partial seizures** have clinical and electroencephalographic onset limited to part of the cerebral hemisphere and cause only focal neurologic symptoms. They were further subclassified into simple partial, complex partial, and those evolving into generalized seizures.

• Simple partial seizures may be manifested by motor symptoms (with or without Jacksonian march), sensory symptoms (somatosensory or special sensory), autonomic, and/or psychic symptoms. Examples include focal clonic seizures or sensory disturbances affecting the face, limb, or hemibody. Auras and *epilepsia partialis continua* are special types. Simple partial seizures do not affect consciousness.

• In contrast, consciousness is impaired to some extent in all complex

Seizures are common in patients with cancer. They can be caused by the tumor itself, metabolic disturbances, radiation injury, chemotherapy-related encephalopathies, cerebral infarctions, or central nervous system infections. Evaluation requires a meticulous history and search for the precipitating cause. Treatment is directed at the underlying etiology and entails the rational and precise use of anticonvulsant drugs.

partial seizures.

• **Generalized seizures** are classified as absence, atypical absence, myoclonic, clonic, tonic, tonic-clonic, atonic, or mixed.

• **Unclassified**—Seizures that do not fit into any of the foregoing categories are labeled as unclassified epileptic seizures.

In 1989, the ILAE again proposed a revised scheme for the classification of epilepsies and epileptic syndromes.³ In this system, epileptic syndromes are classified according to whether they are of known etiology (symptomatic) or idiopathic and whether they are generalized or localized (partial). To date, this classification system has not been widely utilized.

Etiology

In the cancer patient, seizures can result as a complication of a primary CNS malignancy, from metastases, or from treatment (Table 2). Alternatively, a cancer patient may have a preexisting seizure disorder, which may be

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Table 1

Classification of Epileptic Seizures

Partial Seizures

- Simple partial
 - Focal motor
 - With motor (Jacksonian) march
 - Without motormarch
 - Focal sensory
 - Autonomic symptoms
 - Psychic symptoms
- Complex partial
 - Simple partial onset
 - Without automatisms
 - With automatisms
 - Impairment of consciousness at onset
 - Without automatisms
 - With automatisms
- Partial seizures evolving to secondarily generalized seizures

Generalized Seizures

- Absence
- Atypical absence
- Myoclonic
- Clonic
- Tonic
- Tonic-clonic
- Atonic

Unclassified Epileptic Seizures

idiopathic or secondary to a previous CNS injury, such as head trauma or stroke.

• **Primary and Metastatic CNS Tumors**—Seizures may occur as the consequence of diffuse tumor involvement in the CNS, either from a primary malignancy or metastatic systemic cancer. Any primary CNS malignancy may produce seizures; however, low-grade or slow-growing tumors, such as well-differentiated gliomas, oligodendrogliomas, and mixed malignant tumors, are the most likely to do so.⁴ Seizures may occur for some time before a CNS malignancy is detected, and they often herald its presence. Seizures related to parenchymal CNS tumors may be generalized, but are more often partial, with subsequent generalization. The new onset of partial seizures in any patient

Table 2

Cause of Seizures in the Cancer Patient

Idiopathic

Symptomatic

- Tumor
 - Primary CNS neoplasm
 - Metastatic CNS neoplasm
 - Parenchymal metastases
 - Dural-based metastases
 - Carcinomatous meningitis
- Metabolic
 - Hyponatremia
 - Hypoglycemia
 - Hypoxia
 - Hypocalcemia
 - Hypomagnesemia
- Treatment Related
 - Radiation therapy
 - Acute
 - Delayed
 - Early
 - Late
 - Chemotherapy
 - Antimetabolites
 - Methotrexate
 - L-Asparaginase
 - ARA-C
 - Vinca alkaloids
 - Topoisomerase inhibitors
 - Alkylators
 - Ifosfamide
 - Nitrosoureas
 - Cisplatin

- Biological response modifiers
 - Interferon
 - Interleukin-2
- Narcotics
 - Morphine sulfate
 - Meperidine
- Anti-Emetics
 - Phenothiazines
 - Butyrophenones
- Antibiotics
 - Penicillins
 - Imipenem/Cilastin
- Cerebral infarction
 - Hemorrhagic
 - Thrombotic
 - Hypercoagulable state
- Infectious
 - Bacterial
 - Listeria monocytogenes*
 - Viral
 - Cytomegalovirus
 - Herpes simplex
 - Fungal
 - Cryptococcus neoformans*
 - Aspergillus fumigatus*
 - Candida species*
 - Parasites
 - Toxoplasma gondii*

should raise the suspicion of an intraaxial CNS tumor and, in the cancer patient, of parenchymal brain metastases. Solid tumors likely to metastasize to the brain parenchyma include melanoma and lung, breast, renal cell, gastrointestinal, and germ-cell tumors.⁵

Seizures also may be caused by leptomeningeal or dural metastases,⁶ and in such cases may be the initial sign of such metastasis or arise as a late complication. Seizures secondary to meningeal carcinomatous or dural metastases are usually partial initially and often generalize secondarily.

