Short Report

Severe neuropathy after high dose carboplatin in three patients receiving multidrug chemotherapy

Olivier Heinzlef, Jean-Pierre Lotz, Etienne Roullet

Abstract
Three patients are described who developed a severe neuropathy after chemotherapy with high dose cis-diamine-(1,1-cyclobutanedicarboxylato) platinum (carboplatin). This toxic side effect, which is unusual at conventional doses, might become more frequent as increasing doses are administered to overcome drug resistance in cancer treatment, and might limit its use at very high doses before haematopoietic stem cell transplantation.

Keywords: carboplatin; adverse effect; severe neuropathy

Cis-diamine-dichloro-platinum (cisplatin) is effective in treatment of testicular and ovarian carcinomas. As dose related drug resistance is the main cause of treatment failure in these patients, new high dose regimens including platinum derivatives have been developed.

The activity of cis-diamine-(1,1-cyclobutanedicarboxylato) platinum (carboplatin) is similar to that of cisplatin, but its neurotoxicity, nephrotoxicity, and ototoxicity is lower. Carboplatin is successfully used in triple drug regimens combining very high doses of etoposide (VP-16), ifosfamide (IFM), and carboplatin supported by autologous bone marrow transplantation in the treatment of testicular and ovarian tumours unresponsive to conventional regimens containing cisplatin.1 We describe three cases of severe neuropathy occurring in patients receiving high dose carboplatin.

Illustrative case report
A 28 year old hairdresser had been well until February 1994 when a left testicular mass was discovered. Pathological examination showed a non-seminomatous germ cell tumour (stage II C). After orchidectomy, he received four cycles of bleomycin (20 mg/m²), VP-16 (300 mg/m²), and cisplatin (100 mg/m²). He then received a regimen combining cisplatin (100 mg/m²), IFM (6 g/m²), and vinblastin (0.2 mg/kg) for three cycles. After the second cycle (July 1994), he complained of paraesthesiae in the palms and soles together with Lhermitte’s sign (cumulative dose of cisplatin 600 mg/m²). Electrophysiological tests showed mild abnormalities in sensory nerves: conduction velocities were 32.5 m/s in the sural nerve (n>45 m/s) and 37 m/s in the cubital nerve (n>45 m/s). Action potential amplitudes were 8 µV (n>10 µV) in the sural nerve and 5.6 µV in the cubital nerve (n>10 µV). He subsequently received two cycles of VP-16 (500 mg/m²) and IFM (6 g/m²). Lhermitte’s sign disappeared but paraesthesiae persisted and human chorionic gonadotrophin concentration remained high. In October 1994 he was offered tandem high dose chemotherapy consisting of VP-16 (1375 mg/m²), IFM (10 g/m²) and carboplatin (1250 mg/m²) for the first course, and VP-16 (1500 mg/m²), IFM (12 g/m²), and carboplatin (1500 mg/m²) for the second. Each course was followed by autologous bone marrow transplantation.

A few days after the first intensification course the patient complained of burning and aching sensations in the feet, and of lightning pain in the four limbs. He had hand clumsiness, could not stand or walk, and was confined to a chair. On neurological examination, stance and gait were ataxic and Romberg’s sign was positive. He had distal motor deficit and atrophy in the arms and legs. Vibration and joint position sense were absent in the four limbs. There was tactile anaesthesia of the hands and feet and hypoesthesia of the legs and forearms. Temperature and pinprick sensations were normal. Deep tendon reflexes were absent, and bilateral hypoacusia was noted.

Electrophysiological tests showed a severe neuropathy (table 2). A few days before the second intensification course, he could walk unaided but still complained of painful paraesthesiae and weakness of hand muscles. During the first two weeks after the second intensification course (December 1994) paraesthesiae and difficulties in moving the fingers increased. His stance and gait worsened but he could walk unaided. He noticed an increase in Lhermitte’s sign and hypoacusia.

From February to December 1995 he gradually improved. Somatosensory evoked potentials (May 1995) showed associated slight impairment of central conduction. In January 1996, Lhermitte’s sign, paraesthesiae, and pain had disappeared and analgesics were not
necessary. He could stand and walk normally. Vibration sense and pinprick sensitivity were still diminished in the hands and feet, and deep tendon reflexes were absent; the rest of the neurological examination was normal. He still complained of distal tactile anaesthesia, but he resumed work as a hairdresser.

