Fractionated administration of carboplatin/paclitaxel reduces neurotoxicity in patients with advanced non-small cell lung cancer

Yoshiki Ishii, Sakae Fujimoto, Kazumi Okazaki, Masaaki Miyoshi, Tomoe Furihata, Isano Hase, Hidenori Takizawa, Yasuko Kikkawa, Issei Yamada and Takeshi Fukuda

The combination of carboplatin/paclitaxel is commonly used as chemotherapy for advanced non-small cell lung cancer. However, the relatively high incidence of neurotoxicity remains a problem. This study was undertaken to determine whether the fractionated administration regimen can reduce the neurotoxicity. Patients with stage III or IV non-small cell lung cancer were randomized to the nonfractionated (NF) dose group, which received paclitaxel (200 mg/m^2) and carboplatin (area under the concentration–time curve = 6) on day 1, or the fractionated dose (F) group, which received paclitaxel (100 mg/m^2) and carboplatin (area under the concentration–time curve = 3) on days 1 and 8. The cycle was repeated every 3 weeks. Peripheral neuropathy was objectively evaluated by measuring the current perception threshold (CPT) in the median nerve using a neurometer. Fourteen and 13 patients were assigned to the NF and F groups, respectively. The incidence of subjective numbness was significantly lower in the F group (15.4%) than in the NF group (57.1%). The CPT value determined at 2000 Hz showed significant increases in the NF group compared with the pretreatment baseline, but no significant changes were observed in the F group. The response rate was comparable in both groups. The fractionated administration of carboplatin/paclitaxel combination therapy showed a significant reduction in neurotoxicity. Measurement of CPT by a neurometer is a useful tool to evaluate the neurotoxicity of anticancer drugs objectively. *Anti-Cancer Drugs* **22:926–932** © **2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2011, **22**:926–932

Keywords: chemotherapy, current perception threshold, neurotoxicity, non-small cell lung cancer, paclitaxel, pharmacokinetics

Department of Pulmonary Medicine and Clinical Immunology, Dokkyo Medical University School of Medicine, Mibu, Tochigi, Japan

Correspondence to Dr Yoshiki Ishii, MD, PhD, Department of Pulmonary Medicine and Clinical Immunology, Dokkyo Medical University School of Medicine, 800 Kitakobayashi, Mibu, Tochigi 321-0293, Japan
Tel: +81 282 87 2151; fax: +81 282 86 7780;
e-mail: ishiiysk@dokkyomed.ac.jp

Received 11 January 2011 **Revised form accepted** 25 May 2011

Introduction

A combination of two drugs, one from the platinum drugs, such as cisplatin and carboplatin, and the other from novel anticancer drugs, such as paclitaxel, docetaxel, vinorelbine, and gemcitabine, has become a gold standard in chemotherapy for advanced non-small cell lung cancer (NSCLC). A four-arm comparison study [1], which compared cisplatin/paclitaxel, docetaxel, or gemcitabine and carboplatin/paclitaxel in patients with NSCLC, showed no significant differences in the efficacy or survival, but carboplatin/paclitaxel was found to be the most recommendable for daily clinical use in terms of tolerability and adverse reactions. On the basis of the results of this and another study, the carboplatin/paclitaxel combination is commonly used to treat NSCLC at present. Recently, these two agents combined with bevacizumab have been frequently used and have shown higher efficacy [2,3].

In general, the carboplatin/paclitaxel combination therapy is conducted every 3 weeks by administering the drugs on day 1. This therapy has been found to be well tolerated and can be completely managed on an ambulatory basis with sparing effects on thrombopenia, one of the typical dose-limiting toxicity due to carboplatin [4]. However, the relatively high incidence of characteristic toxicities such as peripheral neuropathy, myalgia, and arthralgia remains a problem that needs improvements [4].

Recently, attempts have been made to fractionate the dose of carboplatin and paclitaxel to improve the performance and tolerability of this combination therapy. A study that compared a fractionated dose of carboplatin/paclitaxel regimen and a nonfractionated dose of carboplatin/paclitaxel regimen at the same weekly dose intensity in patients with recurrent ovarian cancer showed that the fractionated-dose regimen produced a response rate comparable with that produced by the nonfractionated dose regimen with significant reductions in adverse reactions, such as peripheral neuropathy, one of the typical adverse reactions associated with paclitaxel [5]. Attempts of fractionated administration of paclitaxel have also been made in patients with NSCLC, and

0959-4973 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e328349313d

fractionated administration was shown, although not in head-on comparison studies [6,7], to produce an efficacy similar to that of the conventional tri-weekly treatment regimen with a reduced toxicity. However, some groups reported no significant differences in either the efficacy or the toxicity between the fractionated and nonfractionated regimens [8].

