Derived pharmacokinetic parameters included the maximum plasma drug concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma drug concentration–time curve from 0 to 24 h (AUC_{0-24}) and to ∞ ($AUC_{0-\infty}$) and terminal half-life ($t_{1/2}$).

Efficacy assessments

We assessed tumor response in accordance with the 'criteria for direct response of solid tumors to chemotherapy' of the Japan Society for Cancer Therapy, which are very similar to those used by the WHO. Measurable lesions were assessed in the same manner before and after dosing, by X-ray, computed tomography (CT) scan, magnetic resonance imaging or echogram. Complete response, partial response or no change in disease status had to be confirmed by a second assessment after 4 weeks.

Serum tumor markers including carcinoembryonic antigen (CEA), prostate-specific antigen, CA 125, CA 19-9, squamous-cell carcinoma-related antigen and thyroglobulin were recorded in patients with relevant tumor types, at screening, on days 1, 8, 15 and 29, and at withdrawal.

Results

Patients

We recruited 31 patients, all of whom had received prior chemotherapy. The median age was 61 years and all patients had a WHO performance status of 0–1 (Table 1). Most patients (74%) had advanced non-small-cell lung cancer (NSCLC) and had been pretreated with chemotherapy (1–4 regimens); 70% of these had received platinum-based regimens.

Of the 31 patients, 30 completed one cycle of treatment (28 days); eight completed ≥2 cycles and six ≥3 cycles. One patient (50 mg group) was withdrawn due to grade 3 atrial fibrillation on day 2 of cycle 1 (due to respiratory failure associated with disease progression); therefore, another patient was added to this group in order that we could collect data on plasma gefitinib concentrations from four patients.

Based on the safety data from the parallel USA/European study, it was judged unnecessary to repeat the 150 and 300 mg dose levels in Japan. In our study, patients in the 50, 100 and 225 mg dose-level groups received the single dose plus the 14-day daily dose. Following comparison of our data with those from the Western study, the pharmacokinetic and adverse effect profiles were found to be similar in the two populations; therefore, the initial single dose was omitted for patients in the 400, 525 and 700 mg dose-level groups.

Table 1. Patient demographics

No. of patients	31
Male/female	19/12
Median age (range), years	61 (40–73)
<65	21
≥65	10
WHO performance status	
0	9
1	22
Prior chemotherapy	31
Prior hormonal therapy	0
Prior radiotherapy	13
Prior chemotherapy and radiotherapy	13
Tumor type	
Non-small-cell lung	23
Adenocarcinoma	18
Squamous	4
Poorly differentiated adenocarcinoma	1
Colorectal	5
Head and neck	2
Breast	1

Dose-limiting toxicity

The highest dose administered was 700 mg/day with two of six patients experiencing DLT [grade 3 diarrhea (one patient) and grade 3 elevation of alanine aminotransferase (ALT; one patient)]. Grade 3 drug-related adverse effects were observed in two additional patients: elevated transaminases in one patient each at 225 and 525 mg/day. Consequently, two additional patients were enrolled, so that a total of six patients were treated at these dose levels. No dose level other than 700 mg/day had more than one of six patients with DLT. No additional DLT occurred.

Tolerability

All 31 patients were evaluable for tolerability and safety. The majority of adverse effects were mild (grade 1/2) and reversible on cessation of treatment. The most frequently reported adverse effects included gastrointestinal tract disorders (77.4%; including diarrhea, nausea, vomiting, anorexia), skin reactions (74.2%; including acne-like rash, seborrhea, dry skin) and increased hepatic enzymes.

Drug-related adverse effects occurring in ≥10% of the patient population are detailed by dose level in Table 2. The most common drug-related adverse effects were grade 1/2 acne-like rash and seborrhea, observed in 32.3 and 22.6% of patients, respectively. Acne-like rash (or folliculitis) covers descriptions such as maculopapular and pustular. These skin disorders tended to occur more often with higher doses of gefitinib and were resolved without treatment or with symptomatic treatments. They tended to recur after the start of treatment with gefitinib in subsequent cycles and often disappeared on cessation of treatment.

Drug-related diarrhea was observed in 19.4% of patients. At doses up to 525 mg/day it was grade 1/2 (loose stools occurring 2–3 days a week) and manageable with routine treatment. Diarrhea generally occurred within the first 2 weeks of a treatment cycle. Drug-related nausea and vomiting were observed in six and four patients, respectively, with most adverse effects resolving on the day of onset or within a few days after treatment cessation with or without adverse effect management.

Drug-related increases in the hepatic transaminases ALT and aspartate aminotransferase (AST) were each seen in 19.4% of patients, and drug-related increases in alkaline phosphatase were seen in 16.4% of patients.

Table 2. Number of patients with drug-related adverse events that occurred in ≥10% of the patient population in all cycles

Gefitinib dose (mg/day)	50		100		225		400		525		700		All		Total	%
No. of patients	5		4		6		4		6		6		31			
NCI-CTC grade	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4		
Adverse event																
Acne-like rash	0	0	1	0	0	0	2	0	4	0	3	0	10	0	10	32.3
Seborrhea	0	0	0	0	0	0	2	0	1	0	4	0	7	0	7	22.6
Diarrhea	0	0	0	0	0	0	2	0	1	0	2	1	5	1	6	19.4
Anorexia	0	0	0	0	0	0	1	0	2	0	3	0	6	0	6	19.4
Nausea	0	0	1	0	0	0	1	0	2	0	2	0	6	0	6	19.4
AST/SGOT increased	0	0	0	0	0	1	1	0	2	1	1	0	4	2	6	19.4
ALT/SGPT increased	0	0	0	0	0	1	1	0	2	1	0	1	3	3	6	19.4
Alkaline phosphatase increased	0	0	0	0	0	0	1	0	1	0	3	0	5	0	5	16.1
Vomiting	0	0	0	0	1	0	0	0	2	0	1	0	4	0	4	12.9

ALT, alanine aminotransferase; AST, aspartate aminotransferase; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

Following frequent and specific ophthalmologic tests, adverse effects were reported in 14 patients (45.2%). Five patients had conjunctivitis (recorded as conjunctivitis, conjunctival congestion and conjunctival epithelial disorder), four had corneal disease (corneal epithelial disorder, corneal erosion and abnormal Rose Bengal staining), keratitis and blepharitis were reported in three patients each and two patients had eye disorders. All ophthalmological events were mild (grade 1/2). In six patients the adverse effects were considered to be drug-related; they resolved in five cases without intervention and in one case following treatment with eye drops (ofloxacin and flavin adenine dinucleotide). Drug-related hematological toxicity occurred in four patients (12.9%) over a range of doses (100–400 mg/day) and was limited to anemia, leukopenia and eosinophilia, all mild in nature (grade 1/2). One patient (gefitinib 400 mg/day) had drug-related prolongation of the PR interval (grade 1), which recovered without intervention. One patient (gefitinib 525 mg/day) had mild alopecia, which also resolved without intervention.

Grade 3/4 adverse effects

No grade 4 adverse effects were observed. A total of 19 grade 3 adverse effects was reported in eight patients. Six of these, in four patients, were considered to be drug related; elevated AST and ALT in one patient each at the 225 and 525 mg/day dose levels, elevated ALT in one patient at 700 mg/day and diarrhea in one patient at 700 mg/day. The grade 3 diarrhea appeared 5 days after withdrawal of treatment. The grade 3 drug-related increases in hepatic enzymes resolved, either with or without treatment. In two of these patients onset of increased hepatic enzymes occurred on day 8 of the second treatment cycle; one (gefitinib 225 mg/day) recovered to normal range within 3 weeks while the other (gefitinib 525 mg/day) recovered 5 days after gefitinib treatment was withdrawn. In the third patient (gefitinib 700 mg/day), onset of increased hepatic enzymes occurred on day 21 of the first cycle (during the treatment interval) and recovered within 1 week. The grade 3 adverse effects in the remaining four patients were considered to be disease related.

