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Neurotoxicity, a common side effect of cytotoxic therapy – how to protect the patient

Administration of cytotoxic drugs can cause central or peripheral nerve damage. Central neurotoxicity after ifosfamide is treatable with 1% methylene blue. The more common peripheral neuropathy is almost impossible to prevent. 10% glutamic acid solution has been tested in Prague.

Neurotoxicity is the second most frequent side effect of cancer therapy after haematological toxicity. Administration of cytotoxic drugs can cause central neurotoxicity or peripheral neuropathy.

Central toxicity

The most common diagnosis of central toxicity is ifosfamide-induced encephalopathy, which can occur in 5–30% of patients. Typical symptoms are disorientation, hallucination, catatonia and seizures, gradually worsening to coma and death. Risk factors include advanced age, hepatic and renal dysfunction, oral ifosfamide and concomitant use of other central nervous system (CNS) depressants [1]. However in our experience, patients with very active metabolism (especially young athletes) are under most threat.

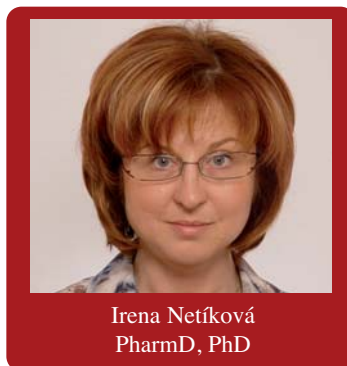
Ifosfamide undergoes secondary metabolism to the dechloroethylated metabolites and chloroacetaldehyde. Chloroacetaldehyde is the metabolite responsible for nephrotoxicity and neurotoxicity by direct nerve damage, depletion of CNS glutathione level and inhibition of mitochondrial oxidative phosphorylation resulting in impaired fatty acid metabolism.

A simple, well-established solution is administration of methylene blue. Methylene blue restores and maintains mitochondrial respiration and therefore can be used to correct or prevent acute neurotoxic effects. IV administration of methylene blue is useful in the treatment of grade 3 or 4 neurotoxicity. Prophylactically methylene blue can prevent encephalopathy in high-risk conditions. However prophylactic or concurrent administration of methylene blue with ifosfamide requires further clinical evaluation [2, 3].

Because many patients in our hospital are at high risk and it is difficult to prepare methylene blue for IV administration, patients have been treated prophylactically with oral methylene blue and concurrently with ifosfamide for the last eight years.

R

Methylenii Caeruleum	0.2
Aquae destillata	ad 20.0
Misce fiat solution	
Dose 5 mL 3–4 times daily	
Stability one month, protect against light	



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PharmD, PhD

For an acute situation slow IV administration is recommended of sterile 50 mg methylene blue in a 10% aqueous solution. After eight years' experience at the General Teaching Hospital Prague we have never had to use it.

Peripheral toxicity

In contrast to ifosfamide-related encephalopathy, chemotherapy-induced peripheral neuropathy (CIPN) cannot be treated easily. Protective strategies are not effective enough and neuropathic symptoms can occur not only as a consequence of antineoplastic and other drugs, but as the result of cancer itself, or other diseases, e.g. diabetes.

Peripheral neuropathy symptoms are different according to the nerves affected. Sensory nerve damage causes pain, numbness and tingling, burning, prickling, pinching or a loss of feeling. Motor nerve damage manifests as weakness or paralysis of the muscles that control those nerves. Dizziness, constipation, difficulty urinating, impotence, vision changes and hearing loss are typical of autonomic neuropathy. Symptoms begin gradually. Prospective studies demonstrate that maximum symptoms and deficit may occur up to a month after discontinuation of treatment [4].

Symptoms reach a plateau at, or soon after, the end of treatment and improve after treatment is discontinued. There is often glove-and-stocking distribution of sensory loss and nerve hyperexcitability. Patients feel their skin is so sensitive that the slightest touch is agonising. They complain of heaviness or weakness in the arms and legs and an unsteady gait and can have difficulty feeling the floor beneath them. Neurotoxicity may develop as a consequence of treatment with platinum analogues (cisplatin, oxaliplatin, carboplatin), taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine, vinorelbine) and more recently thalidomide and bortezomib.

It is paradoxical that non-dividing neurons are susceptible to cytotoxicity. Long peripheral nerve axons are susceptible to agents that interfere with energy metabolism and axonal transport. Cytostatics can affect neuronal cell bodies in the dorsal root ganglion via transport deficits or energy failure and axonal membrane ion channel dysfunction. Patients treated with oxaliplatin have revealed alterations in axonal Na(+) channels. Binding of platinum to mitochondrial DNA is a potential mechanism underlying delayed neuronal death [5].

Peripheral neurotoxicity is a dose-limiting side effect related to cumulative dose and infusion duration. Individual risk factors may also affect the development and severity of neurotoxicity. As more effective multiple drug combinations are used, patients are treated with several neurotoxic drugs. Synergic neurotoxicity has not been extensively investigated yet. Underlying inherited or inflammatory neuropathies as well as focal radiotherapy or intrathecal administration may predispose patients to developing severe symptoms.

