



## Neurologic complications of cancer therapy

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Patients with cancer often take multiple medications. These medications may be directed at underlying neoplasms (eg, chemotherapy, hormonal agents, biologic modifiers) or at secondary symptoms such as cerebral edema or seizures (eg, corticosteroids, anticonvulsants). Given that chemotherapeutic agents are active against rapidly dividing cells and that they are frequently excluded from the central nervous system (CNS) by the blood–brain barrier (BBB), it is surprising that many medications have adverse effects on the nervous system. The various mechanisms underlying neurotoxicity are an area of active investigation in neuro-oncology.

The pace of drug development has progressed rapidly during the past decade. When a patient with cancer presents with new neurologic symptoms, one must consider neurotoxicity related to cancer treatment. The goal of this review is to describe the neurotoxicity associated with established chemotherapeutic agents and with some of newer medications used in the treatment of cancer (Table 1). A number of excellent reviews have been published previously [1–9].

### Clinical findings and diagnosis

The differential diagnosis of a patient with cancer who presents with a new neurologic complaint is broad. Possible causes are listed in the box below. It is important to exclude direct effects of the cancer itself; indirect effects of the cancer such as metabolic, nutritional, opportunistic infections or cerebrovascular disorders; paraneoplastic syndromes; and toxic effects of

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**Causes of Neurologic Symptoms in Patients with Cancer**

Disease progression

Metastasis

Paraneoplastic syndromes

Seizures

Infection

Neurotoxicity of antineoplastic drugs

Radiation effects

Other neurological illnesses (eg, stroke, seizure, migraines, neuropathy)

Other medical illnesses (eg, renal failure, hepatic failure, hypertension)

radiation therapy, in addition to considering potential toxic effects of medications used to treat the cancer. In the majority of cases, there is no diagnostic test to separate iatrogenic causes from other etiologies. The diagnosis of chemotherapy-induced neurotoxicity is made clinically, and is based on three factors: the temporal relationship between drug administration and neurologic complication; knowledge of side effects of specific agents, if known; and exclusion of other possible causes.

**Chemotherapy***Alkylating agents**Nitrosoureas*

The nitrosoureas include BCNU (carmustine), CCNU (lomustine), ACNU, PCNU, streptozocin, and estramustine. They are primarily used to treat gliomas, melanoma, and lymphoma, and as part of the conditioning regimen for bone marrow transplantation. Extramustine is used to treat prostate cancer. These agents are highly lipid soluble, and penetrate the BBB easily. However, rapid clearance of these compounds from the CSF limits their exposure to targets in the CNS [3]. Studies of high-dose intravenous and intraarterial therapy attempt to bypass this hurdle.

*BCNU, CCNU, PCNU, ACNU*

BCNU is the prototype for this group of drugs. At conventional doses, BCNU does not cause neurotoxicity. However, patients who receive high-dose BCNU can develop a profound encephalopathy with or without a myelopathy that may progress to coma and death [149]. Intraarterial BCNU has been associated with significant toxicity. Progressive subacute encephalopathy characterized by confusion, seizures, and contralateral hemiparesis

develops 1-6 months after treatment in 10% of patients [150–152]. Encephalopathy can be distinguished from tumor progression by the lack of clinical response to steroids and by the absence of significant contrast enhancement on neuroimaging. Pathologic studies reveal disseminated foci of necrosis in the perfused territory with softened and expanded white matter consistent with chronic edema [149,152]. These findings resemble radiation necrosis, and in fact, BCNU encephalopathy is more common in those who receive radiation therapy [151].

In addition, about 15% of patients who receive intraarterial BCNU experience visual loss in the ipsilateral eye [151]. Vision can be spared by infusing the drug distal to the origin of the ophthalmic artery. Smaller studies have documented cases of retinopathy after intravenous administration, but this has not been confirmed in large clinical trials [15].

### *Estramustine*

Estramustine is a conjugate of estradiol and mechlorethamine. It binds to tubulin and disrupts formation of microtubules leading to mitotic arrest. Estramustine is primarily used to treat advanced prostate cancer. It has rarely been associated with stroke [153,154].

### *Busulfan*

Busulfan is a bifunctional alkylating agent that crosses the BBB and achieves high concentrations within the cerebrospinal fluid (CSF). It acts by crosslinking strands of nucleic acids and interfering with transcription and translation. Busulfan is used to treat myeloid leukemia, and is part of the conditioning regimen for allogeneic bone marrow transplantation. About 10% of patients who receive high-dose therapy will experience focal or generalized seizures within a day of administration. The most important risk factor is dose. Prophylactic treatment with phenytoin appears to reduce the incidence of this complication [10]. Regardless, seizures are not associated with long-term morbidity [5,11,12].

### *Chlorambucil*

Chlorambucil is a nitrogen mustard derivative that is used to treat lymphoproliferative disorders, ovarian neoplasms, polycythemia vera, and nephrotic syndrome. Seizures can occur with high-dose therapy or after low-dose therapy in patients with a history of seizures; status epilepticus has been reported after accidental overdoses [6,13]. Rarely, patients develop transient myoclonic jerks during treatment [14]. Diplopia and bilateral retinal hemorrhages have been reported [15].

### *Cyclophosphamide (Cytoxan)*

Cyclophosphamide is an alkylating agent with broad spectrum activity against a variety of hematologic disorders and solid tumors. Neurotoxicity related to cyclophosphamide is rare at conventional doses but at high

doses may include transient blurring of vision, dizziness, and confusion [5,15].

#### *Mechlorethamine (nitrogen mustard, Mustargen)*

Mechlorethamine is the prototypic mustard and is used to treat Hodgkin's disease and malignant pleural effusions. Early and late neurotoxicity can develop with high-dose intravenous therapy. Early side effects occur within days, and may include headache, encephalopathy, lethargy, hallucinations, hearing loss, vertigo, and seizures [6,16]. Late toxicity may be delayed by months, and typically occurs in patients who experienced acute toxicity. Symptoms include encephalopathy, personality change, seizures, and hydrocephalus [16]. Intraarterial therapy is associated with significant neurotoxicity. Intracarotid injection for brain tumors can cause necrotizing uveitis in the ipsilateral eye, ophthalmoplegia, necrotizing encephalopathy, coma, and even death [5,6,15].

#### *Ifosfamide (Ifex)*

Ifosfamide is an analog of cyclophosphamide with activity against soft tissue sarcoma and testicular carcinoma. The most common toxicity associated with ifosfamide is encephalopathy [17,18]. Decreased attention, sometimes with agitation, may develop within hours of administration and typically lasts 1–4 days. Estimations of incidence generally range from 10–25% without evidence of a dose–response curve. Renal impairment and hypoalbuminemia may predispose patients to this complication. The pathophysiology of ifosfamide encephalopathy is unknown but intoxication with chloroacetaldehyde, a metabolic product of ifosfamide, is likely the critical factor. Small, nonrandomized trials suggest that diazepam or methylene blue may prevent or treat the encephalopathy [19,20]. Rarely, encephalopathy can progress to coma or death [21,22]. Less commonly, ifosfamide causes extrapyramidal signs, cerebellar signs, weakness, incontinence, or seizures [17,22].

#### *Temozolamide (Temodar)*

Temozolamide is an alkylating agent with improved ability to penetrate the BBB. It has been used in the treatment of gliomas, melanoma, and brain metastases. No significant neurotoxicity has been reported with the use of temozolamide, although headache may be present in up to 25% of patients [23,24].

#### *Thiotepa (Thioplex)*

Thiotepa is an alkylating agent that is used to treat breast cancer and leptomeningeal metastases and as preparative regimen for bone marrow transplantation. Thiotepa is lipid soluble and achieves high concentrations within the CSF. Neurotoxicity is uncommon. Rarely, demyelination of the dorsal columns and nerve roots after intrathecal administration occurs [25].

Somnolence and acute confusional states have been reported after high-dose therapy [5].

### *Antimetabolites*

#### *Capecitabine (Xeloda)*

Capecitabine is an inactive prodrug of 5-fluorouracil (5-FU) that is absorbed intact after oral administration and subsequently converted to 5-FU. Capecitabine has been used to treat breast and colorectal cancer. No significant neurologic toxicity has been noted in human trials [26].