Withdrawals

In addition to patients withdrawn from the trial due to progressive disease, four patients were withdrawn due to adverse effects. A female patient with NSCLC with multiple lung micrometastases receiving the 525 mg/day dose was withdrawn due to grade 3 increased transaminases (AST and ALT) on day 8 of cycle 2. AST returned to normal levels without medical intervention, as did serum ALT 54 days after withdrawal. These events were considered to be related to gefitinib. A male patient with rectal cancer, receiving 700 mg/day, withdrew due to grade 2 diarrhea during cycle 3 (day 7), which resolved after 3 days. The patient experienced grade 3 diarrhea 2 days later and, after a further 2 days, had dehydration associated with grade 2 diarrhea. He was hospitalized 8 days after withdrawal and treated with fluid replacement; the diarrhea and dehydration resolved within 2 days. Diarrhea in this patient was judged to be drug related. A male patient with NSCLC was withdrawn due to grade 3 atrial fibrillation judged to be caused by increased heart burden due to respiratory failure associated with progression of primary NSCLC. A male patient with colorectal cancer receiving gefitinib 225 mg/day was withdrawn due to grade 1 infectious keratoconjunctivitis during cycle 2, which was considered by the investigator to be related to adenovirus infection. In this trial, a total of seven patients remained on study for ≥3 months and three for ≥12 months.

Pharmacokinetics

The derived pharmacokinetic parameters following a single dose and multiple dosing of gefitinib are given in Table 3. At the starting dose of 50 mg/day, absorption of gefitinib was moderately slow, median t_{max} being 3 h from the single dose (range 3–5 h). For the dose range 50–225 mg/day, the mean $t_{1/2}$ was similar for all

Table 3. Derived pharmacokinetic parameters following single dose (50, 100 and 225 mg) and 14 days of multiple dosing of gefitinib

Gefitinib dose (mg/day)	No. of patients	Geometric mean (% CV) C_{max}, ng/ml	Median (range) t_{max}, h	Geometric mean (% CV) $AUC_{0-\infty}$, ng·h/ml	Geometric mean (% CV) AUC_{0-24}, ng·h/ml	Mean (SD) $t_{1/2}$, h
Single dose						
50	5	31 (42)	3 (3–5)	948 (85)	378 (51)	38 (11)
100	4	43 (69)	4 (3–7)	1228 (54)	531 (52)	35 (7)
225	6	150 (92)	4 (3–12)	4623 (43)	1986 (58)	30 (5)
Multiple doses						
50	4	60 (89)	6 (5–7)	3070 (145)	1021 (89)	52 (19)
100	4	105 (35)	5 (5–7)	5258 (58)	1860 (41)	45 (18)
225	6	341 (61)	5 (3–7)	13 868 (77)	5191 (61)	40 (8)
400	4	779 (54)	3 (3–7)	29 691 (138)	11 399 (68)	45 (21)
525	6	850 (71)	5 (3–7)	65 055 (82)	16 350 (65)	59 (10)
700	6	1156 (48)	5 (3–7)	75 620 (66)	21 580 (49)	55 (14)

CV, coefficient of variation; SD, standard deviation.

single doses (30–38 h). Single doses higher than 225 mg/day were not given.

Figure 1 shows the mean plasma concentration–time profile following single and multiple dose administration of 50, 100 and 225 mg/day gefitinib. Multiple dosing resulted in at least a two-fold increase in C_{max} compared with single dosing; for the 50 mg/day dose, exposure (C_{max}) to gefitinib increased two-fold following 14 days of administration compared with the single dose (60 versus 31 ng/ml, respectively) and median t_{max} was 6 h (range 5–7 h).

Multiple dosing with gefitinib (50–700 mg/day) for 14 days resulted in dose-related increases in mean C_{max} (from 60 to 1156 ng/ml) and mean AUC_{0-24} (from 1021 to 21 580 ng·h/ml). Figure 2 shows the mean plasma concentration–time profile following multiple dose administration of 225 and 525 mg/day gefitinib. Day-14 AUC_{0-24} values across the dose range indicate an increase in exposure to gefitinib with dose, with up to six-fold interpatient variability at each dose level (Figure 3). Steady-state plasma concentrations were achieved by days 7–10 at all doses (Figure 4). The mean $t_{1/2}$ across the range 50–700 mg/day was 50.1 h (range 27.8–79.7 h).

Pharmacokinetic parameters were comparable with results from the parallel study in the USA and Europe [13]; for example, Figure 5 compares multiple dose AUC_{0-24} values for the two patient populations. We did not analyze the relationship between pharmacokinetic parameters and toxicity due to the limited sample size.

Antitumor activity

We observed partial responses (duration 35–361 days) in five of the 23 patients with NSCLC. The five patients had adenocarcinoma histology (Table 4) and were receiving a range of gefitinib doses. The first patient, a 51-year-old woman receiving gefitinib 225 mg/day, had previously shown no change in disease status as best response, then progressed on platinum-based combination therapy for 3 months, then progressed following a best response of no change in disease status on cyclophosphamide/etoposide/tegafur–uracil for 1.5 months. Her partial response was observed at the end of cycle 1 and was sustained for 119 days. The second patient, a 63-year-old woman (400 mg/day), had previously had no change in disease status as best response, then progressed on treatment with bleomycin, cisplatin/etoposide and etoposide for 1 month each. Her partial response, initially observed at the end of cycle 2, had a response duration of 361 days. This patient also had a fall in CEA levels over 13 cycles. The third patient was a 70-year-old woman (gefitinib 525 mg/day) who had previously had progressive disease following cisplatin/etoposide/radiotherapy (3 months) followed by no change in disease status as best response, then progression on docetaxel treatment (6 months). This patient experienced a partial response from the end of cycle 1 that was sustained for 35 days. Also at this dose level, a 68-year-old woman who had previously had no change in disease status as best response, then progressed on vindesine/mitomycin C/cisplatin (10 months) followed by docetaxel (2 months) and irinotecan/docetaxel (3 months) had a partial response first observed at the end of cycle 2 (response duration 340 days). This patient demonstrated a partial response on a CT scan (Figure 6A), with a reduction in lesion size visible after 4 months of treatment, and also had a reduction in CEA levels over 12 cycles. This patient continued to receive gefitinib (500 mg/day) for a further 6 months in an open-label extension study (20 months on gefitinib in total). The fifth patient with a partial response (observed from cycle 3; response duration 307 days) was a 67-year-old man receiving gefitinib 700 mg/day, who had previously shown no change in disease status as best response, then progressed after 3 months of treatment with irinotecan/docetaxel. The CT scan demonstrating this partial response is shown in Figure 6B, with a reduction in tumor size visible after 3 months of treatment. This patient continued to receive gefitinib (500 mg/day) for a further 6 months in the open-label extension study (18 months on gefitinib in total).

An additional seven patients [colorectal cancer (three patients), NSCLC (two patients), head and neck cancer (one patient), breast cancer (one patient)] had no change in disease status as their best response (duration 40–127 days). Three of these patients remained

