Table 3 Overall objective response

	Number	%
Number of patients evaluated	101	
Complete response (CR)	1	1.0
Partial response (PR)	19	18.8
Stable disease (SD)	52	51.5
Progressive disease (PD)	25	24.8
Not evaluable	4	4.0
Response rate % (95% CI)	19.8 (12.0–27.6)	
Disease control rate[a] % (95% CI)	71.3 (62.5–80.1)	

[a] CR + PR + S.D.

who had failed several previous chemotherapy regimens, and patients with an ECOG PS score of 3.

3.2. Response to treatment

Table 3 shows an objective response observed in this study. Twenty responders were evaluated and the overall response rate was 19.8%. One patient achieved a complete response, 19 patients exhibited a partial response and 52 patients had stable disease, resulting in a disease control rate (objective responses plus stable disease) of 71.3%. When evaluated using patient characteristics, we determined the response rate detailed in Fig. 1. All patients that responded had adenocarcinoma of the lung as the histological subtype. In addition, for the factors 'female' and 'never-smoker', there were higher response rates than in 'male' and 'smoker' respectively, while RR was similar for age, stage and pre-treatment. The response rate of 'female' and 'never-smoker' were 37.8 and 32.6%, respectively. Using the Fisher's exact test, the predictive factors which were associated with a response were 'female' (37.8% versus 9.4%; $P = 0.0006$), 'adenocarcinoma' (24.7% versus 0%; $P = 0.0104$), 'good PS' (0–1) (26.0% versus 0%; $P = 0.0028$), and never-smoker (32.6% versus 9.1%; $P = 0.0025$). There were no significant differences for age, stage and pre-treatment (Table 4). A multivariate analysis was performed against the four significant predictive factors in univariate analysis (Table 5). Because the incidence of the female factor is very strongly correlated to the never-smoker factor, the statistical assay was rather unstable if the two factors were analyzed simultaneously. We then investigated two patterns of multivariate analysis. One analysis excluded smoking and the other excluded gender. If smoking status was extracted, then female and good performance status were statistically significant. If gender was extracted, then non-smoking and good performance were statistically significant. The odds of a response were over three times higher for patients with adenocarcinoma than for patients with other histologies, however, this is not considered to be statistically significant because the group in this study was of a small size and included a high percentage of adenocarcinoma.

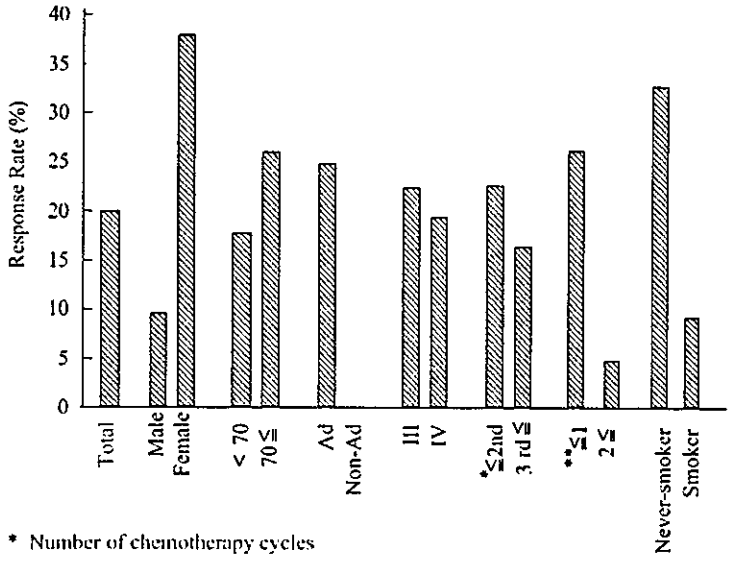

Fig. 1 Tumor response rate of the subgroups.

Table 4 Predictive factors associated with an objective response by univariate analysis

Parameter	*N*	Responder	RR (%)	*P*-value
Smoking index				
Non-smoker	55	15	32.6	
Smoker	46	5	9.1	0.0025
Gender				
Female	37	14	37.8	
Male	64	6	9.4	0.0006
Histology				
Adenocarcinoma	81	20	24.7	
Others	20	0	0.0	0.0104
PS				
0–1	77	20	26.0	
≥2	24	0	0.0	0.0028
Pre-treatment				
≤2 regimens	58	13	22.4	
≥3 regimens	43	7	16.3	N.S.
Age (years)				
≤70	74	13	17.6	
≥71	27	7	25.9	N.S.
Stage				
IIIB	18	4	22.2	
IV	83	16	19.3	N.S.

Abbreviations: N.S., not significant.

3.3. Toxicity

Drug-related AEs of all patients are shown in (Table 6). A total of 101 patients were evaluated for toxicity. The most frequent drug-related AEs were a rash, dry skin and diarrhea. Most of these AEs were mild (Grade 1 or Grade 2) and were controllable. Of all the drug-related AEs evaluated, Grade 3 or Grade 4 AEs were seen in less than 5%, and Grade 4 drug-related AEs were only pneumonitis. Grade 3 or 4 AEs required a treatment interruption, but recovered after discontinuation of gefitinib, except with pneumonitis. Four patients developed greater than Grade 3 pneumonitis requiring hospitalization. All patients had a fever and severe hypoxemia on admission. As soon as possible, all patients were administered steroid therapy. While two patients recovered with the steroid therapy, two patients died within 40 days after the administration of gefitinib. Hematological toxicities were not observed.

3.4. Survival

The median survival time of the patients who were 'good PS' (0 or I) and 'poor PS' (2 or 3) was 353 and 97 days, respectively, and this difference was significant ($P = 0.0001$, log-rank test) (Fig. 2A). The MST of females was significantly longer than that of males (596 days versus 178 days, $P = 0.004$) (Fig. 2B). Furthermore, a low smoking index (<900) significantly prolonged survival (MST: 301 days versus 149 days, $P = 0.031$) (Fig. 2C). Age did not influence the survival benefit of the patients treated with gefitinib (Fig. 2D).

4. Discussion

Gefitinib is an orally active, selective EGFR tyrosine kinase inhibitor that blocks signal transduction pathways, and is one of the promising molecular targeted drugs used in the treatment of advanced NSCLC [16,17,20]. Although the large scale of the phase II study (IDEAL-1) [15] has already confirmed that there were statistically significant differences in efficacy for 'adenocarcinoma' and 'female' by multivariate analysis, the population was essentially biased towards young people with good performance status who had conserved, good organ functions. To clarify the predictive prognostic fac-

Table 5 Predictive factors associated with an objective response by multivariate analysis

Parameter	Odds ratio	95% CI	*P*-value
Extraction of smoking			
Gender (female vs. male)	0.163	0.040–0.585	0.0032
Performance status (1 vs. 2)	0.061	0.000–0.415	0.0018
Histology (Adeno[a] vs. others)	3.326	0.435–infinity	N.S.
Extraction of gender			
Non-smoking (non vs. ≥1)	0.297	0.063–0.959	0.0417
Performance status (1 vs. 2)	0.096	0.000–0.628	0.0101
Histology (Adeno vs. others)	4.385	0.588–infinity	N.S.

Abbreviations: N.S., not significant; CI, confidence interval.
[a] Adenocarcinoma.

Table 6 Patients with drug-related adverse events (NCI-CTC)

Adverse event	Number of patients ($N = 101$)				
	Grade 1	Grade 2	Grade 3	Grade 4/5	Total
Rash	33 (32.6%)	21 (20.8%)	3 (3.0%)	0	57 (56.4%)
Dry skin	24 (23.7%)	3 (3.0%)	0	0	27 (26.7%)
Pruritis	9 (9.0%)	7 (7.0%)	0	0	16 (16.0%)
Diarrhea	19 (18.8%)	4 (4.0%)	0	0	23 (22.8%)
Nausea	6 (6.0%)	1 (1.0%)	0	0	7 (7.0%)
Vomiting	3 (3.0%)	0	0	0	3 (3.0%)
Anorexia	7 (7.0%)	0	0	0	7 (7.0%)
ALT increased	5 (5.0%)	2 (2.0%)	5 (5.0%)	0	12(13.0%)
AST increased	8 (8.0%)	2 (2.0%)	3 (3.0%)	0	13 (13.0%)
Pneumonitis	0	0	2 (2.0%)	2[a] (2.0%)	4 (4.0%)

[a] Treatment-related death (Grade 5).

tors in a practical setting, we retrospectively analysed the patients who received a single regimen of gefitinib at our institute. Multivariate analysis demonstrated that the predictive factors which were associated with a response were 'female', 'good PS' and 'never-smoker'. In survival analyses, the factors 'female', 'good PS', and a low smoking index also significantly prolonged survival.

The mechanism by which these factors produced better prognosis has not been clarified.

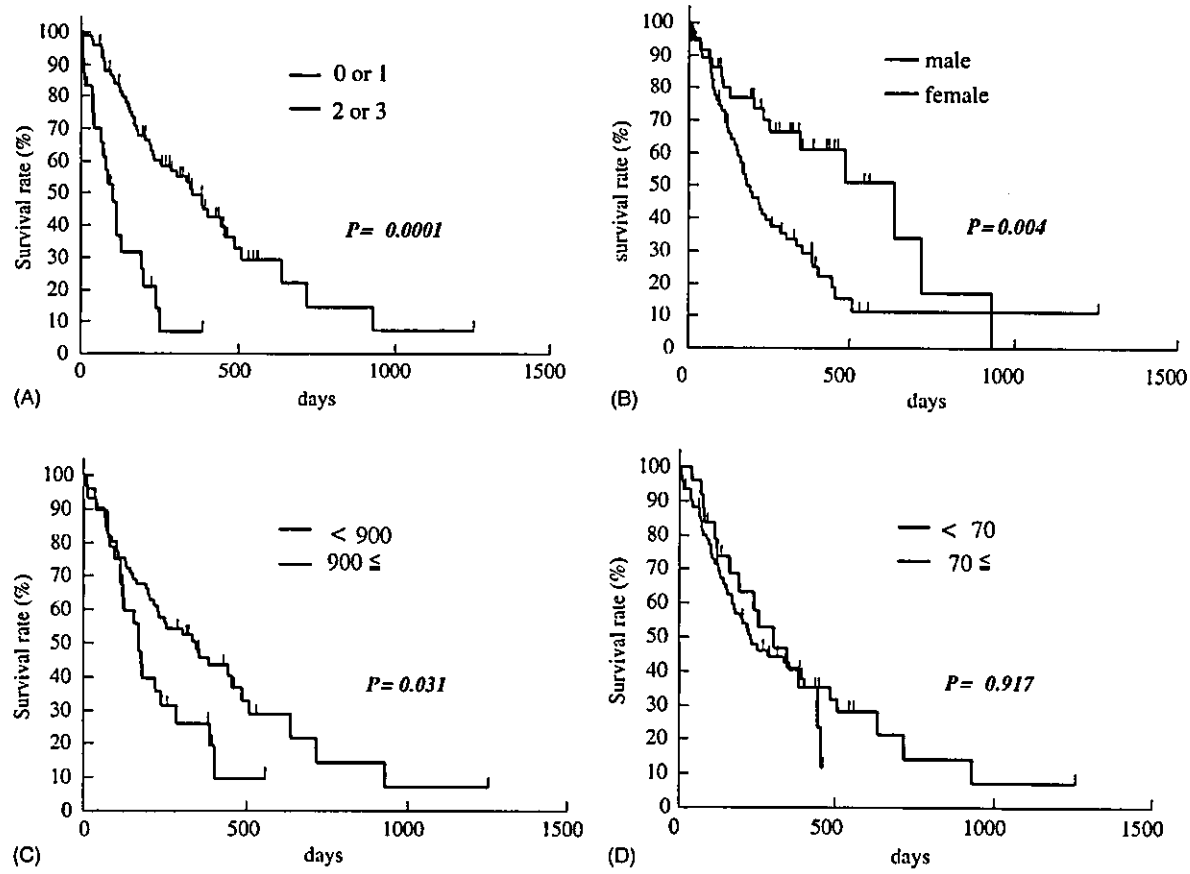

Fig. 2 A comparison of survival of: (A) PS 0, 1 vs. PS 2, 3; (B) gender: male vs. female; (C) smoking index: <900 vs. ≥900; and (D) age: <70 vs. ≥70.