This study was conducted to compare the efficacy and safety of nonfractionated and fractionated dose regimens of carboplatin/paclitaxel in patients with advanced NSCLC. The two regimens were compared in terms of factors, such as the incidence and severity of adverse events, pharmacokinetic parameters, response rates, and mean survival time. To date, peripheral neuropathy has been subjectively evaluated based mainly on subjective symptoms, and it has been difficult to evaluate peripheral neuropathy objectively. In this study, we tried to evaluate it objectively by measuring the perception threshold using electric stimulation.

Patients and methods

Patient eligibility

The eligibility criteria included histologically or cytologically confirmed diagnosis of stage IIIB or IV NSCLC, Eastern Cooperative Oncology Group performance status of 0–2, age of more than 20 years, and anticipated life expectancy of more than 3 months. The stage classification was performed using the sixth edition of the staging system [9]. The following laboratory parameters were required at registration: (a) leukocyte count $\geq 3000/mm^3$, (b) hemoglobin ≥ 9.0 g/dl, (c) platelets $\geq 100\,000/mm^3$, (d) total bilirubin ≤ 1.5 mg/dl, (e) AST and ALT $\leq 3\times$ institutional upper normal limit, (f) serum creatinine ≤ 1.5 mg/dl, and (g) PaO_2 ≥ 70 Torr. Exclusion criteria included previous chemotherapy for lung cancer, brain metastasis, peripheral neuropathy, diabetes mellitus, and serious medical or psychiatric illness.

This protocol was reviewed and approved by the Institutional Review Boards of Dokkyo Medical University School of Medicine. All patients gave written informed consent before study participation.

Treatment schedule

Enrolled eligible patients were randomly assigned to either the nonfractionated (NF) dose group or the fractionated dose (F) group by the secretariat. The F group received paclitaxel (100 mg/m^2, 1 h) and carboplatin [area under the concentration–time curve (AUC) = 3, 1 h] by drip infusion on days 1 and 8 after pretreatment with dexamethasone (16 mg, intravenously), diphenhydramine (50 mg, orally), and ranitidine hydrochloride (50 mg, intravenously). The dose of carboplatin was calculated using the equation of Calvert [dose (mg/body) = target AUC $\times$ (glomerular filtration rate $\times$ (GFR + 25)]. The NF group received paclitaxel (200 mg/ m^2, 3 h) and carboplatin (AUC = 6, 2 h) by drip infusion after the same pretreatment on day 1. Dose intensity was equal in the two groups. Both groups received at least two cycles of treatment (3 weeks per cycle).

Dose modification

Treatment was made after confirming that the WBC was greater than or equal to $3000/mm^3$, the platelet count was greater than or equal to $75\,000/mm^3$, and biochemical parameters were within the range of the eligibility criteria, the day before treatment or the day of treatment. Treatment was postponed in any of the following cases until a recovery was achieved to the above-mentioned criteria: (a) hematological/biochemical abnormality immediately before treatment (until the day before treatment): WBC of less than $3000/mm^3$, platelet counts of less than $75\,000/mm^3$, or biochemical parameters showing deviations from the eligibility criteria; (b) fever of 38°C or higher; (c) performance status ≥ 3; (d) other grade 3 or severer nonhematological toxicity; and (e) other abnormalities that make the treatment undesirable at the discretion of the attending physician. As a rule, the initial dose was continued in the second and subsequent cycles. However, the dose of paclitaxel and carboplatin was reduced by 25% in the subsequent cycle if the following criteria were met as a result of the treatment in the previous cycle: (a) leukopenia of grade 4 (WBC < $1000/mm^3$), (b) grade 3 or severer neutropenia (< $1000/mm^3$) associated with fever (38.5°C or higher), (c) grade 4 decrease in hemoglobin (Hb < 6.5 g/dl), (d) thrombopenia of less than $25\,000/mm^3$; and (e) grade 3 or severer nonhematologic toxicities (excluding nausea and vomiting). The dosage was reduced by 50% or the treatment was discontinued if the above-mentioned criteria were met again after dosage reduction. Treatment was terminated if no recovery was seen 4 weeks after the last administration. Treatment was also discontinued if a new lesion occurred or if apparent progression of the disease was noted.