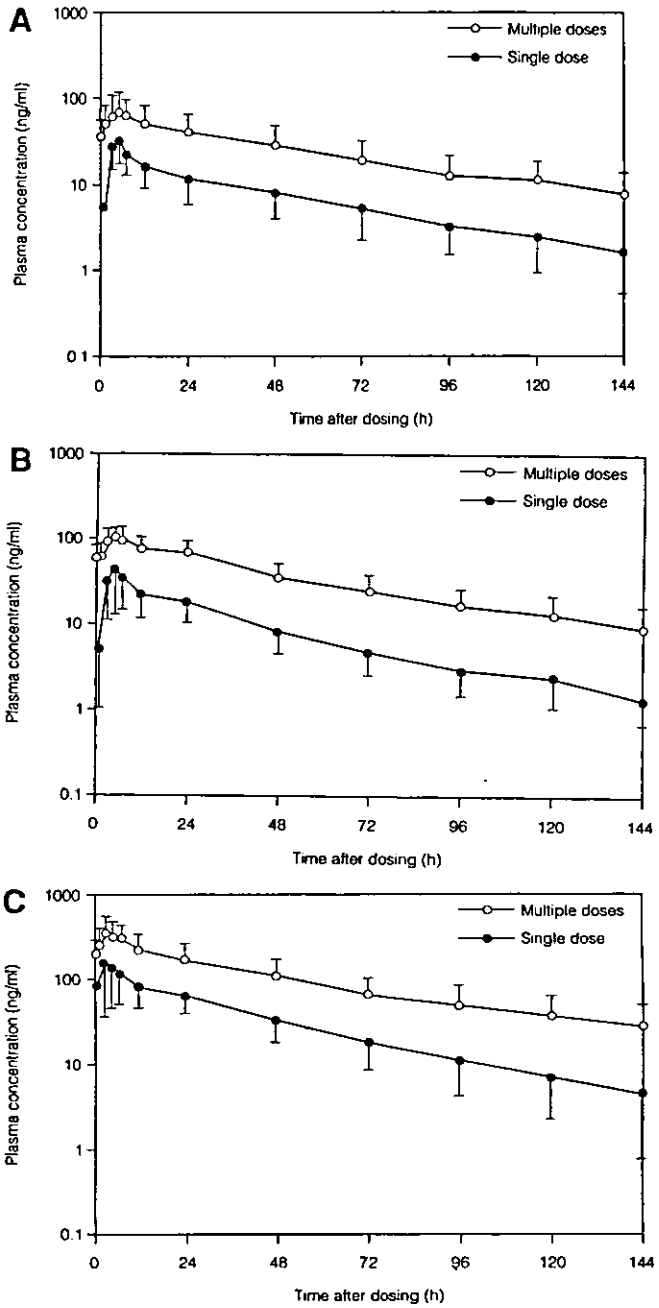

Figure 1. Mean plasma concentration–time profile for gefitinib single dose and multiple doses at (A) 50 mg, (B) 100 mg and (C) 225 mg.

on study for ≥3 months. One of the patients with colorectal cancer (gefitinib 700 mg/day) experienced a considerable fall in CEA and CA 19-9 levels over three cycles.

Discussion

Our study demonstrates that once-daily oral gefitinib, administered for 14 consecutive days every 28 days, has an acceptable tolerability profile in Japanese patients with solid malignant tumors. The safety profile observed in Japanese patients is comparable to that observed in patients from the USA/European phase I trial of gefitinib using similar dose administration and escalation

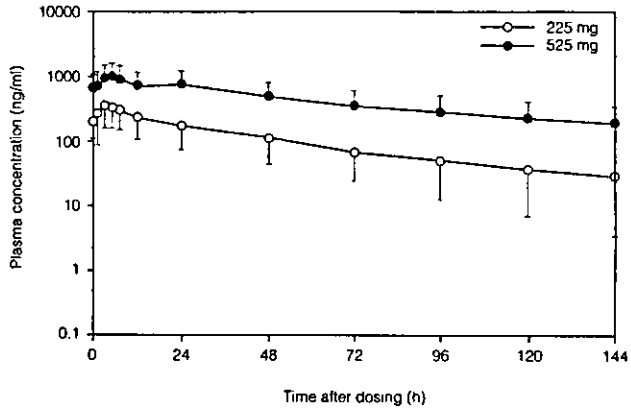

Figure 2. Mean plasma concentration–time profile for gefitinib multiple doses at 225 and 525 mg.

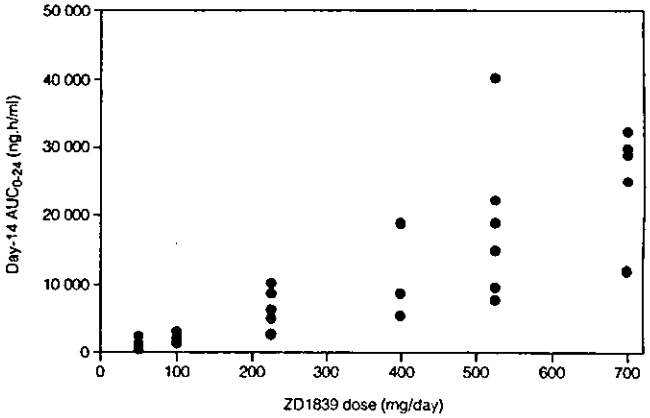

Figure 3. Relationship between exposure to gefitinib (AUC_{0-24}) and dose (mg/day).

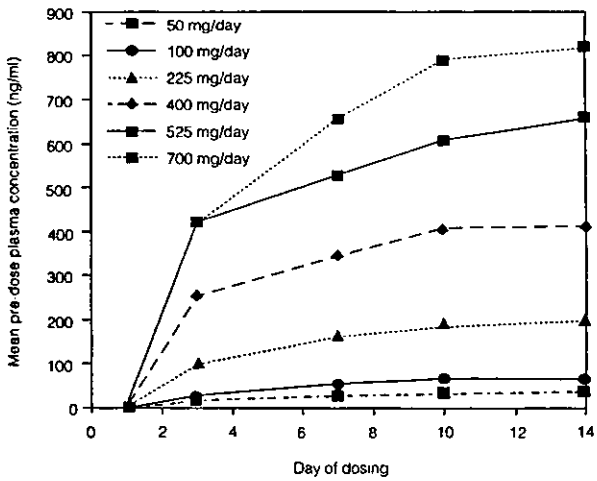

Figure 4. Mean pre-dose plasma concentrations of gefitinib during the multiple dosing phase.

schedules [13]. The incidence of reported drug-related adverse effects was similar in the two studies: 77.4% of patients in our study and 75% in the parallel study, with most adverse effects being grade 1 or 2 in severity. Toxicity increased with dose in both studies and dose escalation stopped at 700 mg/day, with grade 3 diarrhea and increased ALT being the DLTs at this dose.

Table 4. Patients with partial response (PR) or no change in disease status

Gefitinib dose (mg/day)	Tumor type	Response	Duration of PR (days)	Time to progression (days)
50	NSCLC (adeno)	No change	–	58
100	Colorectal	No change	–	43
225	NSCLC (adeno)	Partial response	119	144
	Colorectal	No change	–	57
	NSCLC (squamous)	No change	–	87
	Head and neck	No change	–	40
400	NSCLC (adeno)	Partial response	361	410
525	NSCLC (adeno)	Partial response	35	49[a]
	NSCLC (adeno)	Partial response	340	396[a]
700	NSCLC (adeno)	Partial response	307	362[a]
	Breast	No change	–	127
	Colorectal	No change	–	85

Adeno, adenocarcinoma; NSCLC, non-small-cell lung cancer.
[a]Patients with data cut-off.

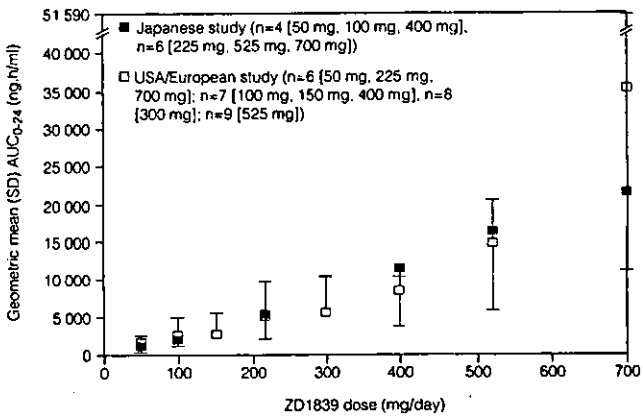

Figure 5. Relationship between dose and exposure in Japanese patients and in USA/European patients after the final dose of the first multiple dosing cycle.

In both our trial and the USA/European trial, among the most frequently reported drug-related adverse effects at doses ≤525 mg/day were an acne-like rash and gastrointestinal adverse effects. The incidence was similar in the two trials for these and other drug-related adverse effects. Results from studies evaluating chronic daily administration of gefitinib also support the conclusions of the present study, that gefitinib is generally well tolerated, with the most frequent adverse effects being grade 1 or 2 skin and gastrointestinal effects [17, 18]. In common with this study, an acne-like rash has been reported as the most common adverse effect of treatment with other EGFR-targeted treatments, including the anti-EGFR antibody cetuximab [19] and the EGFR-TKI erlotinib [4, 20–22], which was also associated with gastrointestinal effects. In our study, all skin-related adverse effects were grade 1/2 and manageable, in some cases without intervention. Similarly, hepatic enzyme elevations resolved with or without management. In our study there were no severe ophthalmological events and all adverse effects considered by the investigators to be possibly related to gefitinib were reversible. Further study will be required in more patients to determine whether any of the observed ophthalmological effects are due to gefitinib. With such intense monitoring in this elderly, ill population, the significance of these findings is not clear. Neither our study nor the parallel trial reported significant or consistent cardiac or renal toxicity. In the USA/European study, hematological toxicity was uncommon and limited to cases of anemia that showed no clear relation to gefitinib dose [13]. We observed a similar low incidence of hematologic effects, contrasting with the tolerability profile of cytotoxic agents. As the tolerability profile of gefitinib was acceptable with the intermittent dosing schedule used in these studies, subsequent studies have been conducted using continuous once-daily oral dosing.