Estrogen and progesterone may up-regulate EGFR in normal tissues [21], and activation of steroid hormones might impact on EGFR function in NSCLC [22]. Another explanation may be that the steroid hormone receptor might interact with EGFR and influence the response of an EGFR inhibitor.

Multivariate analysis in IDEAL-1 showed that PS was not a significant prognostic factor, however, the population of the study was restricted with regards to good PS. Although gefitinib was considered as an effector of symptom improvement in the phase II trial, the indication for patients with poor PS is controversial. Several authors described the case reports about the efficacy of gefitinib in NSCLC patients with poor PS [23,24] or with brain metastases [25]. Although 'good PS' were significant prognostic factor in this trial, gefitinib still might be a candidate drug for patients with poor PS, because of restriction of the use of other anti-cancer drug by their toxicities.

Elderly patients exhibited an equivalent response to young patients in this study. Recent data suggested, gefitinib is safe and well tolerated in elderly pretreated NSCLC patients [26]. A phase II study of gefitinib for elderly patients in NSCLC is needed.

A low smoking index was revealed as a predictive prognostic factor following a single regimen of gefitinib. Erlotinib is also administered orally and is a highly selective EGFR tyrosine kinase inhibitor [27] with a quinazolinamine-based structure similar to that of gefitinib. In the phase II study of erlotinib in NSCLC or bronchial alveolar carcinoma [28], a non-smoking history was also a prognostic factor. Chronic exposure to nicotine increases the expression level and phosphorylation status of EGFR and impairs its function [29]. Moreover, smoking produces overexpression of Her2/neu that binds to EGFR as a hetero-dimer in the tissue of normal bronchus. Expression of EGFR or Her2/neu or both in tissue samples by immunohistochemistry has not correlated in the response of gefitinib [30], however the different type of dimers formed between EGFR families might influence the response to gefitinib.

Four patients (4% of the patients) developed interstitial lung disease (ILD). Continuous smoking disrupted surfactant protein A or D [31,32], and the serum levels of the proteins were increased [33]. As 'smoking history' and 'male' are significant risk factors of ILD and also in treatment with gefitinib [34], a serum level of the surfactant protein A or D might be a predictive marker of ILD. Patients who are female and non-smokers are most likely to receive a high benefit and low risk with gefitinib treatment.

Although more basic biological research is needed to find the mechanism of action, we have found several predictive prognostic factors associated with the practical use of gefitinib. This is necessary clinical information which is important in order to set eligibility criteria for future clinical trials with gefitinib.

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References

[1] Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710–7.
[2] Non-Small-Cell Lung Cancer Collaborative Group. Chemotherapy in non-small-cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Br Med J 311 (1995) 899–909.
[3] Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095–103.
[4] Fossella FV, DeVore R, Kerr RN, et al. Randomized phase II trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum containing chemotherapy regimens. J Clin Oncol 2000;18:2354–62.
[5] Salomon D, Brandt R, Ciardiello F, et al. Epidermal growth factor-related peptides and their receptors in human malignancies. Crit Rev Oncol Hematol 1995;19:183–232.
[6] Rusch V, Baselga J, Cordon-Cardo C, et al. Differential expression of the epidermal growth factor receptor and its ligands in primary non-small-cell lung cancers and adjacent benign lung. Cancer Res 1993;53:2379–85.
[7] Fujino S, Enokibori T, Tezuka N, et al. A comparison of epidermal growth factor receptor levels and other prognostic parameters in non-small-cell lung cancer. Eur J Cancer 1996;32A:2070–4.
[8] Pavelic K, Banjac Z, Pavelic J, et al. Evidence for a role of EGF receptor in the progression of human lung carcinoma. Anticancer Res 1993;13:1133–7.
[9] Volm M, Rittgen W, Drings P. Prognostic value of ERBB-1, VEGF, cyclin A, FOS, JUN and MYC in patients with squamous cell lung carcinomas. Br J Cancer 1998;77:663–9.
[10] Baselga J, Pfister D, Cooper M, et al. Phase I study of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin. J Clin Oncol 2000;18:904–14.
[11] Baselga J, Averbuch S. ZD1839 ('Iressa') as an anticancer agent. Drugs 2000;60(Suppl 1):33–40.
[12] Nakagawa K, Tamura T, Negoro S, et al. Phase I pharmacokinetic trial of the selective oral epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in Japanese patients with solid malignant tumors. Ann Oncol 2003;14:922–30.

[13] Ranson M, Hammond L, Ferry D, et al. ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of phase I trial. J Clin Oncol 2002;20:2240–50.
[14] Herbst R, Maddox AM, Rothenberg M, et al. Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small-cell lung cancer and other solid tumors: results of a phase I trial. J Clin Oncol 2002;120:3815–25.
[15] Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with non-small-cell lung cancer. J Clin Oncol 2003;21:2237–46.
[16] Kris M, Natale R, Herbst R, et al. A phase II trial of ZD 1839 ('Iressa') in advanced non-small-cell lung cancer (NSCLC) patients who had failed platinum- and docetaxel-based regimen (IDEAL 2). Proc Am Soc Clin Oncol 2002;21:292a.
[17] Giaccone G, Johnson DH, Manegold C, et al. A phase III clinical trial of ZD 1839 ('Iressa') in combination with gemcitabine and cisplatin in chemotherapy-naive patients with advanced non-small-cell lung cancer (INTACT I). Ann Oncol 2002;113(Suppl 5):A-4.
[18] Johnson DH, Herbst R, Giaccone G, et al. ZD1839 ('Iressa') in combination with paclitaxel and carboplatin in chemotherapy naive patients with advanced non-small-cell lung cancer (NSCLC): results from a phase III clinical trial (INTACT 2). Ann Oncol 2002;13(Suppl 5):A-468.
[19] Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.
[20] Santoro A, Cavina R, Latteri F, et al. Activity of a specific inhibitor, gefitinib (Iressa™, ZD1839), of epidermal growth factor receptor in refractory non-small-cell lung cancer. Ann Oncol 2004;15:33–7.
[21] Shimomura Y, Matsuo H, Samoto T, Maruo T. Up-regulation by progesterone of proliferating cell nuclear antigen and epidermal growth factor expression in human uterine leiomyoma. J Clin Endocrinol Metab 1998;83:2192–8.
[22] Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2001;2:127–37.
[23] Fujiwara K, Kiura K, Ueoka H, et al. Dramatic effect of ZD 1839 ('Iressa') in a patient with advanced non-small-cell lung cancer and poor performance status. Lung Cancer 2003;40:73–6.
[24] Ranson M, Thatcher N. Commentary on ZD1839 (Iressa) in non small cell lung cancer. Lung Cancer 2003;40:77–8.
[25] Cappuzzo F, Ardizzoni A, Soto-Parra H, et al. Epidermal growth factor receptor targeted therapy by ZD1839 (Iressa) in patients with brain metastases from non-small-cell lung cancer (NSCLC). Lung Cancer 2003;41:227–31.
[26] Cappuzzo F, Bartolini S, Ceresoli GL, et al. Efficacy and tolerability of gefitinib in pretreated elderly patients with advanced non-small-cell lung cancer (NSCLC). Br J Cancer 2004;90:82–6.
[27] Hidalgo M, Siu LL, Nemunaitis J, et al. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. J Clin Oncol 2001;19:3267–79.
[28] Miller VA, Patel J, Shah N, et al. The epidermal growth factor receptor tyrosine kinase inhibitor Erlotinib (OSI-774) shows promising activity in patients with bronchioalveolar cell carcinoma (BAC): Preliminary results of a phase II trial. Proc Am Soc Clin Oncol 2003;22:A-2491.
[29] Wang SL, Milles M, Wu-Wang CY, et al. Effect of cigarette smoking on salivary epidermal growth factor (EGF) and EGF receptor in human buccal mucosa. Toxicology 1992;75:145–57.
[30] Cappuzzo F, Gregorc V, Rossi E, et al. Gefitinib in pretreated non-small-cell lung cancer (NSCLC): analysis of efficacy and correlation with HER2 and epidermal growth factor receptor expression in locally advanced or metastatic NSCLC. J Clin Oncol 2003;21:2658–63.
[31] Subramaniam S, Whitsett JA, Hull W, Gairola CG. Alteration of pulmonary surfactant proteins in rats chronically exposed to cigarette smoke. Toxicol Appl Pharmacol 1996;140:274–80.
[32] Foster DJ, Yan X, Bellotto DJ, et al. Expression of epidermal growth factor and surfactant proteins during postnatal and compensatory lung growth. Am J Physiol Lung Cell Mol Physiol 2002;283:981–90.
[33] Zhang F, Pao W, Umphress SM, Jakowlew SB, et al. Serum levels of surfactant protein D are increased in mice with lung tumors. Cancer Res 2003;63:5889–94.
[34] Tamura K, Yamamoto N, Takeda K, et al. An epidemiological survey for interstitial lung disease induced by gefitinib in patients with advanced non-small-cell lung cancer. West Japan Thoracic Oncology Group (WJTOG). Proc Eur Cancer Soc 2003;1(Suppl 5):A-56.

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Combination phase I study of nedaplatin and gemcitabine for advanced non-small-cell lung cancer

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To establish the toxicities and maximum tolerated dose (MTD) of nedaplatin with gemcitabine, and to observe their antitumour activity, we conducted a combination phase I study in advanced non-small-cell lung cancer (NSCLC). Patients received nedaplatin (60–100 mg m^{-2} given intravenously over 90 min) on day 1, and gemcitabine (800–1000 mg m^{-2} given intravenously over 30 min) on days 1, 8, every 3 weeks. In total, 20 patients with locally advanced or metastatic NSCLC who received no prior chemotherapy or one previous chemotherapy regimen were enrolled. The most frequent toxicities were neutropenia and thrombocytopenia; nonhaematological toxicities were generally mild. Three out of six patients experienced dose-limiting toxicities (neutropenia, thrombocytopenia and delayed anaemia) at dose level 4, 100 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine, which was regarded as the MTD. There were three partial responses, for an overall response rate of 16.7%. The median survival time and 1-year survival rate were 9.1 months and 34.1%, respectively. This combination is well tolerated and active for advanced NSCLC. The recommended dose is 80 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine. This combination chemotherapy warrants a phase II study and further evaluation in prospective randomised trials with cisplatin- or carboplatin-based combinations as first-line chemotherapy for advanced NSCLC.

