

Phase II Study of the Combination of Nedaplatin and Weekly Paclitaxel in Patients with Advanced Non-small Cell Lung Cancer

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Abstract. *Background:* To date, no phase II trial of nedaplatin and weekly paclitaxel in patients with advanced non-small cell lung cancer (NSCLC) has been published. The safety and efficacy of the combination of nedaplatin and weekly paclitaxel in patients with NSCLC was examined. *Patients and Methods:* Patients with previously untreated NSCLC, either stage IIIB with pleural effusion or stage IV, were eligible if they had a performance status of 0 to 2, were 75 years or younger and had adequate organ function. Patients were treated with nedaplatin (80 mg/m² on day 1) and weekly paclitaxel (90 mg/m² on days 1, 8 and 15). *Results:* From March 2005 through March 2008, 47 patients (31 men and 16 women; median age, 66 years; age range, 38 to 75 years) were enrolled. The overall response rate was 53.2% (95% confidence interval, 38.1% to 67.9%). The median survival time was 13 months (range, 1 to 36 months), the 1-year survival rate was 62% and the median time to disease progression was 5 months (range, 1 to 19 months). Grade 3 to 4 hematologic toxicities included neutropenia in 38.3% of patients, thrombocytopenia in 2.1% and anemia in 23.4%. Although frequent non-hematologic toxicities were nausea, hepatic dysfunction and peripheral neuropathy, all cases were of only mild to moderate severity. Although 1 patient had grade 3 pulmonary toxicity due to drug-induced pneumonia, this patient recovered after receiving steroid therapy. *Conclusion:* This combination chemotherapy is

effective and well tolerated and is an acceptable therapeutic option for patients with untreated advanced NSCLC.

For patients with advanced non-small cell lung cancer (NSCLC), systemic chemotherapy constitutes standard care. Platinum-based 2-drug combinations provide a survival benefit for patients with advanced NSCLC and a good performance status (PS) (1, 2). Recently, the addition of bevacizumab to a standard, platinum-based chemotherapy regimen has significantly improved the rates of overall survival, progression-free survival and response in patients with advanced non-squamous cell NSCLC and a good PS (3). However, the addition of bevacizumab is associated with increased number of toxic effects, particularly febrile neutropenia and pulmonary hemorrhage. Bevacizumab cannot be used for patients with non-squamous cell NSCLC in Japan. On the other hand, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib and erlotinib, do not increase the survival rate, time to disease progression (TTP) or the response rate when added to doublet platinum-based chemotherapy for unselected patients with advanced NSCLC (4-7). Therefore, doublet platinum-based chemotherapy has been the standard treatment for patients with previously untreated advanced NSCLC in Japan (1). However, no standard regimen has been established (1, 2). Because standard doublet platinum-based chemotherapy has reached a therapeutic plateau, a combination chemotherapy regimen that is less toxic and more effective is urgently needed.

In vitro experiments have shown that prolonged exposure to paclitaxel, through either continuous infusion or weekly administration, results in increased cytotoxicity (8, 9). In addition, paclitaxel has antiangiogenic and apoptotic activity when delivered with low-dose weekly schedules (10, 11), making this approach of interest for advanced NSCLC. Furthermore, weekly administration of paclitaxel has distinct

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theoretical advantages because a higher dose-intensity can be achieved (12).

Nedaplatin is a second-generation platinum derivative that has shown greater antitumor activity and lower toxicity in mice than has cisplatin (13). In a phase III study in patients with advanced NSCLC the combination of nedaplatin and vindesine produced response rates and an overall survival rate similar to those of cisplatin and vindesine (14). Leukopenia and renal and gastrointestinal toxicities were more frequent in the cisplatin arm than in the nedaplatin arm, although thrombocytopenia was more frequent in the nedaplatin arm (14). The combination of nedaplatin with a new agent, such as gemcitabine or irinotecan, in patients with advanced NSCLC achieves response rates of 30% and 31% (15, 16), indicating similar efficacy to gemcitabine or irinotecan with cisplatin or carboplatin.

