

obstruction, abnormal flow in the spinal canal, or impaired flow over the cerebral convexities may affect distribution of intrathecal chemotherapy, resulting in decreased efficacy or increased toxicity. Radiation therapy may correct CSF flow abnormalities before use of intrathecal chemotherapy. Neoplastic meningitis can also lead to intracranial hypertension and hydrocephalus. Placement of a ventriculoperitoneal shunt may effectively palliate symptoms in these patients.

The development of neoplastic meningitis usually occurs in the setting of uncontrolled cancer outside the CNS; thus, prognosis is poor (median survival 10–12 weeks). However, treatment of the neoplastic meningitis may successfully alleviate symptoms and control the CNS spread.

TREATMENT NEOPLASTIC MENINGITIS

Intrathecal chemotherapy, usually methotrexate, cytarabine, or thiotepa, is delivered by lumbar puncture or by an intraventricular reservoir (Ommaya). An extended-release preparation of cytarabine (Depocyte) has a longer half-life and is more effective than other formulations. Among solid tumors, breast cancer responds best to therapy. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) may be effective in non-small-cell lung cancer patients with *EGFR* mutations and leptomeningeal involvement. Patients with neoplastic meningitis from either acute leukemia or lymphoma may be cured of their CNS disease if the systemic disease can be eliminated.

SEIZURES

Seizures occurring in a patient with cancer can be caused by the tumor itself, by metabolic disturbances, by radiation injury, by cerebral infarctions, by chemotherapy-related encephalopathies, or by CNS infections. Metastatic disease to the CNS is the most common cause of seizures in patients with cancer. However, seizures occur more frequently in primary brain tumors than in metastatic brain lesions. Seizures are a presenting symptom of CNS metastasis in 6–29% of cases. Approximately 10% of patients with CNS metastasis eventually develop seizures. Tumors that affect the frontal, temporal, and parietal lobes are more commonly associated with seizures than are occipital lesions. The presence of frontal lesions correlates with early seizures, and the presence of hemispheric symptoms increases the risk for late seizures. Both early and late seizures are uncommon in patients with posterior fossa and sellar lesions. Seizures are common in patients with CNS metastases from melanoma and low-grade primary brain tumors. Very rarely, cytotoxic drugs such as etoposide, busulfan, ifosfamide, and chlorambucil cause seizures. Another cause of seizures related to drug therapy is reversible posterior leukoencephalopathy syndrome (RPLS). RPLS is associated rarely with administration of cisplatin, 5-fluorouracil, bleomycin, vinblastine, vincristine, etoposide, paclitaxel, ifosfamide, cyclophosphamide, doxorubicin, cytarabine, methotrexate, oxaliplatin, cyclosporine, tacrolimus, and vascular endothelial growth factor inhibitors including bevacizumab, aflibercept, sunitinib, sorafenib, pazopanib, and axitinib. RPLS occurs in patients undergoing allogeneic bone marrow or solid-organ transplantation. RPLS is characterized by headache, altered consciousness, generalized seizures, visual disturbances, hypertension, and posterior cerebral white matter vasogenic edema on CT/MRI. Seizures may begin focally but are typically generalized.

TREATMENT SEIZURES

Patients in whom seizures due to CNS metastases have been demonstrated should receive anticonvulsive treatment with phenytoin or levetiracetam. If this is not effective, valproic acid can be added. Prophylactic anticonvulsant therapy is not recommended. In postcraniotomy patients, prophylactic antiepileptic drugs should be withdrawn during the first week after surgery. Most antiseizure medications including phenytoin induce cytochrome P450 (CYP450), which alters the metabolism of many antitumor agents,

including irinotecan, taxanes, and etoposide as well as molecular targeted agents, including imatinib, gefitinib, erlotinib, tipifarnib, sorafenib, sunitinib, temsirolimus, everolimus, and vemurafenib. Levetiracetam and topiramate are anticonvulsant agents not metabolized by the hepatic CYP450 system and do not alter the metabolism of antitumor agents. They have become the preferred drugs. Surgical resection and other antitumor treatments such as radiotherapy and chemotherapy may improve seizure control.