Assessment of response

Response assessment was performed after two courses of chemotherapy. Analysis of response was based on the Response Evaluation Criteria in Solid Tumors system [10].

Assessment of toxicity

All patients who received at least one course of treatment were included in the analysis of treatment-related toxicities, which were recorded according to the National Cancer Institute-Common Toxicity Criteria, version 2.0 [11].

Current perception threshold

In the first cycle, the current perception threshold (CPT) was measured before the administration of paclitaxel and 3, 5, 7, 10, 12, and 14 days after administration at the same time each day using a neurometer (Neurotron, Baltimore, Maryland, USA). The device emits graded sinusoidal

alternating current stimuli at 5, 250, and 2000 Hz at digitally calibrated levels from 0 to 10 mA. Constant current is maintained throughout the stimulation by feedback circuits. The gold electrode was placed on the right middle finger. CPT for median nerve was measured. At each frequency, the current was increased over a variable time interval until the patient perceived a sensation. Then, the current was decreased and increased until the patient had a sensation that could be identified as the minimal current intensity.

Pharmacokinetic analysis

Blood concentrations were determined after administration of paclitaxel in some patients. Blood samples were collected at 0, 1.5, 3, 12, 24, 48, and 72 h after infusion. Plasma was immediately separated by centrifugation at 3000 rpm for 3 min and stored at –20°C until analysis. Plasma paclitaxel concentrations were determined by high-performance liquid chromatography at SBS Inc., (Sagamihara, Japan).

Statistical consideration

This study compared two treatment regimens in terms of the primary endpoint, adverse events, especially peripheral neuropathy (numbness). As previous studies reported an incidence of peripheral neuropathy of 79% when paclitaxel was administered without dividing the dosage and 0–30% when it was administered in weekly divided doses, the incidence of peripheral neuropathy was assumed to be 25% in the F group and 75% in the NF dose group. On the basis of this assumption, the number of patients necessary in each group was calculated to be 11 at $\alpha = 0.05$ and at a detection power (1–β) of 80%.

All data are expressed as mean ± standard error. To evaluate treatment responses and toxicity, the two groups were compared using Fisher's exact test. Continuous data were compared using Student's *t*-test. Changes in CPT values were analyzed using a two-way analysis of variance for repeated measures. A *P* value of 0.05 was considered significant. The overall survival time was estimated using the method of Kaplan and Meier, and groups were compared by the log-rank test.

Results

Patient characteristics

Between May 2003 and April 2004, a total of 27 patients entered the study. Their characteristics are summarized in Table 1. They were randomly assigned to either of the two groups: 14 to the NF group and 13 to the F group. The two arms were well balanced and there were no statistically significant differences between the two treatment groups at inclusion.

Efficacy

All 27 patients received at least two cycles and were evaluated for the response after the second cycle (Table 2).

Table 1 Patient characteristics

	Nonfractionated dose group	Fractionated dose group	*P* value
Patients (*n*)	14	13	
Sex			
Female	2	4	0.303
Male	12	9	
Age (years)			
Median	63.4	64.0	0.900
Range	35–81	42–77	
Histology			
Squamous cell carcinoma	8	4	0.275
Adenocarcinoma	6	8	
Large cell carcinoma	0	1	
Stage			
IIIB	6	7	0.568
IV	8	6	
ECOG performance status			
0	9	5	
1	5	8	0.123
2	0	0	

ECOG, Eastern Cooperative Oncology Group.

Table 2 Response rate

	n	CR (%)	PR (%)	SD (%)	PD (%)
Nonfractionated dose group	14	0 (0)	4 (28.6)	9 (64.3)	1 (7.1)
Fractionated dose group	13	0 (0)	4 (30.8)	8 (61.5)	1 (7.7)

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

The objective response rate (partial response) was 28.6% (four of 14 patients) in the NF group and 30.8% (four of 13 patients) in the F group. In 64.3% (nine patients) of the NF group and 61.5% (nine patients) of the F group, stable disease status was achieved. The progressive disease was in one patient of each group. There was no significant difference in the response rate between the two groups ($P = 0.901$). The mean survival time was comparable in the NF group (572.4 days) and the F group (517.1 days), and there were no significant differences between the two groups ($P = 0.876$).

Hematological toxicity

Grade 4 hematological toxicity was not seen in either group (Table 3). Grade 3 leukopenia and neutropenia were observed in six (42.9%) and five (35.7%) patients, respectively, in the NF group, compared with seven (53.8%) and six patients (46.2%), respectively, in the F group. Thrombocytopenia was uncommon in both groups. There was no difference in the incidence of hematological toxicity between the two groups.

