Cisplatin-Induced Peripheral Neurotoxicity Is Dependent on Total-Dose Intensity and Single-Dose Intensity

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The authors prospectively evaluated the effects of three different schedules of cisplatin (DDP) administration in 60 patients with advanced epithelial ovarian cancer. The individual total dose of DDP was 450 mg/m² in all three groups, and the anti-cancer response at the end of treatment was similar for the different regimens. The clinical and neurophysiologic results confirmed that axonal sensory neuropathy occurred after the standard administration of DDP (75 mg/m² in 3-week cycles) and probably not only the peripheral, but also the central sensory pathway, was involved. Although the total dose of the drug was identical, the two less conventional schedules were less neurotoxic. These results suggest that not only the total-dose intensity, but also the single-dose intensity are relevant in the onset of DDP-induced sensory neuropathy; therefore, the use of less neurotoxic schedules may prevent or reduce sensory nerve damage. *Cancer* 1992; 69:203–207.

Cisplatin (DDP) is widely used, alone or in combination with other antineoplastic drugs, for its effectiveness in the treatment of malignant tumors of the testis, ovary, neck, and bladder. DDP has a number of toxic effects, the most severe of which involve the kidneys and the nervous system.[1] Hyperhydration and diuretics permit nephrotoxicity to be minimized during DDP administration and higher doses of the drug to be scheduled.[2] Currently, neurotoxicity remains the major dose-limiting side effect of DDP. Neurosensorial hearing loss, retrobulbar optic neuritis, focal encephalopathy, subacute myelopathy, and peripheral neuropathy may all be caused by DDP administration with the schedules currently in clinical use. To date, peripheral neuropathy is the most frequent cause of withdrawal from treatment.[3]

A widely accepted standard schedule of DDP administration is 75 mg/m² of body surface area in 3-week cycles for 6 courses. Peripheral neurotoxicity is generally expected to ensue after the administration of 250 to 350 mg/m² of DDP. Various attempts have been made to reduce the peripheral neurotoxicity of DDP, and promising results have been obtained when DDP has been combined with neuroprotective drugs.[4–6] However, none of these studies has tried to assess the importance of the intensity of the single dose of DDP administered on the onset of neurotoxic side effects. Studies have been mainly aimed at determining the total dose that could be tolerated by patients. In the current study, we prospectively evaluated the clinical and neurophysiologic effects of three different schedules of DDP administration using the same total dose, but different single doses in 60 patients with advanced epithelial ovarian cancer.

Methods

Patients and Treatments

All women affected by histologically confirmed epithelial ovarian cancer at the International Federation of Gynecology and Obstetrics (FIGO) Stages III and IV[7] who were referred to our hospital since December 1988 were considered for inclusion in this study. Patients were excluded if they had had previous chemotherapy or were affected by toxic, metabolic, inflammatory, or hereditary diseases known to damage peripheral nerves. By July 1990, 60 patients had been enrolled and randomly assigned, after informed consent, to one of the three groups that were scheduled to be treated as follows: Group A received DDP (75 mg/m² of body surface area) in 3-week cycles for 6 courses (standard schedule); Group B received DDP (50 mg/m²) weekly

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for 9 courses; and Group C received DDP as in group B plus cyclophosphamide (CTX) (500 mg/m^2) on days 1, 22, and 43. The total dose of DDP was 450 mg/m^2 in all groups. After intravenous (IV) prehydration (2000 ml of 0.9% sodium chloride [NaCl]/sucrose with 60 mEq potassium chloride [KCl] + 3 g magnesium sulfate [$MgSO_4$] in Group A, and 1000 ml of 0.9% NaCl/sucrose with 40 mEq KCl + 2 g $MgSO_4$ in Groups B and C), IV DDP was administered in 250 ml NaCl/glucose for 30 minutes. IV furosemide (5 mg) was administered immediately before DDP. No dose reduction was allowed for DDP. The drug was always given at full scheduled dosage unless the leukocyte count was less than 2000/μl, platelet count was less than 75000/μl, or serum creatinine level was more than 1.5 mg/dl. In such a case, treatment was delayed until there was recovery to the above-mentioned values. The CTX dose in Group C was adjusted to toxicity according to the World Health Organization scales.[8] For oncologic follow-up, a pelvic examination was performed every 3 weeks, with radiograms and computed tomography (CT) scans every 3 months. Patients in whom the tumor did not progress had a second-look laparotomy at the end of treatment. For the evaluation of the antitumor response, the World Health Organization criteria were adopted.[8] Briefly, complete response was defined as the disappearance of all macroscopic and microscopic evidence of disease at second-look laparotomy, and partial response was defined as 50% reduction of the total tumor size.