#### *Cladribine (2-chlorodeoxyadenosine, CdA)*

Cladribine is a purine nucleoside analog used to treat hairy cell leukemia, chronic lymphocytic leukemia, and low-grade lymphomas. At standard doses, profound neutropenia develops in about one-third of patients. This drug may also cause prolonged suppression of CD4 and CD8 positive lymphocytes, increasing the patient's susceptibility to opportunistic infections. Reactivation of herpes simplex and herpes zoster, as well as cases of *Neisseria meningoenephalitis*, have also been reported [27,28]. Neurotoxicity is dose dependent. At low doses, confusion, mood change, headache, and neuropathy may occasionally develop; at high doses, headache, dizziness, paraparesis, and quadraparesis are relatively common [29].

#### *Cytosine arabinoside (Cytarabine, Ara-C)*

Cytosine arabinoside is a pyrimidine analog that exerts its cytotoxic effect via the triphosphate nucleotide, ara-CTP, which terminates DNA replication. Cytosine arabinoside has been used in the treatment of leukemias, lymphomas, and leptomeningeal metastases. Neurotoxicity is related to the dose and the route of administration [5]. At conventional doses (<1 g/m<sup>2</sup>), there is no significant toxicity. At higher doses (>1 g/m<sup>2</sup>), cerebellar signs, encephalopathy, seizures, or leukoencephalopathy affects 10–30% of patients. Neurologic dysfunction usually presents within 24 hours, and resolves within days to weeks after discontinuation of medication [30]. Patients with renal insufficiency are more likely to develop neurotoxicity, and those older than 55 appear to be particularly susceptible to cerebellar dysfunction [31–33]. Pathologic studies of patients with cerebellar signs reveal focal loss of Purkinje cells in the cerebellum [34] (Fig. 1). Further courses of high-dose cytosine arabinoside do not increase the incidence of cerebellar toxicity [32].

High-dose cytosine arabinoside can produce corneal toxicity. Patients may complain of ocular pain, tearing, photophobia, and blurred vision beginning 4 to 8 days after treatment. Examination reveals conjunctival injection and corneal epithelial opacities. Symptoms resolve after 2 to 9 days, and may be prevented by the early use of glucocorticoid eye drops. It is postulated that cytosine arabinoside interferes with DNA synthesis in the cornea [15,35].

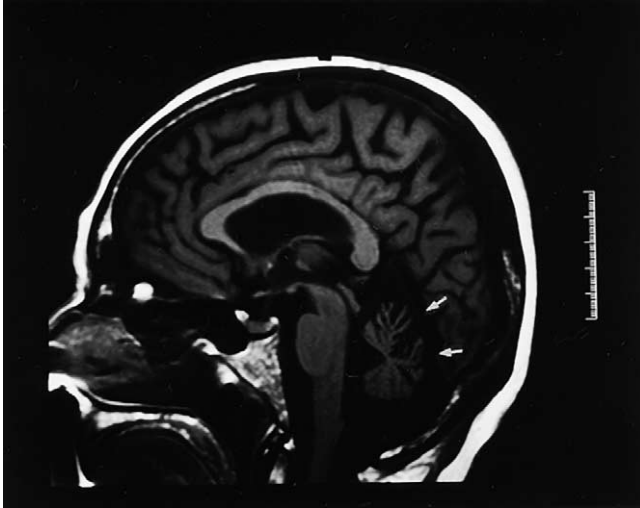


Fig. 1. Sagittal T1-weighted MRI of the brain showing severe cerebellar atrophy in a 66-year-old woman who received high-dose cytosine arabinoside for acute myelogenous leukemia 10 years previously. During her consolidation therapy with cytosine arabinoside she developed severe dysarthria and ataxia. These symptoms improved over the next few months but her speech and balance never returned to normal.

Intrathecal administration of cytosine arabinoside can produce aseptic meningitis, and rarely, myeloencephalopathy or seizures [36,37]. Myeloencephalopathy typically presents as confusion with ascending motor weakness and may extend rostrally to the brainstem and cerebellum [37,38]. The clinical course of myelopathy is variable, ranging from good recovery to death. Findings at necropsy vary from demyelination, axonal degeneration, and gliosis to coagulative necrosis of the spinal cord and brainstem [38,39].

Recently, a sustained-release version of cytosine arabinoside (DepoCyt) has been developed for treatment of leptomeningeal metastases. A single injection of DepoCyt can produce cytotoxic levels of cytosine arabinoside in CSF for up to 2 weeks. Aseptic meningitis is common with DepoCyt, and affects about 25% of treatment cycles. Severe meningitis (grade 3 or 4) is less common, affecting about 5% of cycles. Coadministration of dexamethasone reduces the likelihood of this complication. Other toxicities include headache, altered mental status, seizures, and nausea [40].

#### *Fludarabine (Fludara)*

Fludarabine is a purine analog that was created by rational drug design to resist degradation by the enzyme adenosine deaminase. It has been approved for the treatment of refractory chronic lymphocytic leukemia [29]. In early studies, high-dose fludarabine ( $>50$  mg/m<sup>2</sup>/day) was associated with delayed, progressive neurotoxicity. Affected patients presented 4–8 weeks after treatment with cortical blindness, encephalopathy, and seizures

that often progressed to coma and death. Neuropathological evaluation revealed diffuse leukoencephalopathy with demyelination preferentially affecting the occipital lobes [41–43].

Current treatment with fludarabine utilizes lower doses. Patients receiving doses  $<25 \text{ mg/m}^2/\text{day}$  may experience reversible neurologic dysfunction such as somnolence, hemiparesis, blurred vision, and gait difficulty [29,44]. Reports of progressive multifocal leukoencephalopathy confirmed by biopsy have been reported in patients with chronic lymphocytic leukemia treated with fludarabine [45]. The causal link between fludarabine treatment and development of progressive multifocal leukoencephalopathy is uncertain because patients with chronic lymphocytic leukemia are already at increased risk for progressive multifocal leukoencephalopathy.

### *5-Fluorouracil*

5-Fluorouracil (5-FU) is an analog of the pyrimidine uracil used to treat colorectal and head and neck cancer. It interferes with DNA synthesis by inhibiting the enzyme thymidylate synthetase. Patients with deficiency of dihydropyrimidine dehydrogenase, an enzyme involved in the metabolism of 5-FU, may develop profound encephalopathy and seizures after treatment with 5-FU. Infusion of intravenous thymidine may help these patients [46]. In unaffected patients, 5-FU has been associated with acute confusional states, encephalopathy, and a cerebellar syndrome consisting of horizontal jerk nystagmus, limb ataxia, and gait ataxia [47–49]. Rarely, patients receiving 5-FU may experience focal dystonia [50] or recurrent optic neuropathy with papilledema (Fig. 2) and decreased visual acuity [15,51].

Patients with colorectal adenocarcinoma may receive levamisole, an anti-helminthic, in addition to 5-FU for their disease. Numerous cases of multifocal inflammatory leukoencephalopathy have been reported in patients treated with this combination. Patients present with multifocal neurologic dysfunction such as confusion, weakness, and ataxia. Symptoms typically improve after discontinuation of medication with or without the addition of steroids [52,53].

### *Gemcitabine*

Gemcitabine is a cytidine analog used in the treatment of pancreatic cancer and nonsmall-cell lung cancer. Rarely, autonomic neuropathy or posterior leukoencephalopathy (Fig. 3) can occur [54,55]. Administration of gemcitabine after radiation therapy for brain metastases may increase the risk of neurotoxicity [56].

### *Hydroxyurea (Hydrea)*

Hydroxyurea inhibits DNA synthesis by its effect on the enzyme ribonucleotide reductase. Hydroxyurea is used to treat myeloproliferative disorders and brain tumors. Mild symptoms including drowsiness, headache, and dizziness have been reported [6,57].



Fig. 2. Fundoscopic examination showing papilledema. This may be caused by 5-FU, cisplatin, or retinoids.



Fig. 3. MRI of the brain showing posterior leukoencephalopathy. This may be caused by gemcitabine, methotrexate, vincristine, erythropoietin, and GM-CSF. (Courtesy of Liangge Hsu M.D., Brigham and Woman's Hospital, Boston, MA.)

### *Methotrexate*

Methotrexate is a folic acid antagonist that blocks the conversion of folate to tetrahydrofolate by irreversibly binding the enzyme dihydrofolate reductase. It has a broad spectrum of activity, and is used to treat choriocarcinoma, breast cancer, lymphomas, leukemias, and leptomeningeal metastases. Neurotoxicity associated with methotrexate can be divided into acute, subacute, and late effects.