Nonhematological toxicity

Subjective numbness was reported by eight patients (57.1%) in the NF group: grade 1 in three, grade 2 in four, and grade 3 in one patient. The incidence of subjective numbness was significantly lower in the F group (15.4% with grade 1 numbness in two patients; Table 4). The incidence of myalgia and arthralgia was 42.9 and 35.7%,

Table 3 Hematological toxicity

	Nonfractionated group ($n=14$)		Fractionated dose group ($n=13$)	
	Grade 1/2/3/4 (*n*)	Grade 3 (%)	Grade 1/2/3/4 (*n*)	Grade 3 (%)
Leukopenia	1/2/6/0	42.9	0/2/7/0	53.8
Neutropenia	1/2/5/0	35.7	0/3/6/0	46.2
Thrombopenia	0/0/0/0	0	0/1/0/0	0
Anemia	6/4/1/0	0	5/3/0/0	0

Table 4 Nonhematological toxicity

	Nonfractionated dose group ($n=14$)		Fractionated dose group ($n=13$)		
	Grade 1/2/3 (*n*)	Grade 1+2+3 (%)	Grade 1/2/3 (*n*)	Grade 1+2+3 (%)	*P* value
Numbness	3/4/1	57.1	2/0/0	15.4	0.03
Arthralgia	4/2/0	42.9	2/0/0	15.4	0.13
Myalgia	3/1/1	35.7	2/1/0	23.1	0.38
Nausea/vomiting	3/6/0	64.3	2/2/0	30.8	0.09
Alopecia	3/2/0	35.7	1/1/0	15.4	0.22

respectively, in the NF group and 15.4 and 23.1% in the F group. The incidence was lower for both myalgia and arthralgia in the F group, but it was not significant. Nonhematological toxicities such as nausea/vomiting and alopecia also showed a lower incidence in the F group.

Current perception threshold

There were no significant differences in the baseline CPT values between two groups at any frequency. At 2000 Hz, the CPT value increased significantly in the NF group from days 3 to 15 compared with the baseline values ($P < 0.05$). The F group showed no significant changes during the observation period (Fig. 1a). At 250 and 50 Hz, the CPT value showed no significant changes with time in either group (Fig. 1b and c).

Pharmacokinetics

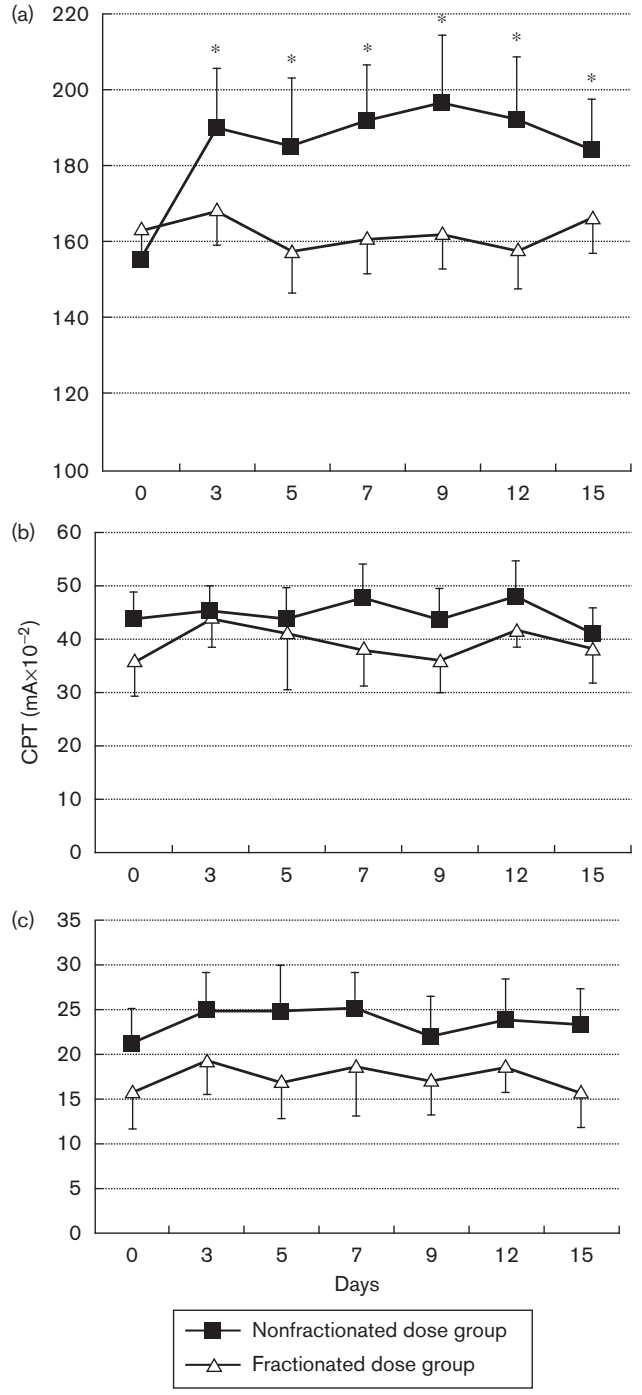
In the pharmacokinetic analysis, the peak blood concentration (C_{max}) was significantly lower in the F group than in the NF group (2.91 ± 0.93 vs. 7.92 ± 0.90 μmol/l; $P < 0.001$; Fig. 2). The length of simulated time during which blood concentrations exceeded 0.05 μmol/l, above which hematological adverse events are likely to occur, was comparable in the NF group (40.5 ± 2.5 h) and in the F group (43.8 ± 3.4 h or 21.9 ± 1.7 h $\times$ 2), but the length of simulated time during which blood concentrations exceeded 0.01 μmol/l, above which antitumor effects are seen, was significantly longer in the NF group (109.0 ± 17.6 h) than in the F group (141.0 ± 3.8 h; $P < 0.05$).

