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Evaluation of the Neurotoxicity of Paclitaxel and Carboplatin by Current Perception Threshold in Ovarian Cancer Patients

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Abstract

Objectives: Combination chemotherapy consisting of paclitaxel and carboplatin has recently started to be given as the regimen of first choice for epithelial ovarian cancer. One of its side effects, however, is neurotoxicity, and this neurotoxicity has been reported to be the dose-limiting factor. Since it is necessary to measure the severity of the neurotoxicity objectively and quantitatively, we evaluated it on the basis of current perception threshold (CPT) values, which is easy and non-invasive.

Method: Sixteen patients with epithelial ovarian cancer were given paclitaxel (175 mg/m^2, 3 hours) and carboplatin (area under the curve of 5) every three weeks, and the CPT values were measured at two sites on the day before and several times after administration.

Results: All patients exhibited mild neurotoxicity, but it was never so severe that chemotherapy could not be continued. The CPT values peaked on day 4 during one course of chemotherapy, but decreased thereafter and returned almost to the baseline by three weeks, in the same way as the patients' complaints. The CPT values decreased with the number of courses, and patients' complaints gradually increased. The CPT values increased more in the cases previously treated with cisplatin than in the other cases. These changes were seen at 2,000 Hz, which generally corresponds to large, myelinated nerves.

Conclusion: There were correlations between the changes in the patients' CPT values and their degree of neurotoxicity. We expect to be able to predict severe neurotoxicity and evaluate the effect of drug therapy for neurotoxicity by measuring CPT values.
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Key words: ovarian carcinoma, paclitaxel, carboplatin, neurotoxicity, CPT

Introduction

Bone marrow suppression, neurotoxicity, muscle pain, and alopecia are known side effects of combination chemotherapy consisting of paclitaxel and carboplatin[1,2]. One of these side effects, neurotoxicity, is difficult to evaluate accurately and objectively[3]. A sensory nerve conduction velocity test and a quantitative vibration test have been used to evaluate neurotoxicity after chemotherapy, but they are not easy or useful, and it is difficult to evaluate neurotoxicity by a fixed standard. By contrast, current perception threshold (CPT) values are obtained noninvasively, nonaversively, and reliably with a Neurometer, and they enable evaluation of neurotoxicity with a fixed standard and by simple scores. They have been utilized to

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evaluate diabetic neuropathy [4,5] and several types of pain in anesthesiology[6,7].

The CPT is a diagnostic transcutaneous electrical stimulation test performed with a neurometer. Variable frequencies of a constant current sinusoid waveform are measured for minimum perceivable intensity at a peripheral nerve site. Testing is performed at frequencies of 5,250, and 2,000 Hz and between 0 and 10 mA[8,9].

Nerve conduction velocity testing is generalized and excites all axons in a peripheral nerve simultaneously, regardless of their function, whereas CPT selectively excites specific subpopulations of afferent axons. Nerve conduction velocity testing is limited in that it reflects only the state of the largest, most rapidly conducting myelinated fibers. The results of examinations for the presence and degree of peripheral neuropathy by CPT at 2,000 Hz correlate with the results obtained by nerve conduction evaluations. Large, middle, and small diameter nerve fibers are selectively evaluated at frequencies of 2,000, 250, and 5 Hz, respectively[4,10].

Increased CPT values are found in hypoesthesia, and they mean that the function of the nerve is greatly impaired. Decreased CPT values, on the other hand, are associated with hyperesthesia and mean that the nerve fibers are inflamed or regenerating[11].

In this study we objectively evaluated the neurotoxicity of combination chemotherapy consisting of paclitaxel and carboplatin by CPT.

Patients and Methods

This study was performed in the Gynecology department of the Nippon Medical School Hospital between August 1998 and September 1999. Seven previously untreated patients with histologically confirmed epithelial ovarian cancer and nine patients with recurrent epithelial ovarian cancer previously treated with a platinum-containing chemotherapy regimen were studied (**Table 1**). The inclusion criteria were age range of 20～75 years inclusive, WHO performance status≦2, life expectancy≧12 weeks and adequate hematologic, renal, and hepatic function at baseline, defined as: leukocyte count≧4.0 $\times 10^9/l$, hemoglobin≧9.5 g/dl, platelet count≧100$\times 10^9/l$, GOT and GPT≦2.0 times the upper normal limit, total bilirubin≦1.5 mg/dl, serum creatinine≦1.5 mg/dl, and 24 hours creatinine clearance≧60 ml/min. Informed consent was obtained in accordance with the requirements of the local Ethics Committee and Helsinki Declaration.