Neurologic Evaluation

All the patients were examined before the chemotherapy, and those who received the full scheduled dose of DDP were reexamined within 1 week of the end of treatment. The physical examination was scored according to the Neurologic Symptom Score (NSS) and Neuropathy Disability Score (NDS) of Dyck *et al.*,[9] which was specifically designed for the detection of peripheral nerve damage. The neurophysiologic evaluation was based on the evaluation with surface electrodes[10] of the sensory nerve conduction (SNC) in the median, ulnar, and sural nerves and of the motor nerve conduction (MNC) in the median, ulnar, and peroneal nerves; the somatosensory evoked potentials (SEP) recorded on the scalp with needle electrodes and obtained after sural nerve stimulation at the ankle and the visual evoked potentials (VEP) obtained with the reversal pattern technique after correction of any visual impairment when present. All neurophysiologic examinations were performed under constant conditions of skin temperature above 34° C using a thermostated infrared lamp. The examiner was always blinded with respect to the group to which each patient belonged. The statistical evaluations of the differences in age and in the neurophysiologic results obtained at baseline and after the treatment in the three groups were performed with the two-tailed Student's *t* test for paired data.

Results

Table 1 shows the main clinical data of the three patient groups. No significant difference in terms of oncologic response was seen at the second-look examination between the two groups treated with DDP alone, and a similar response rate was achieved with the combination DDP and CTX. The general toxicity of the three regimens was also similar, with the exception of severe myelotoxicity that occurred only in Group C (this was expected because of CTX use).

At baseline, patients were comparable from the neurologic point of view. No patients in Groups A and C had clinical polyneuropathy (defined as having NSS score more than 0 or NDS score more than 5), and one patient in Group B had absent ankle jerks and mild symmetrical distal hypoesthesia in the legs (NDS score of 10). Five patients did not undergo the second neurologic examination and were, therefore, excluded from the evaluation (three [one in each group] had tumor progression during the treatment, polytherapy was started, and they dropped out of the study, and two patients in Group C were evaluated later than 1 week after the end of the treatment). At the second neurologic examination, 7 of 19 Group A patients (38.6%), 4 of 19 Group B patients (21.0%), and 2 of 17 Group C (11.7%) had a clinically evident polyneuropathy according to the NSS and NDS scores. The most frequent neurologic symptoms were distal paresthesia and numbness in the legs. At physical examination, a decreased sense of vibration and reduced or absent deep reflexes were most commonly found, and touch and pain sensory impairment were only occasionally seen. Although some patients reported a decrease in strength, no muscle weakness was found on physical examination in such cases.

Neurophysiologically, the pretreatment mean values showed no statistically significant differences among the three groups. Results of the MNC evaluation showed after DDP administration, no changes occurred in velocity, latency, or potential amplitude in any of the nerves in the three groups. Similarly, the sensory conduction velocity and latency were not affected by any kind of treatment, although the sensory amplitude potentials (SAP) were significantly reduced in all the nerves in Group A, but remained unchanged in Groups B and C (Table 2). The mean amplitudes decreased significantly after treatment in Group A (−33.7% in the

Table 1. Summary of the Clinical Data of the Three Groups of Patients

Variable	Group A	Group B	Group C
No. of patients	20	20	20
Mean age (SD) (yr)	58.7 (7.8)	58.5 (8.8)	57.7 (8.5)
Treatment (mg/m^2)			
DDP	75 in 3-week cycles	50 weekly	50 weekly
CTX	—	—	500 on days 1, 22, and 43
Total DDP dose (mg/m^2)	450	450	450
Myelotoxicity			
Leukocytes*	0	0	15/20
Platelets†	0	0	7/20
Nausea and vomiting‡	11/20	12/20	14/20
Nephrotoxicity‡	0	0	0
Tumor response			
Complete	6/20	8/20	7/20
Partial	11/20	9/20	9/20
Overall ratio (%)	85	85	80
Lost at neurologic follow-up	1	1	3
Clinical polyneuropathy§			
Before treatment	0/20	1/20	0/20
After treatment	7/19	4/19	2/17

