SHORT REPORT

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

Olivier Heinzlef, Jean-Pierre Lotz, Etienne Rouillet

Abstract

Three patients are described who developed a severe neuropathy after chemotherapy with high dose *cis*-diamine-(1,1-cyclobutane dicarboxylato) 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.

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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 amyotrophy 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 hypoaesthesia 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

Department of Neurology
O Heinzlef
E Rouillet

Department of Oncology, Hôpital Tenon, Paris, France
J-P Lotz

Correspondence to:
Dr Olivier Heinzlef, Service de Neurologie, Hôpital Tenon, 4 rue de la Chine, 75970 Paris, Cedex 20, France. Telephone 0033 1 40 30 66 21; fax 0033 1 40 30 26 44; email olivier.heinzlef@tnn.ap-hop-paris.fr

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Table 1 Clinical characteristics of three patients with carboplatin neuropathy

	Patient 1	Patient 2	Patient 3
Age/sex	28/Male	29/Male	61/Female
Type of cancer	Non-seminomatous germ cell testicular tumour	Complex non-seminomatous and seminomatous testicular tumour (stage III)	Endometrioid adenocarcinoma with ovarian localisation (stage III C)
Previous neurotoxic chemotherapy	Cisplatin (CD: 700 mg/m ²) Vinblastin (CD: 0.6 mg/m ²)	Cisplatin (CD: 450 mg/m ²) Vinblastin (CD: 0.6 mg/m ²)	Cisplatin (CD: 800 mg/m ²)
Neuropathy before carboplatin	Slight paraesthesiae of palms and soles. Transitory Lhermitte's sign.	Numbness in the feet and the hands during 1 week	Slight paraesthesiae (tingling and numbness) in the hands and feet which remained stable
High dose chemotherapy:			
Carboplatin, CD	2750 mg/m ²	2750 mg/m ²	1000 mg/m ²
Ifosfamide, CD	22 g/m ² in 2 courses	22 g/m ² in 2 courses	7.5 g/m ²
VP-16 or VM 26, CD	3 g/m ² in 2 courses	3 g/m ² in 2 courses	750 mg/m ²
Symptoms:			
Painful distal paraesthesiae	+	+	+
Restless legs syndrome	—	+	—
Lhermitte's sign	+	+	—
Bilateral hypoaesthesia	+	+	+
Confined to wheelchair	+	+	Could walk with two crutches
Impotence	—	+	—
Signs:			
Ataxic gait	+	+	+
Distal motor deficit and amyotrophy	+	—	+
Vibration and joint position sensitivity	Abolished	Abolished	Abolished
Astereognosia	+	+	+
Light touch sensitivity	Distally abolished	Distally abolished	Distally abolished
Pinprick sensitivity	Slight distal impairment	Normal	Slight distal impairment
Thermal sensitivity	Normal	Normal	Normal
Deep tendon reflexes	Abolished	Abolished	Abolished
Time course:			
Outset <7 days after 1st course	+	+	+
Slight improvement after 1st course	+	+	—
Improvement over the next months	++	++†	++‡

*Last visit one year after onset: still improving.

†Last visit eight months after onset: still improving.

‡Return to normal four months after onset. Patient 3 received VM-26 instead of VM-16. CD = cumulative dose.

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. Patients 1 and 2 worsened after the second course. All three patients had a severe sensory ataxic neuropathy with unsteady gait and walking impairment requiring two crutches or a wheelchair. They all complained of painful paraesthesiae in the feet, and two of them had Lhermitte's sign.

Light touch, vibratory, and sensation of joint position were absent in the four limbs. Thermal sense was normal and distal pinprick sensitivity was slightly impaired in two patients. Two patients had astereognosia. All had 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 diagnosis²; By contrast, drug related

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

	Median nerve				Peroneal nerve				Sural nerve		Median nerve (sensory)	
	DL ms	Amplitude mV	NCV m/s	F latency ms	DL ms	Amplitude mV	NCV m/s	F latency ms	Amplitude µV	NCV m/s	Amplitude µV	NCV m/s
Normal values	<3.6	>5	>48	<32	>5	>2	>42	<55	>10	>45	>12	>45
Pt 1	(R) 3.6	10	56	29.2	(R) 6.2	6	45*	56	(R) 8	32.5	(R) 7.2	34.1
Pt 2	(R) 4.1	7.6	54	29	(R) absent				Absent		Absent	
Pt 3	(L) 4	3.3	45.4	ND	(R) 5	0.9	33.6*	50	1.8	37	1.8	33

*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.

neuropathy must be considered, as several potentially neurotoxic drugs had been administered.

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.³ 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).⁴ 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.⁵ 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 cisplatin⁶⁻⁸; neurotoxicity occurred in only 6% of patients receiving carboplatin alone and was clinically mild.⁹ 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.¹⁰

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.^{8, 11} 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.

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