Patients and methods

Protocol objectives

The objectives of this study were: (i) to evaluate the toxicity and antitumor effect of PIE combination regimens administered weekly (arm A) and every 4 weeks (arm B) to patients with extensive stage SCLC; and (ii) to select the right arm for subsequent phase III trials. The primary endpoint was the response rate, with MST and toxicity profiles as the secondary endpoints.

Patient selection

Patients were enrolled in this study if they met the following criteria: (i) a histological or cytological diagnosis of SCLC; (ii) no prior treatment; (iii) measurable disease; (iv) extensive disease, defined as having distant metastasis or contralateral hilar lymph node metastasis; (v) performance status of 0 to 2 on the Eastern Cooperative Oncology Group (ECOG) scale; (vi) predicted life expectancy of ≥3 months; (vii) age between 20 and 70 years; (viii) adequate organ function as documented by a WBC count ≥4.0 × 10^9/l, neutrophil count ≥2.0 × 10^9/l, hemoglobin ≥9.5 g/dl, platelet count ≥100 × 10^9/l, total serum bilirubin ≤1.5 mg/dl, hepatic transaminases ≤100 IU/l, serum creatinine ≤1.2 mg/dl, creatinine clearance ≥60 ml/min, and PaO_2 ≥60 Torr; and (ix) written informed consent.

Patients were not eligible for the study if they had any of the following: (i) uncontrollable pleural, pericardial effusion or ascites; (ii) symptomatic brain metastasis; (iii) active infection; (iv) contraindications for the use of irinotecan, including diarrhea, ileus, interstitial pneumonitis and lung fibrosis; (v) synchronous active malignancies; (vi) serious concomitant medical illness, including severe heart disease, uncontrollable diabetes mellitus or hypertension; or (vii) pregnancy or breast feeding.

Pretreatment evaluation

Pretreatment assessment included a medical history, physical examination, complete blood cell count, differential counts, routine chemistry measurements, creatinine clearance, blood gas analysis, electrocardiogram, chest X-ray, chest computed tomography (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan or ultrasound sonography, and if patients complained of symptoms suggesting bone metastasis, a radionuclide bone scan.

Treatment schedule

In arm A, cisplatin 25 mg/m^2 was administered intravenously (i.v.) over 60 min on day 1 and at 1-week intervals for 9 weeks; irinotecan 90 mg/m^2 was administered i.v. over 90 min on day 1 on weeks 1, 3, 5, 7 and 9; and etoposide 60 mg/m^2 was administered i.v. over 60 min on days 1–3 of weeks 2, 4, 6 and 8. Hydration (2000 ml) and $5HT_3$-antagonist were given on day 1, followed by an additional infusion if indicated. Granulocyte colony-stimulating factor (G-CSF) was administered prophylactically on days when the cytotoxic drugs were not given, unless the WBC count exceeded 10.0 × 10^9/l (Figure 1). In arm B, cisplatin 60 mg/m^2 was administered i.v. over 60 min on day 1; irinotecan 60 mg/m^2 was administered i.v. over 90 min on days 1, 8 and 15; and etoposide 50 mg/m^2 was administered i.v. over 60 min on days 1–3. Hydration (2500 ml) and $5HT_3$-antagonist were given on day 1, followed by an additional infusion if indicated. G-CSF was subcutaneously injected from day 5 to the day when the WBC count exceeded 10.0 × 10^9/l. This treatment was repeated every 4 weeks for a total of four cycles (Figure 1).

