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**Nagio Takigawa · Yoshihiko Segawa · Hiroshi Ueoka
Katsuyuki Kiura · Masahiro Tabata · Takuo Shibayama
Ichiro Takata · Hiroaki Miyamoto · Kenji Eguchi
Mine Harada**

Combination of nedaplatin and vindesine for treatment of relapsed or refractory non-small-cell lung cancer

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Abstract *Purpose*: A phase II study of nedaplatin and vindesine was conducted to evaluate their efficacy and safety for treatment of relapsed or refractory non-small-cell lung cancer (NSCLC). *Methods*: Between August 1996 and September 1998, 48 patients who had previously received chemotherapy, thoracic radiotherapy, and/or surgery were enrolled in the study. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 to 2 and an age between 20 and 79 years. Treatment consisted of nedaplatin (80 mg/m^2, day 1) and vindesine (3 mg/m^2, days 1 and 8) every 3 to 4 weeks. *Results*: Of 48 patients, 7 (14.6%) exhibited an objective response. Four (50%) of eight chemotherapy-naive patients had a partial response. However, of the 40 patients who had received prior chemotherapy, a partial response was observed in only 3 (7.5%). At a median follow-up time of 85.1 weeks, the median survival time was 43.6 weeks (95% confidence interval 34.4–52.7) for patients who had received chemotherapy, with a survival rate of 40% at 1 year. Grade 3 or 4 neutropenia occurred in 43 of 48 patients (90%), and neutropenic fever was observed in 3 of the 43 patients, one of whom died of sepsis. Pharmacokinetic and pharmacodynamic analyses of platinum were performed in 43 patients during the first cycle of chemotherapy. Percent reduction in absolute neutrophil count was correlated not only with the area under the plasma ultrafilterable platinum concentration versus time curve ($r = 0.41$, $P = 0.007$) but also with the duration of ultrafilterable platinum concentration above 1 μg/ml ($r = 0.41$, $P = 0.007$). Patients with progressive disease exhibited a shorter duration of ultrafilterable platinum concentration over 1 μg/ml ($P = 0.046$) than those with other responses. *Conclusion*: A combination of nedaplatin and vindesine was unsatisfactory as second-line chemotherapy for NSCLC, although the combination was well tolerated. The duration of ultrafilterable platinum concentration above 1 μg/ml was an important pharmacokinetic parameter for predicting both chemotherapy-induced neutropenia and treatment outcome.

Key words Nedaplatin · Vindesine · Non-small-cell lung cancer · Pharmacokinetics · Pharmacodynamics

N. Takigawa · Y. Segawa · K. Eguchi
Department of Internal Medicine,
National Shikoku Cancer Center Hospital,
13 Horinouchi, Matsuyama 790-0007, Japan

N. Takigawa (✉) · H. Ueoka · K. Kiura · M. Tabata
T. Shibayama · I. Takata · H. Miyamoto · M. Harada
Second Department of Internal Medicine,
Okayama University Medical School,
2-5-1 Shikata-Cho, Okayama, 700-8558, Japan
e-mail: ntakigaw@hospital.okayama-u.ac.jp
Tel.: +81-86-2357227; Fax: +81-86-2328226

Introduction

The majority of non-small-cell lung cancer (NSCLC) patients relapse after first-line therapy such as surgery, radiotherapy, and chemotherapy. Although cisplatin-containing chemotherapy offers some survival benefit for patients with advanced NSCLC [16], there has been only a small amount of evidence that chemotherapy is effective for relapsed or refractory NSCLC [2]. However, paclitaxel, docetaxel, and gemcitabine have been recently introduced, and have exhibited a promising activity (response rate 18–38%) in the setting of second- or third-line chemotherapy [2, 5, 11]. Gredelli et al. have suggested that cisplatin-based second-line chemotherapy might be useful [10].