*Acute toxicity.* Acute effects typically start within hours of administration. Aseptic meningitis is most common, and occurs in about 10% of patients who receive intrathecal methotrexate. Patients may experience headache, fever, nuchal rigidity, and lethargy consistent with meningeal irritation. Aseptic meningitis can be differentiated from bacterial meningitis by the temporal relationship between symptoms and drug delivery and by examination of CSF, which reveals mild pleocytosis and sterile cultures [3,6]. Symptoms typically last 1–3 days and resolve without long-term sequelae. However, one small study suggests that fever after administration of methotrexate is associated with the development of delayed leukoencephalopathy [58]. This finding has not been confirmed in larger studies. Risk factors for aseptic meningitis include dose, peak concentrations in the CSF, and composition of the vehicle [59]. Patients with impaired or obstructed CSF flow are also at increased risk for severe acute toxicity following normal intrathecal doses of methotrexate.

Massive overdoses of intrathecal methotrexate can produce a fatal myeloencephalopathy characterized by seizures, bilateral pyramidal signs, and coma [60]. Some patients with less severe overdoses may experience only mild neurologic symptoms [61]. Therapies that rapidly decrease levels of methotrexate such as CSF exchange or administration of carboxypeptidase-G2 may be helpful [62,63].

*Subacute toxicity.* Subacute toxicity typically occurs within weeks to months of administration of methotrexate. Patients who receive low-dose methotrexate may describe vague neurologic symptoms in the absence of objective signs [64]. Moderate or high-dose methotrexate has been associated with the abrupt onset of focal neurologic signs such as behavioral abnormalities, dysarthria, aphasia, hemiparesis, and seizures [65–67]. Laboratory studies and CT scans are unremarkable, but EEG reveals focal or generalized slowing. These episodes are self-limited, lasting hours to days, and do not usually recur with retreatment.

Patients who receive a combination of intravenous and intrathecal methotrexate may develop a reversible posterior leukoencephalopathy [68,69] (Fig. 3). These patients present with cortical signs such as seizures, confusion, hemispatial neglect, apraxia, and alexia with characteristic findings on CT and MRI scans. Concurrent hypertension and hypomagnesemia have been associated with this syndrome. Rarely, patients with transient

neurologic signs such as dysarthria and hemiparesis have brain imaging that does not return to baseline. These patients are thought to have a stroke-like syndrome distinct from delayed leukoencephalopathy [70].

Rarely, intrathecal administration of methotrexate is complicated by subacute transverse myelopathy. Patients often complain of lumbar pain followed by the onset of paraparesis with a spinal sensory level and an atonic bladder [3,71]. MRI scan of the spinal cord may reveal focal contrast enhancement [72]. Pathology shows microvacuolization without significant necrosis, inflammation, or neoplastic cells [73]. Significant recovery has been occasionally reported [71,72].

*Late toxicity.* Late neurotoxicity usually develops more than 6 months after treatment, and may occur after intravenous or intrathecal administration. The incidence is increased if methotrexate is given concomitantly with or after radiation therapy. The syndrome is characterized by leukoencephalopathy on neuroimaging (Fig. 4) and presents as progressive dementia, gait ataxia, and urinary incontinence. Concentrations of myelin basic protein in CSF may be elevated [74]. MRI studies reveal diffuse signal abnormality in the white matter of both cerebral hemispheres, cortical atrophy, and ventriculomegaly. In children treated with high-dose methotrexate, IQ scores drop modestly [75]. In adults, quality of life is adversely affected, reflected by a drop in the Karnofsky Performance Scale, and patients may require custodial care. Risk factors include cumulative dose, increasing age, and pretreatment radiation therapy [76]. Pathology usually reveals areas of necrosis and demyelination in the periventricular white matter [53]. The mechanism of late neurotoxicity is not known.

#### *Pentostatin (2'-deoxycoformycin, DCF)*

Pentostatin is a purine analog that inhibits adenosine deaminase. Neurotoxicity is dose related. Early studies using high doses were complicated by encephalopathy or seizures in 60% of cycles. Encephalopathy ranging from mild to severe appeared within days and resolved within weeks. Current regimens use lower doses at which neurotoxicity is less common (about 15%). Side effects include mood disturbance, confusion, and rarely seizures [29].

#### *6-Thioguanine (6-TG, Lanvis)*

6-Thioguanine is an analog of the purine guanine, and is primarily used to treat leukemia and brain tumors. It has not been associated with significant neurotoxicity.

#### *Platinum complexes*

##### *Cisplatin (cis-dichlorodiammine platinum II, DDP)*

Cisplatin is a first-generation platinum complex that crosslinks strands of DNA. It is used to treat solid tumors of the ovary, testicle, lung, and head

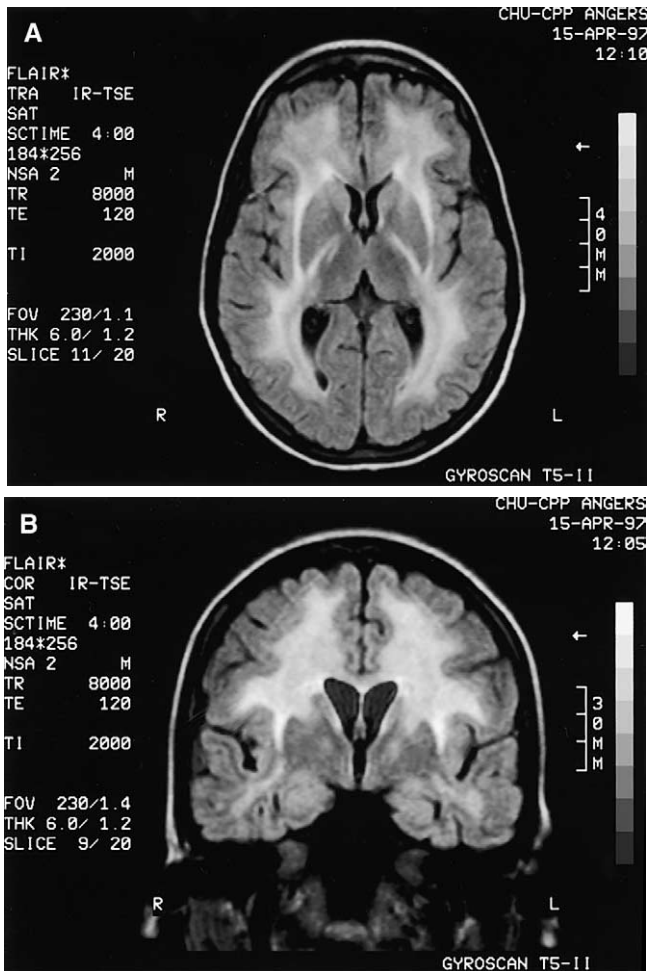


Fig. 4. Axial (A) and Coronal (B) T2-weighted MRI of the brain showing periventricular white matter leucoencephalopathy in a patient who received high-dose methotrexate and radiation therapy for central nervous system lymphoma.

and neck. Neurotoxicity is common, and preferentially affects the peripheral nervous system. This pattern of involvement likely reflects the inability of cisplatin to penetrate the BBB effectively [77,78].

*Peripheral neuropathy.* Sensory neuropathy is the most common complication of cisplatin treatment. Patients report numbness of the hands and feet that spreads proximally with additional courses of treatment. Some patients may experience painful paresthesias. Examination reveals impairment of vibratory sense out of proportion to other sensory modalities. Deep tendon reflexes gradually disappear, first in the ankles and later in the knees. Motor

function is preserved. In severe cases, neuropathy may progress to sensory ataxia and lead to withdrawal of cisplatin from the chemotherapy regimen. Electrophysiologic studies reveal attenuation of distal sensory nerve potentials with relative preservation of conduction velocities. Pathologic examination reveals length-dependent axonal degeneration of large myelinated nerves with secondary demyelination [3,78,79].

The only identified risk factor for neuropathy is cumulative dose. High-risk groups based on patient characteristics have not been identified and, therefore, patient selection is unnecessary [80–82]. Neuropathy usually develops when cumulative doses exceed 400 mg/m<sup>2</sup>, although cases have been reported at lower doses [3,80]. Among long-term survivors (>5 years), the incidence of neuropathy is about 60% [80].

Prevention and treatment of cisplatin-associated neuropathy is an active area of research. Patients with mild neuropathy after moderate doses (<450 mg/m<sup>2</sup>) are unlikely to develop significant neuropathy with additional cycles [83]. In contrast, patients with neuropathy after high doses (>500 mg/m<sup>2</sup>) may continue to worsen after withdrawal of cisplatin [3,84]. Patients who achieve long-term survival may note clinical improvement with time.