SD: standard deviation; DDP: cisplatin; CTX: cyclophosphamide.
* Leukocyte count less than 2000/μl.
† Platelet count less than 75000/μl.
‡ WHO grade 3 (8).
§ According to NSS and NDS scores.[9]

median nerve, −36.6% in the ulnar nerve, and −38.7% in the sural nerve), although they were not statistically different in Groups B and C. This difference was due to a fairly generalized and sharp reduction of the SAP in Group A. Nineteen of 57 SAP recorded in Group A (33.3%) (median nerve, six cases; ulnar nerve, six cases; sural nerve, seven cases) decreased after the treatment by more than 50%. A similar result was seen in 6 of 57 SAP in Group B (10.5%) and in 3 of 51 SAP in Group C (5.1%). When SEP values were compared (Table 2), a significant delay was evident in the cortical p40 (+14.5%) wave latency only in Group A. The VEP were unchanged in all groups when the pretreatment and posttreatment values were compared.

Discussion

Since the first description of Kedar *et al.*,[11] DDP-induced neuropathy has been extensively evaluated clinically and neurophysiologically and a few pathologic and toxicologic studies have been reported.[12–23] The majority of the authors agree that DDP-induced neuropathy is exclusively of the sensory type, generally has an acute or subacute onset during treatment, has a tendency for recovery after withdrawal from DDP administration, and is due to axonal damage.

Our clinical and neurophysiologic assessment of patients treated with DDP confirmed the occurrence of pure sensory neuropathy with the hallmarks of axonopathy. MNC evaluation was unchanged after DDP administration, as were sensory conduction velocity and latency. However, the SAP decreased by more than 50% (as is commonly found during axonopathy) in 28 of 165 nerves evaluated. Evidence of involvement of the central processes of the primary sensory neurones was suggested by the results of the SEP recorded on the scalp after sural nerve stimulation; their mean value was significantly delayed in Group A despite an unchanged sensory peripheral conduction velocity.

To our knowledge, no comparable results in patients treated with the standard schedule of DDP are available, but significant differences in the SEP recorded before and after high-dose DDP treatment (4 to 6 courses of DDP [20 to 50 mg/m^2 daily] for 5 days) have been previously reported.[14,23] These findings are supported by the occurrence of pathologically confirmed cases of dorsal column myelopathy[22] during DDP administration, and spinal ganglia degeneration has been reported in animal models.[24,25] However, none of our patients had Lhermitte's sign as reported by other authors.[21,26–28] VEP were unaffected in all three groups as was expected in view of the rarity of DDP-induced toxicity on the optic nerve and previous study results.[14]

Table 2. Statistical Comparison of the Mean Values (Standard Deviation) of the Sensory Conduction Study and of the p40 Somatosensory Evoked Potentials Before and After Chemotherapy