• **Metabolic Disturbances**—Metabolic derangements, including hypoglycemia, hyponatremia, hypomagnesemia, hypocalcemia, and hypoxia, are common in patients with systemic cancer. These metabolic imbalances may be a

direct effect of the malignancy or may be iatrogenic. Although seizures related to metabolic derangements usually are generalized at onset, occasionally they may be partial initially without any underlying focal CNS pathology.

Hyponatremia most frequently occurs secondary to overhydration, but sodium depletion may also be associated with the syndrome of inappropriate antidiuretic hormone (SIADH). Rapid shifts in serum sodium levels—as may result from overly rapid correction—are more likely to cause seizures than is chronic hyponatremia. Patients with a history of alcoholism are prone to hyponatremia, which may be aggravated with vigorous hydration as with cisplatin chemotherapy.

Hypoglycemia is seen in debilitated cancer patients unable to maintain ade-

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quate nutrition. Patients with a history of alcohol abuse are especially prone to malnutrition and transient hypoglycemia. Hypoglycemia may also occur in cancer patients with diabetes who are receiving insulin, unless special care is taken. Cancer patients treated with hyperalimentation may develop transient hypoglycemia when such therapy is stopped. Less commonly, hypoglycemia may be the direct result of certain malignancies, such as insulinoma.

Hypomagnesemia and hypocalcemia are less frequent causes of seizures in cancer patients. These metabolic disturbances may stem from poor nutritional intake or as a side effect of drugs used in treatment, such as cisplatin (Platinol) or amphotericin B. Hypoxia usually results from cardiopulmonary disease secondary to metastases or treatment-related complications, such as pulmonary fibrosis induced by radiation or certain chemotherapeutic agents (eg, bleomycin [Blenoxane], BCNU) or congestive heart failure induced by doxorubicin (Adriamycin).

Treatment-Related Causes

Seizures often are related to adverse effects or complications, such as coagulopathy and infection, of the different modalities used to treat cancer, including radiation therapy, chemotherapy, narcotics, antiemetics, and antibiotics.

• **Radiation Therapy**—Adverse CNS effects of radiation therapy can be divided into acute, early-delayed, and late-delayed reactions.

• Acute reactions occur during radiation therapy and are thought to be related to CNS edema.⁷ Symptoms include headache, nausea, and vomiting. Exacerbation of preexisting neurologic deficits may occur.

• Early-delayed reactions occur weeks to several months following radiation treatment. Symptoms are transient and include lethargy, somnolence, nausea, vomiting, ataxia, nystagmus, and cerebellar ataxia.⁸ Early-delayed reactions result from CNS demyelination.

• Late-delayed reactions, the most serious adverse effects of CNS radiation, may occur months to years (on average, 12 to 18 months) after radiation treatment.⁹ Two pathologic entities have been described—brain necrosis and large- or small-vessel vasculopathy. Brain necrosis, which affects the white matter, results in bland necrosis, telan-

giectasia, and gliosis. Symptoms are insidious, progressive, and potentially life threatening. Focal neurologic deficits and seizures may occur in conjunction with progressive intellectual decline and an extrapyramidal Parkinson-like disorder.

Vascular injury may be a late-delayed effect of whole-brain irradiation used, for example, as prophylactic treatment in patients with acute lymphocytic leukemia or small-cell lung cancer. Large- or small-vessel strokes may result in focal neurological deficit or progressive intellectual decline.

Factors affecting the degree of radiation damage to the brain include the total radiation dose, size and number of individual fractions, overall treatment time, and volume of CNS irradiated. Concurrent treatment with other modalities, such as chemotherapy, and underlying CNS pathology have a permissive, if not synergistic, role in the pathogenesis of radiation brain injury.