In this phase I study, the maximum tolerated dose (MTD) was determined to be 100 mg/m² of nedaplatin and 90 mg/m² of weekly paclitaxel (17). The dose-limiting toxicities at the MTD were neutropenic fever and grade 3 hepatic dysfunction. A dose of 80 mg/m² of nedaplatin and 90 mg/m² of weekly paclitaxel has been recommended for this phase II study. Although antitumor activity and survival were not the primary end points of the phase I study, the efficacy shown was promising: the response rate at the recommended dose was 44.4%, the MST was 14 months and the overall 1-year survival rate was 52%. To date, no phase II trial of nedaplatin and weekly paclitaxel in patients with advanced NSCLC has been published. Therefore, the present phase II study of the combination of nedaplatin and weekly paclitaxel was performed to assess its antitumor activity and toxicity in patients with advanced NSCLC.

Patients and Methods

Eligibility criteria. The criteria for study entry were: 1) histologically or cytologically confirmed NSCLC; 2) stage IIIB disease with pleural effusion or stage IV disease; 3) age of 20 to 75 years; 4) an Eastern Cooperative Oncology Group PS of 2 or less; 5) a measurable lesion; 6) life expectancy of 3 months or more; 7) adequate bone marrow function (white blood cell [WBC] count from 4000 to 12000/ μ L, neutrophil count of 2000/ μ L or more, platelet count of 100000/ μ L or more and hemoglobin level of 9.0 g/dL or more), renal function (serum creatinine levels less than 1.5 mg/dL and creatinine clearance rate of 50 mL/min or more) and hepatic function (total serum bilirubin level less than the upper limit of the normal range and levels of aspartate aminotransferase and alanine aminotransferase less than or equal to twice the upper limits of the normal ranges) and arterial oxygen pressure of 70 mm Hg or more; and 8) written informed consent. Patients who had previously received chemotherapy were excluded, but patients who had received radiotherapy could be enrolled if it had not been administered to the target lesion used to assess response. Patients were excluded if they had active infections, severe heart disease, interstitial pneumonia, peripheral neuropathy, symptomatic brain metastasis or an active

second malignancy. This study was approved by the institutional review board of the Showa University School of Medicine.

Treatment protocol. Paclitaxel was administered as an intravenous drip infusion in 60 minutes on days 1, 8 and 15. Nedaplatin was given as an intravenous drip infusion over 60 minutes after paclitaxel was administered on day 1. This chemotherapy regimen was administered every 4 weeks for 2 or more courses. If the outcome was progressive disease or if intolerable toxicity developed at any time, chemotherapy was discontinued. If the outcome was stable disease after 2 courses of treatment, subsequent therapy was left to the discretion of the physician in charge of the patient's treatment.

Full doses of paclitaxel were given if the WBC count was greater than 2000/ μ L and the platelet count was more than 75000/ μ L on day 8 or 15 of treatment. If the WBC count was less than 3000/ μ L or the platelet count was less than 100000/ μ L on day 29, the next course was withheld until the count recovered. Nedaplatin was permanently discontinued if the serum creatinine level became greater than 2.0 mg/dL. Doses of paclitaxel were reduced by 10 mg/m² for grade 4 leukopenia or neutropenia lasting 3 days or longer, thrombocytopenia less than 20000/ μ L, neutropenic fever during grade 3 or 4 neutropenia, grade 2 neuropathy, grade 2 arthralgia or myalgia or skip of paclitaxel on day 8 or 15 of treatment because of myelosuppression. Chemotherapy was discontinued for grade 3 or higher non-hematologic toxicity, except for alopecia, nausea or vomiting, anorexia, constipation, fever and fatigue. To prevent hypersensitivity reactions, patients received paclitaxel after receiving intravenous dexamethasone (10 mg), ranitidine (50 mg) and oral diphenhydramine (50 mg). The dexamethasone dose was then progressively decreased to 8, 4, 2 and 1 mg to minimize corticosteroid side effects without severe hypersensitivity reactions. Ondansetron was routinely administered to all patients before nedaplatin as antiemetic prophylaxis. If the WBC or neutrophil count decreased to fulfill grade 4 criteria after chemotherapy, granulocyte colony stimulating factor (G-CSF) was administered until the count recovered.

Toxicity and evaluation of response. Pretreatment evaluation included a baseline history and physical examination, complete blood cell count with differential and routine chemistry profiles, urinalysis, electrocardiograms, chest radiography, chest and abdominal computed tomography (CT), brain magnetic resonance imaging and a radionuclide bone scan. Complete blood cell counts with differential and routine chemistry profiles were obtained at least once a week during chemotherapy.

