Published in final edited form as:

Blood Rev. 2015 March ; 29(2): 93–100. doi:10.1016/j.blre.2014.09.012.

The Double-edged Sword: Neurotoxicity of Chemotherapy

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Abstract

The number of available therapies for hematologic malignancies continues to grow at a rapid pace. Unfortunately, many of these treatments carry both central and peripheral nervous system toxicity, potentially limiting a patient's ability to tolerate a full course of treatment. Neurotoxicity with chemotherapy is common and second only to myelosuppression as a reason to limit dosing. This review addresses the neurotoxicity of newly available therapeutic agents including brentuximab vedotin and blinatumomab as well as classic ones such as methotrexate, vinca alkaloids and platinum. Although peripheral neuropathy is common with many drugs, other complications such as seizures and encephalopathy may require more immediate attention. Rapid recognition of adverse neurologic effects may lead to earlier treatment and appropriate adjustment of dosing regimens. In addition, knowledge of common toxicities may help differentiate chemotherapy-related symptoms from actual progression of cancer into the CNS.

Keywords

Chemotherapy; neuropathy; delirium; encephalopathy; seizure; toxicity

1. Introduction

Many therapies for hematologic malignancies cause both peripheral and central nervous system (CNS) toxicity, and treatment-related effects should be high on the differential for otherwise unexplained neurologic symptoms. Although taste receptors and olfactory neurons do reproduce (and are susceptible to damage with chemotherapy [1, 2]), most cells in the nervous system divide slowly or not at all. It is thus surprising that chemotherapy, which is generally directed towards rapidly-dividing cells, can cause such significant neurotoxicity. In addition, the presence of blood-brain, blood-cerebrospinal fluid (CSF) and blood-nerve barriers should theoretically limit the access of chemotherapeutic agents to the nervous system. Recent studies have shown that chemotherapy agents may damage the nervous

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Conflict of Interest: Dr. DeAngelis and Dr. Magge have no conflict of interest.

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system by other pathways, such as by preferentially targeting non-dividing and post-mitotic oligodendrocytes [3, 4]. Although the mechanisms underlying nervous system damage are still unclear, neurotoxicity with chemotherapy is common and second only to myelosuppression as a reason to limit dosing. The most frequently observed complication is peripheral neuropathy, which is typically caused by direct involvement of the peripheral (usually sensory) nerves. CNS toxicity can present in several ways including headache, seizures, vision loss, speech difficulty or encephalopathy. Drugs that do not penetrate the CNS may indirectly cause neurologic complications; examples include stroke with coagulopathy, or cognitive changes in the setting of metabolic disturbances. It is very important to recognize neurologic complications as soon as possible, as the offending agent may need to be discontinued to prevent irreversible damage. Some agents may require pretreatment or inpatient admission for close monitoring and intervention in case of neurologic decompensation. In addition, quick identification of neurologic symptoms may help differentiate medication-related toxicity from metastatic disease, paraneoplastic syndrome, radiation toxicity or infection.

2. Diagnosis

Neurotoxicity from chemotherapy should be considered a diagnosis of exclusion in the setting of new neurologic deficits. If related to therapy, a reasonable temporal relationship between drug administration and symptom onset can typically be established. In the case of chronic neurotoxicity, a detailed history of prior chemotherapy and drug exposure should be solicited. The most common etiologies of neurologic symptoms should always be excluded. Diabetes mellitus and alcohol abuse are frequent causes of peripheral neuropathy, classically associated with sensory loss and paresthesias. There is a wide differential for cognitive changes; an acute onset with a waxing and waning nature supports delirium, potentially from metabolic causes. More chronic and progressive symptoms indicate a primary degenerative process. Seizures can also cause episodic changes in alertness, and electroencephalography (EEG) is helpful for diagnosis in the absence of additional seizure semiology. Extension of cancer into the central nervous system (CNS) should always be considered with new neurologic problems. Contrast-enhanced magnetic resonance imaging (MRI) can identify both parenchymal and leptomeningeal metastases, while positron emission tomography (PET) imaging is useful for distinguishing tumor from inflammation. Lumbar puncture is helpful in identifying leptomeningeal disease as well as CNS infection. Paraneoplastic syndromes may present as a constellation of neurologic symptoms. These occur in less than 1% of patients with solid tumors and are even rarer in hematologic malignancies such as lymphoma [5]. An important exception is the peripheral neuropathy observed with plasma cell myeloma and Waldenström macroglobulinemia, which in both cases is directly related to the associated paraproteinemia. A detailed history and clinical exam are crucial for evaluating any new deficits, and a neurology consultation may be indicated unless the patient's presentation is straightforward. (Table 1)