• **Chemotherapy-Induced Seizures**—Seizures are a rare complication of chemotherapy, occurring in less than 1% of patients treated.¹⁰ Use of multiple chemotherapeutic agents or the combination of systemic chemotherapy with other modalities, such as intrathecal chemotherapy, radiation therapy, or blood-brain barrier disruption, may significantly increase the incidence of seizures.

Central nervous system toxicity has been reported with a number of antimetabolite chemotherapeutic agents. Methotrexate, in particular, has been associated with acute CNS toxicity when administered at high doses intrathecally or systemically and followed by leucovorin rescue.^{11,12} The most common CNS manifestations of acute CNS methotrexate toxicity are aseptic meningitis and encephalopathy.

A delayed leukoencephalopathy may occur following either long-term intrathecal or repeated, high-dose systemic administration of methotrexate. The risk of this syndrome increases as multiple modalities (eg, systemic and/or intrathecal chemotherapy and brain irradiation) are used.¹³ Symptoms include confusion, forgetfulness, seizures, dysarthria, dysphagia, tremor, ataxia, and spasticity. Some patients who develop this syndrome may progress to irreversible coma and death.¹⁴

Central nervous system toxicity is commonly seen with cytosine arabinoside (ARA-C—Cytosar-U), when given either in high-doses (HD ARA-C) or intrathecally. Seizures may occur in combination with altered mental status, cerebellar dysfunction, and headache following HD ARA-C.¹⁵ An aseptic meningitis similar to that seen with methotrexate has also been observed following intrathecal or HD ARA-C.

L-asparaginase (Elspar) has also been associated with an acute encephalopathy (the common CNS presentation of patients treated with antimetabolites), with focal cerebral dysfunction and seizures.¹⁶ Nonspecific electroencephalogram abnormalities (diffuse slow activity) also have been reported during L-asparaginase therapy.¹⁶

Most nervous system toxicity due to vinca alkaloids relates to peripheral nervous system injury. Vincristine (Oncovin) may cause hyponatremia secondary to SIADH with subsequent seizures. However, seizures also have been reported following accidental intrathecal administration of vincristine, and without evidence of metabolic abnormalities.¹⁷

Etoposide (Vepesid) has been associated with an acute encephalopathy characterized by an altered mental status, with seizures increasing in frequency in a dose-dependent manner.¹⁸

Seizures have been associated with many of the alkylating agents. Chlorambucil (Leukeran) often causes seizures when given in doses greater than 5 mg/kg, as in conditioning therapy for bone marrow transplantation,¹⁹ and has also been associated with seizures in children with renal disease.²⁰ Busulphan (Myleran), too, may cause seizures when administered in high doses.²¹ Ifosamide (Ifex) may cause an acute encephalopathy with associated seizures.²² Transient electroencephalographic abnormalities (characterized by slowing of background activity) can occur and are similar to those associated with any toxic or metabolic encephalopathy.

The nitrosoureas (eg, BCNU and CCNU), when used intraarterially to treat patients with brain tumors, may cause focal seizures immediately or as a delayed complication.²³ A transient encephalopathy associated with seizures has been reported with cisplatin therapy. Such seizures are most commonly

related to metabolic abnormalities secondary to drug-induced renal dysfunction. Occasionally, an encephalopathy characterized by a depressed mental status, cortical blindness, and generalized seizures occurs in patients treated with cisplatin.²⁴

• **Interferon and Interleukin**—Recently, seizures have been reported in several patients treated with interferon.²⁵ In one instance, seizures resolved after discontinuation of interferon and then reoccurred when the drug was restarted.²⁶ Generalized seizures that could not be explained on the basis of metabolic or structural causes have occurred in patients treated with lymphokine activated killer (LAK) cells and interleukin-2 (IL-2).²⁷

Narcotics, Neuroleptics, and Antibiotics

Several narcotic analgesic agents have been implicated in causing seizures. Morphine in high doses is a convulsant agent in neonates and infants.²⁸ In adults, seizures related to morphine are rare and are usually related to epidural or intrathecal administration.²⁹ Systemic administration of meperidine (Demerol), however, has been associated with seizures. Meperidine is metabolized to norpethidine, which may accumulate and have a convulsant action.³⁰ Overdosage of propoxyphene (Darvon) has been associated with status epilepticus.³¹

Neuroleptic agents are commonly used in cancer patients as antiemetics in conjunction with chemotherapy. The phenothiazine and butyrophenone antiemetics have been associated with seizures in a dose-related fashion.³² Seizures are rare, however, with the lower potency agents, such as thioridazine (Mellaril).