Our study confirmed previous reports that gefitinib is orally bioavailable in both healthy volunteers and cancer patients and is suitable for once-daily dosing [12, 13]. The $t_{1/2}$ data following multiple-dose administration, observed in patients from the USA/European study (range 24–85 h) [13] and our study (range 27.8–79.7 h) were similar. Pharmacokinetic analysis of the data from the current study showed dose-related exposure to gefitinib, which is consistent with the results from the USA/European trial.

We observed very encouraging evidence of antitumor activity across a range of gefitinib doses that are well below the MTD. Interestingly, five of 23 patients (22%) with NSCLC (all five with adenocarcinoma) had a partial response. This supports results seen in the USA/European study, in which partial responses were observed in four of 16 patients with NSCLC, each of whom had received at least two prior chemotherapy regimens [13]. There was no tumor regrowth or symptomatic progression observed during the off-treatment period in the Japanese phase I study using the intermittent dosing schedule. This suggests that the efficacy of gefitinib treatment would be maintained in patients requiring treatment interruption for safety reasons during chronic continuous treatment with gefitinib.

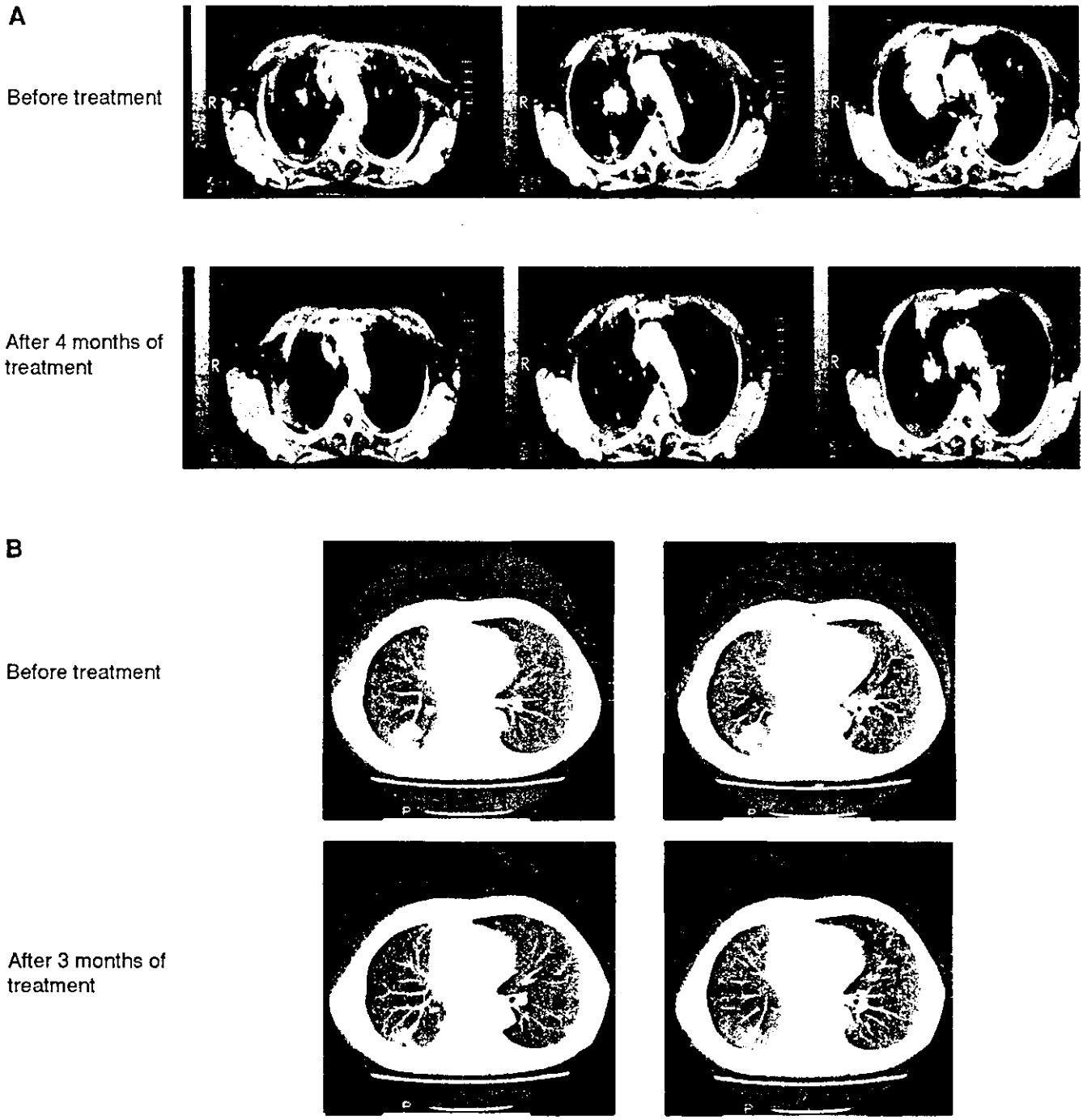

Figure 6. Computed tomography (CT) scan of patients with non-small-cell lung cancer (NSCLC) pre- and post-treatment with gefitinib (**A**) 525 mg/day and (**B**) 700 mg/day.

The findings of this study, in conjunction with those from other phase I studies [13, 17, 18], support the use of 250 and 500 mg/day doses for subsequent trials of gefitinib in advanced NSCLC. The 250 mg/day dose is higher than the lowest dose level at which objective tumor regression was seen, while 500 mg/day is the highest dose that was well tolerated when taken chronically in phase I trials. Two large-scale, randomized, double-blind, phase II studies, 'Iressa' Dose Evaluation in Advanced Lung cancer (IDEAL) 1 and 2, have been undertaken to evaluate the efficacy and tolerability of gefitinib monotherapy in patients with locally advanced or metastatic NSCLC who had previously received platinum-based chemotherapy. In both these studies, gefitinib was generally well tolerated and provided clinically significant antitumor activity [23, 24].

In conclusion, gefitinib is a novel agent designed to inhibit the EGFR signaling pathway, which is a relevant target in cancer biology. Gefitinib has a favorable tolerability profile and has demonstrated promising antitumor activity, especially in patients with NSCLC. The safety profile, pharmacokinetic parameters and antitumor activity observed in our study of Japanese patients are

comparable to those observed in patients from the USA and Europe. Therefore, an international phase II study of gefitinib can include Japanese patients. The potential for gefitinib monotherapy in the treatment of NSCLC has been confirmed by randomized phase II trials.