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Keywords: combination phase I study; maximum tolerated dose; nedaplatin; gemcitabine; non-small-cell lung cancer

Based on the results of a meta-analysis (Non-Small Cell Lung Cancer Collaborative Group, 1995), cisplatin-based chemotherapy is considered the best available therapy for patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC). Although several new agents with novel mechanisms and significant activity against NSCLC have been introduced, such as taxanes, gemcitabine and vinorelbine, any of these agents used in combination with a platinum agent provide equivalent survival improvement (Kelly *et al*, 2001; Schiller *et al*, 2002; Fossella *et al*, 2003). The prognosis of advanced NSCLC patients who receive cisplatin-based chemotherapy is still poor, and the renal and gastrointestinal toxicities caused by cisplatin often limit its clinical use. Therefore, development of different treatment strategies is necessary.

Nedaplatin is a second-generation platinum derivative that has shown equivalent antitumour activity and lower toxicity – less nausea, and lower nephrotoxicity and neurotoxicity – than cisplatin (Kameyama *et al*, 1990; Ota *et al*, 1992). A phase I study demonstrated the maximum tolerated dose (MTD) and the recommended dose (RD) for phase II studies of nedaplatin was 120 and 100 mg m^{-2}, respectively, and the dose-limiting toxicity (DLT) was thrombocytopenia (Ota *et al*, 1992). Two independent phase II studies of nedaplatin for NSCLC showed response rates of 14.7 and 20.5%, respectively, and 16.7 and 12.5% with the patients who had received chemotherapy previously (Fukuda *et al*, 1990; Furuse *et al*, 1992a). Based on these promising results, a randomised study of nedaplatin–vindesine *vs* cisplatin–vindesine was conducted for previously untreated NSCLC patients in Japan and indicated that nedaplatin-based chemotherapy yielded similar response rates and overall survival (Furuse *et al*, 1992b). Leucopenia, renal toxicities and gastrointestinal toxicities were more frequent in the cisplatin–vindesine arm, while thrombocytopenia was more frequent in the nedaplatin–vindesine arm.

Gemcitabine, an analogue of deoxycytidine, is a pyrimidine antimetabolite, that shows a reproducible response rates of >20% with a median survival time of 9 months, offering a quality of life benefit in comparison with best supportive care (Abratt *et al*, 1994; Anderson *et al*, 1994; Gatzemeier *et al*, 1996; Anderson *et al*, 2000). The main toxicity of gemcitabine is mild-to-moderate myelosuppression. The combination of gemcitabine and cisplatin showed synergistic effects in preclinical studies because gemcitabine inhibited the repair of DNA damage caused by cisplatin (Bergman *et al*, 1996), and achieved high response rates along with improvements in median survival time in clinical setting (Sandler *et al*, 2000; Schiller *et al*, 2002; Alberola *et al*, 2003).

Recently, carboplatin has attracted attention ahead of nedaplatin because it has similar activity to cisplatin with fewer nonhaematological toxicities. The available data suggest that carboplatin–paclitaxel or carboplatin–gemcitabine should be considered among standard regimen for advanced NSCLC (Kelly *et al*, 2001; Grigorescu *et al*, 2002; Rudd *et al*, 2002; Schiller *et al*, 2002).

It seems that nedaplatin has activity and toxicity profiles similar to those of carboplatin, although no randomised trial has not been done to allow direct comparison (Fukuda *et al*, 1990; Furuse *et al*,

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1992a; Ota *et al*, 1992). Moreover, Matsumoto *et al* (2001) demonstrated that the combination of nedaplatin and gemcitabine resulted in enhanced inhibition of tumour growth *in vivo* and the antitumour efficacy of the combination was superior to that of cisplatin–gemcitabine or carboplatin–gemcitabine. Based on the results of a preclinical study, we designed the present phase I study of the efficacy of the combination of nedaplatin and gemcitabine for advanced NSCLC. The purpose of this study was to establish the toxicities and MTD of this combination, to determine the RD for phase II studies, and to observe their antitumour activity.

PATIENTS AND METHODS

Patient eligibility

Patients with histologic or cytologic confirmation of locally advanced or metastatic NSCLC who received either no prior chemotherapy or one previous chemotherapy regimen were eligible. The eligibility criteria were as follows; (1) measurable lesions; (2) age $\leqslant$75 years; (3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1; (4) adequate organ function (a white blood count (WBC) $\geqslant 4000\,\mu l^{-1}$, a neutrophil count $\geqslant 2000\,\mu l^{-1}$, a platelet count $\geqslant 100\,000\,\mu l^{-1}$, a haemoglobin count $\geqslant 9.5\,g\,dl^{-1}$, serum total bilirubin $\leqslant 1.5\,mg\,dl^{-1}$, serum transaminase $\leqslant 2\times$ upper normal limits, a serum creatinine $\leqslant$ upper normal limits, blood urea nitrogen (BUN) $\leqslant 25\,mg\,dl^{-1}$, $PaO_2 \geqslant 60$ mmHg or $SpO_2 \geqslant 90\%$]; and (5) normal electrocardiogram (ECG). At least 4 weeks must have passed after the completion of previous therapy and the patients had to have recovered from the toxic effects of previous therapy. The exclusion criteria consisted of pulmonary fibrosis or interstitial pneumonitis with symptoms or apparent abnormalities on chest X-ray, massive pleural effusion or ascites, acute inflammation, pregnancy, lactation, symptomatic brain metastases, active concurrent malignancies, severe drug allergies, severe heart disease, cerebrovascular disease, uncontrollable diabetes mellitus or hypertension, severe infection, active peptic ulcer, ileus, paralysis intestinal, diarrhoea and jaundice. This study was performed at Kinki University School of Medicine and was approved by the Institutional Review Board. Written informed consent was obtained from all patients. This study was conducted in accordance with Declaration of Helsinki.

Pretreatment and follow-up studies

Prior to entry, a complete history was taken and physical examination including age, height, weight, performance status, histological diagnosis, tumour stage, contents of previous treatment and presence of a complication was performed. The pretreatment laboratory investigations included a complete blood cell count, differential WBC count, platelet count, serum electrolytes, total protein, albumin, total bilirubin, transaminase, alkaline phosphatase, lactate dehydrogenase, BUN, creatinine, creatinine clearance and urinalysis. After the initiation of therapy, a complete blood cell count with a differential WBC count was performed at least twice a week. Blood chemistry profiles and chest X-ray films were obtained weekly. The lesion measurements were performed during at least every second course. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2 and tumour responses were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Therasse *et al*, 2000). Time to progression was measured from the date of registration to the date of first progression or death from any cause. Survival time was also measured from the date of registration to the date of death or latest follow-up, and was calculated using the Kaplan–Meier method (Kaplan and Meier, 1958).

Drug administration and dose escalation

The treatment schedule included nedaplatin, diluted with 500 ml of normal saline, given intravenously over 90 min on day 1, and gemcitabine with 100 ml of normal saline, given intravenously over 30 min after the completion of nedaplatin infusion on days 1 and 8, every 3 weeks. All patients were allowed to receive antiemetics with dexamethasone and granisetron, and post-therapy hydration with 1000 ml of normal saline. Granulocyte colony-stimulating factor (G-CSF) prophylaxis was not administered. Doses of gemcitabine on day 8 were given if the WBC count was $>2000\,\mu l^{-1}$ and/or the platelet count was $>750\,000\,\mu l^{-1}$, and/or allergic reaction, fever, elevation of transaminase and pneumonitis were less than grade 2, and/or the other nonhaematological toxicities were less than grade 3. The subsequent courses were withheld until the toxic levels returned to those specified in the eligibility criteria. The doses of both drugs were decreased by one dose level if DLTs occurred. In the case of the initial dose level, the doses of nedaplatin and gemcitabine were reduced by 20 and $200\,mg\,m^{-2}$, respectively.

Dose escalations were performed as listed in Table 1. Intrapatient dose escalation was not allowed. At least three patients were treated at each dose level, and three additional patients were entered at the same dose level if DLT was observed in one of the first three patients. The MTD was defined as the dose level at which more than two of three patients, or three of six patients experienced DLT. The definition of DLT was as follows: (1) grade 4 leukopenia, (2) grade 4 neutropenia for more than 4 days, (3) thrombocytopenia $<20\,000\,\mu l^{-1}$, (4) grade 3 febrile neutropenia, (5) grade 3 nonhaematologic toxicity except for nausea/vomiting, (6) delay of administration of gemcitabine on day 8 over a week for toxicities.

RESULTS

Between August 2001 and February 2003, 20 patients were enrolled in this study. The total and the median number of courses were 56 and 3 (range 1–6), respectively. The patients' characteristics are shown in Table 2. The majority of patients had a PS of 1. There

Table 1 Dose-escalation schema

Dose level	Nedaplatin dose ($mg\,m^{-2}$)	Gemcitabine dose ($mg\,m^{-2}$)	No. of patients (courses)
1	60	800	3 (8)
2	80	800	3 (10)
3	80	1000	8 (18)
4	100	1000	6 (20)

Table 2 Patients' characteristics

No. of patients		20
Age, years	Median	63.5
	Range	36–74
Sex	Male/female	17/3
Performance status	0/1	5/15
Histology	Adeno/squamous	13/7
Stage	IIIB/IV	4/16
Prior therapy	None	5
	Surgery	5
	Radiation	6
	Chemotherapy	14
	CDDP-based	3
	CBDCA-based	4
	Nonplatinum	4
	UFT	2
	Gefitinin	1

were five previously untreated patients (level 3, two patients; level 4, three patients) and 15 (75%) previously treated patients. Of the previously treated patients, five had received prior surgery, five had prior radiotherapy, and 14 had prior chemotherapy. Seven had received platinum-based chemotherapy (cisplatin, three patients; carboplatin, four patients), and four a nonplatinum regimen. Responses to previous chemotherapy included partial response in five patients, stable disease in seven, progressive disease in one, and not evaluable in one. The median interval from previous treatment was 16 weeks (range 4–92.5 weeks). Out of 20 patients, 18 were assessable for toxicity and response. Two patients at level 3 were excluded from the toxicity and response evaluation because they had refused this study after registration.

Toxicities

The haematological and nonhaematological toxicities observed during the first course are shown in Tables 3 and 4, respectively. The most frequent toxicities observed in the first cycle were neutropenia and thrombocytopenia (Table 3). One-third of the patients had grade 3 thrombocytopenia, and one patient received a platelet transfusion during the first course. Three patients had grade 4 neutropenia for no longer than 4 days. The nadir for neutropenia and thrombocytopenia occurred on day 15 (median, range 5–18), and on day 15 (median, range 8–18), respectively. Nonhaematological toxicities generally were mild because none of the patients had experienced more than grade 3 in the first course (Table 4). The major toxicities following all courses are listed in Table 5. Grade 3 thrombocytopenia occurred in 16 out of 56 courses, and three patients received platelet transfusion (one patient at level 1, one at level 3 and one at level 4). However, no patient had haemorrhagic complications. The most frequent nonhaematological toxicities were elevation of transaminase activity, nausea and appetite loss, but all were mild. One previously untreated patient at level 3 experienced grade 3 pneumonitis after the fifth course, probably induced by this treatment, and the patient's condition improved after the administration of steroid. There was no treatment-related death. One of the 18 patients at level 4 underwent dose reduction after the first course due to neutropenia, and two patients at level 3 did not receive gemcitabine on day 8 because they had neutropenia, thrombocytopenia and high transaminase activity. Delays in the commencement of subsequent courses occurred in 11 courses, and the median length of the delay before starting the subsequent course was 21 days (21–35 days).