3. Immunotherapy

3.1 Brentuximab vedotin

Brentuximab vedotin is a CD30-specific antibody-drug conjugate (ADC) that has been shown to have clinical activity in relapsed or refractory Hodgkin lymphoma and anaplastic large cell lymphoma [6]. Binding of the ADC to CD30 on tumor cells initiates internalization of the ADC-CD30 complex with subsequent release of monomethylauristatin E (MMAE) into the lysosomal compartment. Binding of MMAE to tubulin disrupts the microtubule network and induces cell cycle arrest and apoptotic death [7]. Clinical studies indicate that peripheral neuropathy is a frequent complication of treatment (possibly related to the disruption of axonal transport, as seen with vinca alkaloids), and in certain trials this represented the most common reason for discontinuation of the agent [6-10]. In one Phase I study exploring different dosing schedules, there was a significant increase in neuropathy among patients receiving weekly doses compared to those who received the drug every three weeks[8]. A Phase II trial evaluating brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma noted peripheral sensory neuropathy, characterized by numbness and tingling of the fingers and toes, as the most common treatment-related adverse effect (42% of all patients) while peripheral motor neuropathy was less frequent (11%) [10]. The median time to onset of a grade 2 peripheral neuropathy was 27.3 weeks. Complete resolution was seen in 50% of patients while 80% had at least some improvement with a median time to improvement or resolution of 13.2 weeks. Treatment should be held until the neuropathy improves to grade 1, after which it can be restarted at a lower dose. Myalgias are commonly seen with brentuximab vedotin administration, which may be a form of peripheral nerve injury.

A few cases of progressive multifocal leukoencephalopathy (PML) in patients actively receiving treatment have been reported. Activated B and T cells may express CD30 which makes them a target for brentuximab; the resultant immune system deregulation permits reactivation of latent JC virus infection leading to PML [7, 11]. PML can present with subacute onset of cognitive or focal neurologic deficits with associated increased signal on T2-weighted or fluid attenuated inversion recovery (FLAIR) MRI sequences.

3.2 Blinatumomab

Blinatumomab is a novel bispecific T cell receptor-engaging (BiTE) antibody that simultaneously reacts with normal CD3+ T cells and CD19+ acute lymphocytic leukemia cells, allowing lysis of these target tumor cells. Clinical studies have shown significant response rates in minimal residual disease positive B-lineage ALL [12, 13]. These trials have also demonstrated CNS toxicity in 15-20% of patients treated with blinatumomab including seizures, encephalopathy or confusion, and cerebellar symptoms. These events were reversible and resolved with discontinuation of the drug, and may have been related to the rapid release of inflammatory cytokines [12-16]. In a relapsed ALL cohort, six patients with CNS events (3 with seizures and 3 with encephalopathy) restarted treatment at a lower dose after resolution of their CNS symptoms. Although four of the six patients did well after restarting treatment, blinatumomab was permanently discontinued in the two remaining

patients after a recurrent CNS event [16]. Pretreatment with steroids and inpatient admission for close monitoring may help prevent subsequent neurologic toxicity.

3.3 Rituximab

Rituximab is a human monoclonal antibody directed against CD20-positive B cells used for treatment of non-Hodgkin lymphoma and other disorders involving dysfunctional or excess B lymphocytes. Although neurologic side effects are uncommon, headaches, myalgias, and dizziness have been reported [4, 17]. In addition, chronic use of rituximab has been associated rarely with the development of PML [18, 19].

