As neurologic complications of cancer are not uncommon, it is important for the oncologist to be aware of both the common and uncommon neurologic complications of chemotherapy. The clinical aspects of these interactions have been described in detail. A working knowledge of these interactions is helpful in identifying the cause of a patient's symptoms, and help in management, particularly where specific therapies are available. Some are dose-related, while others may arise in the presence of specific risk factors. Last, some are idiosyncratic. Preventative therapies are being investigated and show some promise. Given the impact of neurologic dysfunction on quality of life, this will remain an important topic, particularly in those with good prognosis.

**Peripheral nervous system (PNS) involvement**

The most common effect of chemotherapy on the PNS is a sensory neuropathy. Neuropathies are often classified by the major nerve fibres types affected, eg larger myelinated fibres versus the smaller unmyelinated fibres. Neurophysiologically, they are separated into neuropathies that have significant slowing of motor and/or sensory nerves, often associated with conduction block (demyelinating) and the axonal neuropathies in which the nerve fibre itself is damaged. The demyelinating neuropathies often disproportionately affect proprioception mediated by the large fibres, while the axonal neuropathies tend to affect pain and temperature pathways. Lhermitte's syndrome is sometimes seen, suggesting central involvement. Importantly, patients with pre-existing neuropathies are at increased risk of severe neurotoxicity with any of the compounds listed below. Therefore patients with known familial (Charcot Marie Tooth) or acquired (diabetic, inflammatory neuropathies) neuropathies should in general not be treated with drugs toxic to the PNS.

Vincristine typically causes an axonal neuropathy with loss of small fibre function predominantly, a dying back neuropathy associated with inhibition of microtubule formation. Common as well are muscle pain, often with jaw pain. Autonomic dysfunction can cause constipation, and even postural hypotension. Foot drop occurs in more severe cases. Bulbar dysfunction has been reported in children at high doses. The taxanes also paradoxically stabilise and promote microtubule assembly, and can cause a significant neuropathy that is typically sensory but may in cases involve motor nerves as well. The pattern is predominantly axonal.

Cisplatin causes a demyelinating neuropathy, that may progress even after the cisplatin has been ceased. It is therefore worthwhile to monitor its progress in any patient, looking for a sensory ataxic gait and a positive Romberg's. Oxaliplatin is a new platinum compound that uniquely has activity in colorectal carcinoma, but also has novel neurologic side effects that have been recently reviewed. It has both early and chronic effects, summarised in table one. The pharyngolaryngeal dysaesthesias with feeling of respiratory obstruction or swallowing difficulty, may be disconcerting for the patient but are not dangerous. They may be reduced by slowing the rate of infusion. The features of the acute neuropathy are also summarised in table one. The acute neuropathy is common, but over time merges with the chronic symptoms.

There is good evidence that the chronic neuropathy is related to total dose administered. Dosing up to ~800 mg/m² is associated with 16% grade 3 toxicity, while at doses > 1100 mg/m², 50% of patients will be affected. Usually, tumour response is seen before these levels are reached, and oxaliplatin toxicity generally slowly resolves over 13 weeks, although can be permanent in some patients. At high doses, Lhermitte's phenomenon and urinary retention can be seen.

The acute neurotoxicity seen with oxaliplatin is characterised by electrophysiologic evidence motor nerve hyperexcitability, and the findings are similar to the clinical manifestations of cancer.

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**Table 1: Clinical characteristics of platinum peripheral neuropathy**

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin</th>
<th>Acute</th>
<th>Oxaliplatin</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>45%</td>
<td>85-95%</td>
<td>grade 3/4 in 16%</td>
<td></td>
</tr>
<tr>
<td><strong>DLT</strong></td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>paraesthesia, dysoesthesia, sensory ataxia</td>
<td>paraesthesia, dysoesthesia, sensory ataxia</td>
<td>paraesthesia, dysoesthesia</td>
<td></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>extremities</td>
<td>extremities, oral</td>
<td>extremities</td>
<td></td>
</tr>
<tr>
<td><strong>Trigger</strong></td>
<td>none</td>
<td>cold exposure</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td><strong>Motor symptoms</strong></td>
<td>none</td>
<td>rare muscle spasms</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>delayed</td>
<td>acute</td>
<td>delayed</td>
<td></td>
</tr>
<tr>
<td><strong>Recovery</strong></td>
<td>slow, incomplete</td>
<td>rapid, complete</td>
<td>less slow, more complete</td>
<td></td>
</tr>
<tr>
<td><strong>Schedule dependence</strong></td>
<td>none</td>
<td>yes probably</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>ototoxicity</td>
<td>pharyngolaryngeal dysoesthesia</td>
<td>none</td>
<td></td>
</tr>
</tbody>
</table>

DLT: Dose limiting toxicity

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**For reference:**

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*Note: Insert any additional references and details as necessary.*
neuromyotonia, and has been likened to a channelopathy, i.e. a disturbance of ion channels crucial to nerve function but not associated with morphologic damage.