	Group A (n = 19)		Group B (n = 19)		Group C (n = 17)	
	Before	*After*	*Before*	*After*	*Before*	*After*
Median nerve						
CV	46.08 (5.14)	45.68 (5.72)	49.17 (4.99)	48.83 (5.87)	49.46 (5.35)	46.77 (2.27)
	P = NS		P = NS		P = NS	
L	3.31 (0.51)	3.38 (0.62)	3.25 (0.41)	3.28 (0.50)	2.97 (0.38)	3.11 (0.25)
	P = NS		P = NS		P = NS	
SAP	5.56 (1.67)	3.69 (1.15)	5.08 (1.59)	5.02 (1.32)	5.35 (1.56)	4.89 (1.40)
	P = NS		P = NS		P = NS	
Ulnar nerve						
CV	47.05 (4.61)	45.38 (4.31)	49.24 (4.26)	47.46 (4.32)	48.18 (4.86)	46.32 (4.68)
	P = NS		P = NS		P = NS	
L	2.71 (0.40)	2.87 (0.55)	2.69 (0.49)	2.62 (0.37)	2.58 (0.49)	2.62 (0.28)
	P = NS		P = NS		P = NS	
SAP	5.60 (1.57)	3.55 (1.14)	5.94 (2.60)	5.82 (2.41)	5.48 (1.92)	5.12 (2.13)
	P = 0.011		P = NS		P = NS	
Sural nerve						
CV	48.97 (6.45)	46.13 (4.51)	49.92 (7.07)	47.35 (4.57)	47.95 (5.65)	46.97 (4.79)
	P = NS		P = NS		P = NS	
L	3.00 (0.30)	3.12 (0.51)	2.70 (0.38)	2.78 (0.44)	2.94 (0.37)	2.88 (0.28)
	P = NS		P = NS		P = NS	
SAP	10.14 (2.63)	6.22 (2.30)	10.18 (3.54)	8.96 (3.08)	11.67 (4.21)	11.51 (3.71)
	*P = 0.001		P = NS		P = NS	
SEPs P40	48.3 (2.91)	53.3 (3.05)	47.0 (4.01)	47.7 (3.04)	49.2 (3.52)	51.1 (2.85)
	*P = 0.029		P = NS		P = NS	

CV: conduction velocity (m sec); L: latency (m sec); SAP: potential amplitude (uV); SEPs somatosensory evoked potentials (m sec).
* Significant values at the 95% level.

Despite the long-standing knowledge of the toxic side effects of DDP and the widespread use of this effective drug, most of the studies have been retrospective and only recently has DDP-induced neuropathy been evaluated prospectively on a fairly large series of patients. It must, however, be noticed that DDP was often associated in these studies with other antineoplastic drugs, most of which have been reported as being neurotoxic in humans or in animal models.[19] Therefore, it is extremely difficult to rule out the possibility that part of the abnormal findings previously reported and based on combination chemotherapy might be due to a cumulative effect of DDP and other drug(s). In the current study, one of the largest prospective studies carried out so far, we evaluated the effects of DDP administration as monotherapy and in combination with CTX according to three schedules currently in use in our hospital. The three schedules evaluated in the current study resulted in a similar overall (*i.e.*, complete and partial responses histologically confirmed) tumor response ratio at the end of treatment. The results of the physical and neurophysiologic examinations confirmed that in a relevant number of patients, the standard administration of DDP (Group A) induced the onset of clinical polyneuropathy and a sharp reduction of the SAP in all nerves evaluated. These results accord well with those obtained with similar schedules by other authors[5,18,20,21] and confirm that the administration of 75 mg/m^2 in 3-week cycles induces mild to moderate sensory neuropathy that is less severe than that induced by the high-dose schedule used by other authors.[14,23,29] The administration of 50 mg/m^2/week of DDP, alone or in combination with CTX, induced fewer cases of clinically evident polyneuropathy and failed to induce any significant neurophysiologic change.

There is fairly general agreement that DDP-in-

duced neuropathy is exclusively dose dependent.[3] Nevertheless, a clear effect of the single-dose intensity on the development of DDP-induced nephrotoxicity in humans has been reported.[29] In rats exposed to different schedules of DDP, the tissue concentration of platin in spinal ganglia and peripheral nerves was dependent on the total-dose and single-dose intensity.[30] The results of our study suggest that neurotoxicity in humans may be related to the intensity of the single-dose administration. Although all three groups underwent the same total dose administration of DDP (450 mg/m^2), only Group A (in which the drug was administered with the standard schedule) showed significant sensory changes on neurophysiologic grounds.

In conclusion, our study confirms that the standard administration of DDP induces a sensory neuropathy due to axonal damage that may also be associated with an involvement of the central sensory pathway. It is possible to prevent or reduce the sensory damage, with an equivalent antineoplastic effectiveness, using different schedules such as those used Groups B and C in this study. It is conceivable that the clinical use of these less neurotoxic schedules may allow the use of higher total doses of DDP in an attempt to additionally increase the complete tumor response ratio. It would be interesting to combine these schedules with neuroprotective drugs, with the aim of eliminating the most feared and disabling side effect of a drug that still plays an essential role in the treatment of several tumors.

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