The toxicities of cisplatin, particularly renal and gastrointestinal toxicities, often limit its use. Nedaplatin (cis-diammine-glycolate-*O*,*O*′-platinum II) is a cisplatin analogue with the same carrier ligands of ammine as cisplatin but with a different leaving group, a five-membered ring structure in which glycolate is bound to the platinum ion as a bidentate ligand [20]. It was synthesized in a search for drugs more potent and less toxic than cisplatin [14]. Two independent phase II studies of

nedaplatin for NSCLC have been conducted in Japan [6, 8]. Objective responses were noted in respectively 10 of 68 patients (14.7%) and 8 of 39 patients (20.5%), and response rates were 16.7% and 12.5% for patients who had received prior chemotherapy. In addition, in a phase III study which compared a combination of nedaplatin and vindesine with that of cisplatin and vindesine for previously untreated NSCLC patients, response rates and overall survival were comparable [7]. The cisplatin arm exhibited more toxicities than the nedaplatin arm, in terms of leukopenia, and renal and gastrointestinal toxicities, although the nedaplatin arm exhibited more frequent thrombocytopenia than the cisplatin arm. The nedaplatin arm had the advantage that a smaller volume of hydration was required than for the cisplatin arm. A combination of nedaplatin and vindesine is therefore considered safe and useful for the treatment of NSCLC.

Although leukopenia associated with nedaplatin therapy has been related to the ultrafilterable platinum area under the plasma concentration versus time curve (AUC) [19], this relationship was established from a trial of single-agent nedaplatin with 5-day continuous administration. However, it remains unclear whether this relationship exists for the combination of nedaplatin and vindesine. With this background, we conducted a phase II study to evaluate the efficacy and toxicity of a combination of nedaplatin and vindesine for the treatment of relapsed and refractory NSCLC. In addition, we attempted to determine the pharmacokinetic and pharmacodynamic characteristics of this combination chemotherapy.

Patients and methods

Eligibility criteria

For enrollment in this study, patients were required to have relapsed or refractory disease after chemotherapy, thoracic radiotherapy, and/or surgery. Patients were enrolled at least 4 weeks after completion of prior therapy. Patients were also required to have histologically or cytologically proven NSCLC, measurable disease outside the previously irradiated field, no indication for curative radiation therapy, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, age between 20 and 79 years, and no concomitant malignancies. Patients with severe concurrent medical conditions and those with pleural or pericardial effusion requiring drainage therapy were excluded.

Before enrollment, each patient gave a complete medical history and underwent physical, laboratory, and staging work-up examinations. Laboratory examinations included complete blood cell count, serum chemistry, urinalysis, and electrocardiogram. Staging work-up examinations consisted of chest radiographs, computed tomography scans of the chest and abdomen (ultrasonography of the abdomen was acceptable), magnetic resonance imaging of the brain, radionucleotide bone scintigraphy, and fiberoptic bronchoscopy. Staging was based on the TNM staging system [15]. Eligible patients were required to have a white blood cell (WBC) count ≥3500/μl, a platelet (PLT) count ≥100,000/μl, a hemoglobin concentration ≥9 g/dl, a serum bilirubin level ≤1.5 mg/dl, serum aspartate aminotransferase and alanine aminotransferase levels not more than 2.5 times the upper limit of normal, and a serum creatinine level ≤1.2 mg/dl.

Written informed consent was obtained from all patients. Two institutions participated in the study and their Institutional Review Boards approved the study. The patients were entered into the study after verification of eligibility by the central registration office (Second Department of Internal Medicine, Okayama University Medical School).

Chemotherapy

Nedaplatin 80 mg/m^2 diluted in 500 ml normal saline was given intravenously (i.v.) over 1 h on day 1. Vindesine 3 mg/m^2 diluted in 20 ml normal saline was given i.v. over 5 min, 30 min before commencing the nedaplatin infusion. Vindesine was also given on day 8 if the WBC count was ≥2000/μl on that day. Antiemetic medication consisted of granisetron hydrochloride 3 mg i.v. and dexamethasone 8 mg i.v., each diluted in 100 ml normal saline. They were given over 30 min and followed by infusion of nedaplatin. After the nedaplatin infusion, all patients received 1 l of hydration consisting of 4.3% glucose, 0.09% sodium chloride, 0.149% potassium chloride, and 0.224% sodium lactate over 2 h. The cycle was repeated every 3 to 4 weeks if WBC and PLT counts were ≥3500/μl and ≥100,000/μl, respectively.