Toxicity assessment and treatment modification

During the course of treatment, complete blood cell counts and differential counts were analyzed twice a week, and routine chemistry measurements and

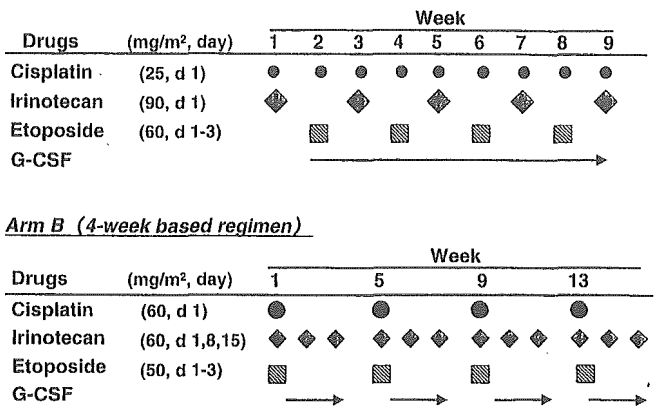

Figure 1. Treatment schema of arm A (weekly regimen) and arm B (4-week based regimen).

a chest X-ray were performed once a week. Toxicity was graded according to the toxicity criteria of the Japan Clinical Oncology Group (JCOG), a modified version of the National Cancer Institutes-Common Toxicity Criteria (NCI-CTC) issued in 1991 [11]. In arm A, subsequent cycles of chemotherapy were delayed for 1 week if one of the following toxicities was noted on day 1: WBC count <2.0 × 10^9/l, platelet count <75 × 10^9/l, serum creatinine level ≥2.0 mg/dl, elevated hepatic transaminase level or total serum bilirubin grade ≥2, fever ≥ 38°C, diarrhea grade 1–3, presence of ileus, massive pleural effusion or ascites, or a performance status of three or greater. The dose of irinotecan was reduced by 25% in all subsequent cycles if grade 2–3 diarrhea was noted. In arm B, irinotecan administration was omitted if one of the following toxicities was noted on day 8 or 15: WBC count <2.0 × 10^9/l, platelet count <75 × 10^9/l, elevated hepatic transaminase level or total serum bilirubin grade ≥2, fever ≥38°C, grade 1–3 diarrhea, presence of ileus, massive pleural effusion or ascites, or a performance status of three or greater. The subsequent cycle of chemotherapy was delayed if one of the following toxicities was noted on day 1: a WBC count <3.0 × 10^9/l, a platelet count <100 × 10^9/l, a serum creatinine level ≥1.6 mg/dl, an elevated hepatic transaminase level or total serum bilirubin grade ≥2, fever ≥38°C, diarrhea of grade 1–3, presence of ileus, massive pleural effusion or ascites, or a performance status of three or greater. If grade 4 leukopenia, grade 4 neutropenia lasting over 7 days, neutropenic fever or grade 4 thrombocytopenia was noted, the doses of irinotecan and etoposide were reduced by 25% in all subsequent cycles, and if grade 2–3 diarrhea was noted, the dose of irinotecan was reduced by 25% in all subsequent cycles. In both arms, treatment was terminated if grade 4 diarrhea, drug-induced interstitial pneumonitis or grade 3–4 peripheral neuropathy was noted.

Response evaluation

Objective tumor response was evaluated according to the World Health Organization (WHO) criteria issued in 1979 [12].

Study design, data management and statistical considerations

This study was designed as a multi-institutional, prospective, randomized phase II trial by 20 institutions in the Lung Cancer Study Group of JCOG. The protocol and consent form were approved by the Clinical Trial Review Committee of JCOG and the Institutional Review Board of each institution. Registration and randomization was conducted at the Registration Center. Data management, periodical monitoring and the final analysis were performed by the Study Coordinator. Simon's randomized phase II selection design was used to determine the sample size. Assuming response rates of a

poor and better arm of 70% and 85%, respectively, and a correct selection probability of 90%, the estimated required number of patients was 26 for each arm [13]. Accordingly, 30 patients for each arm and their accrual period of 24 months were planned for this study.

The dose intensity of each drug was calculated for each patient who received at least two cycles of chemotherapy by using the following formula:

Dose intensity (mg/m^2/week) = Total milligrams of a drug in all cycles per body surface area/[(Total days of therapy)/7]

where total days of therapy is the number of days from day 1 of cycle 1 to day 1 of the last cycle plus 7 days for arm A or 28 days for arm B [14]. The median dose intensity was then calculated.

