TREATMENT **PULMONARY DYSFUNCTION**

Chemotherapy- and radiation-induced pneumonitis is generally very corticosteroid responsive, except in the case of nitrosoureas. Prednisone 1 mg/kg is often used to control acute symptoms and pulmonary dysfunction with a generally slow taper. Prolonged glucocorticoid therapy requires gastrointestinal protection with proton pump inhibitors, management of hyperglycemia, heightened infection management, and treatment of steroid-induced osteoporosis. Antibiotics, bronchodilators, oxygen in only necessary doses, and diuretics may all play an important role in management of pneumonitis, and consultation with a pulmonologist should be routinely undertaken. Amifostine has been studied as a pulmonary radioprotectant, with inconclusive results, and is associated with skin rash, fatigue, and nausea; hence, it is not considered standard therapy at this time. Transforming growth factor β (TGF-β) is believed to be a major inducer of radiation fibrosis and represents a therapeutic target for development of anti-TGF-β therapies.

NEUROLOGIC DYSFUNCTION

CHEMOTHERAPEUTIC AGENTS

Chemotherapy- and radiation-induced neurologic dysfunction is unfortunately increasing in both incidence and severity as a result of improved supportive care leading to more aggressive regimens and longer cancer survivorship allowing the development of late toxicity. Direct effects on myelin, glial cells, and neurons have all been implicated, with alterations in cellular cytoskeleton, axonal transport, and cellular metabolism as mechanisms.

Vinca alkaloids produce a characteristic "stocking-glove" neuropathy with numbness and tingling advancing to loss of motor function, which is highly dose related. Distal sensorimotor polyneuropathy prominently involves loss of deep tendon reflexes with initially loss of pain and temperature sensation, followed by proprioceptive and vibratory loss. This requires careful patient history and physical examination by experienced oncologists to decide when the drug must be stopped due to toxicity. Milder toxicity often slowly completely resolves. Vinca alkaloids may sometimes be associated with jaw claudication, autonomic neuropathy, ileus, cranial nerve palsies, and, in severe cases, encephalopathy, seizures, and coma.

Cisplatin is associated with sensorimotor neuropathy and hearing loss, especially at doses >400 mg/m^2, requiring audiometry in patients with preexisting hearing compromise. Carboplatin is often substituted in such cases given its lesser effect on hearing.

Many of the agents that target kinase enzymes in tumor cells and 5-fluorouracil congeners produce dysesthesias and painful hands and feet known as hand-foot syndrome or palmar-plantar erythrodysesthesia. Symptoms usually abate when the agent is stopped.

Neurocognitive dysfunction has been well described in childhood survivors of acute lymphoblastic leukemia (ALL) treatment, including intrathecal methotrexate or cytosine arabinoside in conjunction with prophylactic cranial irradiation. Methotrexate alone may cause acute leukoencephalopathy characterized by somnolence and confusion that is often reversible. Acute toxicity is dose related, especially at doses >3 g/m^2, with younger patients being at greater risk. Subacute methotrexate toxicity occurs weeks after therapy and is often ameliorated with glucocorticoid therapy. Chronic methotrexate toxicity (leukoencephalopathy) develops months or years after treatment and is characterized clinically as progressive loss of cognitive function and focal neurologic signs, which are irreversible, promoted by synchronous or metachronous radiation therapy, and more pronounced at a younger age.

Neurocognitive decline following chemotherapy alone occurs notably in breast cancer patients receiving adjuvant chemotherapy; this has been referred to as "chemo brain." It is clinically associated with impaired memory, learning, attention, and speed of information processing. There is no clear mechanistic explanation for its cause and no clearly effective therapy. This entity is justifiably attracting more attention and clearly needs to be studied to develop effective therapy or prophylaxis.

Many cancer patients experience intrusive or debilitating concerns about cancer recurrence following successful therapy. In addition, these patients may experience job, insurance, stress, relationship, financial, and sexual difficulties. Oncologists need to ask about and address these issues explicitly with patients and provide appropriate counseling or support systems. Suicidal ideation and suicide have an increased incidence in cancer patients and survivors.

RADIATION THERAPY

Acute radiation central nervous system (CNS) toxicity occurs within weeks; is characterized by nausea, drowsiness, hypersomnia, and ataxia; and is most often associated with recovery. Early delayed toxicity occurring weeks to 3 months following therapy is associated with similar symptoms as acute toxicity and is pathologically associated with reversible demyelination. Chronic, late radiation injury occurs 9 months to up to 10 years following therapy. Focal necrosis is a common pathologic finding, and glucocorticoid therapy may be helpful. Diffuse radiation injury is associated with global CNS neurologic dysfunction and diffuse white matter changes on computed tomography (CT) or MRI. Pathologically, small vessel changes are prominent. Glucocorticoids may be symptomatically useful but do not alter the course. Necrotizing encephalopathy is the most severe form of radiation injury and almost always is associated with chemotherapy, notably methotrexate.

Cranial radiation may also be associated with an array of endocrine abnormalities with disruption of normal pituitary/hypothalamic axis function, and a high index of suspicion needs to be maintained to identify and treat this toxicity.

Radiation-associated spinal cord injury (myelopathy) is highly dose-dependent and rarely occurs with modern radiation therapy. An early, self-limited form involving electric sensations down the spine on neck flexion (Lhermitte's sign) is seen 6–12 weeks after treatment and generally resolves over weeks. Peripheral nerve toxicity is quite rare owing to relative radiation resistance.

HEPATIC DYSFUNCTION

CHEMOTHERAPEUTIC AGENTS

Long-term hepatic damage from standard chemotherapy regimens is rare. Long-term methotrexate or high-dose chemotherapy alone or with radiation therapy, for example, in preparative regimens for bone marrow transplantation, may result in venoocclusive disease of the liver. This potentially lethal complication classically presents with anicteric ascites, elevated alkaline phosphatase, and hepatosplenomegaly. Pathologically, there is venous congestion, epithelial cell proliferation, and hepatocyte atrophy progressing to frank fibrosis. Frequent monitoring of liver function tests during any chemotherapy is necessary to avoid both idiosyncratic and expected toxicities.

Certain nucleoside drugs have been associated with hepatic dysfunction; however, this complication is rare in oncology.

RADIATION THERAPY

Hepatic radiation damage depends on dose, volume, fractionation, preexisting liver disease, and synchronous or metachronous chemotherapy. In general, radiation doses to the liver >1500 cGy can produce hepatic dysfunction with a steep dose-injury curve. Radiation-induced liver disease closely mimics hepatic venoocclusive disease.

RENAL/BLADDER DYSFUNCTION

Cisplatin produces reversible decrements in renal function, but may also produce severe irreversible toxicity in the presence of renal disease and may predispose to accentuated damage with subsequent renal insults. Cyclophosphamide and ifosfamide, as prodrugs primarily