If grade 4 leukopenia or neutropenia, or grade 3 or 4 thrombocytopenia occurred in the preceding cycle, the doses of nedaplatin and vindesine were reduced by 20 mg/m^2 and 0.5 mg/m^2, respectively. The nedaplatin dose was reduced by half when the serum creatinine level increased to ≥1.6 mg/dl but remained ≤3.0 mg/dl. Nedaplatin was not given when the serum creatinine level was higher than 3.0 mg/dl. Chemotherapy was repeated for a maximum of six cycles. If the treatment outcome was progressive disease (PD) after the first cycle of chemotherapy or no change (NC) after the second cycle, chemotherapy was discontinued. When grade 3 or 4 leukopenia or neutropenia occurred, recombinant human granulocyte colony-stimulating factor (rhG-CSF) was administered subcutaneously at a daily dose of 2 μg/kg. This use of rhG-CSF was based on the insurance guidelines in Japan for treating chemotherapy-induced leukopenia or neutropenia.

Response and toxicity evaluations

The patients were evaluated for tumor response and toxicity after the completion of each cycle of chemotherapy by physical examination, complete blood cell count, serum chemistry and follow-up radiographs. Response and toxicity were assessed using the ECOG criteria [17]. Complete response (CR) was defined as the disappearance of all documented lesions for at least 4 weeks. A partial response (PR) was defined as a reduction of ≥50% in the sum of the products of two perpendicular diameters of all measurable lesions lasting for at least 4 weeks without the development of new lesions. PD was defined as a ≥25% increase in the sum of the products of the perpendicular diameters of all measurable lesions or the appearance of new lesions. Unless an objective response or PD occurred, the treatment outcome was considered NC.

Pharmacokinetic analysis

For measurement of platinum concentrations, 6-ml blood samples were taken from the forearm opposite the infusion site immediately before the start of nedaplatin infusion, at the end of infusion, and then at 1, 3, 8 and 24 h postinfusion for the first cycle. Blood was obtained in a heparin-containing syringe and plasma was immediately separated by centrifugation at 3000 rpm for 10 min. The plasma was ultrafiltered (Ultrasento-30 filter; Toso, Japan). Specimens of plasma and ultrafiltrate were stored at −20 °C until analysis. Total platinum and ultrafilterable platinum concentrations were determined with a flameless atomic absorption spectrometer (model AA-400Z; Varian, Australia). Pharmacokinetic parameters were calculated using the least-squares regression method by the NONLIN program. Peak plasma concentrations (Cmax), volume of distribution, total clearance, and half-life were determined using a two-compartment model. AUC of total platinum and ultrafilterable platinum from time 0 to the last sampling time (25 h) were calculated using the trapezoidal rule. Durations of

plasma levels greater than 0.2 μg/ml (T0.2), 1 μg/ml (T1), and 2 μg/ml (T2) were computed.

Study sample size

The minimax two-stage design described by Simon for a phase II clinical trial was used to calculate sample size and to minimize the number of patients required [21]. Sample size was determined based on the following assumptions: alpha error 0.1, beta error 0.1, clinically uninteresting true response rate 5%, sufficiently promising true response rate 20%. According to the two-stage design, this trial had to be stopped if no response was observed in the first 18 patients. Otherwise, the 32 planned patients were enrolled. The treatment was considered effective if four or more responses were observed in 32 evaluable patients. However, at the interim analysis, the patient eligibility criteria were changed since four of eight chemotherapy-naive patients achieved PR. Patients who had received cisplatin-containing chemotherapy were thereafter entered into the study.