Several compounds have shown promise in preventing or reversing neuropathy in experimental models of cisplatin-associated neuropathy. These include WR-2721 (amifostine) [82], Org 2799 [85,86], neurotrophin-3 [87], and nerve growth factor [88]. Human studies have yielded conflicted results with regard to the efficacy of these compounds in preventing cisplatin-induced neuropathy [89–92].

*Muscle cramps.* About one-third of patients with peripheral neuropathy develop muscle cramps that are localized and painful. Routine studies of electrolytes, renal function, and muscle enzymes in these patients are normal [84].

*Cranial neuropathies.* Cisplatin damages hair cells in the Organ of Corti, and commonly produces ototoxicity. This results in hearing loss at higher frequencies (4000–8000 Hz) that develops 3–4 days after treatment. Persistent and symptomatic hearing loss affects 20% of patients treated for testicular cancer and 60% of patients receiving >600 mg/m<sup>2</sup> [93]. Symptoms may improve in patients who receive low cumulative doses of cisplatin [6,93]. Risk factors for ototoxicity include cumulative dose, treatment with other ototoxic medications, hypomagnesemia, and history of noise exposure [93]. Primary cultures of spiral ganglion neurons suggest that members of the nerve growth factor family of proteins (brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin 4/5) block the ototoxic effects of cisplatin [94].

Rarely, ipsilateral palsies of cranial nerves VII–XII can develop after intraarterial administration of cisplatin [95].

*Ophthalmologic toxicity.* Ophthalmologic complications of cisplatin therapy are uncommon. Patients with papilledema (Fig. 2), retrobulbar neuritis, optic nerve swelling, and transient cortical blindness have been reported [15,96–98]. Ipsilateral retinal ischemia or retrobulbar optic neuropathy can occur with intraarterial infusions proximal to the origin of the ophthalmic artery. These complications do not occur with supraophthalmic infusions (5, 7).

*Lhermitte's sign.* The sensation of electrical shock in the neck, back, or limbs triggered by flexion of the neck is called Lhermitte's sign. Traditionally associated with multiple sclerosis, B12 deficiency, and spinal cord tumors, Lhermitte's sign develops in up to 25% of patients treated with cisplatin (5, 7). Associated neuropathology has not been reported.

*Cerebrovascular disease.* Rare cases of myocardial infarction and stroke have been reported with cisplatin treatment [99–101]. The presumed pathophysiology involves injury to the vascular endothelium, activation of local clotting mechanisms, and thrombosis of cerebral vessels [100–102].

*Encephalopathy.* Encephalopathy after administration of cisplatin presents as decreased attention with or without seizures [3,103]. Seizures can occur after intravenous administration, although they are more common after intraarterial administration [104]. Occasionally, seizures are precipitated by electrolyte abnormalities such as SIADH or hypomagnesemia [105,106]. Rarely, in patients with intracranial masses and midline shift, administration of cisplatin can result in cerebral herniation. The pathogenesis is likely multifactorial resulting from preexisting edema, hyponatremia, rigorous intravenous hydration using hypotonic fluids, and seizure activity [107].

### *Carboplatin*

Carboplatin is a second-generation platinum complex with similar activity to cisplatin but with fewer neurologic side effects. Rare cases of peripheral neuropathy have been reported [108]. However, these patients were previously treated with high doses of cisplatin and demonstrated evidence of mild neuropathy prior to carboplatin treatment. Seizures, stroke, and coma have been reported after intraarterial infusion by superselective catheterization [109,110]. Thrombotic angiopathic hemolytic anemia may present as multifocal neurologic deficits with encephalopathy [111]. Blindness has also been reported [112].

### *Oxaliplatin (Eloxatin)*

Oxaliplatin is a third-generation platinum complex used to treat ovarian and colorectal cancer. Peripheral sensory neuropathy is dose related, and may affect patients whose cumulative dose exceeds 200 mg/m<sup>2</sup>. Unlike cisplatin-associated neuropathy, neuropathy associated with oxaliplatin

improves more readily after discontinuation of treatment [113]. Some patients treated with oxaliplatin develop high-frequency hearing loss [113], which is generally milder than that associated with cisplatin.

### *Antineoplastic antibiotics*

#### *Anthracycline antibiotics: doxorubicin, daunorubicin, mitoxantrone*

Doxorubicin (adriamycin) was the first antibiotic used to treat cancers. It acts by intercalating between bases in DNA, leading to uncoiling of the double helix structure. Doxorubicin does not cross the BBB [114], and has no significant toxicity when given in traditional fashion. Accidental administration by intrathecal route can produce transient chemical meningitis, encephalopathy, and myelopathy [115]. Cardiomyopathy due to doxorubicin can predispose patients to formation of ventricular thrombi, which in turn, can lead to transient cerebral ischemia or strokes [116] (Fig. 5). Daunorubicin is an analog of doxorubicin, and has no significant neurotoxicity. Mitoxantrone delivered intrathecally can cause permanent myelopathy in animals and human. For this reason, intrathecal administration is discouraged [117,118].

#### *Bleomycin*

Bleomycin is a mixture of polypeptide antibiotics that cuts DNA strands. Rarely, cardiovascular and cerebrovascular ischemia has been associated with multidrug regimens including bleomycin. A causal link between bleomycin and stroke remains speculative.

#### *Mitomycin C*

Mitomycin C probably acts as an alkylating agent and crosslinks strands of DNA. Neurotoxicity is rare with anecdotal reports of encephalopathy due to thrombotic microangiopathy [119].

#### *Plicamycin (Mithramycin)*

Plicamycin has both antineoplastic and hypocalcemic effects. Its primary use is in the treatment of hypercalcemia of malignancy [3]. Although in recent years, bisphosphonates have superseded plicamycin for treatment of this condition. It may rarely cause headaches and lethargy.

### *Plant alkaloids*

Plant alkaloids include taxanes, vinca alkaloids, and podophyllotoxins. All classes bind tubulin, a component of cellular microtubules, but inhibit cell division through different mechanisms. Taxanes and vinca alkaloids are microtubule poisons that act by stabilizing or degrading microtubules, respectively. Podophyllotoxins bind tubulin but inhibit cell division by interfering with topoisomerase II. The cytoskeleton is involved in disparate cell functions such as signaling transmission, intracellular transport, and