Toxicities were assessed and graded according to the National Cancer Institute Common Toxicity Criteria Version 2.0. Tumor response was classified according to Response Evaluation Criteria in Solid Tumors criteria. All patients who received at least 2 cycles of chemotherapy were assessable for response, and all patients who received at least 1 cycle were assessable for toxicity and survival.

Statistical methods. The TTP was defined as the time from the date of treatment to the date progressive disease was diagnosed. Survival time was measured from the start of treatment until death or latest follow-up. The Kaplan-Meier method was used to calculate survival curves. The trial was designed as a phase II study, with the response rate as the main endpoint. According to the Simons minimax design, the study, with a sample size of 43, had 80% power to accept the

Table I. *Patient characteristics.*

Total number of patients	47
Gender (male/female)	31/16
Age (range), in years	66 (38-75)
PS (0/1/2)	8/34/5
Stage (IIIB/IV)	4/43
Histologic type	
Adenocarcinoma	43
Squamous	4

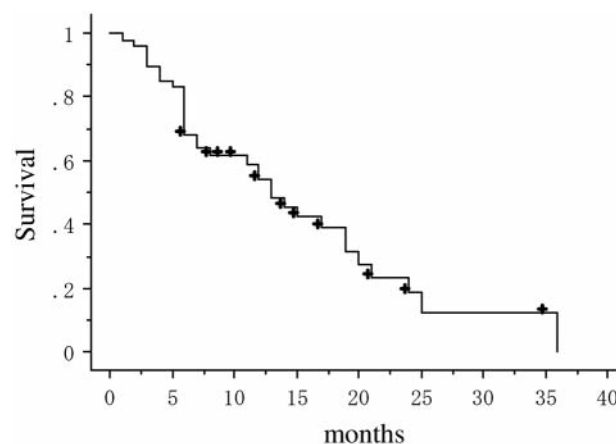
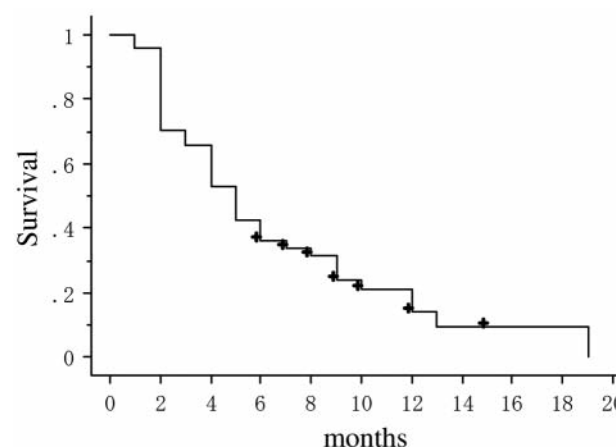
Table II. *Toxicity.*

Toxicity (%)	National Cancer Institute-Common Toxicity Criteria grade				
	1	2	3	4	3 or 4
Leukopenia	12	18	12	1	27.7
Neutropenia	10	12	10	8	38.3
Thrombocytopenia	17	1	1	0	2.1
Anemia	17	17	9	2	23.4
Nausea	10	3	0	0	0
Vomiting	1	4	0	0	0
Diarrhea	1	3	1	0	2.1
Hypersensitivity reaction	3	0	0	0	0
Infection	4	3	1	0	2.1
Elevation of serum creatinine	2	1	0	0	0
Elevation of aminotransferases	13	5	1	0	2.1
Electrolyte	11	3	3	1	8.5
Pulmonary	0	0	2	0	4.3
Arthralgia	3	2	0	0	0
Peripheral neuropathy	20	3	0	0	0

hypothesis that the true response rate was greater than 40% and had 5% significance to reject the hypothesis that the true response rate was less than 20%.