**Summary of cases (table 1)**

Three patients developed a severe sensorimotor neuropathy after very high dose chemotherapy combining carboplatin, IFM, and VP-16 or VM-26. Patients 2 and 3 had a normal neurological examination before this chemotherapy. The neuropathy occurred a few days after the outset of treatment and the maximum deficit was reached in one to two weeks. In patient 1 a discrete improvement was noticed just before the second course. All three patients had a severe sensory ataxia of the limbs and complete deep tendon areflexia. One patient was impotent. Motor deficit and amyotrophy were mild and limited to the hands and feet. Improvement began one to two months after the last course and progressed during the subsequent months in all three cases. Table 2 presents the results of electrophysiological studies.

**Discussion**

We found a severe sensorimotor neuropathy which occurred immediately after multidrug chemotherapy including very high dose carboplatin in three patients (cumulative dose 1000 to 2750 mg/m²). The time course, with immediate occurrence after chemotherapy, and predominant sensory involvement leading to severe ataxia in a few days were distinctive features. Paraneoplastic neuropathy is a very unlikely diagnosis; By contrast, drug related

---

**Table 1** Clinical characteristics of three patients with carboplatin neuropathy

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/sex</td>
<td>28/Male</td>
<td>29/Male</td>
<td>61/Female</td>
</tr>
<tr>
<td>Type of cancer</td>
<td>Non-seminomatous germ cell testicular tumour</td>
<td>Complex non-seminomatous and seminomatous testicular tumour (stage III)</td>
<td>Endometrioid adenocarcinoma with ovarian localisation (stage III C)</td>
</tr>
<tr>
<td>Previous neurotoxic chemotherapy</td>
<td>Cisplatin (CD: 700 mg/m²) Vinblastin (CD: 0.6 mg/m²)</td>
<td>Cisplatin (CD: 450 mg/m²) Vinblastin (CD: 0.6 mg/m²)</td>
<td>Cisplatin (CD: 800 mg/m²)</td>
</tr>
<tr>
<td>Neuropathy before carboplatin</td>
<td>Slight paraesthesia of palms and soles. Transitory Lhermitte’s sign.</td>
<td>Numbeess in the feet and the hands during 1 week</td>
<td>Slight paraesthesiae (tingling and numbness) in the hands and feet which remained stable</td>
</tr>
<tr>
<td>High dose chemotherapy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin, CD</td>
<td>2750 mg/m²</td>
<td>2750 mg/m²</td>
<td>1000 mg/m²</td>
</tr>
<tr>
<td>Ifosfamide, CD</td>
<td>22 g/m² in 2 courses</td>
<td>22 g/m² in 2 courses</td>
<td>7.5 g/m²</td>
</tr>
<tr>
<td>VP-16 or VM 26, CD</td>
<td>3 g/m² in 2 courses</td>
<td>3 g/m² in 2 courses</td>
<td>750 mg/m²</td>
</tr>
<tr>
<td>Symptoms:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful distal paraesthesiae</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Restless legs syndrome</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Lhermitte’s sign</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Bilateral hypeacusia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Confined to wheelchair</td>
<td>+</td>
<td>+</td>
<td>Could walk with two crutches</td>
</tr>
<tr>
<td>Impotence</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

**Table 2** Results of nerve conduction studies in three patients with carboplatin neuropathy latency

<table>
<thead>
<tr>
<th></th>
<th>Median nerve</th>
<th>Prominal nerve</th>
<th>Sural nerve</th>
<th>Median nerve (sensory)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DL ms</td>
<td>Amplitude µV</td>
<td>NCV m/s</td>
<td>F latency ms</td>
</tr>
<tr>
<td>Normal values</td>
<td>&lt;3.6</td>
<td>&gt;5</td>
<td>&gt;48</td>
<td>&lt;32</td>
</tr>
<tr>
<td>Pt 1 (R)</td>
<td>3.6</td>
<td>10</td>
<td>56</td>
<td>29.2</td>
</tr>
<tr>
<td>Pt 2 (R)</td>
<td>4.1</td>
<td>7.6</td>
<td>54</td>
<td>29</td>
</tr>
<tr>
<td>Pt 3 (L)</td>
<td>4.3</td>
<td>3.3</td>
<td>45.4</td>
<td>ND</td>
</tr>
</tbody>
</table>

*No abnormal temporal dispersion.