3.4 Chimeric Antigen Receptor (CAR) T Cells

Adoptive transfer of T cells genetically modified to express chimeric antigen receptors (such as against CD19) has become a potent new immunotherapy for B cell malignancies [20, 21]. This treatment is relatively new and being actively evaluated with several clinical trials; the full toxicity profile is still unclear. However, neurotoxicity such as headache, encephalopathy (including obtundation), and ischemia have been reported after CAR T cell administration [22]. Seizures have also been observed. These adverse effects are probably related to immune system activation with significant elevations in inflammatory cytokines, which are produced by the transferred T cells. Although steroids may help acutely with these symptoms, they would also fully reverse the intended immune activation. Toxicity reports from the active clinical trials should help further clarify the safety profile of CAR T cells.

4. Vinca Alkaloids

Vinca alkaloids bind to tubulin and block its polymerization, which prevents microtubule formation and subsequently arrests cells in metaphase. Tubulin binding interferes with axonal transport which leads to neuropathy [23].

4.1 Vincristine

Vincristine is used to treat multiple hematologic malignancies including both leukemias and lymphomas. It primarily affects the peripheral nerves but it can also contribute to dysfunction of the cranial nerves and autonomic nervous system. A dose-limiting axonal sensorimotor neuropathy is almost universal and is characterized by paresthesias and distal weakness (especially with wrist and foot drop) [4, 23]. Diurnal muscle cramps of the arms and legs may be the first sign of neurotoxicity. The neuropathy is generally reversible, but may require months to improve after vincristine discontinuation, and severely affected patients may have incomplete recovery. Unfortunately, symptoms can progress for several weeks after stopping the drug [23].

Vincristine can occasionally cause focal neuropathies of cranial nerves. Symptoms such as ptosis, vision loss, hoarseness, facial weakness and hearing loss should raise concern for a vincristine-induced cranial neuropathy, although the major differential diagnosis is tumor recurrence in the CNS. Many patients also experience an autonomic neuropathy characterized by colicky abdominal pain and constipation, necessitating the institution of an appropriate bowel regimen in every patient receiving vincristine [23]. This is especially

important when patients are also receiving corticosteroids, as there is increased risk of steroid-induced bowel perforation. Although rare, vincristine may cause CNS toxicity from hyponatremia due to SIADH, potentially resulting in confusion and seizures [24, 25]. However, encephalopathy and seizures unrelated to SIADH have also been reported [26-29]. Additional symptoms including cortical blindness, ataxia, parkinsonism and athetosis have been reported, but usually resolve after treatment discontinuation [30-32] (Table 2)

4.2 Vinblastine, Vindesine, Vinorelbine

These vinca alkaloids tend to be used more in the treatment of solid tumors and are less neurotoxic than vincristine; however all have been reported to cause similar side effects, particularly when combined with or following other neurotoxic agents such as taxanes [33-36]. Vinorelbine appears to be the least toxic.

5. Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) is a key treatment for several hematologic malignancies and can cause multiple neurological toxicities. Although allogeneic hematopoietic cell transplants have been generally thought to have higher risk of adverse effects, a large retrospective study of 425 patients demonstrated a similar incidence of neurological problems in autologous and allogeneic HCT recipients [37, 38]. Initial cell harvesting is generally safe but neurotoxicity can occur during all phases of transplantation [37-41]. Most complications during conditioning can be attributed to high-dose chemotherapy, prophylactic drugs against graft versus host disease (GvHD), or total body irradiation. Seizures and encephalopathy are most common immediately after the actual hematopoietic cell infusion [23]; seizures are typically generalized and do not recur, even without antiepileptic drugs. This is probably related to toxicity from dimethyl sulfoxide used as a cryopreservative, and may be associated with diffuse white matter changes on MRI that resolve over days to weeks [42, 43]. Many patients experience delirium without focal neurologic deficits within 30 days of HCT [44, 45]. Risk factors for development of delirium include elevated pre-transplant levels of alkaline phosphatase and blood urea nitrogen, as well as post-transplant use of opiates [46]. Strokes, intracranial hemorrhage, transient global amnesia and posterior reversible encephalopathy syndrome (PRES) have also been reported after transplantation (Fig. 1).