Results

Patients characteristics. Forty-seven patients were enrolled from March 2005 through March 2008 (Table I). All patients could be assessed for toxicity and survival and 44 patients could be assessed for response. Three patients could not be assessed for response because they had not received 2 courses of chemotherapy owing to intolerable toxicity or death during the first course of chemotherapy; these patients were considered to be non-responders. When disease progressed, 24 (51%) patients received an additional course of chemotherapy. Both docetaxel and an EGFR-TKI were administered in 8 (17%) patients, docetaxel without an EGFR-TKI was administered in 12 (26%) patients and an EGFR-TKI without docetaxel was administered in 4 (9%) patients.

Figure 1. *Overall survival time.*Figure 2. *Time to disease progression.*

Response to treatment and survival. The overall response rate was 52.3% (95% confidence interval, 38.1% to 67.9%), as outcomes were as follows: complete responses in 0 patients, partial responses in 25 patients, stable disease in 5 patients and progressive disease in 14 patients. Survival analysis was performed when the median follow-up time of all assessable patients was 11 months. At present, 14 patients (29.8%) are alive and no patients have been lost to follow-up. The MST was 13 months (range, 1 to 36 months), and the 1-year survival rate was 62% (Figure 1). The median TTP was 5 months (range, 1 to 19 months; Figure 2).

Toxicity. A total of 138 courses of chemotherapy were given. The median number of courses given per patient was 3 (range, 1 to 6). The most frequent toxicity of grade 3 to 4 was neutropenia, which developed in 38.3% of patients (18 of 47 patients; Table II). However, the myelosuppressive

effects of nedaplatin and weekly paclitaxel were likewise mild: G-CSF was administered during only 10 (7.2%) of the 138 assessable courses for a median time of 3 days. No patients had grade 3 or 4 thrombocytopenia or received a platelet transfusion. Although 11 (23.4%) patients had grade 3 or 4 anemia, only 3 patients received an erythrocyte transfusion.

Table II shows the more severe non-hematologic toxicity that developed during treatment. Frequent non-hematologic toxicities were hepatic dysfunction, electrolyte abnormality, nausea and peripheral neuropathy; all cases were of only mild to moderate severity. All cases of hepatic dysfunction were manifested only by transient increases in serum aminotransferase levels. Although 3 patients had grade 3 or 4 hyponatremia and 1 patient had grade 3 hypokalemia, all cases of electrolyte abnormality were transient decreases. No patients had grade 3 or 4 nausea and vomiting, hypersensitivity reactions, neurotoxicity or arthralgia. One patient had grade 3 pulmonary toxicity due to drug-induced pneumonia during the first course which resolved after treatment with steroid therapy and supplemental oxygen. One patient had grade 3 hypoxia due to lymphangitis of carcinomatosa during the fourth course. One patient who had diabetes mellitus suddenly died of a cerebral infarction on day 17 of the first course of chemotherapy. This patient's death was not considered to be related to treatment.

Dose intensity. No doses of nedaplatin were reduced. Doses of paclitaxel were reduced in only 1 patient because of neutropenic fever. During a total of 138 courses, a total of 8 (5.8%) doses of paclitaxel were skipped on day 8 (2 doses) or 15 (6 doses). The most frequent reason for skipped doses was neutropenia. The next cycle was delayed in 15 courses. The main reason for delay was also neutropenia. The actual delivered dose intensities were 97.5% and 95.5%, respectively, of the planned doses of nedaplatin and paclitaxel.

Discussion

A recent meta-analysis has shown that combination chemotherapy with cisplatin plus a new agent yields a substantial survival advantage over that with carboplatin plus a new agent in patients with advanced NSCLC (18). However, cisplatin-based chemotherapy frequently causes nausea and vomiting and nephrotoxicity and necessitates additional hydration, which might lead to deterioration in quality of life (QOL). Because the primary role of chemotherapy in patients with advanced NSCLC is palliation, the effect on QOL is an important issue in determining the true value of any new therapy. Nedaplatin is a second-generation platinum derivative whose mechanism of action and a toxicity profile appear to be similar to those

of carboplatin, although the 2 agents have not been directly compared. Combination therapy with paclitaxel and nedaplatin inhibits tumor growth in mice to a significantly greater degree than does monotherapy with paclitaxel or nedaplatin (19). Furthermore, the antitumor activity of the combination of paclitaxel and nedaplatin is superior to that of the combination of paclitaxel plus cisplatin or carboplatin (19). In addition, a study in sheep has shown that distribution in the lung after infusion is greater with nedaplatin than with cisplatin (20). These findings suggest that nedaplatin would have greater efficacy than other platinum compounds in patients with NSCLC.