Discussion

This study compared the nonfractionated and fractionated dose regimens of carboplatin/paclitaxel. Adverse reactions such as peripheral neuropathy, one of the typical adverse reactions associated with paclitaxel were significantly reduced in the F group. This finding was objectively corroborated by the measurement of CPT values using a neurometer. Meanwhile, no significant differences were noted between the two groups in the incidence of hematological adverse events.

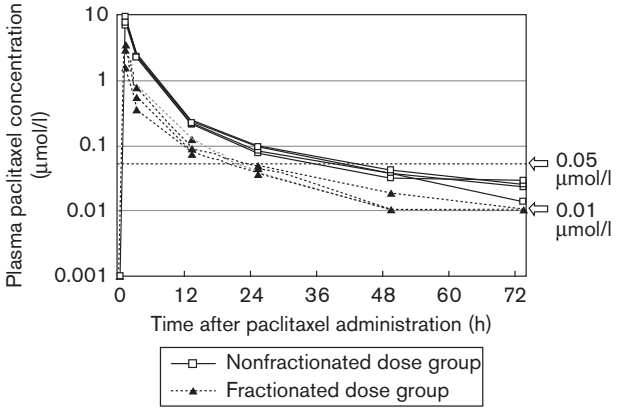
A combination of carboplatin and paclitaxel is the most commonly used chemotherapy for NSCLC, and its usefulness has been established. In general, paclitaxel (175–225 mg/m^2) and carboplatin (AUC: 5–6) are administered on day 1, and this treatment is repeated every 3 weeks. It is reported to be effective with response rates of 17–55% and median survival time (MST) of 8–12.8 months [1,12–15]. However, this therapy is characteristically associated with peripheral neuropathy, which is associated with subjective symptoms such as burning distal paresthesia, often associated with myalgia, arthralgia, and restless legs syndrome. Both sensory and motor fibers seem to be involved in this neuropathy [16]. The toxicity is related to alteration in axonal transport due to the activity of the drug on microtubule kinetics and a subsequent alteration in the axoplasmic cytoskeleton [17]. Paclitaxel leads to microtubule aggregation in cultured mouse dorsal root-ganglion cells and in rat Schwann cells and axons, with subsequent demyelination and loss of axoplasmic transport [18,19]. However, in humans, it is not clear whether the primary site of paclitaxel toxicity is the nerve cell body or the axon. Toxicity by higher doses of paclitaxel may involve the neuronal cell body as well as the axon [20]. Clinical and neurophysiological data suggest that both small (painful sensitivity) and large fibers (vibratory sensitivity) are involved [16]. Nerve biopsy conducted in patients with neuropathy due to paclitaxel showed demyelination and secondary remyelination in the axon [21,22]. Paclitaxel-induced neuropathy occurs in a dose-dependent manner. Neuropathic symptoms were observed in 50, 79, and 100% of patients treated with 135, 175, and 250–300 mg/m^2 of

Fig. 1



Changes of current perception threshold (CPT) values at 2000 Hz (a), 250 Hz (b), and 50 Hz (c) after chemotherapy with carboplatin and paclitaxel in the nonfractionated dose group or in the fractionated dose group. The CPT was measured before administration of paclitaxel and 3, 5, 7, 10, 12, and 14 days after administration in the first cycle. *$P<0.005$ vs. baseline value.