MTD and DLTs

At levels 1 and 2, none of the patients had developed a DLT. Haematological and nonhaematological toxicities were generally mild at these levels, although one patient had grade 3 thrombocytopenia at level 1. At level 3, two of six assessable patients had developed DLTs. Both could not receive their scheduled dose of gemcitabine on day 8 because they had neutropenia, thrombocytopenia and high transaminase activity. At level 4, three of six patients had developed DLTs. One patient received G-CSF for neutropenia, not lasting more than 4 days, which was considered as the DLT. Another patient required a platelet infusion because of thrombocytopenia $<20\,000\,\mu l^{-1}$. The third patient could not receive the second course due to the delayed anaemia, also considered as DLT. Therefore, dose level 4, 100 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine was regarded as the MTD. The recommended dose level for further phase II study was determined to be 80 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine (dose level 3 in this study).

Response and survival

There were three partial responses, for an overall response rate of 16.7%. As for squamous cell carcinoma, only one out of seven

Table 3 Haematological toxicity following first course of nedaplatin and gemcitabine

		WBC grade					ANC grade					plt grade					Hb grade				
Dose level	No. of patients	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1	3	0	2	1	0	0	0	1	2	0	0	0	1	1	1	0	0	2	1	0	0
2	3	1	0	2	0	0	1	0	1	1	0	0	3	0	0	0	0	1	2	0	0
3	6	1	1	2	1	0	2	0	0	3	1	1	2	1	2	0	3	3	0	0	0
4	6	1	0	3	2	0	0	0	3	1	2	0	2	1	3	0	0	3	3	0	0

Table 4 Nonhaematological toxicity following first course of nedaplatin and gemcitabine

		Nausea grade					Vomiting grade					Fatigue grade					Transaminase grade				
Dose level	No. of patients	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1	3	3	0	0	0	0	3	0	0	0	0	2	1	0	0	0	3	0	0	0	0
2	3	1	1	1	0	0	3	0	0	0	0	1	2	0	0	0	1	2	0	0	0
3	6	2	3	1	0	0	5	1	0	0	0	4	2	0	0	0	3	1	2	0	0
4	6	2	2	2	0	0	6	0	0	0	0	6	0	0	0	0	1	5	0	0	0

		Infection grade					Fever grade					Appetite loss grade					Constipation grade				
Dose level	No. of patients	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1	3	3	0	0	0	0	3	0	0	0	0	3	0	0	0	0	3	0	0	0	0
2	3	2	0	1	0	0	2	1	0	0	0	1	2	0	0	0	3	0	0	0	0
3	6	6	0	0	0	0	6	0	0	0	0	2	4	0	0	0	4	2	0	0	0
4	6	4	0	2	0	0	6	0	0	0	0	2	4	0	0	0	4	2	0	0	0

Table 5 Toxicities following all courses of nedaplatin and gemcitabine (56)

	Grade			
	1	2	3	4
WBC	13	26	10	0
ANC	15	15	13	3
Hb	24	27	1	0
Plt	22	14	16	0
Nausea	17	4	0	0
Vomiting	6	0	0	0
Appetite loss	21	0	0	0
Fatigue	15	0	0	0
Constipation	6	7	0	0
Transaminase	27	5	0	0
Neuropathy	5	0	0	0
Pneumonitis	0	0	1	0
Fever	1	0	0	0
Infection	0	3	1	0

patients had a partial response. The median progression-free survival time was 5.1 months. The median survival time and 1-year survival rate were 9.1 months and 34.1%, respectively. Out of 15 patients who had received prior treatment, two (13.3%) achieved a partial response, and there was no clear relationship between responses to previous treatment and responses to this regimen. For previously treated patients, the median survival time and 1-year survival rate were 9.2 months and 40.3%, respectively. Among five previously untreated patients, one (20%) achieved a partial response and the median survival time and 1-year survival rate were 12.0 months and 50.0%, respectively.

DISCUSSION

Many recent randomised clinical trials have shown that the combinations of cisplatin with one of the new agents, such as gemcitabine, taxanes or vinorelbine, is the standard therapy for patients with locally advanced or metastatic NSCLC (Non-Small Cell Lung Cancer Collaborative Group, 1995; Kelly *et al*, 2001; Schiller *et al*, 2002; Fossella *et al*, 2003). As it is known that cisplatin strongly promotes nephrotoxicity, neurotoxicity and gastrointestinal toxicity, second-generation platinum-containing compounds including carboplatin have attracted attention. Based on several randomised trials that have shown that the combination of carboplatin with paclitaxel produces similar response rates and overall survival with a more favourable toxicity profile than the combination of cisplatin with new agents (Kelly *et al*, 2001; Scagliotti *et al*, 2002; Schiller *et al*, 2002), combined therapy of carboplatin and paclitaxel is considered to be a standard therapy. More recently, the combination of carboplatin with gemcitabine has become attractive as a therapy for advanced NSCLC. Some randomised studies have indicated that carboplatin–gemcitabine regimen offers equivalent median survival compared with cisplatin–gemcitabine or mitomycin–vinblastine–cisplatin /mitomycin–ifosfamide–cisplatin (Danson *et al*, 2003; Zatloukal *et al*, 2003), and results in significant improvements in overall survival over those for gemcitabine alone or the older cisplatin-containing regimens (Grigorescu *et al*, 2002; Rudd *et al*, 2002; Sederholm, 2002). However, neutropenia and thrombocytopenia were more common in carboplatin–gemcitabine regimens than others; thrombocytopenia was particularly common.

Like carboplatin, nedaplatin is also a second-generation platinum derivative that appears to have a similar mechanism and toxicity profile to carboplatin, although direct comparison has not been performed. Moreover, *in vivo* study suggested that nedaplatin–gemcitabine resulted in more enhanced inhibition of tumour growth than cisplatin–gemcitabine or carboplatin–gemcitabine. These results prompted us to investigate nedaplatin-based combinations and to conduct this phase I study.

With respect to toxicities, the most frequent toxicities were haematological toxicities, especially neutropenia and thrombocytopenia. Eight of 18 patients (44.4%) developed more than grade 3 neutropenia after the first courses, and after 16 out of 56 (28.6%) courses overall. On the other hand, six out of 16 patients (37.5%) developed grade 3 thrombocytopenia after the first courses, and after 16 out of 56 courses (37.5%) overall. However, patients required platelet transfusions during only three courses. In addition, one previously untreated patient developed drug-related pneumonitis, which improved with the administration of steroid, at level 3 after the fifth course.

Overall, the toxicities of the combination of nedaplatin with gemcitabine were generally mild and this combination chemotherapy is both well tolerated and active against advanced NSCLC.

The overall response rate of 16.7%, the median survival time of 9.1 months, and 1-year survival rate of 34.1% in this study were quite acceptable because most patients had been given prior chemotherapy. As evaluation of antitumour activity was not a primary objective, and our patient population was small and heterogeneous, we are unable to draw definitive conclusions about the activity of this regimen. Currently, it is still controversial whether novel platinum compounds such as carboplatin and nedaplatin could replace cisplatin for the treatment of advanced NSCLC. However, when not only antitumour activity but also palliation are the main goals of treatment, these new platinum compounds might play a useful role because of their favourable toxicity profile. Therefore, nedaplatin–gemcitabine warrants a phase II study, and further evaluation in prospective randomised trials with cisplatin- or carboplatin-based combinations as a first-line chemotherapy for advanced NSCLC in order to investigate whether nedaplatin could replace cisplatin or carboplatin.

In conclusion, the combination of nedaplatin with gemcitabine is well tolerated and active for advanced NSCLC. The MTD and recommended dose level are 100 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine and 80 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine, respectively.

REFERENCES

Abratt RP, Bezwoda WR, Falkson G, Goedhals L, Hacking D, Rugg TA (1994) Efficacy and safety profile of gemcitabine in non-small-cell lung cancer: a phase II study. *J Clin Oncol* 12: 1535–1540

Alberola V, Camps C, Provencio M, Isla D, Rosell R, Vadell C, Bover I, Ruiz-Casado A, Azagra P, Jimenez U, Gonzalez-Larriba JL, Diz P, Cardenal F, Artal A, Carrato A, Morales S, Sanchez JJ, de las Penas R, Felip E, Lopez-Vivanco G (2003) Cisplatin plus gemcitabine versus a cisplatin-based triplet versus nonplatinum sequential doublets in advanced non-small-cell lung cancer: a Spanish Lung Cancer Group phase III randomized trial. *J Clin Oncol* 21: 3207–3213

Anderson H, Hopwood P, Stephens RJ, Thatcher N, Cottier B, Nicholson M, Milroy R, Maughan TS, Falk SJ, Bond MG, Burt PA, Connolly CK, McIllmurray MB, Carmichael J (2000) Gemcitabine plus best supportive care (BSC) *vs* BSC in inoperable non-small cell lung cancer – a randomized trial with quality of life as the primary outcome. *Br J Cancer* 83: 447–453

Anderson H, Lund B, Back F, Thatcher N, Walling J, Hansen HH (1994) Single-agent activity of weekly gemcitabine in advanced non-small cell lung cancer. A phase II study. *J Clin Oncol* 12: 1821–1826

Bergman AM, Ruiz van Haperen VW, Veerman G, Kuiper CM, Peters GJ (1996) Synergistic interaction between cisplatin and gemcitabine *in vitro*. *Clin Cancer Res* **2**: 521–530

Danson S, Middleton MR, O'Byrne KJ, Clemons M, Ranson M, Hassan J, Anderson H, Burt PA, Fairve-Finn C, Stout R, Dowd I, Ashcroft L, Beresford C, Thatcher N (2003) Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced nonsmall cell lung carcinoma. *Cancer* **98**: 542–553

Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szczesna A, Fidias P, Millward M, Belani CP (2003) Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer : the Tax 326 Study Group. *J Clin Oncol* **21**: 3016–3024

Fukuda M, Shinkai T, Eguchi K, Sasaki Y, Tamura T, Ohe Y, Kojima A, Oshita F, Hara K, Saijo N (1990) Phase II study of (glycolato-O, O') diammineplatinum (II), a novel platinum complex, in the treatment of non-small-cell lung cancer. *Cancer Chemother Pharmacol* **26**: 393–396

Furuse K, Fukuoka M, Asamoto H, Niitani H, Kimura I, Sakuma A, Yamaguchi Y (1992a) A randomized comparative study of 254-S plus vindesine *vs* cisplatin plus vindesine in patients with advanced non-small cell lung cancer. *Jpn J Cancer Chemother* **19**: 1019–1026

Furuse K, Fukuoka M, Kurita Y, Ariyoshi Y, Niitani H, Yoneda S, Fujii M, Hasegawa K, Nishiwaki Y, Tamura M, Kimura I, Inoue S, Oshima S, Kusume K, Sugimoto K (1992b) A phase II study of *cis*-diammine glycolate platinum, 254-S, for primary lung cancer. *Jpn J Cancer Chemother* **19**: 879–884

Gatzemeier U, Shepherd FA, Le Chevalier T, Weynants P, Cottier B, Groen HJM, Rosso R, Mattson K, Cortes-Funes H, Tonato M, Burkes RL, Gottfried M, Voi M (1996) Activity of gemcitabine in patients with non-small cell lung cancer: a multicentre, extended phase II study. *Eur J Cancer* **32**: 243–248