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Randomised phase II study of docetaxel/cisplatin *vs* docetaxel/irinotecan in advanced non-small-cell lung cancer: a West Japan Thoracic Oncology Group Study (WJTOG9803)

N Yamamoto*[,1], M Fukuoka[1], S-I Negoro[1], K Nakagawa[1], H Saito[1], K Matsui[1], M Kawahara[1], H Senba[1], Y Takada[1], S Kudoh[1], T Nakano[1], N Katakami[1], T Sugiura[1], T Hoso[1] and Y Ariyoshi[1] for the West Japan Thoracic Oncology Group

[1]*Department of Medical Oncology, Kinki University School of Medicine, 377-2 Ohnohigashi, Osakasayama, Osaka 589-8511, Japan*

Docetaxel plus cisplatin and docetaxel plus irinotecan are active and well-tolerated chemotherapy regimens for advanced non-small-cell lung cancer (NSCLC). A randomised phase II study compared their efficacy and toxicity in 108 patients with stage IIIb/IV NSCLC, who were randomised to receive docetaxel 60 mg m^{-2} and cisplatin 80 mg m^{-2} on day 1 (DC; $n=51$), or docetaxel 60 mg m^{-2} on day 8 and irinotecan 60 mg m^{-2} on day 1 and 8 (DI; $n=57$) every 3 weeks. Response rates were 37% for DC and 32% for DI patients. Median survival times and 1- and 2-year survival rates were 50 weeks (95% confidence interval: 34–78 weeks), 47 and 25% for DC, and 46 weeks (95% confidence interval: 37–54 weeks), 40 and 18% for DI, respectively. The progression-free survival time was 20 weeks (95% confidence interval: 14–25 weeks) with DC and 18 (95% confidence interval: 12–22 weeks) with DI. Significantly more DI than DC patients had grade 4 leucopenia and neutropenia ($P<0.01$); more DC patients had grade $\geqslant 2$ thrombocytopenia ($P<0.01$). Nausea and vomiting was more pronounced with DC ($P<0.01$); diarrhoea was more common with DI ($P=0.01$). Three treatment-related deaths occurred in DC patients. In conclusion, although the DI and DC regimens had different toxicity profiles, there was no significant difference in survival.
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Keywords: combination chemotherapy; doublets; irinotecan; cisplatin; docetaxel; non-small-cell lung cancer; carboplatin

Unfortunately, non-small-cell lung cancer (NSCLC) is a member of the group of neoplastic diseases that is relatively chemoresistant. Recent meta-analyses show that cisplatin-based chemotherapy improves survival (Non-Small Cell Lung Cancer Collaborative Group, 1995), and it is considered a standard treatment for NSCLC, Most cisplatin-based regimens have substantial toxicities that require close monitoring and supportive care. Thus, there is a need to develop active and less toxic chemotherapy regimens that include new active compounds with novel mechanisms of action.

In the 1990s, several new, active therapies with single-agent response rates of 15–30% became available for NSCLC, including irinotecan, docetaxel, paclitaxel, vinorelbine, and gemcitabine. Because irinotecan and docetaxel were approved for NSCLC earlier than the other drugs in Japan, development of regimens containing irinotecan or docetaxel is more advanced. Docetaxel 60 mg m^{-2} showed good antitumour activity against advanced NSCLC (Kunitoh *et al*, 1996), and the combination of docetaxel plus cisplatin (DC) is one of the most effective regimens for advanced NSCLC (Rodriguez *et al*, 2001; Schiller *et al*, 2002). Studies in Japan included a phase II study in which DC yielded a response rate of 42% (Okamoto *et al*, 2002), and a phase III study in which DC was associated with better survival than the vindesine and cisplatin (VC) combination (Kubota *et al*, 2002).

Irinotecan demonstrated activity similar to that of VC in stage IIIb/IV NSCLC (Negoro *et al*, 2003), and significant longer overall survival time than VC in stage IV NSCLC (Fukuoka *et al*, 2000). We reported a phase I study of docetaxel plus irinotecan (DI) in patients with advanced NSCLC, in which a promising response rate of 48% and the median survival time of 48 weeks were achieved with acceptable toxicities (Masuda *et al*, 2000). Thus, DI appeared to be a promising non-cisplatin-containing regimen.

Based on the above findings, we conducted a randomised trial of DC *vs* DI in patients with advanced NSCLC to compare the respective response rates, survival data, and toxicity profiles of the two regimens. This was a multicentred phase II study.

PATIENTS AND METHODS

Patients

Patients enrolled in this trial had histologically or cytologically confirmed stage IIIb or IV NSCLC. Patients with stage IIIb disease who were not candidates for thoracic radiation and patients with stage IV disease were eligible if they had not received previous therapy, had measurable disease, and had a life expectancy of at least 3 months. Additional entry criteria were age $\geqslant 20$ years, performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale, adequate bone marrow function (leucocyte

*Correspondence: N Yamamoto, Thoracic Oncology Division, Shizuoka Cancer Center Hospital, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka, 411-8777, Japan; E-mail: n.yamamoto@scchr.jp
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count 4000–12 000 μl^{-1}, haemoglobin concentration $\geqslant 9.5\,g\,dl^{-1}$ platelet count $\geqslant 100\,000\,\mu l^{-1}$), kidney function (creatinine $\leqslant$ upper limit of normal, 24-h creatinine clearance $\geqslant 60\,ml\,min^{-1}$), liver function (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leqslant 2.0$ times the upper limit of normal, total bilirubin $\leqslant 1.5\,mg\,dl^{-1}$), and pulmonary function ($PaO_2 \geqslant 60$ torr). Patients with active concomitant or a recent (<3 years) history of any malignancy, symptomatic brain metastases, past history of drug allergy reactions, complication by interstitial pneumonia, watery diarrhoea, ileus, treatment with nonsteroidal anti-inflammatory drugs, or other serious complications, such as uncontrolled angina pectoris, myocardial infarction within 3 months, heart failure, uncontrolled diabetes mellitus or hypertension, massive pleural effusion or ascites, or serious active infection were excluded. All patients gave written informed consent, and the institutional review board for human experimentation approved the protocol.

Study evaluations

Pretreatment studies included a complete medical history and physical examination, chest X-ray, electrocardiography, computed tomography (CT) scan of the brain and chest, CT or ultrasound examination of the abdomen, and bone scintigraphy. Blood and blood chemistry studies included complete blood cell count, liver function test, serum electrolytes, serum creatinine, and blood urea nitrogen. Chest X-ray, blood and blood chemistry analyses, and urinalysis were repeated weekly.

Randomisation and treatment schedule

Patients were randomly assigned to receive the DC regimen or the DI regimen by a minimisation method using stage (IIIB/IV) and treatment institution. The DC regimen was consisting of docetaxel 60 mg m^{-2} on day 1 and cisplatin 80 mg m^{-2} on day 1, and the DI regimen was consisting of docetaxel 60 mg m^{-2} as a 60-min intravenous infusion on day 8 and irinotecan 60 mg m^{-2} as a 90-min intravenous infusion on days 1 and 8 (Figure 1). Both regimens were repeated every 3 weeks. Participating researchers at each institution decided the amount of fluid replacement and the type of antiemetic therapy to administer. Standard antiemetic treatment in the DC arm consisted of 5-HT_3 receptor antagonist plus 16 mg dexamethasone intravenously on day 1, before cisplatin administration. In the DI arm, standard antiemetic treatment consisted of 5-HT_3 receptor antagonist intravenously before chemotherapy administration on days 1 and 8. Patients received at least two treatment cycles, and those with a complete or partial response after two cycles had treatment continued until there was evidence of disease progression, intolerable toxicity, or patient refusal.

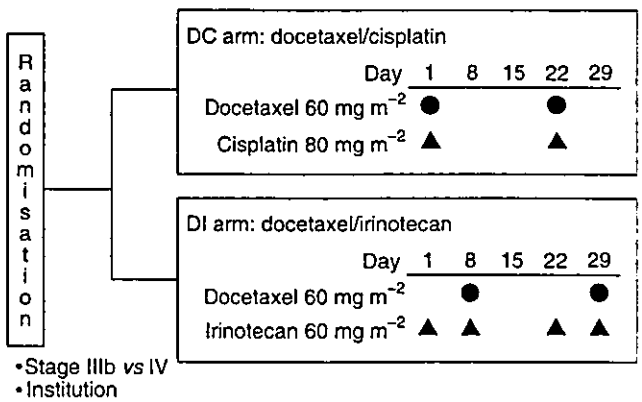

Figure 1 *Treatment schema*: after stratification by stage and institution, enrolled patients were randomly allocated to receive docetaxel plus cisplatin (DC) or docetaxel plus irinotecan (DI).

Dose modifications

Toxicity assessment was based on the National Cancer Institute–Common Toxicity Criteria version 2.0. Dose levels and treatment schedule were modified to avoid severe adverse effects. Patients receiving DI had the day-8 docetaxel and irinotecan doses postponed to day 15 if any of the following toxicities was present on day 8: leucocyte count $<3000\,\mu l^{-1}$, platelet count $<100\,000\,\mu l^{-1}$ diarrhoea consisting of bloody or watery stools, or increased to two or more diarrhoea within 24 h, abdominal pain rated mild or worse, hepatic toxicity $\geqslant$ grade 3, or fever >38°C. If these toxicities occurred on day 15 after skipping the day-8 treatment, DI was stopped in that course.