Fig. 2



Time versus concentration curves of paclitaxel. Blood samples were collected at 0, 1.5, 3, 12, 24, 48, and 72 h after infusion. ($n=4$ in each group).

paclitaxel, respectively [20]. Neurotoxicity was more pronounced when the administration was made for more than 3 h than when the same dose was administered for more than 24 h, suggesting that the adverse event is related to the AUC [23]. In general, dose-limiting neurotoxicity is believed to be unlikely to occur at 250 mg/m^2 or smaller doses, but mild sensorimotor neuropathy was reported to be seen in 84% of cases [24–26]. The incidence of grade 3 or severer neuropathy due to triweekly administration of carboplatin/ paclitaxel, the most commonly used regimen for NSCLC, is reported to be 5–13%, but the incidence rises to 40–60% including mild cases [1,4,12,14,15,27].

In recent years, various attempts have been made to reduce toxicity of paclitaxel by administering it in divided doses. The incidence of paclitaxel-related hematotoxicity is reported to be related to how long its blood concentrations remain above 0.05–0.1 μmol/l [28], whereas its antitumor efficacy depends on how long its blood concentrations exceed 0.01 μmol/l [29]. Fractionated dose treatment regimens are expected to shorten the time during which hematotoxic blood concentrations are maintained while prolonging the duration of antitumor blood concentrations. Rosenberg *et al.* [5] compared biweekly administration of paclitaxel alone at 67 mg/m^2 and triweekly administration of 200 mg/m^2 in patients with ovarian cancer, and reported that although response rates were comparable, adverse events such as hematotoxicity, arthralgia, myalgia, neuropathy, and alopecia were significantly reduced in the F group. Ichiki *et al.* [7] conducted a phase II study in patients with an advanced NSCLC by bi-weekly fractionated dose administration of paclitaxel and carboplatin and reported a response rate of 35.1%, a rate comparable with that reported with the conventional tri-weekly carboplatin/ paclitaxel therapy, with reduced hemotoxicity and nonhemotoxicity such as neuropathy. In this study, fractionated administration significantly reduced neuropathy and alopecia, although hematotoxicity showed no significant reduction. This finding may be explained by the

fact that blood concentrations of paclitaxel exceeded 0.05 μmol/l, the threshold above which hematological adverse events are likely to occur, for an average of about 40 h per cycle in both the NF and F groups. C_{max} decreased significantly from 7.92 ± 0.90 μmol/l in the NF group to 2.91 ± 0.93 μmol/l in the F group, resulting in the reduction in neurotoxicity in the F group. This finding is consistent with the report that neurotoxicity depends on C_{max} [30]. Blood concentrations remained above the antitumor effect concentration of 0.01 μmol/l, for a significantly longer period of time in the F group (141 h/cycle) than in the NF group (109 h/cycle). As continued exposure to paclitaxel is expected to result in the induction of apoptosis of cancer cells and the manifestation of antitumor effects through inhibition of neoangiogenesis, the F group was expected to show a better response rate and MST than the NF group. However, no significant differences were noted between the two groups in this respect in this study.

This study used a neurometer to determine CPT to more objectively evaluate neuropathy. CPT measurement has been shown to be useful in evaluating peripheral neuropathy associated with diseases such as diabetes [31,32], but it has seldom been used to evaluate peripheral neuropathy caused by anticancer drugs. The neurometer makes it possible to detect disorders of the C-unmyelinated fibers, Aδ small myelinated fibers, and Aβ large myelinated fibers by stimulation of three wavelengths (5, 250, and 2000 Hz).

In this study, neither the NF group nor the F group showed any significant changes in CPT until day 15 after treatment at 5 or 250 Hz, whereas at 2000 Hz, CPT increased in only the NF group from day 3 after treatment. This finding suggests that neuropathy due to paclitaxel is most likely to be associated with injury of Aβ large-myelinated fibers.

In general, mild neurological symptoms improve or resolve completely within several months after discontinuation of therapy [33]. Meanwhile, the symptoms and deficits persist longer in patients who develop severe neuropathy [33]. In this study, we evaluated only the early phase of neuropathy at the first course, because when patients complain of neurological symptom at the first course, we have to use antisymptomatic or preventive medication, which makes it difficult to evaluate neurotoxicity precisely thereafter. As evaluation of the duration and reversibility of neuropathy and cumulative effect of drugs are very important, further studies will be required.