Grigorescu AC, Draghici IN, Nitipir C, Gutulescu N, Corlan E (2002) Gemcitabine (GEM) and carboplatin (CBDCA) versus cisplatin (CDDP) and vinblastine (VLB) in advanced non-small-cell lung cancer (NSCLC) stage III and IV: a phase III randomised trial. *Lung Cancer* **37**: 9–14

Kameyama Y, Okazaki N, Nakagawa M, Koshida H, Nakamura M, Gemba M (1990) Nephrotoxicity of a new platinum compound, evaluated with rat kidney cortical slices. *Toxicol Lett* **52**: 15–24

Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observation. *J Am Stat Assoc* **53**: 457–481

Kelly K, Crowley J, Bunn PA, Presant CA, Grevstad PK, Moinpour CM, Ramsey SD, Wozniak AJ, Weiss GR, Moore DF, Israel VK, Livingston RB, Gandara DR (2001) 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* **19**: 3210–3218

Matsumoto M, Takeda Y, Maki H, Hojo K, Wada T, Nishitani Y, Maekawa R, Yoshioka T (2001) Preclinical *in vivo* antitumor efficacy of nedaplatin with gemcitabine against human lung cancer. *Jpn J Cancer Res* **92**: 51–58

Non-Small Cell Lung Cancer Collaborative Group (1995) Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. *BMJ* **311**: 899–909

Ota K, Wakui A, Majima H, Niitani H, Inuyama Y, Ogawa M, Ariyoshi Y, Yoshida O, Taguchi T, Kimura I, Kato T (1992) Phase I study of a new platinum complex 254-S, *cis*-diammine (glycolato)-platinum (II). *Jpn J Cancer Chemother* **19**: 855–861

Rudd RM, Gower NH, James LE, Gregory W, Eisen T, Lee SM, Harper PG, Spiro SG (2002) Phase III randomised comparison of gemcitabine and carboplatin with mitomycin, ifosfamide, and cisplatin in advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* **21**: 292a

Sandler AB, Nemunaitis J, Denham C, von Pawel J, Cormier Y, Gatzemeier U, Mattson K, Manegold Ch, Palmer MC, Gregor A, Nguyen B, Niyikiza C, Einhorn LH (2000) Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* **18**: 122–130

Scagliotti GV, De Marinis F, Rinaldi M, Gridelli CC, Ricci S, Matano E, Boni C, Marangoro M, Failla G, Altavilla G, Adamo V, Ceribelli A, Clerici M, Costanzo F Di, Frontini L, Tonato M (2002) Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol* **20**: 4285–4291

Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH (2002) Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* **346**: 92–98

Sederholm C (2002) Gemcitabine compared with gemcitabine plus carboplatin in advanced non-small cell lung cancer: a phase III study by the Swedish Lung Cancer Study Group. *Proc Am Soc Clin Oncol* **21**: 291a

Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* **92**: 205–216

Zatloukal P, Petruzelka L, Zemanova M, Kolek V, Skrickova J, Pesek M, Fojtu H, Grygarkova I, Sixtova D, Roubec J, Horenkova E, Havel L, Prusa P, Novakova L, Skacel T, Kuta M (2003) Gemcitabine plus cisplatin *vs* gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: a phase III randomized trial. *Lung Cancer* **41**: 321–331

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Effect of re-treatment with gefitinib ('Iressa', ZD1839) after acquisition of resistance

A 70-year-old man with adenocarcinoma of the lung developed pulmonary metastases 7 months after middle and lower lobectomy of the right lung in October 1998. He received four courses of first-line chemotherapy with docetaxel/irinotecan from June to September 1999. The best response was stable disease and, after 6 months of treatment, there was evidence of progressive disease with increase in size and number of pulmonary metastases. Therefore, we recommended enrollment in a phase I study of gefitinib ('Iressa') [1], an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor.

The patient began to take gefitinib 700 mg/day in March 2000. Remarkable tumor regression was immediately achieved in April 2000 (Figure 1). This response lasted for 18 months. However, pulmonary metastases again developed (considered to be progressive disease), and gefitinib was discontinued in October 2001. The patient received a combination of nedaplatin, a second-generation platinum complex with high antitumor activity against non-small-cell lung cancer [2], and gemcitabine in November 2001. Significant tumor regression was achieved, and a total of six courses from November to April 2002 were administered. Pulmonary metastases progressed again and pulmonary effusion developed in August 2002. Although progressed, he had few symptoms, and was considered to have a performance status of 0. We planned to use a chemotherapy regimen that had not previously been used for this patient, but instead commenced re-treatment with gefitinib at the patient's request on September 3, 2002 (gefitinib 250 mg/day had by this time been approved for use in Japan). One month later, a significant response had been achieved (Figure 1).

This is an interesting case in which acquired resistance to gefitinib could be overcome. There are some possible explanations. First, resistance to gefitinib might naturally change over time, but there is no report of this so far. Secondly, because platinum-based cytotoxic chemotherapy was administered after the first treatment with gefitinib, the proportion of sensitive or resistant cells might have been modified. Thirdly, treatment with cytotoxic chemotherapy might produce genetic changes in EGFR or other unknown associated genes that regulate resistance to gefitinib. Saltz et al. reported that a combination of the EGFR inhibitor cetuximab (C225) and irinotecan produced a 22.5% partial response in patients with irinotecan-refractory colorectal cancer with high EGFR expression [3]. In contrast to that report, cytotoxic agents have the possibility of modifying resistance to cytostatic agents. Recently, two large phase III studies to compare concurrent use of conventional platinum-based chemotherapy (carboplatin/paclitaxel or cisplatin/gemcitabine) and gefitinib with conventional chemotherapy alone were reported [4, 5]. No differences in overall survival were found. These results suggested that gefitinib and chemotherapy may be targeting the same cells with the possibility of overlapping activity. If cytotoxic agents altered sensitivity to gefitinib by genetic modification, chemotherapy followed by gefitinib might be superior to concurrent use. Gefitinib is a very promising agent, but little knowledge is available concerning the types of cases for which gefitinib should be administered, or how gefitinib should be combined with conventional cytotoxic agents. Further investigations are needed to answer these questions.

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References

1. Negoro S, Nakagawa K, Fukuoka M et al. Final results of a phase I intermittent dose-escalation trial of ZD1839 ('Iressa') in Japanese patients with various solid tumors. Proc Am Soc Clin Oncol 2001; 20: 324a.
2. Kameyama Y, Okazaki N, Nakagawa M et al. Nephrotoxicity of a new platinum compound, 254-S, evaluated with rat kidney cortical slices. Toxicol Lett 1990; 52: 15–24.
3. Saltz L, Rubin M, Hochster H et al. Cetuximab (IMC-C225) plus irinotecan (CPT-11) is active in CPT-11-refractory colorectal cancer (CRC) that express epidermal growth factor receptor (EGFR). Proc Am Soc Clin Oncol 2002; 20: 3a.
4. Giaccone G, Johnson DH, Manegold C et al. A phase III clinical trial of ZD1839 ('Iressa') in combination with gemcitabine and cisplatin in chemotherapy-naive patients with advanced non-small-cell lung cancer (INTACT 1). Ann Oncol 2002; 13 (Suppl 5): 2.
5. Johnson DH, Herbst R, Giaccone G et al. ZD1839 ("Iressa") in combination with paclitaxel and carboplatin in chemotherapy-naive patients with advanced non-small-cell lung cancer (NSCLC): results from a phase III clinical trial (INTACT 2). Ann Oncol 2002; 13 (Suppl 5): 127.

10.1093/annonc/mdh006

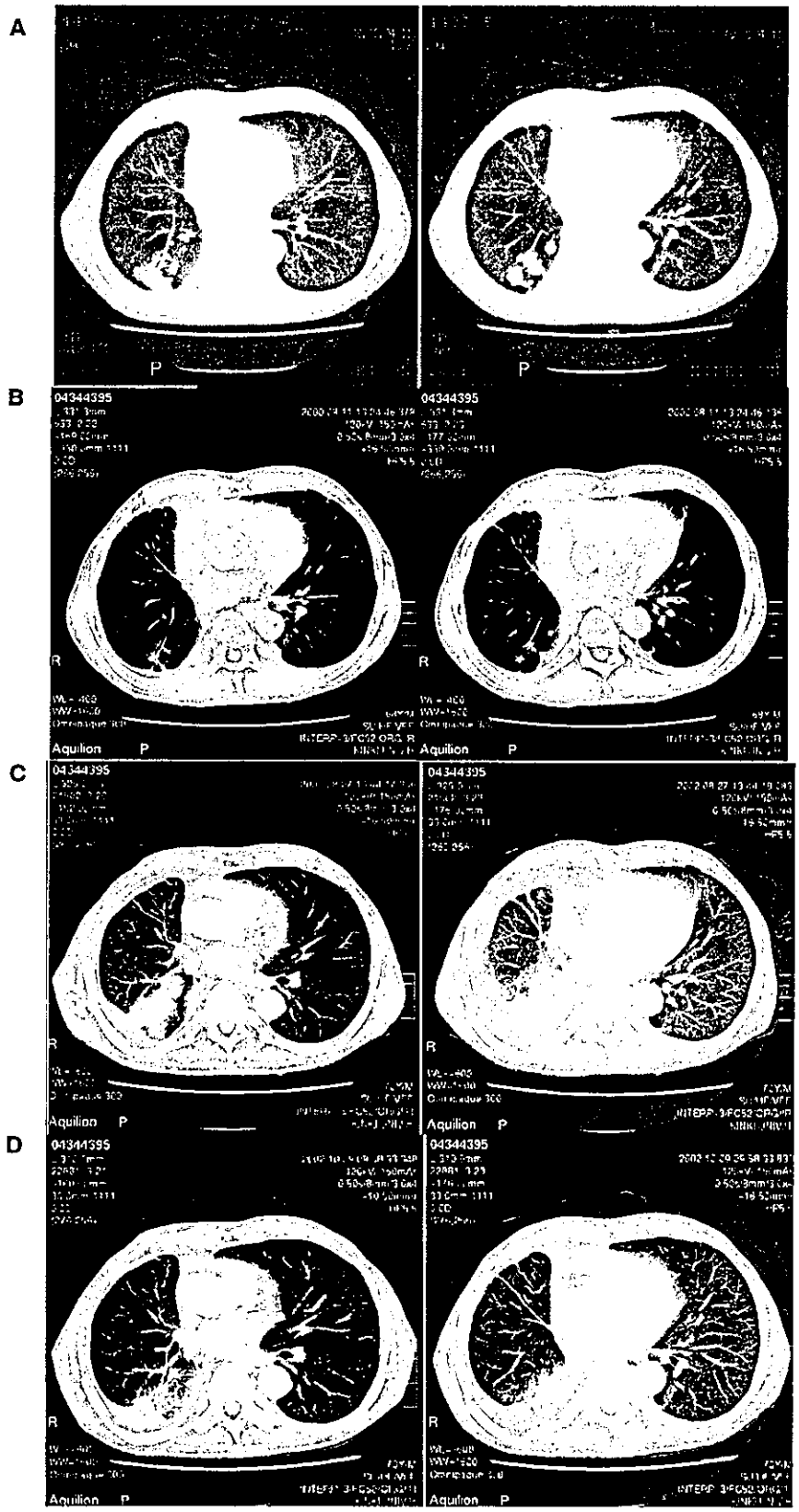

Figure 1. A 70-year-old man with adenocarcinoma of the lung. CT scan before treatment of gefitinib (A), after initiation of treatment (B), before re-treatment (C) and after initiation of re-treatment (D).