The survival distribution was estimated by the Kaplan–Meier method [15]. The final analysis was planned 15 months after the last patient accrual. The investigational arm in a phase III trial was proposed based on the response rate, survival, toxicity and compliance data in the final analysis.

Results

Patient characteristics

From August 1999 to October 2000, 30 patients each were entered in arms A and B, and the last follow-up was performed in February 2002. All enrolled patients were included in the analyses of toxicity, tumor response and patient survival. The demographic details are listed in Table 1. Information on weight loss during the 6-month period before study entry was available for all patients. There were no differences between the two arms in any characteristics listed.

Treatment delivery

Treatment with respect to the number of cycles delivered was well tolerated in both arms. Of the 30 patients in arm, 22 (73%) in arm A and 21 (70%) in arm B received full cycles of chemotherapy, i.e. nine cycles in arm A and four cycles in arm B (Table 2). Therapy was stopped because of toxicity in four (13%) patients in arm A and in six (20%) patients in arm B, and because of tumor progression in three (10%) patients each in both arms. The treatment delays in arm A and skipping in arm B, however, were significant (Table 2). Only eight (27%) patients in arm A completed the treatment without delay, and only seven (23%) patients in arm B received all doses planned in the protocol. A total of 105 chemotherapy cycles were administered to 30 patients in arm B, but eight (8%) doses of irinotecan on day 8, and 33 (31%) doses of irinotecan on day 15 were omitted because of toxicity according to the criteria in the protocol.

The median total doses of cisplatin and etoposide administered per patient were maintained at the planned dose levels in both arms (Table 3). The median total dose of irinotecan as a percent-

Table 1. Patient characteristics

Characteristics	Arm A (n = 30)		Arm B (n = 30)	
	n	(%)	n	(%)
Sex				
Female	3	(10)	3	(10)
Male	27	(90)	27	(90)
Age				
Median	64		63	
Range	(47–70)		(46–68)	
Performance status				
0	2	(7)	3	(10)
1	25	(83)	25	(83)
2	3	(10)	2	(7)
Body weight loss				
<5%	23	(77)	21	(70)
5–10%	6	(20)	8	(27)
>10%	1	(3)	1	(3)

Table 2. Treatment delivery

No. of cycles	n	(%)
Arm A (n = 30)		
9	22	(73)
8	4	(13)
5	1	(3)
4	1	(3)
2	1	(3)
1	1	(3)
Delay (weeks)		
0	8	(27)
1	7	(23)
2	6	(20)
3	4	(13)
4	3	(10)
7	1	(3)
NE	1	(3)
Arm B (n = 30)		
4	21	(70)
3	5	(17)
2	2	(7)
1	2	(7)
Delay (weeks)		
0	22	(73)
1	3	(10)
2	2	(7)
3	1	(3)
NE	2	(7)
No. of missed cycles		
0	7	(23)
1	11	(37)
2	4	(13)
3	6	(20)
4	2	(7)

NE, not evaluable.

Table 3. Actual total dose and dose intensity delivered

	Median (range) total dose or dose intensity administered per patient			
	Arm A		Arm B	
	Actual	Relative (%)[a]	Actual	Relative (%)[a]
Total dose (mg/m^2)				
Cisplatin	225 (25–225)	100 (11–100)	240 (60–240)	100 (25–100)
Irinotecan	450 (90–450)	100 (20–100)	563 (60–720)	78 (8–100)
Etoposide	720 (0–720)	100 (0–100)	600 (150–600)	100 (25–100)
Dose intensity (mg/m^2/week)				
Cisplatin	21 (13–25)	82 (52–100)	15 (12–15)	100 (80–100)
Irinotecan	40 (21–50)	80 (41–100)	35 (19–45)	77 (42–100)
Etoposide	70 (47–80)	88 (59–100)	37 (28–38)	99 (75–100)

[a]Relative (%): actual/planned × 100.