Certain antibiotics have been associated with seizures. High-dose penicillin, for example, as used in the treatment of CNS infections, may cause seizures, and imipenem/cilastatin (Primaxin) has been associated with a significant tendency to do so.³³ The

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cephalosporins, on the other hand, almost never cause seizures. Patients with structural CNS lesions or renal failure appear to be at higher risk for antibiotic-induced seizures, as are patients treated with intrathecal antibiotics.

Hematologic abnormalities, both hypercoagulable and hypocoagulable, are common in patients with neoplastic disease. Thrombocytopenia may result from chemotherapy induced bone marrow suppression, bone marrow infiltration by tumor, or peripheral consumption. Disseminated intravascular coagulopathy (DIC), particularly the chronic type, may occur in patients with advanced disseminated cancer. Intracerebral hemorrhage may occur in cancer patients with coagulation abnormalities. Furthermore, CNS metastases, particularly melanoma, renal cell carcinoma, and germ-cell tumors, may undergo hemorrhagic transformation. These events may be catastrophic, resulting in death, or result in less severe focal neurological deficit and seizures.³⁴ Sinus or venous thrombosis related to a hypercoagulable state may cause either hemorrhagic or non-hemorrhagic venous infarctions and result in seizures. Non-bacterial thrombotic endocarditis (NTBE) also occurs in patients with cancer, particularly in those with mucinous adenocarcinomas, and may result in cerebral emboli, infarction, and seizures.³⁵

CNS Infections

Patients with neoplastic disease are often immunosuppressed and susceptible to CNS infections, which may be atypical.³⁶ Meningitis in immunocompromised patients may be caused by common bacterial pathogens or by esoteric agents such as *Listeria monocytogenes* and *Cryptococcus neoformans*. *Candida* in the CNS are usually seen in the setting of widely disseminated infection. *Aspergillus* brain abscess may occur as a result of CNS seeding from an invasive pulmonary infection. Viral meningitis in the cancer patient is more often caused by cytomegalovirus or herpes simplex. Parasitic infections with *Toxoplasma gondii* may occur, particularly in patients with lymphoma or leukemia. Seizures related to CNS infections are most likely to occur in patients with a focal brain lesion (such as an abscess or *T gondii* infection) or with a diffuse meningoencephalitis.

Points to Stress in the History and Physical

In the patient with a known neoplastic disorder, it is critical to determine whether the seizures are related to a structural CNS lesion or a transient metabolic or infectious process. Other nonepileptic paroxysmal events, such as syncope, also must be excluded. A careful, thorough medical history, followed by a general and neurological examination are crucial in making these determinations. Laboratory, radiologic, and electroencephalographic tests will help confirm the diagnosis.

• **History**—A careful history is often neglected, yet is essential in pinpointing the cause of a seizure. Details of the event should be obtained both from the patient and, if possible, from a reliable observer who was a witness. Information about the seizure and the periods prior to and after it should be obtained. The patient should be asked if there was any forewarning. Abnormal sensations, such as tastes, odors, or tactile, visual or auditory phenomena may indicate an aura or a simple partial seizure at the onset, while psychic phenomena, such as *deja vu*, may indicate a focal onset in the temporal lobe. Other symptoms, such as cardiac palpitations, shortness of breath, and diaphoresis, may be related to a nonepileptic event, such as syncope.

Accurate details of the seizure are essential for proper classification. Any focal features usually indicate a focal cerebral onset. In particular, localizing motor or sensory symptoms are indicative of a focal onset in the hemisphere contralateral to the symptoms. Versive eye deviation, especially at the onset of the seizure, are highly suggestive of a partial onset in the cerebral cortex opposite the direction of eye deviation. Urinary incontinence and lateral tongue lacerations are common in generalized convulsive seizures; however, they may also be seen in other paroxysmal nonepileptic events, such as syncope.

The duration of the seizure and of the postictal period are often important diagnostic clues and should be carefully recorded. The majority of seizures are self-limited events and subside within minutes. A prolonged period of lethargy or confusion may occur following a generalized convulsion. Details of the patient's activity prior to and at the onset of the seizure should also be ob-

tained to determine if there were any precipitating factors. Any treatment or medication recently administered should be noted. Factors such as sleep deprivation, emotional stress, and medical problems (eg, infections, metabolic derangements) should be elicited.