Pancytopenia before bone marrow reconstitution greatly increases the risk of CNS infection, which can present with headache, meningismus, confusion or more focal neurological deficits. However, patients receiving HCT can also experience an engraftment syndrome characterized by fever, rash, and headache which may look like CNS infection. This may be catalyzed by cytokine upregulation by neutrophils with administration of hematopoietic colony-stimulating factors [37, 47]. Patients who require long-term immunosuppression remain at risk for delayed CNS infections, such as fungal disease or *Nocardia asteroides*. Prophylaxis against GvHD with drugs such as cyclosporine and tacrolimus can contribute to neurologic toxicity including PRES, which may be caused by uncontrolled hypertension induced by these agents. In addition, autoimmune type phenomena such as polymyositis, myasthenia, and peripheral neuropathy have been reported with chronic GvHD; these

typically do not require additional intervention other than standard treatment of the GvHD [48, 49]. Post-transplant lymphoproliferative disorder (PTLD) can develop after allogeneic HCT; it can affect the CNS in isolation where it may mimic primary CNS lymphoma or can affect the CNS as part of widespread systemic disease [50]. Treatment usually requires reducing immunosuppressive therapy as well as implementing anti-lymphoma therapy.

6. Small Molecule Inhibitors

6.1 Bortezomib and Carfilzomib

Bortezomib is a proteasome inhibitor effective in multiple myeloma. The most common adverse effect is a dose-dependent, predominantly sensory, painful peripheral neuropathy, which is usually reversible with dose reduction or drug discontinuation [51]. However, full recovery may take many months to years. This is also associated with increased susceptibility to compression neuropathies. Although CNS toxicity is less common, dizziness, aphasia and confusion have been observed. Carfilzomib, a second-generation proteasome inhibitor, usually causes a less severe peripheral neuropathy [52].

7. Angiogenesis Inhibitors

7.1 Thalidomide, Lenalidomide, and Pomalidomide

Thalidomide is an angiogenesis inhibitor, first developed as a sedative, used to treat myeloma and some lymphomas. Not surprisingly, the most common side effect is somnolence [23]. It is also associated with a predominantly sensory peripheral neuropathy characterized by pain and dysesthesias [53]. This appears to be more dependent on duration of use than the dose [54]. Encephalopathy and seizures are rare [55]. Lenalidomide and pomalidomide, both thalidomide analogs, are less neurotoxic but have been shown to contribute to peripheral neuropathy as well [56-59].

8. Platinums

8.1 Cisplatin

Cisplatin, like all the platinums, contains a heavy-metal moiety and often causes peripheral neuropathy. Patients complain of numbness, tingling, and pain in the extremities. These symptoms usually begin in the distal legs but spread proximally with subsequent involvement of the arms [60, 61]. Strength is usually spared. The neuropathy is dose-dependent and typically only follows cumulative cisplatin doses $>400\text{mg/m}^2$ [60, 62]. Initial symptoms usually begin during treatment but they can continue to progress several months after completion of therapy. Maximal nerve injury is not seen until months after drug discontinuation, making dose-adjustment difficult. Although symptoms can improve slowly, some patients are left with permanent sensory deficits, particularly a sensory ataxia because large fiber sensory modalities (e.g. position sense) are preferentially affected. Unfortunately, there are no clear treatments or preventative interventions that are effective [63, 64].

Some patients may experience electrical sensations down their back and limbs during or after treatment, consistent with Lhermitte symptom. This represents a transient

demyelinating lesion in the posterior columns of the spinal cord [65, 66]. Imaging is usually negative and symptoms resolve completely without permanent damage.

Cisplatin can also cause ototoxicity with high-frequency hearing loss and less commonly vestibular dysfunction [67]. Hearing loss usually occurs at doses above 60mg/m², but patients may not notice any change (although high-dose cisplatin can rarely cause acute deafness). Tinnitus often presents before hearing loss. Unfortunately, drug-related hair cell damage is irreversible, but multiple prophylactic and therapeutic treatments such as amifostine, Vitamin E, sodium thiosulfate and intratympanic corticosteroids are being investigated [68-71].