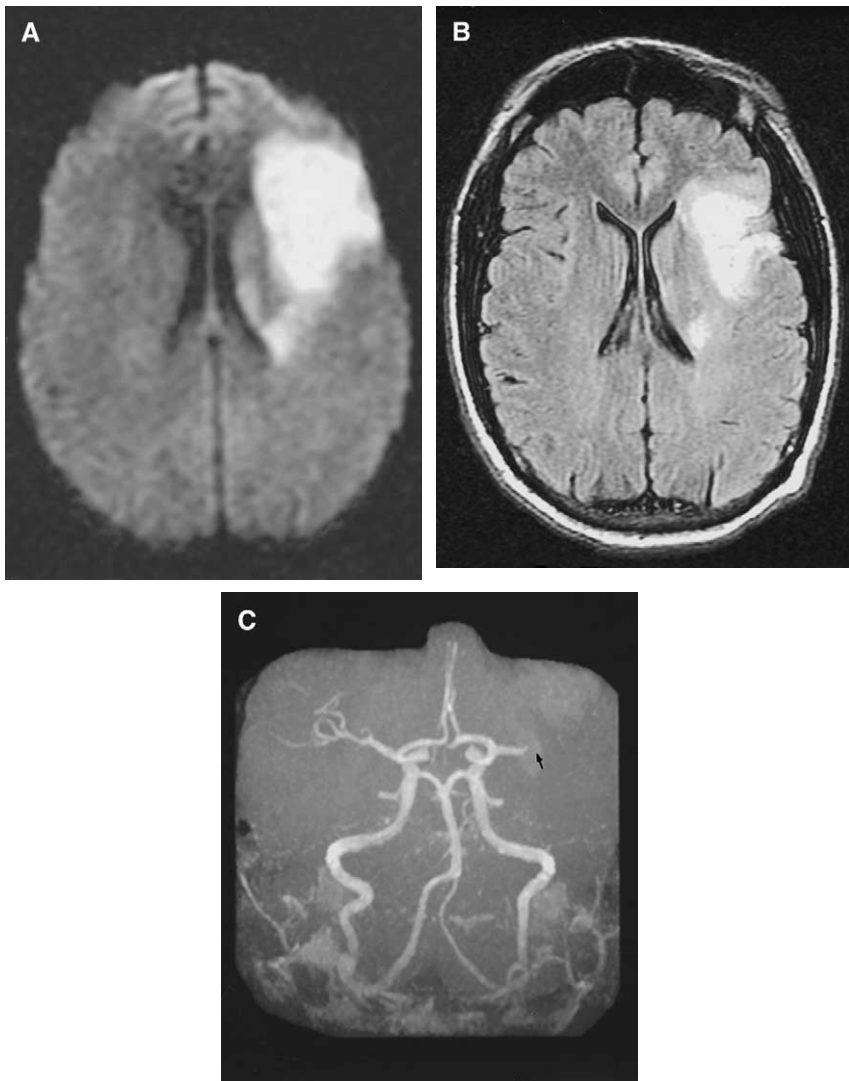


Fig. 5. A 29-year-old man with non-Hodgkins lymphoma who received chemotherapy including doxorubicin (adriamycin). Treatment was complicated by the development of a dilated cardiomyopathy with an ejection fraction of 20%. He was not treated with warfarin. Subsequently he presented with right-sided facial and arm weakness and aphasia. MRI showed a large left middle cerebral artery (MCA) stroke. (A) Diffusion MRI showing restricted diffusion, consistent with a stroke, in the left frontal lobe. (B) FLAIR MRI showing the left frontal stroke. (C) Magnetic resonance angiography showing cutoff of the left MCA (suggesting embolus).

maintenance of cell shape [120]. Neurotoxicity of these agents is related to disruption of these functions.

#### *Taxanes: paclitaxel (Taxol), docetaxel (Taxotere)*

Paclitaxel is a derivative of the Pacific yew, and is used to treat ovarian, breast, and lung cancer. Paclitaxel produces a predominantly sensory neuropathy that may be dose limiting. Examination reveals loss of pain and temperature sensation (small fiber) as well as vibration and position sense (large fiber) [121,122]. Mild proximal or distal weakness may develop 1–3 days after treatment in patients with sensory symptoms, but usually does not interfere with ambulation [3,121,123]. Electrophysiologic studies reveal evidence of axonal degeneration and demyelination [122]. Cumulative dose is the main risk factor. Greater than 50% of patients who receive doses in excess of 250 mg/m<sup>2</sup> develop significant neuropathy. Sensory and motor symptoms often improve after discontinuation of treatment. Proximal myalgias affect 25–50% of patients, and can detract from quality of life [123,124]. Patients with amputated limbs can develop reversible phantom-limb pain after administration of paclitaxel [125]. Rarely, patients who receive high doses (>600 mg/m<sup>2</sup>) develop profound encephalopathy that may be fatal [126,127].

Ophthalmic toxicity can occur with administration of paclitaxel. About 20% of patients describe transient scotomas near the end of paclitaxel infusions. A minority of these patients note subjective decrease in visual acuity, which correlates with optic neuropathy on visual evoked responses [128].

#### *Docetaxel*

Docetaxel is a semisynthetic analog of paclitaxel used to treat a variety of solid tumors. Like its parent compound, docetaxel induces a symmetric, peripheral neuropathy that primarily affects sensation [129]. Weakness and myalgias have been reported [123]. Sural nerve biopsies demonstrate an axonal neuropathy preferentially affecting large myelinated fibers [130]. Spontaneous improvement after discontinuation of treatment is common. Neuropathy associated with docetaxel is less well characterized but appears to be less frequent than that associated with paclitaxel. A subset patients with neuropathy may experience Lhermitte's sign upon flexion of the neck [131].

#### *Vinca alkaloids: vincristine, vinblastine, vindesine, vinorelbine*

Vinca alkaloids are derived from the periwinkle plant. Vincristine produces an axonal sensorimotor peripheral neuropathy. Paresthesias of the hands and feet are the first signs of neuropathy, and are usually associated with loss of ankle reflexes. Further treatment may cause impairment of fine movements and mild weakness of ankle dorsiflexors. Occasionally, patients may develop unilateral or bilateral foot drop. Autonomic neuropathy, which presents as abdominal pain, constipation, and urinary retention, may affect up to one-third of patients [3]. Electrophysiologic studies and nerve

biopsies support a length-dependent axonal neuropathy [132–134]. Risk factors include dose, increasing age, compromised nutritional state, and treatment with neuropathy-inducing medications. Clinical signs may improve with time [3]. Occasionally, treatment with vincristine may unmask unrecognized hereditary motor and sensory neuropathy (Charcot-Marie-Tooth) [134], or may present as fulminant acute inflammatory demyelinating neuropathy [135]. Patients who receive granulocyte- or granulocyte-macrophage-colony stimulating factor along with vincristine are at increased risk for developing a transient but severe neuropathy characterized by excruciating pain and profound foot drop [136].

CNS toxicity is uncommon. Cranial neuropathies presenting as ptosis, diplopia, facial weakness, or vocal cord paralysis may appear early or late in the course of treatment [137,138]. Rarely, patients may develop unilateral or bilateral optic atrophy associated with the loss of tubulin in the optic nerves [15,137]. Visual hallucinations have been reported with vincristine therapy, although the patient was receiving concurrent corticosteroids [139]. Encephalopathy, seizures, and blindness suggestive of posterior leukoencephalopathy (Fig. 3) may also occur [140,141].

Accidental administration of vincristine into the CSF produces a myeloencephalopathy that is usually fatal, even with rapid drainage of CSF [142,143]. Occasionally, patients may survive intrathecal vincristine, although they remain neurologically devastated [144]. Pathologic examination of the brain and spinal cord reveals widespread necrosis in regions of brain exposed to vincristine [143].

Vinblastine, vindesine, and vinorelbine are derivatives of vincristine with fewer neurologic complications. Patients may develop peripheral and autonomic neuropathies, although they are less frequent than with vincristine [145]. Vinorelbine produces less peripheral neuropathy than vindesine [146].

#### *Podophyllotoxins: etoposide (VP-15) and tenoposide (VM-26)*

Etoposide and tenoposide are semisynthetic derivatives of the May apple or mandrake plants. Etoposide is used to treat lung cancer, germ cell tumors, brain tumors, and lymphoma. It penetrates the BBB poorly and rarely causes neurotoxicity. Occasionally, etoposide may produce a mild and reversible neuropathy [3,147]. At high doses, it has been associated with encephalopathy and worsening of neurologic deficits in patients with gliomas [148]. Intraarterial administration with carboplatin may produce headache, seizures, confusion, blurred vision, and urinary retention [104]. Tenoposide has been used for acute lymphoblastic leukemia, Kaposi sarcoma, and cutaneous T-cell lymphoma. It has been rarely associated with peripheral neuropathy [3].

#### *Topoisomerase inhibitors*

##### *Irinotecan (Camptosar, CPT-11)*

Irinotecan is a semisynthetic analog of camptothecin that inhibits topoisomerase I, thereby delaying DNA replication and cell division. It is used to

treat colon cancer. Neurotoxicity is rare, but may include transient dysarthria [155,156] and cholinergic symptoms when coadministered with oxaliplatin [157].

#### *Topotecan (Hycamtin)*

Topotecan is a topoisomerase I inhibitor used to treat ovarian cancer, lung cancer, and Ewing's sarcoma. Topotecan is not associated with significant neurotoxicity, but some patients experience debilitating lethargy that can be dose limiting [158].

#### *Miscellaneous agents*

##### *L-asparaginase (Elspar)*

L-asparaginase catalyzes the hydrolysis of asparagine to aspartate and ammonia. This effect reduces synthesis of proteins and glycoproteins needed for cell division. L-asparaginase is used to treat acute lymphocytic leukemia. Depression, personality changes, and encephalopathy may develop in patients who receive L-asparaginase [159,160]. Encephalopathy is likely caused by hepatic dysfunction. The degree of encephalopathy typically correlates with the amount of slow wave activity on electroencephalogram (EEG) but not with hyperammonemia [160,161]. Some patients with normal mental status may have abnormal electroencephalograms [161].

L-asparaginase produces deficiencies of antithrombin III, plasminogen, and fibrinogen that predispose patients to cerebrovascular disease, especially venous sinus thrombosis (3, 5, 7). Patients who present with headache, focal seizures, hemiparesis, or obtundation should be suspected of harboring a thrombosis or hemorrhage until proven otherwise.