Several recent randomized phase III trials in patients with NSCLC have achieved overall response rates of 17% to 38%, with MSTs of 6.6 to 14 months, 1-year survival rates of 16% to 59.6% and TTPs of 3.1 to 7.2 months (1, 2, 21-24). In the present study, the overall response rate was 52.3%, with a MST of 13 months, a 1-year survival rate of 62% and TTP of 5 months. These results compare favorably with those of most published trials in patients with NSCLC. However, comparing these results with those of other studies of second-line treatment is difficult because of the inclusion of patients with different prognostic factors.

In recent randomized phase III trials for advanced NSCLC, rates of grade 3 to 4 neutropenia, thrombocytopenia and anemia have ranged from 13% to 88%, 1% to 50% and 4% to 31%, respectively (1, 2, 21-24). In this study, most hematologic toxicities were only mildly to moderately severe: grade 3 to 4 hematologic toxicities included neutropenia in 38.3% of patients, thrombocytopenia in 2.1% and anemia in 23.4%. These rates of toxicity compare favorably with those in most recently published trials in patients with advanced NSCLC.

In the above mentioned randomized phase III trials, rates of grade 3 to 4 nausea, vomiting and neurotoxicity have ranged from 1% to 37%, 1% to 35% and 0% to 18%, respectively (1, 2, 21-24). In this study, no patients had grade 3 to 4 nausea, vomiting, arthralgia or neurotoxicity. A previous study has reported that if the weekly paclitaxel dose is 100 mg/m² or less, neurotoxicity is absent or mild in most patients (25). Although the rates of hepatic dysfunction and electrolyte abnormality were higher in this trial than in other recent trials, all cases in this trial were transient and only mildly to moderately severe. In a previous phase I study, hepatic dysfunction developed in 48% of patients (17). The rate of hepatic dysfunction when nedaplatin is used in combination with other agents has ranged from 20% to 55% (14, 16). Therefore, nedaplatin could be responsible for hepatic dysfunction. Although grade 3 drug-induced interstitial pneumonia developed in 1 patient, it resolved with steroid therapy.

Recent randomized phase II or III trials in patients with NSCLC have found that the regimen of weekly paclitaxel and

weekly or 3-weekly carboplatin is as effective as the regimen of 3-weekly paclitaxel with carboplatin (22, 24, 26). However, the regimens had different toxicity profiles. Belani *et al.* have reported that grade 3 to 4 anemia is more frequent with weekly paclitaxel, although grade 2 to 3 neuropathy and arthralgia were more frequent with 3-weekly paclitaxel (22). Other studies have found that grade 3 to 4 sensory neuropathy or severe myalgias and arthralgias occur more frequently with 3-weekly paclitaxel and carboplatin, whereas grade 3 to 4 diarrhea, thrombocytopenia and anemia occur more frequently with the regimen of weekly paclitaxel (24, 26). In this study, no patients had grade 3 to 4 thrombocytopenia or diarrhea, although grade 3 to 4 anemia did develop in 23.4% of patients. Therefore, the combination of nedaplatin and weekly paclitaxel is an acceptable therapeutic option for patients with advanced NSCLC.

The tolerability of nedaplatin and weekly paclitaxel is further supported by the similarity of the planned and the actual dose intensities of the 2 drugs. The dose intensity of paclitaxel in the study was 50% higher than that of the combination of nedaplatin and monthly paclitaxel previously reported (27, 28). Nevertheless delivered dose intensities as percentages of planned dose intensities were 97.5% for nedaplatin and 95.5% for paclitaxel.

In conclusion, the present phase II study is the first to examine the combination therapy of nedaplatin and weekly paclitaxel for advanced NSCLC. The efficacy and toxicity documented in this trial compare favorably with those of other trials in patients with advanced NSCLC. It is believed that the combination of nedaplatin and weekly paclitaxel is an acceptable therapeutic option for patients with untreated advanced NSCLC.