Table 4. Grade 3 and 4 toxicity

Toxicity	Arm A (n = 30)				Arm B (n = 30)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	n	(%)	n	(%)	n	(%)	n	(%)
Leukocytopenia	9	(30)	6	(20)	12	(40)	4	(13)
Neutropenia	5	(17)	12	(40)	14	(47)	12	(40)
Anemia	12	(40)	5	(17)	12	(40)	2	(7)
Thrombocytopenia	8	(27)	0	(0)	3	(10)	0	(0)
Elevated creatinine	1	(3)	0	(0)	1	(3)	0	(0)
Hyponatremia	4	(13)	0	(0)	6	(20)	0	(0)
Hypokalemia	0	(0)	0	(0)	2	(7)	0	(0)
Infection	1	(3)	1	(3)	2	(7)	2	(7)
Nausea/vomiting	1	(3)	0	(0)	2	(7)	0	(0)
Stomatitis	0	(0)	0	(0)	1	(3)	0	(0)
Diarrhea	2	(7)	0	(0)	1	(3)	2	(7)
Arrhythmia	2	(7)	0	(0)	0	(0)	1	(3)
Dyspnea	0	(0)	1	(3)	1	(3)	1	(3)

age of the scheduled dose (the relative total dose) was 100% in arm A, but only 78% in arm B, reflecting the skips of irinotecan on days 8 and 15. The dose intensity was evaluable in 29 patients in arm A and 28 patients in arm B (Table 3). Median relative dose intensity was well maintained at a level of 80% or higher except that of irinotecan in arm B (77%). The median actual dose intensity of etoposide was 70 mg/m^2/week in arm A and 37 mg/m^2/week in arm B.

Toxicity

Toxicity was evaluated in all patients. The major toxicity was neutropenia in both arms: grade 3 or 4 neutropenia was noted in 17 (57%) patients in arm A and in 26 (87%) patients in arm B (Table 4). The median duration of G-CSF administration was 33 days (range 0–59) in arm A and 27 days (range 3–65) in arm B. One patient in arm A developed grade 4 septic shock, grade 3 diarrhea, arrhythmia, dyspnea and elevated serum creatinine, and died 16 days after the start of the treatment. There was a protocol violation in this case because the patient was given the second cycle of chemotherapy despite the presence of grade 1 diarrhea and decreased performance status of three. Two patients in arm B also developed grade 4 septic shock in the first and third chemotherapy cycle, respectively, but recovered completely from the toxicity. There were three episodes of grade 3 infection consisting of neutropenic fever, pneumonia and phlegmon. In all, grade 3 or 4 infection developed in two (7%) patients in arm A and four (13%) patients in arm B. The percentage of patients who developed grade 3 or 4 anemia was almost the same in both arms: 43% in arm A and 47% in arm B. Red blood cell transfusion, however, was required in 13 (43%) patients in arm A and four (13%) patients in arm B. Thrombocytopenia was mild in both arms. Diarrhea was mild in most patients, and grade 3 or 4

Table 5. Clinical responses

Response	Arm A		Arm B	
	n	(%)	*n*	(%)
Complete response	2	(7)	5	(17)
Partial response	23	(77)	18	(60)
No change	1	(3)	0	(0)
Progressive disease	3	(10)	4	(13)
Not evaluable	1		3	

diarrhea was noted in two (7%) patients in arm A and three (10%) patients in arm B. Grade 3 arrhythmia in one patient in arm A resolved shortly after treatment with an antiarrhythmic agent. The other two episodes of grade 3 or 4 arrhythmia were associated with septic shock. Three episodes of grade 3 or 4 dyspnea were associated with pneumonia and septic shock. All episodes of grade 3 hyponatremia and hypokalemia not associated with infection were asymptomatic and transient.