The dosage of paclitaxel was 175 mg/m^2 dissolved in 500 ml normal saline and infused intravenously over 3 hours. The carboplatin was dissolved in 500 ml

Table 1 patient characteristics

	f	p	total
n	7	9	16
age	54.0 ± 5.4	53.6 ± 7.4	53.8 ± 6.6
clinical stage			
Ⅰ	1	2	3
Ⅱ	2	0	2
Ⅲ	2	6	8
Ⅳ	2	1	3
pathological findings			
S.A.	3	7	10
E.A.	1	0	1
C.A.	2	1	3
P.A.	1	1	2

f; new patients who had not been given cisplatin, p; the patients who had previously been given cisplatin, S.A.; serous adenocarcinoma, E.A.; endometrioid adenocarcinoma, C.A.; clear cell adenocarcinoma, P.A.; poorly differentiated adenocarcinoma

of normal saline and infused intravenously over 2 hours in a dose calculated thus: target area under the free carboplatin plasma concentration versus time curve (AUC＝5) × (GFR＋25). Before treatment patients were premedicated with 20 mg dexamethasone p.o. 12 hours and 6 hours prior to paclitaxel infusion, and 5 mg dexchlopheniramine and 300 mg cimetidine, both intravenously, 30 minutes prior to the infusion. The chemotherapy was done every three weeks.

The neurotoxicity of chemotherapy was measured with a Neurometer (Neurotron Inc., USA), as a portable battery-operated (6 V) device that generates graded sinusoid waves at 5,250, and 2,000 Hz at a constant current of from 0 to 10 milliamperes (mA) (**Fig. 1**). The current is delivered to the skin surface via a pair of 1-cm diameter gold electrodes, 1.7 cm apart, covered with a thin layer of electrode paste. The Neurometer measures neuro-selective current perception threshold values, which quantify peripheral nerve function. The CPT values were examined on the day before each course of chemotherapy and on days 4, 7, and 14 after it. The sites of examination were the middle finger of the right hand for median nerve toxicity and the medial malleolus of the right leg for peroneal nerve toxicity.

Data are presented as mean±SD. Statistical analyses were performed with the unpaired *t* test and one way ANOVA. Differences were considered significant at $p<0.05$.

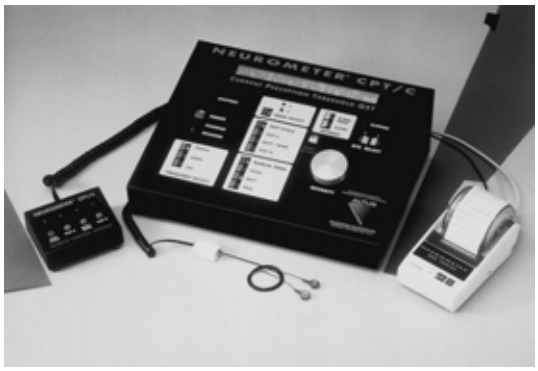

Fig. 1 neurometer

Results

The patients' symptoms were sensory disturbances in the tips of their fingers and toes as early as two days after the chemotherapy that peaked at 4～6 days, then gradually decreased, and resolved by three weeks in almost all patients. The grade of the sensory disturbances as classified by the WHO were 1 or 2; there was no severe sensory disturbance corresponding to grade 3, and all patients were able to continue the chemotherapy. The patients' symptoms grew slightly worse with the number of courses.

The changes in CPT values were as follows. On the day before chemotherapy, at 2,000Hz, the CPT value was 167.3 ± 7.9 mAmp$\times10^{-2}$ in the median nerve, and 114.1 ± 16.0 mAmp$\times10^{-2}$ in the peroneal nerve. On day 4 after administration, the CPT value peaked at 242.9 ± 16.4 mAmp$\times10^{-2}$ in the median nerve and 181.8 ± 25.5 mAmp$\times10^{-2}$ in the peroneal nerve.