CIPN related to platinum compounds causes complaints of paresthesias in the distal extremities. All sensory modalities are involved, but loss of large fibre sensory function is often prominent. This may progress to severe sensory ataxia. The limiting dose for cisplatin is $\geq 400\text{--}500\text{ mg/m}^2$, typically 3–6 months into treatment 60–80% of patients develop a stereotypical cold-induced acute toxicity that involves reversible paresthesias in the throat, mouth, face, and hands occurring within 30–60 minutes of oxaliplatin administration. Other alkylating agents such as cyclophosphamide, procarbazine and thiotepa can cause mild peripheral neuropathy. Paresthesias, pain in the feet and general sensory loss have occurred; recovery is slow and incomplete over years after drug withdrawal.

Mitotic spindle inhibitors vinca alkaloids, taxanes and podophyllin analogues (etoposide and teniposide) interfere with microtubule assembly and mitotic spindle formation. The disruption of microtubule function in axons also inhibits axonal transport. Sensory, motor and autonomic fibres are all affected. Because the cell body is usually spared, function can recover well, especially in children and young adults [6].

Treatment of CIPN pain

Pain relievers such as aspirin and ibuprofen can be used only for mild symptoms and are not very effective. More severe symptoms are treated with COX II inhibitors, e.g. nimesulid or preferably opioids (tramadol, oxycodone, morphine). Mild to moderate symptoms can also be treated by antidepressants (amitriptyline, nortriptyline, imipramine, citalopram, venlafaxine, paroxetine and bupropion). Antiepileptic drugs (carbamazepine, gabapentin, pregabalin, lamotrigine) are helpful for jabbing, shooting pain. Other drugs, like for example mexiletine, a drug normally used to treat irregular heart rhythms, may help to relieve burning pain.

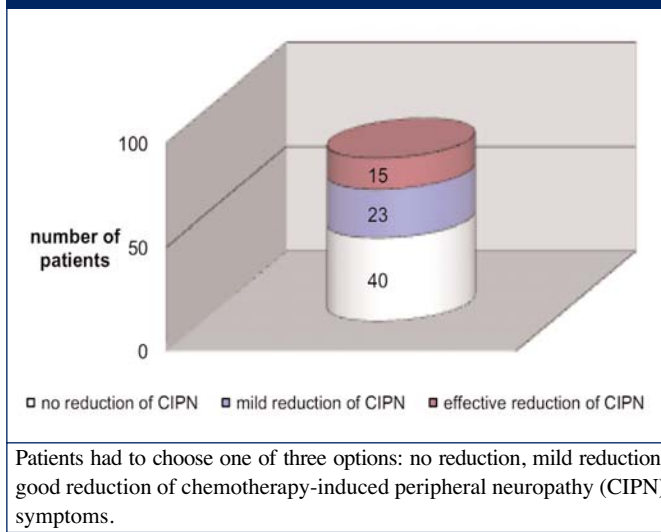
Prophylactic strategies

Many clinical trials have attempted prophylactic treatment of CIPN with, e.g. amifostine, vitamin E and glutathione [7]. Unfortunately, a recent Cochrane review [8] concluded that there was insufficient evidence to recommend the use of any preventative treatment for platinum toxicity.

The experimental agents acetyl-L-carnitine (ALC), glutamate and glutamine have been studied intensively. ALC plays an essential role in intermediary metabolism. Its neuroprotective and neurotrophic actions, antioxidant activity, positive actions

on mitochondrial metabolism, and stabilisation of intracellular membranes are still being investigated [9, 10]. Glutamate in animal studies significantly protected against both sensory and motor neuropathy. No intrinsic neurotoxicity and no interference with the cytotoxic efficacy of vincristine were observed [11, 12]. Glutamine has been tested as a neuroprotective agent in high-dose paclitaxel-induced peripheral neuropathy [13]. Using oral glutamine concomitant to chemotherapy significantly reduces the incidence and severity of peripheral neuropathy of patients receiving oxaliplatin without affecting response and survival [14, 15] (see Figure 1).

Figure 1: Efficacy of 10% glutamic acid solution



Ten percent glutamic acid solution is made in the General Teaching Hospital Prague and is being tested for CIPN symptoms after treatment with taxanes and oxaliplatin.

R
 Acidum glutamicum 15.0
 Sirupus plantaginis 45.0
 Aqua purificata ad 150.0
 Dose 10 mL three times daily

Conclusion

Neurotoxicity after cytostatics is a serious side effect, very often dose limiting and in advanced cases possibly demanding a change of chemotherapy. We can prevent central neurotoxicity after ifosfamide administration relatively well, but we are not able to prevent or to treat peripheral neuropathic symptoms. It is very important to continue clinical trials and research projects to improve supportive care in oncology therapy.

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