Response and survival

Two complete responses (CRs) and 23 partial responses (PRs) were obtained in arm A, resulting in the overall clinical response rate of 83% with 95% confidence interval (CI) of 65–94%, whereas five CRs and 18 PRs were obtained in arm B, and the overall response rate was 77% (95% CI 58% to 90%) (Table 5). The MST and 1-year survival rate were 8.9 months and 40%, respectively, in arm A, and 12.9 months and 57%, respectively, in arm B (Figure 2).

Discussion

This is the first study to evaluate PIE combinations in patients with extensive SCLC. Myelosuppression was the major toxicity observed frequently, and was comparable in both arms. We observed one (3%) treatment-related death in arm A, but it was associated with a protocol violation, and there were two (7%) and four (13%) grade 3 or 4 infections in arms A and B, respectively. Diarrhea and other non-hematological toxicities were not significant. Thus, toxicity was acceptable in both arms, and the recommended doses determined in our previous combination phase I studies proved reasonable [9, 10]. The clinical response and survival in both arms were comparable with those reported in the literature [3–8]. The results of this study suggested that the PIE combinations in both schedules have significant activity against extensive SCLC with acceptable toxicity.

Randomized phase II trials are a useful method of selecting one arm for subsequent phase III trials [13]. It is not always easy, however, to determine the right arm on the basis of the results of this kind of study, because the sample size is not large enough to detect statistically significant differences between the arms. The response rate, the primary endpoint of this study, was slightly higher in arm A (83% in arm A and 77% in arm B), but the CR rate and MST were both higher in arm B (7% and 8.9 months in arm A, and 17% and 12.9 months in arm B, respectively). Since

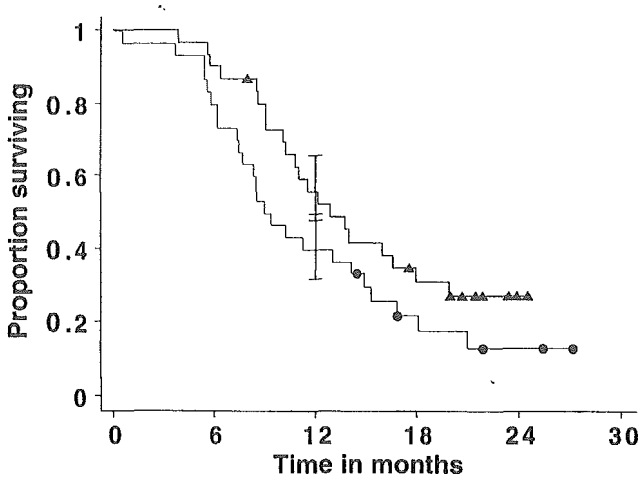

Figure 2. Survival by treatment arm. Arm A, thin line with closed circle; arm B, thick line with closed triangle.

patients with various characteristics were equally distributed in the two arms, it seems reasonable to attribute the difference in survival to the difference in treatment arms. We therefore concluded that arm B should be selected for future phase III studies. The CR rate and MST in arm B were more promising than the historical control data [3–8].

The reasons for the difference in survival between the arms are unknown. The proportion of patients who discontinued treatment because of severe toxicity did not differ between the arms. The cumulative total doses of cisplatin, irinotecan and etoposide were comparable in both arms. Since the dose intensity of the three agents in arm A was higher than in arm B, the dose intensity did not contribute to the better survival in arm B. Because of the negative results of recent phase III studies comparing dose intensive versus standard chemotherapy [16–18], increasing dose intensity is not considered a major strategy for the treatment of extensive SCLC.

Although compliance with the treatment cycles appeared good in arm B, irinotecan administration often needed to be skipped, especially on day 15. Thus, a 3-week schedule in which irinotecan is administered only on days 1 and 8 and the chemotherapy cycle is repeated every 3 weeks may improve treatment delivery and antitumor efficacy. A recent randomized phase II study of cisplatin and gemcitabine chemotherapy in patients with non-small cell lung cancer showed that a 3-week schedule was better than a 4-week schedule [19].