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Efficacy and Tolerability of Cancer Pain Management with Controlled-release Oxycodone Tablets in Opioid-naïve Cancer Pain Patients, Starting with 5 mg Tablets

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Background: We conducted an open-label, dose titration study to assess the efficacy and tolerability of controlled-release oxycodone in the therapy of cancer pain management, starting with a newly developed 5 mg tablet every 12 h.
Methods: Twenty-two Japanese cancer patients with pain who had not been taking opioid analgesics over the previous 2 weeks were enrolled. The length of time and the dose needed to attain stable and adequate pain control were evaluated in addition to the assessment of analgesic efficacy and safety during the study period.
Results: Eighteen patients in the efficacy population (18 out of 20, 90%) attained stable, adequate pain control. Two-thirds of the patients attained stable, adequate pain control without any dose titration. The mean length of time was 1.2 days. In these patients, the pain was significantly reduced in intensity, even at 1 h after the initial dose intake. Fifteen patients (68%) reported at least one side effect, but only one patient had to withdraw from the study because of a side effect.
Conclusion: The results suggest that controlled-release oxycodone tablets offered stable and adequate pain control within a short period of time in most Japanese cancer patients who have not been taking opioid analgesics, and could be effectively titrated against pain from a starting dose of 5 mg every 12 h. This indicates that a lower strength controlled-release oxycodone formulation may make it possible to start and titrate the dose more appropriately and carefully in patients who are sensitive to opioid analgesics.

Key words: oxycodone – 5 mg controlled-release tablets – titration – analgesia – cancer pain

INTRODUCTION

Oxycodone is a semi-synthetic opioid analgesic drug that has been in clinical use for >80 years (1). It effectively relieves both non-cancer and cancer pain in patients (2–4), and has been widely acknowledged as one of the invaluable alternatives to morphine, the parent drug of strong opioid analgesics (5,6).

The strengths of controlled-release (CR) oxycodone tablets legalized in Japan in April 2003 are 5, 10, 20 and 40 mg tablets. Since 1997, however, they have been widely available in the USA and Europe. We anticipated that a starting dose of lower than 10 mg would provide effective analgesia in cancer

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patients with moderate pain who had not previously been exposed to opioid analgesics, based on the dose ratio between morphine and oxycodone calculated in previous studies (7–10), which suggested that 5–7.5 mg of CR oxycodone would provide adequate analgesic effects comparable with those of 10 mg CR morphine tablets.

It should also be considered that a lower starting dose may be better tolerated in Japanese cancer patients with moderate pain, because the average body weight of Japanese individuals is much lower than that of Western individuals. Therefore, the starting dose of 10 mg may possibly lead to an overdose for some Japanese patients who have not been exposed to opioid analgesics previously. In addition, a lower starting dose should also be recommended for patients with renal and/or hepatic impairment in comparison with those with normal functions (11). These are the reasons why the 5 mg CR oxycodone tablets were developed to control slight to moderate pain that was not relieved with non-opioid analgesics. The tablet was also expected to be useful for cancer patients for whom a lower starting dose should be considered or a sensitive dose titration should be performed during the opioid treatment.

This was an open-label, 7 day dose titration study in cancer patients with pain who had not been taking opioid analgesics over the previous 2 weeks. The aim of this study was to determine the length of time and the dose needed for attaining stable and adequate pain control, and to evaluate the efficacy and safety of CR oxycodone tablets, with a starting dose of 5 mg every 12 h.

SUBJECTS AND METHODS

PATIENTS

This study was conducted over a 3 month period in adult in-patients with cancer pain recruited from 11 centers (13 divisions) in Japan. They were receiving non-opioid analgesics to manage their pain, but with little effect. The patients eligible for the study had to be cooperative, able to take oral medication and able to keep a pain diary. The patients enrolled scored their pain intensity as slight to severe pain on a 4-point categorical (CAT) scale (where 0 = no pain, 1 = slight pain, 2 = moderate pain and 3 = severe pain). They had been treated with non-opioid analgesics until entering the study, e.g. paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs), but they had not taken any opioid analgesics over at least the previous 2 weeks. The values of their clinical laboratory tests for liver function (glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and total bilirubin) and kidney function (serum creatinine) should not exceed the upper limit of the in-house normal reference range by more than five and six times, respectively. Patients were excluded if they had a history of hypersensitivity to opioid analgesics or if the use of oxycodone or morphine was contraindicated for any reasons. Also excluded were patients who had undergone surgery or palliative radiotherapy for pain over the previous 2 weeks, or who were scheduled to undergo such treatments during the study period.

This study was designed mainly to assess pharmacokinetic profiles of CR oxycodone 5 mg tablet in a single dose as well as to evaluate the safety and efficacy of the CR oxycodone during the titration. For that purpose, 20 cases were considered necessary for the pharmacokinetic analysis and, therefore, we set the target number at 25 cases with the premise that there might be some cases to be excluded from the analysis set. However, infact, we decided to discontinue the study when 22 patients were accumulated, because we judged the number of patients to be sufficient to conduct the pharmacokinetic analysis. The relationship between pharmacokinetics of oxycodone and pain intensity after the first dose will be published separately (in preparation).

All patients gave written informed consent before being enrolled in the study. The institutional review board at each center approved the protocol before the study was initiated. The study was carried out in accordance with the guideline of Good Clinical Practice (GCP) and the ethical principles originating from the Declaration of Helsinki.

TREATMENTS

This was an open-label, dose titration study starting with a 5 mg CR oxycodone tablet given every 12 h. The initial dose was 5 mg and the dose could be titrated against the intensity of pain. If the patient reported their pain intensity as 'moderate' or 'severe' on the CAT scale, the dose could be titrated with the use of 5 and 20 mg CR oxycodone tablets every 24 h. Conversely, the doses could be reduced if the patient experienced intolerable adverse events. Dose titration against the intensity of pain was continued until a stable and adequate pain control with minimal adverse effect was obtained. We considered that adequate pain control was attained when the following conditions were fulfilled: pain-free period lasted at least 48 h; the dose every 12 h was unchanged; no supplemental analgesic dose was taken; the dosing regimen for any non-opioids or adjuvants was unchanged; the patients rated their pain intensity as 'no' or 'slight' on the CAT scale; and any adverse events were tolerable.

Throughout the study, patients were allowed to take immediate release oral morphine preparations as rescue medication whenever breakthrough pain or incident pain occurred. If patients took the rescue medication, an equivalent amount of oxycodone was added to their total daily dose of CR oxycodone tablets. The maximum daily dose of oxycodone (i.e. CR oxycodone tablets plus any rescue dose) permitted in this study was 240 mg.

Patients were not allowed to take any other opioid analgesic during the study. They were allowed to take non-opioid analgesics and adjuvant medications for their specific needs if these drugs had been given before study entry. The dose and route of administration of these drugs had to remain the same throughout the study course as they had been taking until study entry. The use of anti-side effect agents was recommended during the

study. In particular, anti-emetics and laxative agents were commonly used from study entry.

Pain Intensity

Each day, the patients themselves assessed their pain intensity over the previous 24 h. They were also requested to assess their pain intensity at 0 h (i.e. immediately before taking their initial dose of study medication), and at 1, 3, 5, 8 and 12 h after the initial dose intake. At the same points, blood samples were collected concomitantly and assayed for plasma oxycodone and noroxycodoen. They rated their pain intensity on the CAT scale described above, and on a 100 mm visual analogue scale (VAS), where 0 mm = a painless state and 100 mm = worst possible pain. Patients also recorded the number of hours that they were in pain each day and also the number of hours of sleep they had each day.

Evaluation of Pain Control and Length of Time to Attain Stable and Adequate Pain Control

The investigator at each center assessed whether the patient was under stable and adequate pain control in accordance with the criteria described above. The first assessment by the investigator was made 48 h after the initial intake of the study medication. Subsequent assessment was conducted each morning until the patient had attained a stable and adequate pain control.

When the patient attained a stable and adequate pain control within the first 48 h without any dose titration, the time to stable and adequate pain control was recorded as 0 day.

Acceptability of Therapy

Acceptability of therapy was an index based on analgesic effect and side effect of the study medication assessed by patients. Each day, the patients themselves assessed the acceptability of the therapy to them over the previous 24 h and recorded this in a diary. They rated the acceptability of therapy on the 5-point acceptability CAT scale (1 = very poor, 2 = poor, 3 = fair, 4 = good, 5 = excellent). The overall assessment was done in accordance with pain intensity and the occurrence of any adverse events.

Safety Assessments

Safety was evaluated based on the frequency and severity of adverse events, the data for which were obtained by questioning and/or examining the patients and by reviewing the patient's pain diaries and also the results of clinical laboratory tests at study entry and completion of, or withdrawal from, the study. The severity (slight, mild or severe) and seriousness (serious and non-serious) of adverse events was assessed by the investigators.

Statistical Analyses

The percentage of patients who gave a rating of 'good' or 'excellent' for acceptability of therapy were analyzed using the Clopper–Pearson method with a 95% confidence interval (CI).

Changes in the percentage of patients whose pain intensity was 'slight' and 'no' pain were assessed using the McNemar method. Changes in pain intensity (CAT scale and VAS scores) were assessed using the Wilcoxon signed rank test. The following parameters were analysed using the paired *t*-test: number of painful hours per day, number of hours sleep and acceptability of therapy ratings. The percentage of patients attaining stable and adequate pain control and the associated 95% CIs were estimated using the Kaplan–Meier method and Greenwood's method, respectively.

RESULTS

Patient Population

Of the twenty-two cancer patients enrolled in the study, 20 completed the 7 day study period. The efficacy population included 20 patients who were enrolled and did not infringe any of the inclusion or exclusion criteria. Two patients were excluded from the efficacy population because of infringement of the inclusion criteria: one patient had received a fentanyl injection (0.1 mg/day) for pain relief during biopsy 4 days before study entry; and the other patient had not been treated with any analgesic agents before the study. The safety population included all of the 22 patients who were enrolled and had received at least one dose of the study medication.

The mean age and mean body weight of all of the 22 patients were 69.1 years (range 49–80) and 54.5 kg (range 38.0–82.0), respectively. Nineteen patients (86.3%) were male. The most common diagnosis was lung cancer (25.0%), followed by stomach and esophageal cancer. The most common sites of pain were the chest and abdomen.

Two patients withdrew from the study. One withdrew because of the complication of serious pneumonia, which was not considered to be related to the study medication. The other withdrew because of somnolence, which was considered to be related to the study medication. This patient had attained stable and adequate pain control before the withdrawal.

Time Course of Pain Intensity After the Initial Dose

Table 1 shows patients' pain intensity scores (CAT scale) up to 12 h after the initial dose intake of the study medication (one 5 mg tablet). The patients' pain intensity scores decreased significantly by 1 h after the intake and the decreases continued up to 12 h after.

A similar time course of pain intensity was observed when assessed using the VAS. No patient needed supplemental medication until the next dose was given.