PULMONARY AND INTRACEREBRAL LEUKOSTASIS

Hyperleukocytosis and the leukostasis syndrome associated with it is a potentially fatal complication of acute leukemia (particularly myeloid leukemia) that can occur when the peripheral blast cell count is $>100,000/\text{mL}$. The frequency of hyperleukocytosis is 5–13% in acute myeloid leukemia (AML) and 10–30% in acute lymphoid leukemia; however, leukostasis is rare in lymphoid leukemia. At such high blast cell counts, blood viscosity is increased, blood flow is slowed by aggregates of tumor cells, and the primitive myeloid leukemic cells are capable of invading through the endothelium and causing hemorrhage. Brain and lung are most commonly affected. Patients with brain leukostasis may experience stupor, headache, dizziness, tinnitus, visual disturbances, ataxia, confusion, coma, or sudden death. On examination, papilledema, retinal vein distension, retinal hemorrhages, and focal deficit may be present. Administration of 600 cGy of whole-brain irradiation can protect against this complication and can be followed by rapid institution of antileukemic therapy. Hydroxyurea, 3–5 g, can rapidly reduce a high blast cell count while the accurate diagnostic workup is in progress. Pulmonary leukostasis may present as respiratory distress and hypoxemia, and progress to respiratory failure. Chest radiographs may be normal but usually show interstitial or alveolar infiltrates. Hyperleukocytosis rarely may cause acute leg ischemia, renal vein thrombosis, myocardial ischemia, bowel infarction, and priapism. Arterial blood gas results should be interpreted cautiously. Rapid consumption of plasma oxygen by the markedly increased number of white blood cells can cause spuriously low arterial oxygen tension. Pulse oximetry is the most accurate way of assessing oxygenation in patients with hyperleukocytosis. Leukapheresis may be helpful in decreasing circulating blast counts. Treatment of the leukemia can result in pulmonary hemorrhage from lysis of blasts in the lung, called *leukemic cell lysis pneumopathy*. Intravascular volume depletion and unnecessary blood transfusions may increase blood viscosity and worsen the leukostasis syndrome. Leukostasis is very rarely a feature of the high white cell counts associated with chronic lymphoid or chronic myeloid leukemia.

When acute promyelocytic leukemia is treated with differentiating agents like tretinoin and arsenic trioxide, cerebral or pulmonary leukostasis may occur as tumor cells differentiate into mature neutrophils. This complication can be largely avoided by using cytotoxic chemotherapy or arsenic together with the differentiating agents.

HEMOPTYSIS

Hemoptysis may be caused by nonmalignant conditions, but lung cancer accounts for a large proportion of cases. Up to 20% of patients with lung cancer have hemoptysis some time in their course. Endobronchial metastases from carcinoid tumors, breast cancer, colon cancer, kidney cancer, and melanoma may also cause hemoptysis. The volume of bleeding is often difficult to gauge. Massive hemoptysis is defined as $>200\text{--}600\text{ mL}$ of blood produced in 24 h. However, any hemoptysis should be considered massive if it threatens life. When respiratory difficulty occurs, hemoptysis should be treated emergently. The first priorities are to maintain the airway, optimize oxygenation, and stabilize the hemodynamic status. If the bleeding side is known, the patient should be placed in a lateral decubitus position, with the bleeding side down to prevent aspiration into the unaffected lung, and given supplemental oxygen. If large-volume bleeding continues or the airway is compromised, the patient should be intubated and undergo emergency bronchoscopy. If the site of bleeding is detected, either the patient undergoes a definitive surgical procedure or the lesion is treated with a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, argon plasma coagulation, or electrocautery. In stable