• **Physical Exam**—The general medical examination should include a careful cardiac exam, which may detect murmurs or arrhythmias. Skin lesions may indicate evidence of systemic infection or septic emboli. A complete neurologic examination is critical. Any focality found on neurological examination is suggestive of a structural CNS lesion. A focal motor deficit may persist for a period following the seizure and then resolve. This phenomenon, known as a Todd's paralysis, rarely persists for more than several hours.

• **Laboratory examination** should look for evidence of metabolic or infectious etiology. Routine studies following a seizure should include a complete blood count and serum and urine chemistry screen, with particular attention being paid to glucose and electrolyte levels and measurements of renal and hepatic function. Magnesium and calcium should be included, since these are commonly abnormal in cancer patients, especially in the presence of renal failure or amphotericin B treatment. These electrolyte abnormalities are possible, albeit rare, causes of seizures.

A coagulation screen should include a platelet count and determinations of a prothrombin time and activated partial thromboplastin time. If a coagulopathy is suspected, a DIC panel should be included. Cerebral spinal fluid analysis by lumbar puncture should be performed if there is any evidence of infection. Cytology should be included to exclude the possibility of leptomeningeal spread of metastatic cancer; if this diagnosis is a serious consideration, however, two or three cytology screenings may be necessary.

All cancer patients who suffer a seizure should undergo a neuroimaging study to exclude CNS metastases. Magnetic resonance imaging (MRI) of the brain with gadolinium enhancement is more sensitive than contrast-enhanced computerized tomography (CT).³⁷ Special imaging sequences may be necessary to detect infections or vascular events, such as a superior sagittal throm-

Table 3
Management of Status Epilepticus

Time, min	Therapy	Action
0		Obtain history, secure IV line access with normal saline, obtain blood for anticonvulsant serum levels, chemistry panel, CBC, and toxicology screen; finger stick glucose monitor respirations, blood pressure, EKG
5	Bolus IV: 50 ml of 50% glucose and thiamine, 100 mg Lorazepam (Ativan), 4-8 mg IV (max rate, 2 mg/min)	Use if patient is actively seizing, while primary anticonvulsant is being loaded; monitor respiratory status
10	Load with phenytoin, 18-20 mg/kg IV (max rate, 50 mg/min)	Monitor blood pressure and cardiac status closely
30-40	Start second anticonvulsant: phenobarbital, 20 mg/kg (max rate, 50-100 mg/min)	If seizures persist, determine underlying etiology Electively intubate
60	General anesthesia Pentobarbital coma	Continuous EEG monitoring Burst suppression pattern ICU monitoring

Table 4
Major Oral Antiepileptic Dosages and Serum Levels

Drug	Usual Daily Dose, mg	Loading Dose, mg/kg	Serum Level, µg/ml
Phenytoin	300-400	15-18	10-20
Phenobarbital	120-250	10-20	15-351
Carbamazepine	600-1,200	8	6-12
Valproic Acid	1,000-3,000	20-30	50-100

basis. If MRI is unavailable, a CT scan should be done. Intravenous contrast is necessary to increase sensitivity for the detection of metastatic lesions. Because of the high incidence of parenchymal brain metastases in patients with cancer and seizures, either contrast-enhanced brain MRI or CT should be performed on a semi-urgent basis. The neuroimaging study should precede a lumbar puncture to exclude a structural lesion.

Finally, an electroencephalogram may be of diagnostic assistance. Specific patterns may indicate a particular etiology, eg, a persistent focal delta wave may reflect a structural lesion or lateralized periodic discharges may suggest herpes simplex encephalitis.

Treatment

If a seizure is witnessed, initial care should ensure that the patient is not

injured, especially during a generalized tonic-clonic convulsion. Care should be taken so that the patient does not fall or strike his or her head. Soft objects, such as pillows or blankets, should be placed to protect the patient, and sharp objects should be removed. Nothing should be placed in the patient's mouth—not a tongue depressor, nor fingers, nor a wallet.

• **Initial Therapy**—Medical management should begin by evaluating and stabilizing the patient's cardiorespiratory status. If there is airway obstruction, the patient's head should be turned to the side and secretions drained. If seizure activity continues or the patient does not recover to a normal alert state between seizures, status epilepticus should be considered and appropriately treated (Table 3).