Although it is difficult to affirm because of a small number of cases in this study, the response rate was comparable in the two groups: 28.6% in the NFgroup and 30.8% in the F group. MST also did not show any significant difference between the two groups: 572.4 days in the NF group and 517.1 days in the F group. These therapeutic results are comparable or superior to those reported for the carboplatin/paclitaxel therapy so far.

In conclusion, administration of carboplatin/paclitaxel in divided doses may be useful because the dose division is expected to reduce neurotoxicity without reducing the antitumor effects of the combination therapy. The measurement of CPT by a neurometer is a helpful tool to evaluate the neurotoxicity of anticancer drugs objectively.

Acknowledgement

The authors thank Dr Kitajima for his technical support and advice to measure CPT.

Conflicts of interest

There are no conflicts of interest.

References

1 Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, *et al.* Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002; **346**:92–98.
2 Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, *et al.* Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004; **22**:2184–2191.
3 Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, *et al.* Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006; **355**:2542–2550.
4 Hainsworth JD, Urba WJ, Hon JK, Thompson KA, Stagg MP, Hopkins LG, *et al.* One-hour paclitaxel plus carboplatin in the treatment of advanced non-small cell lung cancer: results of a multicentre, phase II trial. *Eur J Cancer* 1998; **34**:654–658.
5 Rosenberg P, Andersson H, Boman K, Ridderheim M, Sorbe B, Puistola U, *et al.* Randomized trial of single agent paclitaxel given weekly versus every three weeks and with per oral versus intravenous steroid premedication to patients with ovarian cancer previously treated with platinum. *Acta Oncol* 2002; **41**:418–424.
6 Belani CP, Barstis J, Perry MC, La Rocca RV, Nattam SR, Rinaldi D, *et al.* Multicenter, randomized trial for stage IIIB or IV non-small-cell lung cancer using weekly paclitaxel and carboplatin followed by maintenance weekly paclitaxel or observation. *J Clin Oncol* 2003; **21**:2933–2939.
7 Ichiki M, Kawasaki M, Takayama K, Ninomiya K, Kuba M, Iwami F, *et al.* A multicenter phase II study of carboplatin and paclitaxel with a biweekly schedule in patients with advanced non-small-cell lung cancer: Kyushu Thoracic Oncology Group Trial. *Cancer Chemother Pharmacol* 2006; **58**:368–373.
8 Socinski MA, Ivanova A, Bakri K, Wall J, Baggstrom MQ, Hensing TA, *et al.* A randomized phase II trial comparing every 3-weeks carboplatin/paclitaxel with every 3-weeks carboplatin and weekly paclitaxel in advanced non-small cell lung cancer. *Ann Oncol* 2006; **17**:104–109.
9 Sobin LH, Wittekind C. International Union Against Cancer (UICC): TNM classification of malignant tumours. 6th ed. New York, NY: Wiley-Liss. pp. 99–103.
10 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, *et al.* New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**:205–216.
11 Trotti A, Byhardt R, Stetz J, Gwede C, Corn B, Fu K, *et al.* Common toxicity criteria: version 2.0. an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int J Radiat Oncol Biol Phys* 2000; **47**:13–47.
12 Belani CP, Lee JS, Socinski MA, Robert F, Waterhouse D, Rowland K, *et al.* Randomized phase III trial comparing cisplatin-etoposide to carboplatin-paclitaxel in advanced or metastatic non-small cell lung cancer. *Ann Oncol* 2005; **16**:1069–1075.
13 Laohavinij S, Maoleekoonpairoj S, Cheirsilpa A, Maneechavakajorn J, Sirachainant E, Arpornvivat W, *et al.* Phase II study of paclitaxel and carboplatin for advanced non-small-cell lung cancer. *Lung Cancer* 1999; **26**:175–185.

14 Hensing TA, Peterman AH, Schell MJ, Lee JH, Socinski MA. The impact of age on toxicity, response rate, quality of life, and survival in patients with advanced, stage IIIB or IV nonsmall cell lung carcinoma treated with carboplatin and paclitaxel. *Cancer* 2003; **98**:779–788.

15 Kelly K, Crowley J, Bunn PA Jr., Presant CA, Grevstad PK, Moinpour CM, *et al*. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. *J Clin Oncol* 2001; **19**:3210–3218.