Patients could receive the next treatment course only if the following criteria were met: leucocyte count $\geqslant 4000\,\mu l^{-1}$, platelet count $\geqslant 100\,000\,\mu l^{-1}$ AST/ALT <2.0 times the upper limit of normal, total bilirubin $\leqslant 1.5\,mg\,dl^{-1}$ serum creatinine $\leqslant$ the upper limit of normal, ECOG PS $\leqslant 2$, neurotoxicity $\leqslant$ grade 1, no diarrhoea or oedema. However, if more than 6 weeks passed before these criteria were satisfied, the patient was removed from the study.

Dose modification criteria for each drug are shown in Table 1. If during the previous course, grade 4 leucopenia, grade 4 neutropenia lasting $\geqslant 3$ days, or grade 4 thrombocytopenia had occurred, doses of all drugs were reduced by 10 mg m^{-2}. Doses of both cisplatin and docetaxel were reduced by 10 mg m^{-2} in subsequent cycles if chemotherapy induced grade $\geqslant 2$ neurotoxicity. Moreover, dose of docetaxel was reduced by 10 mg m^{-2} if grade $\geqslant 2$ hepatic toxicity or grade $\geqslant 3$ stomatitis had occurred. Dose of cisplatin was reduced by 20/mg/m^2 if grade $\geqslant 2$ renal toxicity occurred. Dose of irinotecan was reduced by 5 mg m^{-2} if grade $\geqslant 2$ hepatic toxicity had occurred and by 10 mg m^{-2} if grade $\geqslant 2$ diarrhoea or cancellation of day-8 treatment had occurred.

Evaluation of response and survival

Tumour response was classified according to World Health Organization (WHO) criteria (World Health Organization, 1979). Complete response was defined as complete disappearance of all measurable and assessable disease for at least 4 weeks, Partial response was a $\geqslant 50\%$ decrease in the sum of the products of the two IL largest perpendicular diameters of all measurable tumours lasting at least 4 weeks and without appearance of any new lesions. No change was defined as a <50% decrease or a <25% increase of tumor lesions for at least 4 weeks with no new lesions.

Table 1 Dose modification criteria

Toxicities in previous cycle	Decrease in docetaxel dose (mg/m^{-2})	Decrease in cisplatin dose (mg/m^{-2})	Decrease in -irinotecan dose (mg/m^{-2})
Grade 4 neutropenia lasting $\geqslant 3$ days, leucopenia or thrombocytopenia	10	10	10
Grade $\geqslant 2$ neurotoxicity	10	10	—
Grade $\geqslant 2$ renal toxicity	—	20	—
Grade $\geqslant 2$ hepatic toxicity	10	—	5
Grade $\geqslant 3$ stomatitis	10	—	—
Grade $\geqslant 2$ diarrhoea	—	—	10
Cancellation of day-8 treatment	—	—	10

Progressive disease was defined as development of new-lesions or a 25% increase in the sum of the products of the two largest perpendicular diameters of all measurable tumors. Duration of response in patients who achieved complete or partial response was measured from the start of treatment to the date of disease progression.

Statistical methods

Results of this study were evaluated to determine whether the docetaxel plus irinotecan combination warranted further assessment in a phase III trial. Thus, this study was designed to conduct two randomised phase II studies concurrently. We calculated the number of patients required for each of the two studies based on the Fleming's single-stage procedure (Fleming, 1982). In both studies, we set response rates of 40% as target activity level and 20% as the lowest level of interest with a power of 0.9 at a one-sided significance level of 0.05. As a result, a total of 100 qualified patients were to be enrolled, with 50 patients in each treatment arm. The primary objective was to estimate the response rate to both regimens, particularly to irinotecan plus docetaxel.

Overall survival and progression-free survival were analysed by the Kaplan–Meier method. The overall survival was measured from study entry to death. The progression-free survival was measured from study entry until the day of the first evidence of disease progression. If the disease had not progressed by the time of this analysis, progression-free survival was considered censored at the time of the analysis. All comparisons between patient characteristics, response rates, and toxicity incidences were performed by Pearson's χ^2 contingency table analysis.

RESULTS

Patient characteristics

From October 1998 to August 1999, 108 patients were assigned to receive DC ($n=51$) or DI ($n=57$). Baseline patient characteristics according to treatment arm are shown in Table 2. Patients were well balanced between the two treatment arms in terms of gender, age, performance status, disease stage, and histologic subtypes. There were 23% stage IIIb patients and 74% had adenocarcinoma. All patients were included in the survival evaluation, and all were assessable for antitumor efficacy and toxicity.

Treatment delivery

Patients in both treatment arms received a median of two treatment courses. Two or more courses were delivered to 72.5 and 71.9%, and four courses to 17.6 and 19.1% of patients in the DC and DI arms, respectively. Differences between arms in the number of chemotherapy courses administered were not statistically significant.

Table 2 Baseline patient characteristics

		Docetaxel/ cisplatin	Docetaxel/ irinotecan	χ^2 text
No. of patients		51	57	
Gender	Male/female	37/14	38/19	$P=0.537$
Age (years)	Median	62	60	
	Range	39–74	42–77	
PS	0/1	15/36	15/42	$P=0.830$
Histology	Adenocarcinoma	36	44	$P=0.520$
	Squamous cell carcinoma	13	9	
	Others	2	4	
Disease stage	IIIb/IV	11/40	14/43	$P=0.820$
Brain metastasis	(+)/(−)	4/47	11/46	$P=0.086$

PS = performance status.

Response to treatment and survival

There were no complete responses. In the DC arm, 19 patients had partial responses for an overall response rate of 37% (Table 3). Among DI patients, 18 had partial responses for an overall response rate of 32%. The difference in response rate between arms was not significant ($P=0.55$). Progressive disease was noted in twice as many DI (25%) than DC (12%) patients. Early deaths within 3 months of treatment initiation occurred in 10% ($n=5$) of DC and 5% ($n=3$) of DI patients. The early deaths were treatment-related (three patients, all in the DC arm) or due to disease progression (five patients).

Overall and progression-free survival curves for the two treatment arms are shown in Figures 2 and 3. The median progression-free survival time was 20 weeks (95% confidence interval: 14–25 weeks) in the DC arm *vs* 18 weeks (95% confidence interval: 12–22 weeks) in the DI arm. Median survival times, 1-year survival rates, and 2-year survival rates were 50 weeks (95% confidence interval 34–78 weeks), 47 and 25%, respectively, in the DC arm, and 46 weeks (95% confidence interval: 37–54 weeks), 40 and 18%, respectively, in the DI arm. No significant differences were noted between groups in progression-free survival ($P=0.33$) or overall survival ($P=0.50$), although there were trends toward higher 1-year and 2-year survival rates in the DC.

Table 3 Overall response to docetaxel/cisplatin (DC) or docetaxel/irinotecan (DI) in patients with stages IIIb/IV non-small-cell lung cancer

Response	DC ($n=51$) No. pts	DI ($n=67$) No. pts
Complete response	0	0
Partial response	19	18
No change	23	25
Progressive disease	6	14
NE (TRD)	3	0
Response rate	37.3%*	31.6%*
95% Confidence intervals	24.1–51.9%	19.9–45.2%

pts = patients; NE = not evaluable; TRD = treatment-related death. *$P=0.55$.

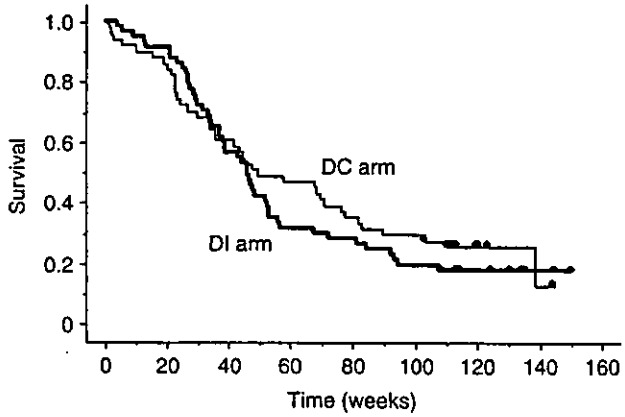

Figure 2 Overall survival according to treatment group, calculated by Kaplan–Meier method. Median survival times were 50 weeks for DC (docetaxel plus cisplatin) and 46 weeks for DI (docetaxel plus irinotecan). $P=0.50$ between treatment groups.