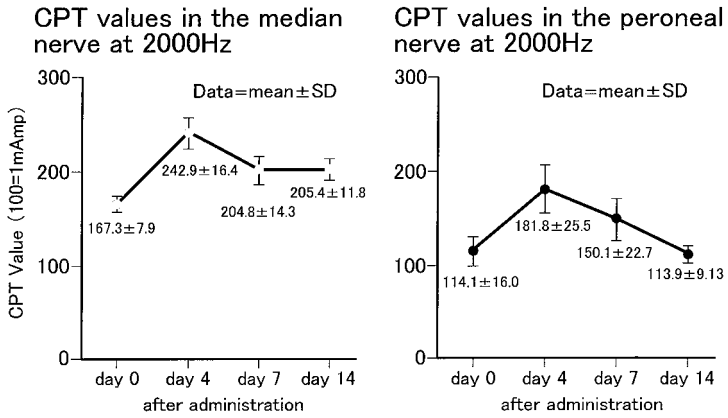

Fig. 2 The changes in CPT values after administration at 2,000 Hz. On day 4 after administration, the CPT values peaked in the median nerve and peroneal nerve, and then returned roughly to the values before chemotherapy ($p<0.05$).

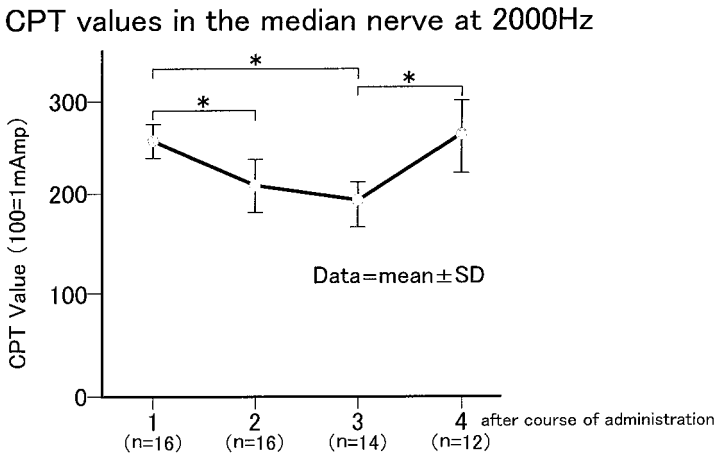

Fig. 3 The changes in CPT values according to number of administrations. At 2,000 Hz, the CPT values of median nerve on day 4 after the first, second, and third administration decreased, but they rebounded after the third ($p<0.05$).

On day 7, it decreased to 204.8 ± 14.3 mAmp$\times 10^{-2}$ and 150.1 ± 22.7 mAmp$\times 10^{-2}$, respectively, and on day 14, 205.4 ± 11.8 mAmp$\times 10^{-2}$ and 113.9 ± 9.13 mAmp$\times 10^{-2}$, and it subsequently returned roughly to the values before chemotherapy (**Fig. 2**). These changes were consistent with the patients' symptoms. There were no significant changes at 250Hz or 5Hz.

We then examined the changes in CPT values as the number of administrations increased. The patients' complaints gradually increased. At 2,000 Hz, the CPT value of the median nerve on day 4 after the first administration was 258 ± 18.5 mAmp$\times 10^{-2}$. After the second administration, it decreased to 212 ± 27.2 mAmp$\times 10^{-2}$, and after third it decreased further to 194 ± 22.8 mAmp$\times 10^{-2}$. After the fourth, however, it increased to 269 ± 40.2 mAmp$\times 10^{-2}$ (**Fig. 3**) ($p<0.05$). There were no significant changes at 250 Hz or 5 Hz.