16 Pace A, Bove L, Aloe A, Nardi M, Pietrangeli A, Calabresi F, *et al*. Paclitaxel neurotoxicity: clinical and neurophysiological study of 23 patients. *Ital J Neurol Sci* 1997; **18**:73–79.

17 Vuorinen Versus, Roytta M. Taxol-induced neuropathy after nerve crush: long-term effects on regenerating axons. *Acta Neuropathol (Berl)* 1990; **79**:663–671.

18 Roytta M, Raine CS. Taxol-induced neuropathy: further ultrastructural studies of nerve fibre changes in situ. *J Neurocytol* 1985; **14**:157–175.

19 Roytta M, Raine CS. Taxol-induced neuropathy: chronic effects of local injection. *J Neurocytol* 1986; **15**:483–496.

20 Postma TJ, Vermorken JB, Liefting AJ, Pinedo HM, Heimans JJ. Paclitaxel-induced neuropathy. *Ann Oncol* 1995; **6**:489–494.

21 Wiernik PH, Schwartz EL, Strauman JJ, Dutcher JP, Lipton RB, Paietta E. Phase I clinical and pharmacokinetic study of taxol. *Cancer Res* 1987; **47**:2486–2493.

22 Sahenk Z, Barohn R, New P, Mendell JR. Taxol neuropathy: electrodiagnostic and sural nerve biopsy findings. *Arch Neurol* 1994; **51**:726–729.

23 Huizing MT, Keung AC, Rosing H, Van der Kuij V, ten Bokkel Huinink WW, Mandjes IM, *et al*. Pharmacokinetics of paclitaxel and metabolites in a randomized comparative study in platinum-pretreated ovarian cancer patients. *J Clin Oncol* 1993; **11**:2127–2135.

24 Reichman BS, Seidman AD, Crown JP, Heelan R, Hakes TB, Lebwohl DE, *et al*. Paclitaxel and recombinant human granulocyte colony-stimulating factor as initial chemotherapy for metastatic breast cancer. *J Clin Oncol* 1993; **11**:1943–1951.

25 Schiller JH, Storer B, Tutsch K, Arzoomanian R, Alberti D, Feierabend C, *et al*. Phase I trial of 3-hour infusion of paclitaxel with or without granulocyte colony-stimulating factor in patients with advanced cancer. *J Clin Oncol* 1994; **12**:241–248.

26 Seidman AD, Reichman BS, Crown JP, Yao TJ, Currie V, Hakes TB, *et al*. Paclitaxel as second and subsequent therapy for metastatic breast cancer: activity independent of prior anthracycline response. *J Clin Oncol* 1995; **13**:1152–1159.

27 Giorgio CG, Pappalardo A, Russo A, Giuffrida D, Santini D, Petralia G, *et al*. A phase II study of carboplatin and paclitaxel as first line chemotherapy in elderly patients with advanced non-small cell lung cancer (NSCLC). *Lung Cancer* 2006; **51**:357–362.

28 Gianni L, Kearns CM, Giani A, Capri G, Vigano L, Lacatelli A, *et al*. Nonlinear pharmacokinetics and metabolism of paclitaxel and its pharmacokinetic/pharmacodynamic relationships in humans. *J Clin Oncol* 1995; **13**:180–190.

29 Chang YF, Li LL, Wu CW, Liu TY, Lui WY, P'Eng FK, *et al*. Paclitaxel-induced apoptosis in human gastric carcinoma cell lines. *Cancer* 1996; **77**:14–18.

30 Cagnoni PJ, Shpall EJ, Bearman SI, Matthes S, Ross M, Taffs S, *et al*. Paclitaxel-containing high-dose chemotherapy: the University of Colorado experience. *Semin Oncol* 1996; **23**:43–48.

31 American Association of Electrodiagnostic Medicine EaCC. Technology review: the Neurometer Current Perception Threshold (CPT). *Muscle Nerve* 1999; **22**:523–531.

32 Kempler PKE, Marton A, Vargha P, Hermanyi Z, Keresztes K. Sensory nerve dysfunction in NIDDM and in newly diagnosed NIDDM detected by neurometer: relation to automatic function. In: Hotta NGD, Ward JD, Sima AAF, Boulton AJM, editors. *Diabetic neuropathy: new concepts and insights*. Amsterdam: Elsevier Science; 1995. pp. 291–296.

33 Rowinsky EK, Chaudhry V, Cornblath DR, Donehower RC. Neurotoxicity of taxol. *J Natl Cancer Inst Monogr* 1993;107–115.