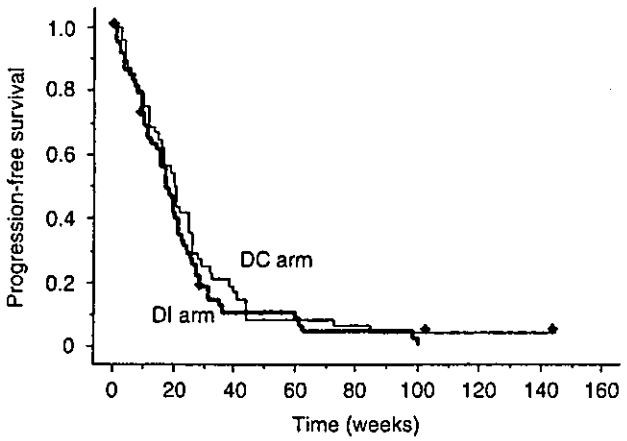

Figure 3 Progression-free survival according to treatment group, calculated by Kaplan–Meier method. Median progression-free survival times were 20 weeks for DC (docetaxel plus cisplatin) and 18 weeks for DI (docetaxel plus irinotecan). $P=0.33$ between treatment groups.

Table 4 Haematologic toxicity: maximum toxicity grade in any course

	Docetaxel/ cisplatin (% pts)			Docetaxel/ irinotecan (% pts)		
Toxicity/grade	**2**	**3**	**4**	**2**	**3**	**4**
Leucopenia*	31	43	4	26	40	16
Neutropenia*	10	31	43	4	23	61
Anaemia	47	10	2	46	7	0
Thrombocytopenia**	10	4	0	0	0	0
Febrile neutropenia		20			28	

pts = patients. *$P<0.01$ for grade 4; **$P<0.01$ for the sum of grades 2 and 3.

Second-line chemotherapy was administered to 61 patients (24 DC and 37 DI patients). A total of 22 patients in the DI group received cisplatin-based second-line chemotherapy and five had partial responses to this treatment (overall response rate, 23%). In particular, nine patients were subsequently treated with vinorelbine containing regimen and three patients had a partial response. Only two patients in the DC group received an irinotecan-containing regimen, one of whom had a partial response. Concerning as second-line chest irradiation, 8 patients in the DC group and 13 patients the DI group received.

Toxicity

Haematologic and nonhaematologic toxicities are listed in Tables 4 and 5. Grade 4 leucopenia and neutropenia occurred in a significantly higher percentage of DI than DC patients (leucopenia 16 *vs* 4%, $P<0.01$; neutropenia 61 *vs* 43%, $P<0.01$). On the other hand, there was a higher rate of grade $\geqslant 2$ thrombocytopenia in the DC than in the DI arm (14 *vs* 0%, $P<0.01$). Rates of anaemia (decrease in haemoglobin) and febrile neutropenia were similar in both groups.

Nonhaematologic toxicities including grade $\geqslant 2$ nausea (88 *vs* 51%, $P<0.01$), vomiting (39 *vs* 14%, $P<0.01$), and renal toxicity (increased serum creatinine; 12 *vs* 2%, $P<0.01$) were significantly more prevalent in the DC than in the DI arm, respectively. On the other hand, grade $\geqslant 2$ diarrhoea occurred significantly more often in DI than in DC patients (24 *vs* 42%, $P=0.01$). Other nonhaematologic toxicities, such as hepatic toxicity and peripheral neuropathy, were mild and occurred with similar frequency in both groups.

Table 5 Nonhaematologic toxicity: maximum toxicity grade in any course

	Docetaxel/ cisplatin (% pts)			Docetaxel/ irinotecan (% pts)		
Toxicity/grade	**2**	**3**	**4**	**2**	**3**	**4**
Diarrhoea*	18	6	0	26	12	4
Nausea*	53	33	0	33	18	0
Vomiting**	33	2	4	14	0	0
Peripheral neuropathy	2	0	0	2	0	0
AST increase	8	2	2	7	0	2
ALT increase	14	4	0	9	2	2
ALP increase	8	2	0	4	0	0
Creatinine increase*	10	0	2	0	0	2

pts = patients; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase. *$P<0.01$ for the sum of grades 2, 3, and 4; **$P=0.01$ for the sum of grades 2, 3, and 4.

There were three treatment-related deaths in the DC arm, which were due to febrile neutropenia and sepsis (one of these patients also developed perforation of the oesophagus). No treatment-related deaths occurred in the DI arm. The difference in incidence of treatment-related deaths was not significant.

DISCUSSION

Results of this randomised phase II study showed that the doublet chemotherapy regimens DC and DI had comparable activity in patients with advanced NSCLC. A primary goal of this study was to determine whether the DI combination should be studied in the phase III setting. Although there were no differences between DI and DC – a third-generation cisplatin-containing regimen – in overall and progression-free survival, patients who received DI tended to have lower 1-year and 2-year survival rates. Furthermore, overall toxicity was not reduced in the DI arm compared with the DC arm. Leucopenia and neutropenia were the major toxicities in both groups. As expected, emesis and renal toxicity were more prevalent in patients receiving DC, and diarrhoea occurred more frequently with DI.

Cisplatin has played a prominent role in the treatment of NSCLC, despite a relatively unimpressive single-agent response rate and a relatively severe toxicity profile. In 1995, the Non-Small Cell Lung Cancer Collaborative Group published a pivotal meta-analysis of chemotherapy in lung cancer and demonstrated the advantage of cisplatin-based regimens over best supportive care (Non-Small Cell Lung Cancer Collaborative Group, 1995). In the 1990s, third-generation chemotherapeutic agents, including paclitaxel, docetaxel, vinorelbine, gemcitabine and irinotecan, were shown to have higher response rates often coupled with fewer adverse effects (no renal toxicity, no massive dehydration, less emesis, etc.) than cisplatin. For example, single-agent paclitaxel (Ranson *et al*, 2000), docetaxel (Roszkowski *et al*, 2000), or vinorelbine (The Elderly Lung Cancer Vinorelbine Italian Study Group, 1999) significantly improved survival compared with best supportive care in patients with advanced NSCLC. Studies of single-agent gemcitabine (Perng *et al*, 1997) or irinotecan (Negoro *et al*, 2003) demonstrated a survival benefit comparable to that of second-generation chemotherapy regimens (cisplatin plus vindesine, cisplatin plus etoposide). Based on the above results, we thought that combination chemotherapy consisting of third-generation agents might improve outcome for patients with advanced NSCLC.

Only one published study compared cisplatin-based and noncisplatin-based regimens that included third-generation

agents. Georgoulias *et al* (2001) conducted a randomised study of cisplatin plus docetaxel (CD) *vs* gemcitabine plus docetaxel (GD) in 441 advanced NSCLC patients. The noncisplatin regimen provided a comparable response rate (CD 32.4%, GD 30.2%) and median survival time (CD 10 months, GD 9.5 months) but with less toxicity. The authors stated that the non-cisplatin GD regimen would likely be more acceptable to patients based on convenience of administration. However, several randomized trials reported at recent international meetings showed slightly shorter survival times with noncisplatin compared with cisplatin-based combinations. Preliminary results of the EORTC-Lung Cancer Group phase III study of cisplatin plus paclitaxel *vs* cisplatin plus gemcitabine *vs* paclitaxel plus gemcitabine in 480 patients with advanced NSCLC revealed superior overall survival and progression-free survival with the cisplatin-based regimens (Van Meerbeeck *et al*, 2001). Moreover, in a recent Italian–Canadian intergroup study of 501 patients comparing gemcitabine plus vinorelbine with cisplatin plus vinorelbine or gemcitabine, the noncisplatin regimen provided only short-term and sporadic advantages in some quality-of-life components, but there were no significant differences in overall and progression-free survival (Gridelli *et al*, 2002).