Although more common with intra-arterial infusion, an encephalopathy characterized by seizures and focal neurologic symptoms (including cortical blindness) is seen rarely after intravenous administration of cisplatin [72, 73]. However, encephalopathy due to cerebral herniation (with water intoxication after vigorous hydration) or hyponatremia from SIADH may present in a similar manner.

Vascular toxicity with resultant strokes is occasionally observed when cisplatin is administered in combination with other chemotherapy agents. The exact pathophysiology is unclear, but this can contribute to both acute and late complications [74-76]. Lastly, cisplatin may also cause muscle cramps, loss of taste, myelopathy and a myasthenic syndrome.

8.2 Oxaliplatin

Like cisplatin, oxaliplatin can cause a peripheral sensory neuropathy. This usually follows cumulative dose >540mg/m² and can also present with eye and jaw pain, ptosis, vision loss, voice changes, sensory ataxia, and muscle cramps [77]. These symptoms may persist for several months and necessitate drug discontinuation. Oxaliplatin can also produce an acute neuropathy immediately after infusion consisting of paresthesias, dysesthesias, and jaw tightening; these symptoms usually improve within 24 hours. Calcium and magnesium supplementation were thought to prevent both the acute and chronic neuropathies of oxaliplatin, but a recent randomized controlled trial failed to confirm this initial impression [78]. Lhermitte symptom and ototoxicity are less common with oxaliplatin [79].

8.3 Carboplatin

Peripheral neuropathy has been reported rarely with high-dose carboplatin, but it is generally less neurotoxic than cisplatin or oxaliplatin [80] (Table 3).

9. Antimetabolites

9.1 Methotrexate

Methotrexate is the most widely used antimetabolite and can cause acute, subacute and delayed neurotoxicity. Many patients receiving weekly low-dose methotrexate will experience headaches, dizziness, and transient cognitive difficulties [81]. Although rare, oral methotrexate has been reported to cause acute dysarthria as well as PRES, both of which resolve after stopping treatment [82, 83].

Systemic high-dose IV methotrexate sometimes induces a stroke-like syndrome with transient focal neurologic deficits (such as alternating hemiparesis), aphasia, encephalopathy, and even seizures [84, 85]. This generally develops several days after treatment, typically after the second or third cycle, and is of variable duration. Neuroimaging is often negative but brain MRI can show hyperintense foci on FLAIR and diffusion-weighted (DWI) sequences, which may be reversible [86]. CSF studies tend to be normal although EEG may demonstrate diffuse slowing. Symptoms mostly resolve spontaneously within two to three days, and methotrexate can be given again without recurrence of the syndrome.

Leukoencephalopathy is the major delayed complication of methotrexate, appearing months to years after therapy [23]. This typically follows repeated doses of IV high-dose methotrexate and may present clinically as slowly progressive cognitive dysfunction or personality changes. The syndrome is exacerbated by cranial radiation therapy (RT), especially if the methotrexate is given at the same time or immediately following RT. Brain MRI classically shows diffuse periventricular white matter hyperintensity with possible temporary focal enhancement, as well as subsequent cerebral atrophy and ventricular dilatation (Fig. 2). The clinical course is variable—although some patients may recover slowly or stabilize, the syndrome may also progress resulting in severe weakness, dementia, coma or even death. Unfortunately, no effective treatment has been identified (Table 4).

9.2 Fludarabine

Neurotoxicity is uncommon with fludarabine, but symptoms such as headache, sedation, and paresthesias have been reported with low doses of the drug. A more severe progressive and delayed encephalopathy consisting of cortical blindness, ataxia, seizures, paralysis and even coma can be seen with higher doses (usually >90 mg/m²/day); recovery is variable [87-90]. As fludarabine is highly immunosuppressive, it may increase the risk of PML, especially in older patients and those on higher doses [91-93].