Needle EMG showed no spontaneous activities. During maximal voluntary contraction, there was reduced recruitment and the rate of firing was increased in tibialis anterior (patients 1 and 2) and in gastrocnemius (patient 3).

ND = not done; R = right; L = left; NCV = nerve conduction velocity; DL = distal latency.
Severe neuropathy after high dose carboplatin in multidrug chemotherapy

Peripheral neuropathies caused by VP-16 and VM-26 are usually confined to paraesthesiae and leg areflexia. We could only find one report of ifosfamide peripheral neurotoxicity.¹

In that report, four patients with cisplatin neuropathy had short lived (few hours to few days) exacerbations of painful paraesthesiae after high dose IFM (14 g/m²), but none had the severe long lasting disability with ataxia and severe sensory loss found in our three patients.

Our patients received cisplatin before carboplatin and all developed a mild sensory neuropathy while taking cisplatin (one had Lhermitte’s sign). This neuropathy appeared at a cumulative dose of 400 to 600 mg/m², remained stable in two patients, and fluctuated in the third. Delayed cisplatin neurotoxicity has been reported but seems improbable in our cases. Siegal and Haim described 14 patients who had late onset cisplatin neuropathy (2.5 to 5.5 months after withdrawal of cisplatin).² In addition, Mollman et al described three patients whose symptoms began three to eight weeks after the last dose of cisplatin and progressed over one or two months to moderate or pronounced disability before improving.³

However, none of the patients in these two studies had a rapid worsening over a few days or weeks, or a severe disabling neuropathy after cisplatin withdrawal such as that found in our patients. We therefore think that cisplatin alone cannot account for the severe neuropathy, but may have acted as a predisposing factor.

Clinical peripheral neuropathy is a rare complication of treatment with carboplatin. Three comparative studies confirmed that carboplatin at conventional doses is less neurotoxic than cisplatin⁴; neurotoxicity occurred in only 6% of patients receiving carboplatin alone and was clinically mild.⁵ To our knowledge there are no detailed reports of severe peripheral neuropathy in patients given carboplatin. In one study involving very high dose therapy with carboplatin (2 g/m²), cyclophosphamide (6 g/m²), and etoposide (625 mg/m²) followed by autologous bone marrow transplantation for metastatic breast cancer, one patient (out of 28) had a “severe peripheral neuropathy”, but no clinical details were provided.⁶

The occurrence of severe neuropathy with very high dose carboplatin is in keeping with the dose related neurotoxicity of platinum compounds. In one study, five of 13 patients receiving “ultra high dose” cisplatin (30 to 40 mg/m²/day for five days) developed a severe ataxic neuropathy (requiring the use of a cane or wheelchair in four) nine to 12 weeks after the outset of chemotherapy.⁷ ⁸ The mode of onset was different from that in our patients but, interestingly, they had a very similar severe ataxia.

In conclusion, although our patients had a mild neuropathy before carboplatin treatment, we think that the severe neuropathy we found was mainly caused by carboplatin, for the following reasons: (1) the onset of the neuropathy closely followed the administration of carboplatin;(2) in clinical terms, the large sensory fibres were predominantly affected, as with platinum compounds, and the neuropathy resembled that found with very high dose cisplatin; (3) the other drugs in the high dose regimen cannot alone explain this neuropathy. However, a synergistic effect of VP-16 and IFM and a cumulative effect with cisplatin are conceivable.

Although carboplatin is less neurotoxic than cisplatin at conventional doses, its use at a very high dose in multidrug chemotherapy in patients previously treated by cisplatin for advanced carcinomas should be carefully clinically monitored. The rapid occurrence or worsening of symptoms and signs of neuropathy should lead to the consideration of withdrawal of carboplatin from treatment, to avoid a long lasting disabling neuropathy.

Severe neuropathy after high dose carboplatin in three patients receiving multidrug chemotherapy
Olivier Heinzlef, Jean-Pierre Lotz and Etienne Roullet

*J Neurol Neurosurg Psychiatry* 1998 64: 667-669
doi: 10.1136/jnnp.64.5.667

Updated information and services can be found at:
http://jnnp.bmj.com/content/64/5/667

These include:

**References**
This article cites 9 articles, 3 of which you can access for free at:
http://jnnp.bmj.com/content/64/5/667#ref-list-1

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/