Statistical analysis

Survival time was defined as the period from the start of treatment to death or last follow-up evaluation. Time to progression was defined as the period from the start of treatment to PD. Survival curves were calculated using the method of Kaplan and Meier. Correlation coefficients were determined by Spearman's rank correlation test. The significance of differences between two independent groups was assessed using the Mann-Whitney *U*-test. The statistical analyses mentioned above were performed with the SPSS Base System and Advanced System programs (SPSS, Chicago, Ill.). Stepwise multivariate regression analysis was performed to assess the influence of pretreatment parameters (age, creatinine, albumin, aspartate aminotransferase, alanine aminotransferase, and creatinine clearance levels, weight, and body surface area) on the total and ultrafilterable platinum AUC and T1. The inclusion criterion for the backward stepwise procedure was an *F*-value of ≥4.000. This analysis was performed with the STATVIEW 4.0 program (Brainpower, Calabasas, Calif.). *P*-values less than 0.05 from two-tailed analyses were considered to indicate statistical significance.

Results

Patients characteristics

Between August 1996 and September 1998, 48 patients were enrolled in this trial. The patient characteristics are shown in Table 1. There were 36 men and 12 women with a median age of 66 years. All patients but one had an ECOG PS of 0 to 1. The diagnoses were as follows: 30 adenocarcinoma, 15 squamous cell carcinoma, 2 large cell carcinoma, and 1 adenosquamous cell carcinoma. In terms of clinical stage, 5 patients were IIIA, 8 IIIB, and 35 IV. Of the 35 patients with stage IV disease, the number of metastatic sites was one in 21 patients, two in 11, three in 2, and four in 1. Of the 48 patients, 40 had received prior chemotherapy with or without other modalities of treatment (37 one regimen and 3 two regimens), 2 had received thoracic radiotherapy and 6 surgery. Cisplatin-containing chemotherapy had previously been administered to 33 patients (8 cisplatin plus vindesine, 7 cisplatin plus docetaxel, 7 cisplatin plus irinotecan, 6 cisplatin plus 5-fluorouracil, 2 cisplatin, mitomycin C plus vindesine, 1 cisplatin, ifosfamide plus vindesine, 1 cisplatin plus Adriamycin, and 1 cisplatin alone). Responses to the first-line chemotherapy included PR in 13 patients, NC in 9, PD in 11 and not evaluable in 7. The median interval between previous and present chemotherapies was 13 weeks (range 4–153 weeks).

Table 1 Patient characteristics (*CT* chemotherapy, *OP* operation, *RT* radiation therapy)

Total patients enrolled (*n*)		48
Age (years)	Median	66
	Range	41–77
Sex (*n*)	Men	36
	Women	12
ECOG performance status (*n*)	0–1	47
	2	1
Histology (*n*)	Adenocarcinoma	30
	Squamous cell carcinoma	15
	Large cell carcinoma	2
	Adenosquamous cell carcinoma	1
Stage (*n*)	IIIA	5
	IIIB	8
	IV	35
Pretreatment (*n*)	CT	21
	CT plus RT	9
	CT plus OP	10
	RT	2
	OP	6

Treatment accomplishment

The 48 patients received a median of two cycles of chemotherapy (range, one to five). In the 100 cycles performed in total, vindesine on day 8 was given in 86 cycles. The median interval between cycles was 4 weeks (range 3–7 weeks). Dose intensities (milligrams per meter squared per week; mean ± SD) of nedaplatin and vindesine in each cycle were as follows: 20.3 ± 2.6 and 1.45 ± 0.34 in the first cycle, 20.4 ± 6.7 and 1.42 ± 0.28 in the second cycle, 18.8 ± 2.7 and 1.30 ± 0.34 in the third cycle, 20 ± 0 and 1.5 ± 0 in the fourth cycle, and 20 and 1.5 in the fifth cycle.

Responses

Responses to chemotherapy are summarized in Table 2. Of the 48 patients entered, 7 achieved PR, 30 NC and 10 PD, and 1 was not evaluable because of early death. The overall response rate was 14.6%, with a 95% confidence interval (CI) of 4.4% to 24.8%. The histological types of the responders were adenocarcinoma in three patients, squamous cell carcinoma in three, and adenosquamous cell carcinoma in one. Of the 40 patients who had received previous chemotherapy, 3 (7.5%) achieved a PR with response durations of 17.0, 18.9 and 24.7 weeks. All previous chemotherapies used for the three

Table 2 Response to chemotherapy (*CDDP-CC* cisplatin-containing chemotherapy, *NC* no change, *NE* not evaluable, *PD* progressive disease, *PR* partial response)

Response	Overall (no.)	Prior chemotherapy (no.)	Prior CDDP-CC (no.)
PR	7 (14.6%)	3 (7.5%)	3 (9.1%)
NC	30	26	21
PD	10	10	8
NE	1	1	1
Total	48	40	33

responders consisted of cisplatin-containing regimens, in which two PRs had been noted.