References

- Ohe Y, Ohashi Y, Kubota K, Tamura T, Nakagawa K, Negoro S, Nishiwaki Y, Saijo N, Ariyoshi Y and Fukuoka M: Randomized phase III study of cisplatin plus irinotecan *versus* carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small cell lung cancer: four-arm cooperative study in Japan. *Ann Oncol* 18: 317-323, 2007.
- Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J and Johnson DH: Eastern Cooperative Oncology Group Comparison of four chemotherapy regimens for advanced non-small-cell cancer. *N Engl J Med* 346: 92-98, 2002.
- Sandler A, Gray R, Perry M, Brahmer J, Schiller JH, Dowlati A, Lilienbaum R and Johnson DH: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 355: 2542-2550, 2006.
- Giaccone G, Herbst RS, Manegold C, Scagliotti G, Rosell R, Miller V, Natale RB, Schiller JH, Von Pawel J, Pluzanska A, Gatzemeier U, Grous J, Ochs JS, Averbuch SD, Wolf MK, Rennie P, Fandi A and Johnson DH: Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial-INTACT 1. *J Clin Oncol* 22: 777-84, 2004.
- Herbst RS, Giaccone G, Schiller JH, Natale RB, Miller V, Manegold C, Scagliotti G, Rosell R, Oliff I, Reeves JA, Wolf MK, Krebs AD, Averbuch SD, Ochs JS, Grous J, Fandi A and Johnson DH: Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial-INTACT 2. *J Clin Oncol* 22: 785-94, 2004.
- Herbst RS, Prager D, Hermann R, Fehrenbacher L, Johnson BE, Sandler A, Kris MG, Tran HT, Klein P, Li X, Ramies D, Johnson DH and Miller VA: TRIBUTE Investigator Group.: TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 23: 5892-5899, 2005.
- Gatzemeier U, Pluzanska A, Szczesna A, Kaukel E, Roubec J, De Rosa F, Milanowski J, Karnicka-Mlodkowski H, Pesek M, Serwatowski P, Ramlau R, Janaskova T, Vansteenkiste J, Strausz J, Manikhas GM and Von Pawel J: Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: The Tarceva Lung Cancer Investigation trial. *J Clin Oncol* 25: 1545-1552, 2007.
- Georgiadis MS, Russell EK, Gazdar AF and Johnson BE: Paclitaxel cytotoxicity against human lung cancer cell lines increases with prolonged exposure durations. *Clin Cancer Res* 3: 449-454, 1997.
- Liebmann JE, Cook JA, Lipschultz C, Teague D, Fisher J and Mitchell JB: Cytotoxic studies of paclitaxel (Taxol) in human tumor cell lines. *Br J Cancer* 68: 1104-1109, 1993.
- Belotti D, Vergani V, Drudis T, Borsotti P, Pitelli MR, Viale G, Giavazzi R and Tarabozetti G: The microtubule-affecting drug paclitaxel has antiangiogenic activity. *Clin Cancer Res* 2: 1843-1849, 1996.
- Reshkin SJ, Bellizzi A, Cardone RA, Tommasino M, Casavola V and Paradiso A: Paclitaxel induces apoptosis *via* protein kinase A- and p38 mitogen-activated protein-dependent inhibition of the Na(+)/H(+) exchanger (NHE) isoform 1 in human breast cancer cells. *Clin Cancer Res* 9: 2366-2373, 2003.
- Akerley W, Glantz M, Choy H, Rege V, Sambandam S, Joseph P, Yee L, Rodrigues B, Wingate P and Leone L: Phase I trial of weekly paclitaxel in advanced lung cancer. *J Clin Oncol* 16: 153-158, 1998.
- Shiratori O, Kanai H and Uchida N (eds.): Recent advances in chemotherapy: Antitumor activity of 254-S, a platinum complex, in rodents. University of Tokyo Press, Tokyo, 1985.
- Furuse K, Fukuoka M, Asamoto H, Niitani H, Kimura I, Sakuma A and Yamaguchi Y: A randomized comparative study of 254-S plus Vindesine (VDS) *vs.* Cisplatin plus VDS in patients with advanced non-small cell lung cancer. *Jpn J Cancer Chemother* 19: 1019-1026, 1992 (in Japanese).
- Oshita F, Yamada K, Kato Y, Ikehara M, Noda K, Tanaka G, Nomura I, Suzuki R and Saito H: Phase I/II study of escalating doses of nedaplatin in combination with irinotecan for advanced non-small cell lung cancer. *Cancer Chemother Pharmacol* 52: 73-78, 2003.
- Shirai T, Hirose T, Noda M, Ando K, Ishida H, Hosaka T, Ozawa T, Okuda K, Ohnishi T, Ohmori T, Horichi N and Adachi M: Phase II study of the combination of gemcitabine and nedaplatin for advanced non-small cell lung cancer. *Lung Cancer* 52: 181-187, 2006.
- Okuda K, Hirose T, Ishida H, Kusumoto S, Sugiyama T, Ando K, Shirai T, Ohnishi T, Horichi N, Ohmori T and Adachi M: Phase I study of the combination of nedaplatin and weekly paclitaxel in patients with advanced non-small cell lung cancer. *Cancer Chemother Pharmacol* 61: 829-835, 2008.