It is important to realize that the majority of seizures are self-limited. Evaluation of the patient should be focused on determining if there is evidence of a structural CNS lesion(s) or determine if the seizure was caused by a potentially reversible toxic metabolic or infectious process. If the evaluation reveals a structural CNS lesion, oral anticonvulsant therapy should be started (Table 4). In some cases, a short course of anticonvulsant therapy may be needed to control seizures while metabolic, toxic, or infectious problems are being corrected. In the case of an isolated seizure without a clear etiology, it may not be necessary to start anticonvulsant therapy, as the risk of recurrent seizure is probably no more than 40%.³⁸

• **Choice of Anticonvulsant**—Consideration of the choice of anticonvulsant drug should include the type of seizure to be treated, concurrent medical conditions, the route of administration, the time to reach therapeutic serum levels, dosage frequency, potential side effects and drug interactions, the likelihood of patient compliance, and the expense of the agent. Anticonvulsant therapy should always begin with a single drug. The majority of seizures can be easily controlled with monotherapy, and a second anticonvulsant should be added only after a trial of the first agent at therapeutic serum levels has failed. If seizure control is attained after adding the second agent, tapering the dosage of the initial agent should be considered. There is little difference in the therapeutic efficacy of phenytoin

(Dilantin), carbamazepine (Tegretol), and phenobarbital in the treatment of partial and secondarily generalized seizures,³⁹ the types most commonly seen in patients with cancer.

• Phenytoin has the advantages that it is relatively inexpensive, has a long serum half life and therefore can usually be given as a single daily dose. It is well tolerated and can be administered as a loading dose, both parentally and orally, thereby achieving therapeutic serum levels in 12 to 24 hours. However, phenytoin, in combination with whole-brain cranial radiation, has been associated with an increased incidence of Stevens-Johnson syndrome in patients with metastatic brain cancer; therefore it may be contraindicated in this setting.⁴⁰

• Phenobarbital is also inexpensive and has a long serum half-life, thereby allowing single daily dosing. It can be sedating in some patients and, when given orally, may require several weeks to reach a therapeutic serum level.

• Carbamazepine has a short serum half-life and therefore requires multiple daily dosing (two to three times a day). A mild decrease (approximately 10%) in white blood cell count occurs in nearly all patients, which may limit its use in patients with bone marrow suppression resulting from tumor invasion or chemotherapy.

• Valproic acid (Depakote/Depakene) is the anticonvulsant agent of choice for the treatment of primary generalized seizures. Although these seizures are idiopathic, they may occur concurrently with neoplastic disease. Recent data suggests that valproic acid is also a highly effective anticonvulsant for the treatment of partial and secondary generalized seizures. Be aware, though, that valproic acid has been associated with hepatic dysfunction, particularly in patients under two years of age or when used in combination with other anticonvulsant agents. Valproic acid also may prolong bleeding time and may result in a dose-dependent thrombocytopenia. Despite these side effects, the agent is well tolerated and, unlike phenobarbital and phenytoin, causes minimal cognitive dysfunction.

Monitoring serum anticonvulsant drug levels is important because chemotherapy may produce lower levels than would otherwise be anticipated.⁴¹ Possible mechanisms include decreased

gastrointestinal absorption (phenytoin, carbamazepine, valproic acid), increased metabolic rate (phenytoin), and increased volume of distribution (phenytoin).

• **Refractory seizures**—Occasionally, seizures may be difficult to control and persist for an extended period or recur without the patient returning to a normal level of alertness between seizures. In this situation, the patient should be aggressively treated for status epilepticus (Table 3). Overall morbidity and mortality usually relate to the underlying cause and may be high in the cancer patient with structural CNS lesions or with complicated medical problems. Central nervous system hemorrhages and frontal lobe structural lesions are common etiologies of status epilepticus in this patient group. Accidental anticonvulsant withdrawal may also precipitate status epilepticus and may occur in the confused or debilitated cancer patient.

Conclusions

Seizures occur commonly in the patient with neoplastic disease and may result from multiple etiologies, including tumor, metabolic derangements, radiation injury, chemotherapy-related encephalopathies, cerebral infarctions, and CNS infections. A rational classification of seizures facilitates diagnosis and helps direct evaluation. A systematic approach directed at the etiology of the seizure ensures proper therapy and management.

*This article is reviewed
on pages 40 and 47.*

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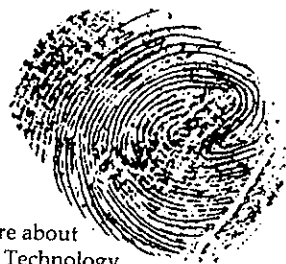
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