Survival

At the median follow-up time of 85.1 weeks (range 42.2–150.4 weeks), 36 patients (75%) had died and 12 were still alive. The survival rate was 40% at 1 year, with a median survival time (MST) of 43.6 weeks (95% CI 36.4–50.8). The median time to progression was 22.4 weeks (95% CI 16.0–28.9). For the 40 patients who had received previous chemotherapy, the survival rate was also 40% at 1 year, with a MST of 43.6 weeks (95% CI 34.4–52.7). The median time to progression was 25.0 weeks (95% CI 15.0–35.0).

Toxicity

Toxicities are shown in Table 3. The major toxicity was myelosuppression. Grade 3 or 4 leukopenia and neutropenia were observed in 34 (71%) and 43 (90%) of 48 patients, respectively. rhG-CSF was administered to 35 of 48 patients (73%) and in 58 (58%) of 100 cycles of chemotherapy with a median duration of 7 days (range 1–17 days). Neutropenic fever was observed in three patients, one of whom died of sepsis. Nonhematological toxicities were generally mild, although one patient experienced myocardial infarction on day 8 of the first cycle. This patient was conservatively treated and recovered.

Pharmacokinetic/pharmacodynamic analyses

Pharmacokinetic parameters determined using plasma specimens from 43 patients are listed in Table 4. In general, pharmacokinetic parameters for ultrafilterable platinum exhibited better correlations with patient pretreatment parameters than did those for total platinum (data not shown). Coefficients of correlation between AUC and T1 and pretreatment factors are shown in Table 5. Age exhibited weak correlations with ultrafilterable platinum AUC ($r = 0.34$, $P = 0.025$) and T1 ($r = 0.39$, $P = 0.009$). Creatinine clearance level was also weakly correlated with ultrafilterable platinum AUC ($r = -0.33$, $P = 0.030$) and T1 ($r = -0.51$, $P = 0.001$). In a stepwise multiple regression analysis, age was confirmed to be the only factor significantly predicting ultrafilterable platinum AUC ($r^2 = 0.15$, $F = 4.4$, $P = 0.042$). In addition, age and creatinine clearance level were significant predictors of ultrafilterable platinum T1 ($F = 7.3$, $P = 0.010$; $F = 7.7$, $P = 0.008$, respectively). The overall F, P and r^2 values for the model were 8.8, 0.0007 and 0.31, respectively.

The pharmacodynamic analysis (Fig. 1) showed that the percent reduction in absolute neutrophil count (ANC) was correlated with ultrafilterable platinum AUC ($r = 0.41$, $P = 0.007$) and T1 ($r = 0.41$, $P =$

Table 4 Pharmacokinetic parameters (*AUC* area under the plasma concentration versus time curve; *Cl* total clearance; *Cmax* peak plasma concentration; $t_{1/2}$ half-life; *T0.2*, *T1*, *T2* duration of exposure over 0.2, 1, and 2 μg/ml of platinum concentration, respectively; *Vd* volume of distribution)

Parameter	Total platinum		Ultrafilterable platinum	
	Mean	SE	Mean	SE
AUC (μg · h/ml)	17.6	0.75	13.1	0.55
Cmax (μg/ml)	4.48	0.15	4.15	0.16
$t_{1/2}$ (h)	8.37	1.52	3.87	0.55
Cl (l/h)	6.46	0.36	9.56	0.56
Vd (l)	20.2	1.22	19.3	1.37
T0.2 (h)	20.0	1.85	11.2	0.94
T1 (h)	5.23	0.28	4.17	0.20
T2 (h)	2.33	0.13	1.92	0.12