##### *Dacarbazine (DTIC)*

Dacarbazine is used to treat metastatic melanoma. Isolated reports of hemiparesis, dementia, and seizures exist, but the causative role of dacarbazine in these cases is unclear [6,162].

##### *Hexamethylmelamine (Altretamine)*

Hexamethylmelamine achieves its antieoplastic effect by unknown mechanisms. It is occasionally used to treat ovarian cancer, lung cancer, and lymphoma. Toxicity is dose related and reversible. The most common side effect is peripheral neuropathy, occurring in about 30% of patients. Other side effects include mood changes, tremor, ataxia, seizures, and parkinsonism [3,6,163].

##### *Levamisole (Ergamisol)*

Levamisole is an antihelminthic drug used in conjunction with 5-FU to treat colorectal cancer. Some patients treated with both levamisole and 5-FU develop subacute confusion and focal neurologic signs associated with

multifocal lesions on MRI [52,53]. A similar presentation has been reported in a patient receiving levamisole monotherapy [164].

#### *Procarbazine (Matulane)*

Procarbazine is a methylhydrazine derivative whose mechanisms of activity has not been defined. It is used to treat gliomas, lymphomas, and lung cancer. Procarbazine crosses the BBB and achieves high concentrations within the CNS. High-dose therapy ( $>75 \text{ mg/m}^2$ ) has been associated with depression of mental status ranging from drowsiness to stupor [165]. However, many of these patients also received sedating medications such as phenothiazines for treatment-associated nausea and vomiting. In patients with gliomas, a range of neuropsychologic findings including memory disturbance, apathy, and personality change associated with cortical atrophy can occur with intensified regimens of procarbazine. This occurs in the absence of disease progression [166]. Reversible peripheral neuropathy characterized by paresthesias and loss of deep tendon reflexes has been documented [165].

#### *Pyrazolonacridine (PZA)*

Pyrazolonacridine is an acridine derivative that exerts its antineoplastic effects by intercalating between bases of DNA. It is used to treat ovarian, cervical, and colorectal cancer. Neurotoxicity is relatively common, affecting about 20–30% of patients in phase I and phase II trials. The most common symptoms are anxiety, restlessness, and agitation [167,168]. Occasionally, neuropsychiatric symptoms are severe enough to be dose limiting. Reducing the total dose, lengthening the time of infusion, and pretreating with benzodiazepines help minimize the symptoms. Many patients also experience involuntary movement of the limbs during infusion that resembles myoclonus [167,168].

#### *Retinoids: tretinoin (retin-A), isotretinoin (accutaine), and alitretinoin*

Retinoids are analogs of vitamin A (retinal) that include all-trans-retinoic acid (ATRA, tretinoin), 13-cis-retinoic acid (isotretinoin), and 9-cis-retinoic acid (alitretinoin). These agents arrest cell growth and induce differentiation in some tumors. Headaches are a common side effect of all three medications, and can lead to dose reduction [169,170]. Some patients with headaches may develop increased intracranial pressure and papilledema suggestive of idiopathic intracranial hypertension (Fig. 2) [169,171,172]. Rare cases of depression, mononeuritis multiplex, or cerebellar dysfunction have been reported [169,173,174].

#### *Suramin*

Suramin is a polysulfonated naphthylurea that has traditionally been used to treat parasitic diseases and more recently to treat metastatic prostate carcinoma. It acts by inhibiting the binding of growth factors and interfering with the activity of cellular enzymes. Suramin has been associated with two

distinct forms of neuropathy. The first is a mild sensorimotor axonal neuropathy that affects 20–80% of patients being treated for prostate carcinoma [175]. Patients develop impaired sensibility to pain and vibration with mild distal weakness and absent reflexes. Ambulation is not affected. The second is a demyelinating polyneuropathy similar to Guillain-Barre syndrome that develops in 10–20% of patients 1–2 months after delivery of suramin [176,177]. Patients typically note proximal weakness affecting the legs more than the arms, with absent reflexes and variable amounts of sensory symptoms. Progression to quadraparesis with ventilatory support and death have been documented [175,177]. Withdrawal of suramin and plasma exchange appear to be helpful. Risk factors include peak concentrations of suramin >350 µg/mL but not total cumulative dose [175,176]. Other neurotoxicities reported with suramin use include visual and hearing disturbances, disorientation, and mood changes [178].

### *Thalidomide*

Thalidomide was introduced in Europe in 1954 as a sedative agent. Seven years later it was withdrawn due to the high incidence of limb malformations in children born to women who received the drug. In 1998, thalidomide was approved by the Federal Drug Administration for treatment of erythema nodosum leprosum. Thalidomide has antiangiogenic properties, and has been used to treat multiple myeloma, gliomas, Kaposi's sarcoma, and breast cancer. The most common side effect is somnolence, affecting 40–60% of patients [179–182]. Tachyphylaxis to this side effect often develops after 2 or 3 weeks, but sedation remains an important cause of dose limitation. Peripheral neuropathy occurs in 3–32% of patients, and does not appear to be dose related [179,182,183]. Thalidomide neuropathy typically presents as distal paresthesias, often with sensory loss. Electrophysiologic studies suggest an axonal sensory neuropathy that may improve slightly after withdrawal of therapy [183,184]. Seizures can occur in a minority of patients with gliomas and a past history of seizures [179]. Other side effects include depression, incoordination, tremors, and headache [180–182].

### *Hormonal therapy*

#### *Antiestrogens: tamoxifen (Nolvadex) and toremifene citrate (Fareston)*

Tamoxifen and toremifene are nonsteroidal antiestrogens that are used to treat breast cancer. Neurotoxicity is uncommon with tamoxifen. Visual complaints, including decreased central vision, are reported in less than 5% of patients. Retinal changes on ophthalmologic exam include small, refractile deposits in the region surrounding the macula with macular edema. This complication is more common in patients receiving high-dose therapy or those with large cumulative doses [185–187]. Discontinuation of tamoxifen usually results in clinical improvement, although retinal deposits may persist.

Tamoxifen has been associated with increased risk of arterial and venous thrombosis [188]. The increased risk of stroke, however, remains small. In a large phase III multicenter trial, the incidence of stroke was 1.45 events per 1000 women per year. This rate slightly exceeded that for women treated with placebo (0.92), but the difference was not significant [189].

Toremifene is structurally similar to tamoxifen, differing only by a single atom of chlorine. Toremifene has not been studied as extensively as tamoxifen. The side effects of toremifene are similar to tamoxifen but appear to be less common [190].

#### *Aromatase inhibitors: aminoglutethimide, anastrozole (Arimidex), and Letrozole (Femara)*

These agents are examples of nonsteroidal, competitive, aromatase inhibitors that block the synthesis of steroid hormones. They are used to treat breast cancer, adrenocortical carcinoma, and ectopic Cushing's disease. Aminoglutethimide is a nonselective inhibitor of aromatase that reduces the production of estrogen, aldosterone, and cortisol. Therefore, concurrent treatment with corticosteroids is required. In contrast, anastrozole and letrozole are selective inhibitors of aromatase and do not require routine corticosteroid replacement. The most common side effect of these drugs is lethargy and somnolence that may affect up to 10% of patients [191].

#### *Corticosteroids*

Corticosteroids are commonly used in the treatment of cancer. They may be included in chemotherapy regimens for their cytotoxic effects, as in the treatment of leukemias and lymphomas, or for their ability to alleviate secondary symptoms of cancer. For example, steroids reduce peritumoral edema in primary and metastatic tumors of the CNS and provide symptomatic relief from mass effect. Steroids have also been used to treat chemotherapy-induced nausea, to relieve pain, and to improve mood and appetite.

Complications of steroid therapy have been recognized since their introduction in the 1950s. One of the most common side effects is myopathy. Estimations of incidence vary from 10% to 60% [192,193]. Characteristic proximal weakness develops weeks to months after institution of steroid treatment, and often interferes with quality of life. Patients who can tolerate a reduction in dose typically improve [192,193].

Neuropsychiatric symptoms are common in patients treated with steroids. Estimations of incidence are limited because much of the data comes from studies in the 1950s when application of strict definitions of psychiatric disease were not universal. Given these limitations, the incidence of mild/moderate and severe affective disease occurs in 27% and 5% of patients, respectively [194,195]. Depression and mania are the most common symptoms; psychosis and delirium occur less frequently. Symptoms often appear within 2 weeks of starting therapy. In general, higher doses are more likely

to precipitate psychiatric disease, although steroid withdrawal can also precipitate psychosis [3].