9.3 Cytarabine

Cytarabine can cause both peripheral and central nervous system toxicity [23, 94, 95]. Most concerning is cerebellar dysfunction consisting of nystagmus, dysarthria, ataxia, and possible confusion or lethargy. This typically occurs at a cumulative dose ≥ 36 gm/m²; older age, renal dysfunction, prior neurologic disorders, or elevated alkaline phosphatase all predispose to this toxicity [96-98]. There is usually complete resolution of symptoms within two weeks of discontinuing the drug, but some patients suffer permanent impairment due to loss of Purkinje cells in the cerebellum as a direct consequence of cytarabine toxicity. Neuroimaging is by and large normal but EEG may demonstrate slowing. Anosmia, ocular problems, lateral rectus palsy, bulbar palsy, Horner syndrome, aseptic meningitis, locked-in syndrome, encephalitis and extrapyramidal syndromes have been anecdotally reported with cytarabine administration [4]. Peripheral nervous system toxicity is uncommon, but peripheral neuropathies and brachial plexopathy have been described [99-101].

9.4 Nelarabine

Somnolence and fatigue can present about one week after treatment with nelarabine. Furthermore, about 20% of patients develop motor or sensory peripheral neuropathy. Additional CNS toxicity includes memory loss, headache, seizure, ataxia, tremor, and weakness which may not be reversible. Drug discontinuation may be necessary [102, 103].

10. Antibiotics

10.1 Bleomycin

Bleomycin sulfate inhibits DNA synthesis via production of free radicals. The drug has been shown to cause delayed vascular toxicity, especially in combination with cisplatin, with subsequent cerebral and myocardial infarcts. Low magnesium levels may be a risk factor [104, 105].

11. Alkylating Agents

11.1 Procarbazine

Procarbazine interferes with DNA, RNA and protein biosynthesis and rapidly crosses the blood-brain barrier [4, 23]. Encephalopathy of varying severity (from drowsiness to stupor) can occur rarely. In addition, some patients may develop confusion or psychosis. Procarbazine may cause a reversible peripheral neuropathy characterized by paresthesias and myalgias [106].

12. Intrathecal Chemotherapy

Intrathecal (IT) chemotherapy via lumbar puncture or an Ommaya reservoir is used for both treatment and prophylaxis against leptomeningeal metastases. It is generally contraindicated in patients with hydrocephalus or elevated intracranial pressure (ICP), both of which impair CSF circulation compromising drug distribution and enhancing toxicity. IT methotrexate and cytarabine can cause an aseptic meningitis characterized by headache, neck stiffness, nausea, vomiting and potential fever and encephalopathy [94]. This is very common with liposomal cytarabine (DepoCyt), and dexamethasone should be given prophylactically the day prior and for two to three days after each treatment dose [107]. Transverse myelopathy can also develop after administration of either IT methotrexate or cytarabine. Symptoms include back pain with subsequent weakness, sensory loss and bladder or bowel incontinence [23, 94]. Other complications of these agents include seizures, headaches, and encephalopathy. Use of IT rituximab has been associated with headaches, back pain, weakness, and paresthesias [108, 109] (Table 5).

Acknowledgments

Funding: There was no funding for this manuscript.

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Practice Points

- Many therapeutic agents for hematologic malignancy are associated with both central and peripheral nervous system toxicity.
- Identification of adverse neurologic effects may allow earlier treatment and adjustment of dosing to prevent worsening neurotoxicity.
- Patients receiving newer agents must be monitored closely for neurologic side effects, as their toxicity profiles may not yet be fully understood.

Figure 1.
Example of posterior reversible encephalopathy syndrome (left) with subsequent resolution (right) on MRI.

Figure 2.
Example of chemotherapy-induced leukoencephalopathy on MRI.

Table 1
Recommended Diagnostic Studies for Evaluation of Common Neurologic Symptoms

Signs/Symptoms	Recommended Diagnostic Testing
Sensory loss	Glucose, Hgb A1c, TFTs, vitamin B12, SPEP, UPEP, EMG/NCS
Cognitive deficits	Vitamin B12, LFTs/ammonia, TFTs, creatinine/BUN, EEG (if episodic), CT Head and/or MRI Brain,
Seizures	Glucose, sodium, EEG, CT Head and/or MRI Brain, LP (if suspicion for infection)

TFTs, thyroid function tests; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; EMG/NCS, electromyogram/nerve conduction studies; LFTs, liver function tests; BUN, blood urea nitrogen; EEG, electroencephalogram; CT, computed tomography; MRI, magnetic resonance imaging; LP, lumbar puncture