Requirements for Titration

Eighteen of the 20 patients (90%) attained stable and adequate pain control during the 7 day study period. Table 2 shows the

Table 1. Changes in pain intensity up to 12 h after the initial dose

Time points (time after initial dose, h)	CAT pain intensity score*		VAS pain intensity score	
	Mean ± SD	*P*-value**	Mean ± SD	*P*-value**
0	1.7 ± 0.8	–	44.0 ± 24.8	–
1	1.3 ± 0.9	0.0078	33.0 ± 31.2	0.0022
3	1.2 ± 0.9	0.0078	32.1 ± 31.8	0.0100
5	1.0 ± 0.9	0.0020	27.1 ± 29.9	0.0016
8	1.2 ± 0.9	0.0156	31.8 ± 30.8	0.0314
12	1.3 ± 0.9	0.0469	32.1 ± 30.1	0.0285

$n = 20$ at all time points.
*CAT pain score: 0 = no pain; 1 = slight pain; 2 = moderate pain; 3 = severe pain.
**P-value for change from 0 h after the initial dose.

Table 2. Mean length of time to stable, adequate pain control and mean dose needed for stable, adequate pain control*

	Mean ± SD	Minimum	Median	Maximum
Length of time to adequate, stable pain control (days)	1.2 ± 1.9	0	0	5
Dose needed for adequate, stable pain control (mg/day)	16.7 ± 10.8	10.0	10.0	40.0

*Patients attained stable, adequate pain control, $n = 18$.

mean (±SD), minimum, median and maximum length of time and the dose needed to obtain stable and adequate pain control. Mean (±SD) and median length of the time to stable, adequate pain control were 1.2 ± 1.9 and 0 days, respectively. Mean (±SD) and median doses needed for stable and adequate pain control were 16.7 ± 10.8 and 10 mg/day, respectively. The dose ranged from 5 to 20 mg every 12 h. Two patients were unable to attain stable adequate pain control during the study period: one withdrew because of an adverse event (pneumonia), and the other did not want to increase the study medication because of adverse events (sleepiness, itching, sweating and dry mouth). The estimated rate of achievement of stable and adequate pain control at the end of the study was 93.8% (95% CI 82.1–100.0).

Table 3 shows the number and percentage of patients who attained stable and adequate pain control at each dose level. Twelve (68%) of the 18 patients attained it at the dose of 5 mg every 12 h (10 mg/day). All of these patients required no dose titration and attained pain relief that met the criteria for stable and adequate pain control. They attained it within the first 48 h after study entry (length of time to stable and adequate pain control is 0 days).

Change in Pain Intensity During the Study

At study entry, 13 patients (65%) reported their pain intensity to be 'moderate' to 'severe' and seven patients (35%) reported it to be 'slight'. Table 4 shows the patient mean (±SD) CAT scores at study entry reported by the patients, 24 h after their initial dose intake of the study medication, and at the end of the study. The decrease in patients' pain intensity between study entry and 24 h after their first dose of study medication, and that between study entry and at the end of study were both statistically significant. Similar decreases were also observed and found to be statistically significant in making an assessment of patients' pain intensity with the use of the VAS.

Table 3. Number and percentage of patients attaining stable, adequate pain control at each daily dose

Daily dose (mg)	No. (%) of patients attaining stable, adequate pain control
10	12* (68)
20	2 (11)
30	2 (11)
40	2 (11)

*All 12 patients attained stable, adequate pain control on the first day.

The percentage of patients whose pain intensity was 'slight' and 'no' increased during the study. At the study entry, this rate was 35.0% (95% CI 15.4–59.2). The corresponding values at 24 h after the initial dose intake and at the end of the study were 70% (95% CI 45.7–88.1) and 87.5% (95% CI 61.7–98.4), respectively. The increase in the percentage of the patients whose pain was 'slight' and 'no' was statistically significant between study entry and 24 h after their initial dose intake, and between study entry and the end of the study ($P = 0.0082$).

As rescue medication, more than one dose of immediate-release morphine was used in four patients (20%) during the 7 day study period. The mean of the rescue doses per day was 1.3 ± 0.5. Eighty percent of the patients required no rescue medication.

The number of hours each day that the patients were in pain decreased during the study period. At study entry, the median (range) number of painful hours per day was 12.0 h (1.0–24.0). At 24 h after the initial dose intake, it had decreased to 3.5 h (0.1–24.0), and this decrease was statistically significant ($P = 0.0155$). At the end of study, the corresponding value was 1.0 h (0.0–18.0), and this decrease from baseline (at study entry) was also statistically significant ($P = 0.0022$).

There was no change in the number of hours of sleep patients had each night during the study period. At study entry, the mean (SD) number of hours of sleep was 7.4 h (2.1). The corresponding values at 24 h after the first dose intake of the study medication and at the end of study were 7.7 h (2.3) and 7.3 h (1.9), respectively.

Acceptability of Therapy

Figure 1 shows the acceptability of the therapy to patients at study entry and at the end of the study. At study entry, the number of patients who rated the acceptability of the therapy as 'poor' or 'very poor' was 11 (55%); at the end of the study, this decreased to 1 (5%). The change in acceptability of therapy to patients measured on a 5-point acceptability CAT scale

Table 4. Pain intensity at study entry, at 24 h after the first dose and at the end of study

	VAS pain intensity score		CAT pain intensity score		Percentage of 'slight' or 'none' patients (%)	*P*-value**
	Mean ± SD	*P*-value**	Mean ± SD	*P*-value**		
At study entry	47.7 ± 26.4	-	1.8 ± 0.7	-	35.0	-
24 h after first dose	28.8 ± 22.3	0.0053	1.2 ± 0.8	0.0098	70.0	0.0588
At the end of the study*	15.7 ± 16.6	0.0025	0.9 ± 0.6	0.0010	87.5	0.0082

$n = 20$ at study entry and 24 h after first dose.
*$n = 16$: at the end of the study (i.e. at 12 h after the final dose), four patients were excluded from the analysis set as "non-evaluated" cases.
**P-value for change from study entry.

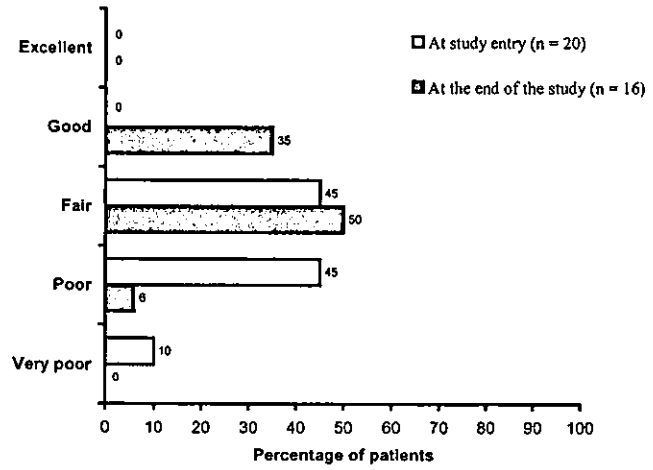

Figure 1. Patients' ratings of the acceptability of therapy at study entry and at the end of the study.

between study entry and at the end of study was statistically significant ($P = 0.0024$).

The percentage of patients whose rating of acceptability on a 5-point acceptability CAT scale was 'good' or 'excellent' was 0% (95% CI 0–16.8) at study entry. However, at the end of study, it increased to 43.8% (95% CI 19.8–0.1).

Safety Evaluations

At least one adverse event, which was considered by investigators to be at least possibly related to study medication (side effect), was observed in 15 of 22 patients (68%; 95% CI 45–86), and 41 cases occurred in total. The common (>10%) side effects were as follows: sleepiness (11 patients, 50%), constipation (seven patients, 32%), nausea (five patients, 28%) and anorexia (four patients, 18%). Most of the reported side effects were slight to moderate in severity. Six cases of severe side effects were reported. Except for one patient who had to discontinue the study due to severe somnolence, all of the patients were able to continue the treatment with the study medication in spite of the side effects. It should be noted that no serious side effects were reported.

Only one patient withdrew from the study because of somnolence that might be related to the study medication. There was no other serious side effect.

Abnormal changes either in white blood cell count or blood creatinine were seen in two patients (9%). Abnormal changes in glutamic oxaloacetic transaminase, glutamaic pyruvic transaminase or positive urinary protein were seen in one patient. Changes in glutamic oxaloacetic transaminase and glutamaic pyruvic transaminase were considered to be clinically significant and considered to be related to the study medication.

Both of the clinical laboratory test values were 21 U before study entry and 51 U at the end of study. The investigator considered that it was impossible to deny the causal relationship between the study medication and the change in laboratory values, although many other drugs were used concomitantly with study medication and, therefore, the exact cause of this abnormal change in laboratory values could not be determined. These changes returned to normal after the medication was stopped.

The value of daily risk was calculated by the method of dividing the total number of incidents of seven common adverse events associated with the opioid, namely constipation, vomiting, nausea, sleepiness, dizziness, dry mouth and pruritus, by the total number of days on which the tablets were taken. The mean value of daily risk in the safety population was 0.19 (29 occurrences in 151 days). The mean value of daily risk in patients who attained stable and adequate pain control was 0.19 (23 occurrences in 125 days).

DISCUSSION

The World Health Organization three-step analgesic ladder has been widely used in cancer pain management (12). In many clinical settings, pharmacological treatment for mild, and sometimes moderate, cancer pain may often be initiated with non-opioid analgesic medication. It may progress to weak and then strong opioid medication in combination with non-opioid treatments as the pain increases in intensity. The only weak opioid analgesics available in Japan are codeine and hydrocodeine. Their analgesic effect is due to their conversion to morphine (13) and they have a ceiling effect. This makes treatment with weak opioid analgesics inappropriate for severe cancer pain management. Hence, the strong opioids are prescribed occasionally when treatment with non-opioid analgesics is ineffective, skipping a trial of weak opioid analgesics in clinical practice. Sometimes, small doses of strong opioids, such as morphine and oxycodone, are used

instead of weaker ones in step 2 for patients who are resistant to or no longer responding to NSAIDs. On the other hand, fixed-dose combination tablets of oxycodone and acetaminophen have been used effectively as weak opioid analgesics to control mainly non-opioid-irresponsive cancer pain in some countries including the USA. We thus conducted an open-label, dose titration study in Japanese cancer patients with pain who had not been taking opioid analgesics, with the starting dose of a 5 mg CR oxycodone tablet every 12 h.

Prior to this study, another study of similar design was conducted in Japanese cancer patients with pain (in preparation). Ninety-two opioid-naïve patients were enrolled in that study and the starting dose was 10 mg every 12 h (twice as high as this study). Twenty-four of 92 patients (26.1%) had to withdraw from the study within 10 days and half of them had to withdraw from the study within 2 days after the study started because of the adverse events (nausea, vomitting, sleepiness, dizziness, etc.) that are commonly associated with opioid analgesics, and most of these withdrawals (21 out of 24) occurred at the starting dose. However, 19 of the 24 patients (79.2%) reported that their pain was less than or equal to 'slight pain' on the pain score (CAT). It should be admitted that the study drug was administered without enough provisions against the side effects. However, a high incidence of sleepiness (five out of 24) and dizziness (three out of 24) associated with the study drug, which ultimately led to discontinuation of the study, suggested that the starting dose of a 10 mg CR oxycodone tablet might be too high for some Japanese cancer patients with pain who had not been taking opioid analgesics. This was possibly because the average weight of Japanese patients is less than that of Western patients.