We also examined the differences in CPT values according to whether the patients had previously been given cisplatin. At 2,000 Hz, the CPT value in the median nerve of the patients previously given cisplatin ($n=9$, 53.6 ± 7.4 y) was 263 ± 27.1 mAmp$\times 10^{-2}$ mAmp$\times 10^{-2}$, as opposed to 203 ± 24.5 mAmp$\times 10^{-2}$ in those who were not ($n=7$, 54.0 ± 5.4 y) ($p<0.05$). At 250 Hz, the CPT value of the patients given cisplatin previously was 85.5 ± 9.04 mAmp$\times 10^{-2}$, as opposed to 62.1 ± 9.30 mAmp$\times 10^{-2}$ in those who were not ($p<0.05$) (**Fig. 4**). At 5 Hz, there were no significant differences.

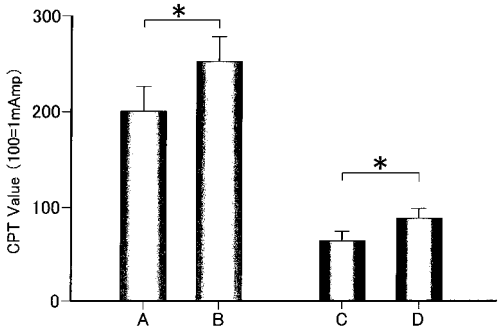

Fig. 4 The differences in CPT values according to whether the patients had previously been given cisplatin. This study revealed that the CPT values increased more in the cases treated with cisplatin previously ($p<0.05$)
A: the CPT values in the median nerve of the patients not given cisplatin at 2,000 Hz, B: the CPT values in the median nerve of the patients previously given cisplatin at 2,000 Hz, C: the CPT values in the median nerve of the patients not given cisplatin at 250 Hz, D: the CPT values in the median nerve of the patients previously given cisplatin at 250 Hz
Data = mean ± SD

Discussion

Paclitaxel is an antineoplastic drug whose cytotoxicity is attributable to promotion of intracellular tubulin polymerization and stabilization of abnormal microtubule structures against

depolymerization[12]. The neurotoxicity of paclitaxel is thought to be due to the presence of many microtubules in nerve cells and Schwann cells, and pathological studies have shown nerve fiber loss, axonal atrophy, and secondary demyelination[13]. This neurotoxicity is one of its dose-limiting factors[3], and although treatment with neurotoxicity, amitryptiline[14], vitamin B[15], etc., has been reported, no treatment has been effective.

The CPT values obtained with the Neurometer in epithelial ovarian cancer patients revealed significant changes due to the neurotoxicity of the combination chemotherapy with paclitaxel and carboplatin only at 2,000 Hz, but not at 250 Hz or 5 Hz. The selectivity of the CPT values has been confirmed pathologically[16], physiologically[17], and pharmacologically[18], and the significant changes in CPT values at only 2,000 Hz, which estimate large and myelinated nerve function, suggested that large myelinated nerves were damaged by paclitaxel plus carboplatin.

During one course of chemotherapy, the CPT values were highest on day 4. They decreased thereafter (on days 7 and 14) and had almost recovered at three weeks after chemotherapy, in the same way as the patients' symptoms that peaked at 4～6 days, then gradually decreased. Increased CPT values mean hyposensitivity, suggesting that sensory dullness was one of the causes of the neurotoxicity of paclitaxel plus carboplatin combination chemotherapy.

On the other hand, the CPT values decreased with the number of courses, and the patients' complaints gradually increased. Decreased CPT values mean hypersensitivity, and the CPT values decreased in the process of repairing nerve fibers momentary[11]. It was thought the CPT values decreased for this reason. In fact, after the third chemotherapy, the CPT values increased, which was expected to be hyposensitivity. It has been reported that the CPT values decreased in mild diabetic neuropathy, and increased in severe diabetic neuropathy[19,20].

It appears that cumulative, but not dose-limiting, neurotoxicity occurs when paclitaxel is used in patients previously treated with cisplatin[21]. This study revealed that the CPT values increased more in the cases treated with cisplatin previously. It is necessary to care the neurotoxicity to those patients.

The changes in the neurotoxicity of paclitaxel plus carboplatin combination chemotherapy were investigated by measuring CPT values. CPT values are expected to be used clinically to diagnose the neurotoxicity and evaluate the side effects of antineoplastic drugs, easily, non-invasively, and objectively.

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