Table 2
Vincristine Neurotoxicity

Toxic Effect	Subacute (1 Day to 2 Weeks)	Intermediate (1 to 4 Weeks)	Chronic (>3 Weeks)
Peripheral neuropathy	Paresthesias	Paresthesias	Sensory loss, weakness, foot-drop
Myopathy?	Muscle pain, tenderness (especially quadriceps), jaw pain	-	-
Autonomic neuropathy	Ileus with cramping abdominal pain	Constipation, urinary hesitancy, impotence, orthostatic hypotension	-
Cranial neuropathy (uncommon)	-	-	Vision loss, ptosis, facial weakness, hearing loss, hoarseness, dysphagia
“Central” toxicity	-	Seizure, SIADH	-

SIADH, syndrome of inappropriate antidiuretic hormone secretion

Table 3**Platinum Neurotoxicity**

Peripheral sensory neuropathy *
Lhermitte symptom
Hearing loss (high frequency)
Tinnitus
Muscle cramps
Encephalopathy
Visual loss (retinal, optic nerve, cortical)
Seizure
Taste loss
Herniation (hydration-related)
Electrolyte imbalance (Na ⁺ , SIADH, Ca ²⁺ , Mg ²⁺)
Vestibular toxicity
Autonomic neuropathy
Myelopathy
Myasthenic syndrome

* Primarily large fiber with ataxia

SIADH, syndrome of inappropriate antidiuretic hormone secretion

Table 4
Methotrexate Toxicity

Route of Administration	Dose	Toxic Effect
Oral or intravenous	Standard	Headache, dizziness, transient encephalopathy
Intravenous	High	Transient encephalopathy, stroke-like syndrome, leukoencephalopathy (chronic)
Intra-arterial	Standard	Hemorrhagic stroke
Intrathecal	Standard	Aseptic meningitis, seizure, transverse myelopathy, leukoencephalopathy (chronic)

Table 5
Neurotoxicity Caused by Agents Commonly Used in Patients with Hematologic Malignancies

Acute Encephalopathy (Delirium)	Chronic Encephalopathy (Dementia)	Seizures	Cerebellar Dysfunction (Ataxia)	Aseptic Meningitis	Peripheral Neuropathy
5-Azacytidine Asparaginase Blinatumomab Capecitabine Carmustine Chlorambucil Cisplatin Cladribine Corticosteroids Cyclophosphamide Cyclosporin A Dacarbazine Etoposide Fludarabine Gemcitabine Hydroxyurea Ifosfamide Imatinib Methotrexate (HD, IV, IT) Mitomycin C Nelarabine Nitrosoureas (HD) Procarbazine Tacrolimus Thalidomide Thiotepa (HD) Vincristine	Carmustine Cisplatin Corticosteroids Cytarabine Dacarbazine Fludarabine Ifosfamide Methotrexate Rituximab (IT)	Asparaginase Busulfan (HD) Carmustine Chlorambucil Cisplatin Corticosteroids Cyclophosphamide (HD) Cyclosporin A Cytarabine Dacarbazine Dimethyl sulfoxide Erythropoietin Etoposide (HD) Fludarabine (HD) Gemcitabine Hydroxyurea Ifosfamide Methotrexate Nelarabine Teniposide Thalidomide Vincristine	Blinatumomab Cyclosporin A Cytarabine Nelarabine Procarbazine	Cytarabine (IT) Liposomal cytarabine (IT) Methotrexate (IT) Rituximab (IT) IVIg Monoclonal antibodies NSAIDs Trimethoprim-sulfamethoxazole	5-Azacytidine Bortezomib Brentuximab Cabazitaxel Capecitabine Carboplatin Carfilzomib Cisplatin Cladribine Cytarabine Etoposide Fludarabine Gemcitabine Ifosfamide Ipilimumab Ixabepilone Lenalidomide Nab-paclitaxel Nelarabine Oxaliplatin Procarbazine Sorafenib Sunitinib Taxotere Teniposide Thalidomide Vinka alkaloids

HD, high-dose; IT, intrathecal; IV, intravenous; IVIg, intravenous γ -globulin; NSAIDs, nonsteroidal anti-inflammatory drugs