Other common complications of steroid therapy include tremor, insomnia, visual blurring, and cerebral atrophy [5,196]. Rare effects include hiccups or spinal cord compression due to epidural lipomatosis [197–199]. Withdrawal of steroids can produce a variety of symptoms including headache, lethargy, nausea, anorexia, and pseudotumor cerebri. These symptoms may prevent tapering, and can lead to steroid dependence.

#### *Danazol (Danocrine)*

Danazole is an anabolic androgen that inhibits gonadotropin release. Occasionally, woman taking danazol may experience muscle cramps, headache, and irritability [3,200].

#### *Goserelin (Zoladex)*

Goserelin is an analog of lutenizing hormone releasing hormone (LHRH) that suppresses the secretion of sex steroids. It is used to treat breast and prostate cancer. Significant neurotoxicity has not been reported, although there is a theoretical risk of exacerbating spinal cord compression due to bony metastases when the drug is first used [3].

#### *Leuprolide acetate (Leupron)*

Leuprolide acetate is an analog of gonadotropin-releasing hormone that suppresses the hypothalamic-pituitary-gonadal axis. It is used to treat advanced breast and prostate cancer. As with goserelin, there is a theoretical risk of worsening spinal cord compression when the drug is first used [3].

#### *Mitotane (O,P'-DDD)*

Mitotane suppresses adrenocorticosteroid production and is used to treat adrenocortical carcinoma. The most common side effect is lethargy, which can affect up to one-third of patients [3]. Other side effects are related to serum levels. When concentrations exceed 15 mg/L, patients may experience ataxia and problems with language, memory, and visuospatial tasks [201]. When concentrations exceed 20 mg/L, severe somnolence, dizziness, vertigo, or seizures may occur [202,203].

#### *Octreotide (Sandostatin)*

Octreotide is an analog of somatostatin that is used to treat endocrine tumors such as carcinoid tumors, vasoactive intestinal peptide (VIP)-secreting tumors, and growth hormone-secreting pituitary adenomas. Rarely, it can exacerbate headache and cause dizziness and seizures.

### **Biologic agents**

#### *Interferons: -alpha, -beta, and -gamma*

Interferons are naturally occurring cytokines that have both anti-neoplastic and immunomodulatory effects. They induce enzymes that

polyadenylate mRNA, thereby identifying them for degradation. Interferon-alpha and -beta induce expression of HLA class I antigens and activate lymphocytes; interferon-gamma induces expression of HLA class II antigens and activates macrophages.

Interferon-alpha is used to treat hairy cell leukemia, melanoma, Kaposi's sarcoma, renal cell carcinoma, multiple myeloma, non-Hodgkin's lymphoma, and chronic myelogenous leukemia. Neurotoxicity is dose related. At low doses, interferon-alpha has few side effects except for influenza-like symptoms such as headache, myalgias, and lethargy [204]. At higher doses, a significant percentage of patients develop a change in mental state ranging from lethargy and somnolence to frank encephalopathy [205,206]. EEG studies typically reveal diffuse slowing and, rarely, generalized sharp-wave discharges [205,207]. EEG abnormalities may exist in asymptomatic patients. Intraventricular administration of interferon-alpha may produce seizures, hearing loss, hiccups, and a vegetative state that progresses to death [208].

In patients referred for neuropsychologic evaluation, cognitive deficits are consistent with frontal-cortical dysfunction [209]. Depression, psychosis, and suicidal ideation occur in up to 25% of patients and those with a history of preexisting psychiatric disease are at particular risk [209,210]. Pretreatment with paroxetine may be helpful in reducing the incidence of this complication [211]. Discontinuation of treatment usually results in complete recovery, although some patients have persistent deficits [209].

Motor symptoms such as parkinsonism and intention tremor are common with interferon-alpha therapy [204,208,209]. Rarely, spastic diplegia may develop in children receiving interferon-alpha [212,213].

Interferon-beta and -gamma have been used primarily for nonneoplastic diseases such as multiple sclerosis. Neurotoxicity with these agents is less well characterized but resembles that of interferon-alpha.

### *Interleukins*

Interleukins are naturally occurring cytokines that have antineoplastic and immunomodulatory effects. Interleukin-1 (IL-1) is primarily used to minimize hematologic toxicity of chemotherapy agents. Its efficacy is limited by dose limitation due to hypotension. Influenza-like symptoms, headache, and hypotension are the primary side effects [214,215].

Interleukin-2 (Aldesleukin, Proleukin, IL-2) has an antineoplastic effect and is used to treat metastatic melanoma and renal cell carcinoma. Neurotoxicity is dose related. Towards the end of treatment, some patients may experience lethargy, somnolence, agitation, delusions, encephalopathy, or depression [216,217]. Symptoms may be severe in some cases but resolve after discontinuation of treatment. Rarely, patients who receive intraventricular IL-2 develop a chronic subcortical dementia associated with white matter abnormalities on MRI [218]. Patients treated with interleukin-2 may also

develop focal neurologic deficits. Transient monocular vision loss and homonymous quadrantsanopia may develop in the absence of abnormalities on neuroimaging. The etiology of this syndrome is unknown, but may represent activation of endothelial cells [219]. Focal signs may develop in patients with gliomas who receive interleukin-2 directly into the tumor bed. These signs correlate with increased peritumoral edema on neuroimaging [220]. Rarely, patients given systemic interleukin-2 develop hemiparesis, ataxia, seizures, aphasia, or cortical blindness several days after treatment. MRI reveals multiple gray and white lesions. Most patients improve after discontinuation of treatment, but rarely death may occur [221]. Neuropathology reveals foci of perivascular demyelination [222]. One patient treated with a combination of IL-2 and GM-CSF died from a venous infarct with hemorrhage [223].

Interleukin-4 (IL-4) has minimal antineoplastic effect in phase I and II studies. Toxicity includes influenza-like symptoms.

#### *Tumor necrosis factor*

Tumor necrosis factor is a cytokine with antitumor effects in vitro and in vivo. It has been used with hyperthermic limb perfusion to treat soft tissue sarcomas and melanomas of the extremities. Neurotoxicity is mild, and consists of decreased sensation and absent reflexes in the perfused limb. Electrophysiologic evidence of neuropathy is scant [224]. Systemic administration has been associated with influenza-like symptoms, hypotension, lethargy, or headaches [225].

#### **Growth factors**

*Colony-stimulating factors: granulocyte colony-stimulating factor (G-CSF, Filgrastim, neupogen), granulocyte-macrophage colony-stimulating factor (GM-CSF, Sargramostim, Leukine, Prokine S, Molgramostim), pegfilgrastim (neulasto)*

These agents are used to boost levels of granulocytes in patients with nonmyeloid tumors receiving chemotherapy. Acute disorientation, cortical blindness, and symptoms suggestive of posterior leukoencephalopathy has been described in a patient receiving GM-CSF [226] (Fig. 3). A similar presentation in a patient receiving G-CSF has been reported although the specific role of G-CSF is unclear because the patient also received ifosfamide, vincristine, and etoposide prior to treatment [227].

*Erythropoietin (Procrit, Epogen), Darbepoetin Alfa (Aranesp)*

Erythropoietin is used to increase red blood cell mass. Some patients may experience fatigue, dizziness, and paresthesias. Rarely, patients may experience seizures, venous sinus thrombosis associated with polycythemia [228],

or develop posterior leukoencephalopathy associated with hypertension [229] (Fig. 3). Darbepoetin Alfa (Aranesp) has a longer half-life but similar side effects.

#### *Oprelvekin (IL-11, Neumega)*

Oprelvekin, or IL-11, stimulates the production of platelets, and has been licensed for the treatment of chemotherapy-induced thrombocytopenia. Experience with this growth factor is limited. Reported side effects include headache, nausea, and systemic neuropathy [230].

### **Monoclonal antibodies**

#### *Gemtuzamab ozogamicin (Mylotarg)*

Gemtuzamab ozogamicin is composed of an anti-CD33 monoclonal antibody linked to an antibiotic derivative that cleaves DNA. It is used to treat acute myelogenous leukemia. Severe thrombocytopenia is common and may lead to fatal intracranial hemorrhage in up to 4% of patients [231].