This has led to a number of approaches in small series using anticonvulsants (carbamazepine, gabapentin), calcium and magnesium supplements, glutathione and amifostine. All of these appear to have some efficacy but need to be tested more extensively. This may be even more important as oxaliplatin is moved into the adjuvant setting. It may be possible that similar approaches could be used for the other drugs as well.

Central effects of systemic chemotherapy

Chemotherapy may affect the central nervous system in a number of ways, such as acute encephalopathy, that is often reversible, or a chronic CNS toxicity that may be additive with radiotherapy, such as with methotrexate or intra-arterial chemotherapy. Focal disorders include cerebellar syndromes, such as with high dose cytarabine. Levamisole when combined with 5-FU may cause a multifocal leukoencephalopathy, with enhancing subcortical white matter lesions that can be mistaken for cerebral metastases. Transverse myelopathy may occur with intrathecal therapy, or as mentioned above, Lhermitte's phenomenon may be seen with oxaliplatin. Of interest recently neuropsychologic deficits have been reported in patients in association with standard chemotherapy. This is controversial but needs more precise data. It is important to exclude other causes of these syndromes, such as metastases, leptomeningeal malignancy, or metabolic disturbance.

Acute encephalopathy

The encephalopathy may be characterised by delirium, myoclonus or seizures.

Cisplatinum has been associated with an acute encephalopathy that may include seizures and focal signs such as cortical blindness, with characteristic MRI appearances of white matter T2 hyperintensities, that may include a posterior leukoencephalopathy. Three patients were recently described, including one patient who died and was found at post-mortem to have an ischaemic L temporal lesion, consistent with the hypothesis that endothelial cell damage may be a pathophysiologic event. Cisplatinum encephalopathy is commonly associated with hypomagnesaemia, which also should be treated, and seizure control is important.

Of the mustard alkylating agents ifosfamide is the most neurotoxic. It is usually reversible and associated with delirium and seizures and may occur four to six days after therapy. It usually resolves but persistent symptoms have been reported. Risk factors include renal or hepatic dysfunction, low albumin and pleural or peritoneal effusions. Methylene blue has been reported to be effective in reversing the encephalopathy perhaps by compensating for the mitochondrial toxicity of ifosfamide metabolites.

We have seen a small number of patients with encephalopathy in association with cyclophosphamide who have partially responded to methylene blue. This has been in the context of relatively intense cyclophosphamide dosing. Thus it may be worthwhile considering this drug in other chemotherapy-related acute encephalopathies.

Methotrexate can cause an acute encephalopathy (<48 hours), a subacute encephalopathy in the week following administration and a chronic leukoencephalopathy, most commonly associated with whole brain radiotherapy. Usually, the last syndrome is not common if the methotrexate is given prior to cranial radiotherapy.

Neurocognitive effects of adjuvant chemotherapy

The long-term neurocognitive effects of whole brain radiotherapy have been reasonably studied, although more needs to be understood. With the increasing use of adjuvant therapy for breast cancer in particular, in a wider group of patients for relatively small gains in cure and survival rates, a more careful assessment of subtle effects of therapies needs to be performed. The field has been well reviewed recently.

These studies are not easy to perform. Detailed neuropsychologic assessment is complex and time-consuming and therefore difficult to perform repeatedly. Other factors may intrude such as anxiety, fatigue, disease progression and hormonal changes. In brief, it can be said that neuropsychologic deficits have been found in patients given adjuvant chemotherapy that are not seen in breast or lymphoma patients treated with local therapy, or compared to healthy controls. There is not a close correlation between cognitive changes measured and recognised quality of life measurements.

As a result, longitudinal studies are now being performed. Screening tools sensitive to change such as Cogstate (www.cogstate.com) are being used in studies in Australia. It is important to stress that these effects do not equate with “brain damage” (Darby, personal communication).

References