Table 3 Toxicity according to ECOG criteria

	Grade			
	1 No. (%)	2 No. (%)	3 No. (%)	4 No. (%)
Leukopenia	3 (6)	11 (23)	30 (63)	4 (8)
Neutropenia	3 (6)	1 (2)	13 (27)	30 (63)
Anemia	13 (27)	24 (50)	11 (23)	0
Thrombocytopenia	5 (10)	4 (8)	2 (4)	1 (2)
Liver damage	0	0	1 (2)	0
Renal damage	1 (2)	0	0	0
Cardiac damage	0	0	0	1 (2)
Nausea/vomiting	20 (42)	8 (17)	1 (2)	0
Peripheral neuropathy	6 (13)	0	0	0
Extravasation injury	0	1 (2)	0	0
Infection	0	2 (4)	0	1 (2)

Table 5 Correlation coefficients between pharmacokinetic parameters and pretreatment factors (*ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *AUC* area under the plasma concentration versus time curve, *BUN* blood urea nitrogen, *C-Cr* creatinine clearance, *T1* duration of exposure over 1 μg/ml of platinum concentration)

Factor	Total platinum		Ultrafilterable platinum	
	AUC	T1	AUC	T1
Age	0.13	0.37	0.34	0.39
Weight	0.11	0.11	0.03	0.04
Body surface area	0.14	0.13	0.04	0.07
Total protein	−0.22	−0.26	−0.14	−0.20
Albumin	−0.29	−0.37	−0.24	−0.37
BUN	0.21	0.28	0.23	0.30
Creatinine	0.32	0.39	0.28	0.40
C-Cr	−0.33	−0.50	−0.33	−0.51
AST	0.12	0.18	0.22	0.18
ALT	−0.09	−0.08	−0.09	−0.13

0.007). In the patient who died of sepsis due to neutropenia, ultrafilterable platinum AUC was 17.2 μg · h/ml, the fifth highest value among 43 patients studied. Ultrafilterable platinum T1 also exhibited the third longest value (6.15 h) in this patient. Concerning the relationships between response to chemotherapy and pharmacokinetic parameters, patients with PD had a shorter ultrafilterable platinum T1 than did those with PR or NC, or those not evaluable (4.36 h vs 3.52 h, $P = 0.046$; Fig. 2). There were no significant correlations between response to chemotherapy and other parameters examined in this study.

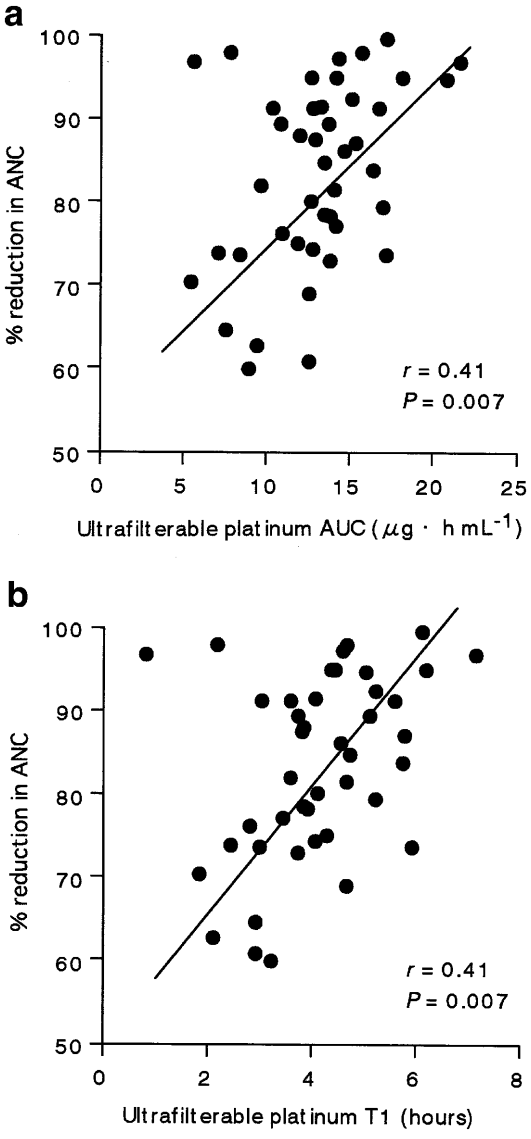

Fig. 1a,b Scatterplots of (**a**) percent reduction in absolute neutrophil count (ANC) versus area under the plasma ultrafilterable platinum concentration versus time curve (AUC) and (**b**) duration of ultrafilterable platinum exposure above 1 μg/ml (T1) during the first cycle of chemotherapy