#### *Rituximab (IDEC-C2B8, Rituxan)*

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen found on cells of B-cell lineage. It is used to treat low-grade or follicular B-cell lymphomas. Neurotoxicity is uncommon, but may include headache, dizziness, and paresthesias [232]. Reactivation of herpes zoster can occur when rituximab is coadministered with CHOP chemotherapy [233].

#### *Iodine-131 tositumomab*

Iodine-131 tositumomab is a radiolabeled murine monoclonal antibody directed against the CD20 antibody. The targeted delivery of beta particles to B-lymphocytes exploits the extreme radiosensitivity of hematologic malignancies. It is used to treat relapsed or refractory non-Hodkin's lymphoma. Significant neurotoxicity has not been reported, but some patients may experience headache, fatigue, or dizziness [234,235].

#### *Trastuzumab (Herceptin)*

Trastuzumab is a humanized monoclonal antibody directed against human epidermal growth factor receptor-2. It is used alone or in combination with chemotherapy to treat patients with metastatic breast cancer overexpressing human epidermal growth factor receptor-2. Patients may experience headaches, dizziness, or insomnia.

Table 1  
Selected CNS complications of cancer therapy (by symptoms)

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Acute encephalopathy

Asparaginase	Fludarabine	Mitomycin C
BCNU (IA or HD)	5-Fluorouracil	Paclitaxel
Carboplatin	GM-CSF	Pentostatin
Cisplatin	Ifosfamide	Procarbazine (HD)
Cyclophosphamide	Interferons	R115777
Cytosine arabinoside (HD)	Interleukins	Suramin
Denileukin	Levamisole	Thalidomide
Doxorubicin (IT)	Mechloramine	Thiotepa (HD)
Etoposide (HD or IA)	Methotrexate	Vinca alkaloids

Mood/Personality change

Asparaginase		Pyrazolonacridine
Cladribine	Interferons Interleukin-2	Retinoic acids
Corticosteroids	Mechlorethamine	Suramin
Danazole	Pentostatin	Thalidomide
Hexamethylmelamine	Procarbazine	

Headache

Asparaginase	Gemtuzumab (Mylotarg)	Retinoic acids
Cisplatin	Hydroxyurea	Rituximab (Rituxan)
Cladribine	Interferons	SU5416
Corticosteroids	Interleukins	Temozolomide
Cytosine arabinoside	Imatinib (Gleevec)	Thalidomide
Danazol	Mechlorethamine	Tositumomab
Denileukin	Methotrexate (IT)	Trastuzumab (Herceptin)
Etoposide (IA)	Ocreotide	Tumor necrosis factor
Fludarabine	Oprelvekin (Neumega)	ZD1839

Seizures

Asparaginase	Etoposide (IA)	Interleukin-2
Busulphan (HD)	Erythropoietin	Levamisole
BCNU	5-Fluorouracil	Mechloramine
Carboplatin (IA)	Fludarabine	Methotrexate
Chorambucil (HD)	GM-CSF	Mitotane
Cytosine arabinoside (HD or IT)	Hexamethylmelamine	Pentostatin
Dacarbazine	Ifosfamide	Thalidomide
	Interferon (IT)	Vinca alkaloids

Dementia

BCNU (IA and HD)	Fludarabine	Methotrexate
Dacarbazine	Interferon-alpha	Procarbazine
Cytosine arabinoside	Interleukin-2	

Peripheral neuropathy

Carboplatin	Oprelvekin	Suramin
Cisplatin	Oxaliplatin	Tenoposide
Cladribine	Paclitaxel	Thalidomide

Table 1 (continued)

Docetaxel	Procarbazine	TNF
Etoposide	R115777	Vinca alkaloids
Hexamethylmelamine		
Cranial neuropathy		
Cisplatin	Methotrexate	Vincristine
Hearing loss		
Cisplatin	Mitotane	Oxaliplatin
Interferons (IT)	Mechlorethamine	Suramin
Visual disturbance		
BCNU (IA)	Etoposide	Retinoic acids
Carboplatin	5-Fluorouracil	Suramin
Chlorambucil	Fludarabine	Tamoxifen
Cisplatin (IA)	Interleukin-2	Toremifene
Corticosteroids	Paclitaxel	Vincristine
Cyclophosphamide	Pamidronate	ZD1839
Cytosine arabinoside	R115777	Zoledronic acid
Cortical blindness		
Carboplatin	Fludarabine	Methotrexate (HD)
Cisplatin	GM-CSF	Vinca alkaloids
Erythropoietin	Interleukin-2	
Myelopathy		
BCNU (HD)	Doxorubicin (IT)	Methotrexate (IT)
Cisplatin	Goserelin	Mitoxantrone (IT)
Corticosteroids	Interferon-alpha	Thiotepa (IT)
Cytosine arabinoside (IT)	Leuprolide	Vincristine (IT)
Docetaxel (Lhermitte's sign)		
Extrapyramidal syndromes		
5-Fluorouracil	Ifosfamide	Retinoic acids
Hemamethylmelamine	Interferon-alpha	Vincristine
Cerebellar syndrome		
Cytosine arabinoside (HD)	Interleukin-2	R115777
5-Fluorouracil	Mitotane	Thalidomide
Hexamethylmelamine	Procarbazine	Vinca alkaloids
Ifosfamide	Retinoic acid	
Dizziness		
Cladribine	Mitotane	Tositumomab
Cyclophosphamide	Octreotide	Trastuzumab
Hydroxyurea	Rituximab	

(continued on next page)

Table 1 (continued)

Vasculopathy and stroke		
Asparginase	Doxorubicin	Imatinib (Gleevec)
Bleomycin	Erythropoietin	Methotrexate
Carboplatin (IA)	Estramustine	Tamoxifen
Cisplatin	Gemtuzumab	Toremifene
Aseptic meningitis		
Cytosine arabinoside (IT)	Doxorubicin (IT)	Methotrexate (IT)

*Abbreviations:* HD, high-dose; IT, intrathecal; IA, intraarterial.

### Small molecule inhibitors

#### *Imatinib mesylate (STI-571, Gleevec, Glivec)*

Imatinib is a small-molecule inhibitor of bcr-abl tyrosine kinase and receptors for platelet-derived growth factor and c-kit. Imatinib is approved by the Federal Drug Administration for the treatment of gastrointestinal stromal tumors and chronic myelogenous leukemia refractory to interferon therapy. Neurologic side effects are usually mild, and may include headache and fatigue. In a recent phase II study including 532 patients with chronic myelogenous leukemia, one patient each died of ischemic stroke, subarachnoid hemorrhage, and cerebral hemorrhage [236]. A causal link to imatinib has not been established. Rarely, patients develop cerebral edema.

#### *Zarnestra (R115777)*

Zarnestra is an inhibitor of farnesyl protein transferase. This enzyme transfers a 15-carbon farnesyl group to the protein Ras, which is involved in the signal transduction of proliferative signals. Zarnestra has been used as an experimental treatment for refractory and relapsed acute leukemia and advanced solid tumors. In phase I and II studies, patients receiving high-dose zarnestra experienced moderate to severe confusion, ataxia, and neuropathy. Mild to moderate fatigue and visual changes were also noted [237,238].

#### *SU5416*

SU5416 is an inhibitor of the tyrosine kinase vascular endothelial growth factor receptor-2. SU5416 is currently under study in phase I and II clinical trials. Preliminary results suggest that it can cause migraines.

#### *ZD1839 (Iressa)*

ZD1839 is an inhibitor of the tyrosine kinase epidermal growth factor receptor. ZD1839 is currently under study in phase I and II clinical trials. Preliminary results suggest that it can cause headaches and visual loss.

## Other agents

### *Amifostine (WR-2721, Ethyol)*

Amifostine is a cytoprotectant agent used to reduce the toxicity associated with platinum agents. Toxicity associated with amifostine is mild, and may include somnolence and hypotension [3].

### *Bisphosphonates: pamidronate (Aredia) and zoledronic acid (Zometa)*

Pamidronate and zoledronic acid are bisphosphonates used to treat malignancy-associated hypercalcemia and osteolytic bone lesions. Rarely, patients may experience drowsiness, insomnia, or abnormal vision.

### *Denileukin diftoz (Ontak)*

Denileukin diftoz is a recombinant fusion protein of interleukin-2 and diphtheria toxin. It binds to cells expressing interleukin-2 receptor, and causes cell death by inhibiting protein synthesis. Neurotoxicity, including headaches, myalgias, and confusion may occur [239].

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