- 18 Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M and Tanimoto M: Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 22: 3852-3859, 2004.
- 19 Yamada H, Uchida N, Maekawa R and Yoshioka T: Sequence-dependent antitumor efficacy of combination chemotherapy with nedaplatin, a newly developed platinum, and paclitaxel. *Cancer Lett* 172: 17-25, 2001.
- 20 Koizumi T, Kubo K, Shinozaki S, Koyama S, Amari T, Hayano T, Fujimoto K, Kobayashi T, Sekiguchi M and Sakai R: Pharmacokinetic evaluation of (glycolato-O,O') diammine platinum (II) in lung lymph in sheep. *Jpn J Cancer Res* 84: 468-473, 1993.
- 21 Kelly K, Crowley J, Burn PA Jr., Presant CA, Grevstad PK, Moinpour CM, Ramsey SD, Wozniak AJ, Weiss GR, Moore DF, Israel VK, Livingston RB and Gandara DR: Randomized phase III trial of paclitaxel plus carboplatin *versus* vinorelbine plus cisplatin in the treatment of patient with advanced non-small-cell lung cancer: A Southwest Oncology Group trial. *J Clin Oncol* 19: 3210-3218, 2001.
- 22 Belani CP, Ramalingam S, Perry MC, LaRocca RV, Rinaldi D, Gable P and Tester WJ: Randomized phase III study of weekly paclitaxel in combination with carboplatin *versus* standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated non-small-cell lung cancer. *J Clin Oncol* 26: 468-473, 2008.
- 23 Scagliotti GV, Marini F, Rinaldi M, Crinò L, Gridelli C, Ricci S, Matano E, Boni C, Marangolo M, Failla G, Altavilla G, Adamo V, Ceribelli A, Clerici M, Di Costanzo F, Frontini L and Tonato M: Italian Lung Cancer Project: Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol* 20: 4285-91, 2002.
- 24 Schuette W, Blankenburg T, Guschall W, Ditttrich I, Schroeder M, Schweisfurth H, Chemaissani A, Schumann C, Dickgreber N, Appel T and Ukena D: Multicenter randomized trial for stage IIIB/IV non-small-cell lung cancer using every 3-week *versus* weekly paclitaxel/ carboplatin. *Clin Lung Cancer* 7: 338-343, 2006.
- 25 Seidman AD, Hudis CA, Albanel J, Tong W, Tepler I, Currie V, Moynahan ME, Theodoulou M, Gollub M, Baselga J and Norton L: Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. *J Clin Oncol* 16: 3353-3361, 1998.
- 26 Socinski MA, Ivanova A, Bakri K, Wall J, Bagstrom MQ, Hensing TA, Mears A, Tynan M, Beaumont J, Peterman H and Niell HB: 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* 17: 104-109, 2006.
- 27 Yoshiike F, Koizumi T, Kitaguchi Y, Hatayama O, Yasuo M, Sasabayashi M, Wakamatsu H, Fujimoto K and Kubo K: Phase I trial of nedaplatin and paclitaxel for patients with non-small cell lung cancer. *J Chemother* 17: 550-554, 2005.
- 28 Sekine I, Nokihara H, Horiike A, Yamamoto N, Kunitoh H, Ohe Y, Tamura T, Kodama T and Saijo N: Phase I study of cisplatin analogue nedaplatin (254-S) and paclitaxel in patients with unresectable squamous cell carcinoma. *Br J Cancer* 90: 1152-1158, 2004.

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