Discussion

The overall response rate in the present study was 14.6%, but disappointingly decreased to 7.5% when the study population was limited to patients who had received prior chemotherapy. This indicates that this combination is inappropriate in most previously treated patients. However, the MST of patients who had received prior chemotherapy was 43.6 weeks, which is comparable to that (8.9 months) found for the nedaplatin plus vindesine arm of a phase III study of chemotherapy-naive patients [7]. In previous reports of second-line chemotherapy trials for NSCLC, MST and median time to progression have ranged from 3 to 11 months and from 3 to 8 months, respectively [2, 5, 10, 18]. Survival time and time to progression in the present study therefore appear to be nearly equal to or better than those reported previously. An ECOG study has demonstrated that the platinum analogue carboplatin yields longer survival and time to progression than other regimens, although the response rate was only 9% for the carboplatin arm [3]. A combination of nedaplatin, a platinum analogue, and vindesine may increase survival.

The major toxicities such as leukopenia and neutropenia in this trial were generally tolerable, although one patient died of sepsis. No grade 2 or greater renal toxicity or neurotoxicity was observed in this study. Although myocardial infarction occurred in one patient, it is unclear whether this adverse event was treatment-related or not. There have been no reports describing treatment-related cardiac damage in previous studies [6, 7, 8].

The pharmacokinetic analysis in this study suggest that pretreatment parameters might predict ultrafilterable platinum AUC and T1. In a multiple regression analysis, age was found to be the sole predictor of ultrafilterable platinum AUC, although the coefficient of correlation between these two was small. Yamamoto et al. also found that age was an independent and significant predictor of ultrafilterable platinum AUC in a

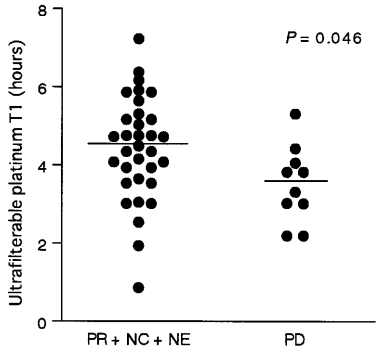

Fig. 2 The relationship between response to chemotherapy and duration of plasma ultrafilterable platinum exposure above 1 μg/ml (T1). *Bars* indicate mean values (*NE* nonevaluable, *NC* no change, *PD* progressive disease, *PR* partial response)

cisplatin pharmacokinetic study [23]. In addition, both age and creatinine clearance level were independent predictors of ultrafilterable platinum T1 in the present study. Pharmacokinetic analyses of taxanes such as paclitaxel and docetaxel have shown a significant correlation between time of exposure to drugs above a threshold level and neutropenia [4, 9, 12]. Similarly, with 5-day continuous administration of nedaplatin, ultrafilterable platinum AUC is correlated with percent change in WBC count [19]. In the present study, a significant correlation was found between percent reduction of ANC and ultrafilterable platinum AUC or T1 in the first cycle of chemotherapy. Concerning treatment response, patients with PD had shorter ultrafilterable platinum T1 than did those achieving other responses. Indeed, 1 μg/ml of nedaplatin has been demonstrated to be a pharmacologically active concentration in experiments using lung cancer cells [13, 22].

In conclusion, the therapeutic effect of a combination of nedaplatin and vindesine was unsatisfactory as second-line chemotherapy for NSCLC, although this combination was well tolerated. Paclitaxel, docetaxel, and gemcitabine, have been reported to be active in salvage chemotherapy [2, 5, 11]. Combination chemotherapy including these new agents will be investigated in a future study. The duration of ultrafilterable platinum concentration above 1 μg/ml was an important pharmacokinetic parameter in predicting both chemotherapy-induced neutropenia and response to chemotherapy.

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