The best known noncisplatin platinum-based chemotherapy regimen is the paclitaxel plus carboplatin doublet. A Southwest Oncology Group study compared vinorelbine plus cisplatin with paclitaxel plus carboplatin. No differences in the overall survival or quality of life were noted between the two treatment groups, but toxicity rates were significantly lower in patients who received paclitaxel plus carboplatin (Chen *et al*, 2002). Results of a recent ECOG randomised phase III trial evaluating four platinum-based chemotherapy regimens showed no significant differences in the overall survival, while the paclitaxel plus carboplatin combination was less toxic than cisplatin-based chemotherapy (Schiller *et al*, 2002). Based on these findings, the paclitaxel plus carboplatin regimen is considered a standard therapy for previously untreated patients with advanced NSCLC, with activity comparable to that of cisplatin-based regimens and better tolerability.

The utility of doublet regimens containing third-generation chemotherapeutic agents for advanced NSCLC thus needs to be evaluated against the paclitaxel plus carboplatin combination, and several such studies were reported or are ongoing. The Hellenic Cooperative Oncology Group is conducting a phase III randomised study of paclitaxel plus carboplatin *vs* paclitaxel plus gemcitabine, and final results indicate comparable activity, toxicity and total cost of the two regimens in patients with inoperable NSCLC (Kosmidis *et al*, 2002). The Taiwan group conducted a similar study and found that paclitaxel plus carboplatin and paclitaxel plus gemcitabine had similar efficacy in the treatment of NSCLC, but that paclitaxel plus carboplatin was more cost-effective (Chen *et al*, 2002).

As mentioned in the introductory paragraphs, we conducted a phase I study of docetaxel plus irinotecan (DI) in patients with advanced NSCLC, and had a promising response rate of 48% and median survival time of 48 weeks (Masuda *et al*, 2000). Although we recommended docetaxel 50 mg m^{-2} on day 1 plus irinotecan 50 mg m^{-2} on days 1, 8, and 15 in the phase I study, more than half of patients could not receive irinotecan on day 15 because of haematologic toxicities. Accordingly, the day-15 irinotecan dose was omitted and the day-2 docetaxel dose moved to day 8 and increased from 50 to 60 mg m^{-2} in this randomised phase II trial.

It has been reported that second-line chemotherapy compared with best supportive care may increase the overall survival in patients with advanced NSCLC, and more studies in this regard are needed. In a recent study in which patients received cisplatin-based chemotherapy followed by docetaxel or supportive care alone, the median survival was significantly longer in the docetaxel-treated patients (Shepherd *et al*, 2000). In our study, 52% of patients were treated with second-line chemotherapy. Of these, 19 (33%) DI patients received cisplatin-based second-line chemotherapy, five of whom (26%) responded. Thus, cisplatin-based chemotherapy is capable of exerting antitumour activity in patients who have relapsed after having received noncisplatin-containing regimens.

Only two patients in the DC group received an irinotecan-containing regimen, one of whom had a partial response. As there were only two patients, we cannot judge whether irinotecan-containing regimen is effective for the patients after having received cisplatin-containing regimen.

In conclusion, docetaxel plus irinotecan combinations may be reasonable treatment options for NSCLC patients who cannot tolerate cisplatin. However, as there was no significant difference in the overall survival and no reduction in overall toxicity, DI has not improved on results obtained with DC. Thus, we will not select docetaxel/irinotecan as the experimental regimen in the next phase III study of first-line treatment of advanced NSCLC.

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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.

T. Kurata, K. Tamura, H. Kaneda, T. Nogami, H. Uejima, G. Asai, K. Nakagawa & M. Fukuoka*

*Department of Medical Oncology, Kinki University School of Medicine, 377-2 Ohno-Higashi Osaka-Sayama, Osaka 589-8511, Japan (*E-mail: mfukuoka@med.kindai.ac.jp)

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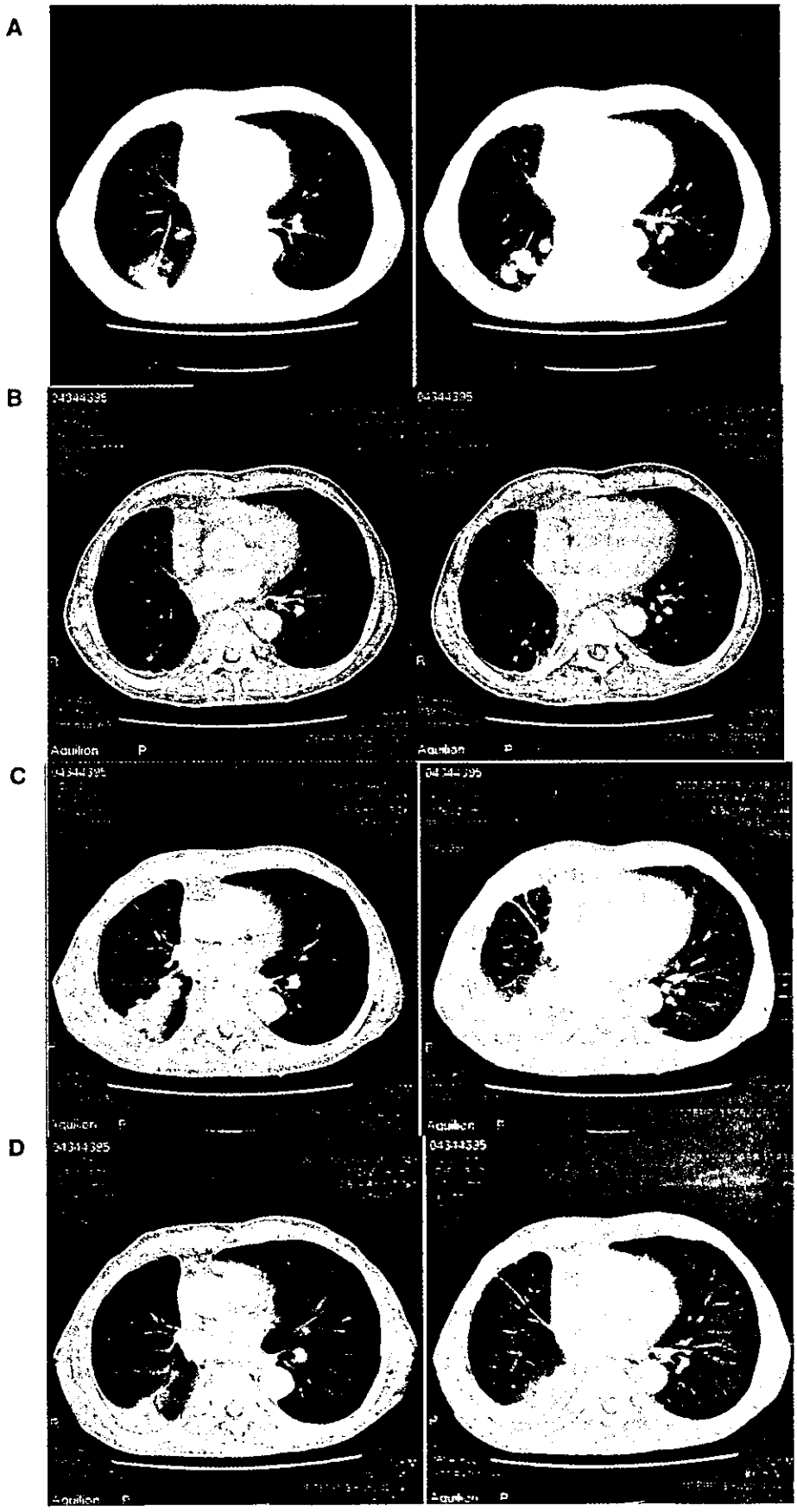

Figure 1. A 70-year-old man with adenocarcinoma of the lung. CT scan before treatment of gefitinib (**A**), after initiation of treatment (**B**), before re-treatment (**C**) and after initiation of re-treatment (**D**).

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

T Kurata[1], K Tamura[1], N Yamamoto[1], T Nogami[1], T Satoh[1], H Kaneda[1], K Nakagawa[1] and M Fukuoka*[,1]

[1]*Department of Medical Oncology, Kinki University School of Medicine: 377-2, Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan*

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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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*,

*Correspondence: Dr M Fukuoka; E-mail: mfukuoka@med.kindai.ac.jp
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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.

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