Furthermore, since oxycodone elimination is delayed by renal (14) or hepatic impairment (15), lower dose CR oxycodone should be considered in determining the starting dose for those patients sensitive to opioids with renal or hepatic impairment. These are the main reasons for development of the 5 mg CR oxycodone tablet in Japan in addition to introduction of 10, 20 and 40 mg CR oxycodone tablets. In the present study, we tried to evaluate the clinical efficacy and safety of CR oxycodone tablets with a starting dose of 5 mg every 12 h in those Japanese cancer patients with non-opioid-irresponsive pain.

Patients who still had a pain unsatisfactorily treated with non-opioid analgesics were enrolled in this study. The aim of this inclusion criterion is to include potential target patients for the 5 mg tablet. Although seven patients (35%) reported baseline pain intensity to be 'slight' at study entry on a 4-point CAT scale, we considered that these patients needed opioid therapy. This was eventually shown by the fact that none of them rated their acceptability of therapy at study entry as 'satisfactory' or 'very satisfactory' on a 5-point acceptability CAT scale. However, at the end of the study, three patients showed satisfaction with the lower dose oxycodone treatment and, moreover, there was no patient who rated their acceptability of therapy as 'poor' or 'very poor'. These results suggest that opioid therapy was indeed needed for the patients with slight pain at study entry in this study.

The 5 mg CR oxycodone tablet (a newly developed formulation) gave significant pain relief 1 h after the first dose, and the subsequent pain scores were kept significantly lower than the pre-dose scores during the following 12 h period. In addition, score for pain intensity was significantly reduced over the 24 h after the first dose intake of 5 mg of study medication as compared with that at study entry. These data indicate that the 5 mg tablet is effective for controlling cancer pain and can be administered quite safely as the starting dose for Japanese cancer patients who have not previously been taking any opioid analgesics.

In this study, 18 (90%) of the 20 patients attained stable and adequate pain control throughout the study period. Two-thirds of them did so on a dose of 5 mg every 12 h without further titration within the initial 48 h (at 0 day). The mean length of time to achieve stable and adequate pain control was 1.2 days. This result was consistent with the findings in two previous studies with CR oxycodone which showed that the mean length of time to stable and adequate pain control was 1.6–2 days (8,16). Although it is common practice to start opioid therapy with an immediate-release formulation and titrate the dose against pain intensity, Salzman and colleagues reported that CR oxycodone was also as readily titrated as an immediate-release formulation (16). Our results support their findings. Moreover, both the patients' rating of their acceptability of therapy on a 5-point acceptability CAT and the overall improvement assessment by the investigator were significantly improved at the end of this study. These results suggest that the use of 5 mg CR oxycodone tablets, if necessary with titration, is acceptable for cancer patients who had not been taking opioid analgesics and is effective for them to achieve stable and adequate pain control in a short period of time.

The 5 mg CR oxycodone tablet was developed to offer a lower starting dose for patients who might experience intolerable adverse events with a starting dose of 10 mg every 12 h. Although a high percentage of patients reported adverse events during this study, most of them were reported to be slight to moderate in severity and only one patient withdrew because of an adverse event (somnolence). Sleepiness, constipation and nausea were the three most common adverse events, all of which are widely known side effects of most opioid analgesics. Another adverse event commonly observed in this study was anorexia, which is commonly reported by cancer patients with pain and can be exacerbated by opioid administration (17).

In conclusion, CR oxycodone tablets offered stable and adequate pain control within a short period of time in most Japanese cancer patients who have not been taking opioid analgesics, and could be effectively titrated against pain from a starting dose of 5 mg every 12 h. Most of the side effects were tolerable. This indicates that a lower strength CR oxycodone formulation may make it possible to start and titrate the dose more appropriately and carefully in patients who are sensitive to opioid analgesics, including Japanese cancer patients who have a relatively lighter body weight, or patients with renal and/or hepatic impairment.

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References

1. Falk E. Eukodal, ein neues Narkotikum. *Muench Med Wchnschr* 1917;64:381–4.
2. Roth SH, Fleischmann RM, Burch FX, Frederick D, Bockow B, Rapoport RJ, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain. *Arch Intern Med* 2000;160:853–60.
3. Parris WCV, Johnson BW Jr, Croghan MK, Moore MR, Khojasteh A, Reder RF, et al. The use of controlled-release oxycodone for the treatment of chronic cancer pain: a randomized, double-blind study. *J Pain Symptom Manage* 1998;16:205–11.
4. Citron ML, Kaplan R, Parris WCV, Croghan MK, Herbst LH, Rosenbluth RJ, et al. Long-term administration of controlled-release oxycodone tablets for the treatment of cancer pain. *Cancer Invest* 1998;16:562–71.
5. Heiskanen TE, Ruismäki PM, Seppälä TA, Kalso EA. Morphine or oxycodone in cancer pain? *Acta Oncol* 2000;39:941–7.
6. Kaplan R, Parris WCV, Citron ML, Zhukovsky D, Reder RF, Buckley BJ, et al. Comparison of controlled-release and immediate-release oxycodone tablets in patients with cancer pain. *J Clin Oncol* 1998;16:3230–7.
7. Bruera E, Belzile M, Pituskin E, Fainsinger R, Darke A, Harsanyi Z, et al. Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. *J Clin Oncol* 1998;16:3222–9.
8. Mucci-LoRosso P, Berman BS, Silberstein PT, Citron ML, Bressler L, Weinstein SM, et al. Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain: a randomized, double-blind, parallel-group study. *Eur J Pain* 1998;2:239–49.
9. Heiskanen T, Kalso E. Controlled-release oxycodone and morphine in cancer related pain. *Pain* 1997;73:37–45.
10. Cherny N, Ripamonti C, Pereira J, Davis C, Fallon M, McQuay H, et al. Strategies to manage the adverse effects of oral morphine: an evidence-based report. *J Clin Oncol* 2001;19:2542–54.
11. Davis MP, Varga J, Dickerson D, Walsh D, LeGrand SB, Lagman R. Normal-release and controlled-release oxycodone: pharmacokinetics, pharmacodynamics, and controversy. *Support Care Cancer* 2003;11:84–92.
12. World Health Organization. Cancer Pain Relief, 2nd edn. Geneva: World Health Organization, 1996.
13. Jaffe JH, Martin WR. Opioid analgesics and antagonists. In: Gilman AG, Rall TW, Nies AS, Taylor P, editors. Goodman and Gilman's the Pharmacological Basis of Therapeutics, 8th edn. New York: Pergman Press 1990;485–521.
14. Kirvela M, Lindgren L, Seppala T, Olkkola KT. The pharmacokinetics of oxycodone in uremic patients undergoing renal transplantation. *J Clin Anesth* 1996;8:13–8.
15. Kaiko RF. Pharmacokinetics and pharmacodynamics of controlled-release opioids. *Acta Anaesthesiol Scand* 1997;41:166–74.
16. Salzman RT, Roberts MS, Wild J, Fabian C, Reder RF, Goldenheim PD. Can a controlled-release oral dose form of oxycodone be used as readily as an immediate-release form for the purpose of titrating to stable pain control? *J Pain Symptom Manage* 1999;18:271–9.
17. Bruera E, Walker P, Lawlor P. Opioids in cancer pain. In: Stein C, editor. Opioids in Pain Control. Basic and Clinical Aspects. Cambridge: Cambridge University Press, 1999;309–324.

S-1 Plus Cisplatin Combination Chemotherapy in Patients with Advanced Non–Small Cell Lung Cancer: A Multi-Institutional Phase II Trial

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ABSTRACT

Purpose: **To evaluate the efficacy and toxicity of a novel combination chemotherapeutic regimen including cisplatin with an oral anticancer agent, S-1 that consisted of tegafur, 5-chloro-2, 4-dihydroxypyridine, and potassium oxonate, for non–small-cell lung cancer (NSCLC) patients.**

Experimental Design: **In this phase II trial, patients with locally advanced and metastatic NSCLC were treated with the oral administration of S-1 at 40 mg/m^2 twice a day for 21 consecutive days while cisplatin (60 mg/m^2) was administered intravenously on day 8. This schedule was repeated every 5 weeks.**

Results: **Of 56 patients enrolled in the study, 55 patients were eligible and analyzed. The median number of cycles administered was 3 (range, 1–12 cycles). Among these 55 patients, one complete response and 25 partial responses were observed with an overall response rate of 47% (95% confidence interval, 34–61%). The median survival time was 11 months and the 1-year survival rate was 45%. Hematologic toxicities of grades 3 and 4 included neutropenia (29%) and anemia (22%). No grade 4 nonhematologic toxicity was observed. Grade 3 toxicity included anorexia (13%), vomiting (7%), or diarrhea (7%).**

Conclusions: **S-1 plus cisplatin combination chemotherapy showed a promising effectiveness with acceptable toxicity rates in patients with advanced NSCLC. These results warrant further investigations of this regimen including a randomized controlled trial for its use as a first line treatment for NSCLC.**

INTRODUCTION

S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) is an oral anticancer agent comprised of tegafur, 5-chloro-2, 4-dihydroxypyridine, and potassium oxonate, in a molar ratio of 1:0.4:1 (1). Tegafur is a prodrug that generates 5-fluorouracil (5-FU) in the blood primarily via metabolism by liver enzyme cytochrome P450. 5-Chloro-2, 4-dihydroxypyridine enhances the serum 5-FU concentration by the competitive inhibition of dihydropyrimidine dehydrogenase, an enzyme responsible for 5-FU catabolism. The inhibitory effect of 5-chloro-2, 4-dihydroxypyridine on dihydropyrimidine dehydrogenase *in vitro* is reported to be 180 times higher than that of uracil (2). Potassium oxonate is a reversible competitive inhibitor of orotate phosphoribosyl transferase, a phosphoenzyme for 5-FU. Diarrhea induced by 5-FU administration is thought to be attributable to the phosphorylation of 5-FU by the enzyme in the gastrointestinal tissue. After the oral administration of potassium oxonate, the concentration of potassium oxonate in the gastrointestinal tissue is high enough to inhibit the enzyme, and the concentration in blood and tumor is reported to be either slight or nil (3). Because of these mechanisms, oral S-1 administration generates a higher concentration of 5-FU than protracted intravenous injection of 5-FU given in a dose equimolar to the tegafur in S-1 whereas the incidence of adverse events concerning the gastrointestinal tract does not increase (4, 5).

In a phase II trial of S-1, which was orally administered at approximately 40 mg/m^2 twice a day for 28 days followed by a 2-week rest period in 59 advanced non–small-cell lung cancer (NSCLC) patients without prior chemotherapy, the response rate was 22% [95% confidence interval (CI), 12–35%] and the median survival time was 10.2 months. As expected, the incidence of severe gastrointestinal adverse events was low: *i.e.*, the incidence of grade 3 was 10% in anorexia, 8% in diarrhea, and 2% in stomatitis whereas no grade 4 nonhematologic adverse events were observed. In addition, there were few severe hematologic adverse events. The incidence of grade 3 or 4 was 7% in neutropenia, 2% in anemia, and 2% in thrombocytopenia (6).

UFT is another dihydropyrimidine dehydrogenase-inhibitory fluoropyrimidine consisting of tegafur and uracil in a 1:4 molar concentration (7). UFT has a similar profile of adverse events but a weaker antitumor activity against NSCLC than S-1 (8). However, combination chemotherapy consisting of a daily

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