In conclusion, combinations of cisplatin, irinotecan and etoposide on two schedules were effective against extensive SCLC with acceptable toxicity. Arm B, in which these agents were administered on a 4-week basis, was considered to be more appropriate as the investigational arm in phase III trials.

Acknowledgements

This work was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare of Japan.

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Original contribution

A Phase II Study of Topotecan in Patients with Relapsed Small-Cell Lung Cancer

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Abstract

An early phase II study of topotecan produced favorable results in a small number of untreated and previously treated patients with small-cell lung cancer (SCLC). This multicenter study was conducted in patients with relapsed SCLC at 19 medical institutions in Japan. Topotecan 1.0 mg/m²/day was administered for 5 consecutive days every 3 weeks. Fifty-three patients were enrolled in the study. One patient was withdrawn before the commencement of study treatment, and 2 patients were unable to continue study treatment due to an interruption in the supply of study medication. The response rate was 26.0% in 13 of the 50 evaluable patients who were eligible and completed protocol-specified treatment and procedures. The median time to progression and overall survival were 133 days and 262 days, respectively. The most frequently reported toxicity was reversible myelosuppression, such as leukopenia, neutropenia, anemia (decreased hemoglobin), and thrombocytopenia. Nonhematological toxicity was also reported but the incidence of grade 3/4 symptoms was low. The results of this study indicate that topotecan is effective against relapsed SCLC with good tolerability.

Clinical Lung Cancer, Vol. 4, No. 4, 224-228, 2003

Key words: Chemotherapy, Camptothecin analogue, Topoisomerase I inhibitor, Myelosuppression, Granulocyte colony-stimulating factor

Introduction

Small-cell lung cancer (SCLC) is characterized by its high sensitivity to chemotherapy and radiotherapy. At present, combination chemotherapy with cisplatin/etoposide is used as the standard therapy for SCLC, and the response rate (RR) is as high as 81%-86% in previously untreated patients.[1,2] However, relapse inevitably follows in most responders, and the cancer progresses within 2 years in many patients. In order to improve survival in SCLC patients, new anticancer agents with a unique mechanism of action are needed.[3]

Topotecan is a semisynthetic camptothecin analogue. Preclinical data show that topotecan is particularly active against lung cancer with a broad spectrum of antitumor activity but without cross resistance to various anticancer agents.[4,5] The efficacy of topotecan alone has been reported in patients with SCLC treated in clinical studies conducted in the United States and Europe.[6-8] A phase I study in Japan was started in 1992 in patients with solid tumors.[9] The maximum tolerated dose was estimated to be 1.5 mg/m²/day for a 5-consecutive-day dosing schedule with a dose-limiting toxicity (DLT) of leukopenia. Subsequently, an early phase II study was conducted between 1993 and 1997 in a small number of patients and produced favorable results in untreated and previously treated patients with SCLC. The RRs in untreated (n = 6) and previously treated (n = 15) patients were 33.3% and 26.7%, respectively. In this early phase II study in patients with SCLC, the starting dose was reduced to 1.0 mg/m²/day after 1 death was reported at 1.2 mg/m²/day. The response to topotecan, which was defined as a complete response (CR) or partial response (PR), was observed at both the 1.2 mg/m²/day and 1.0 mg/m²/day dose levels. Based on these safety and efficacy data from the early phase II

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Submitted: Sep 17, 2002; Revised: Nov 25, 2002; Accepted: Dec 10, 2002

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study, 5 daily administrations of 1.0 mg/m^2/day with a 3-week interval was selected as the recommended regimen for the phase II study in patients with SCLC, and the dose could be increased to 1.2 mg/m^2/day if the starting dose was tolerated.

The clinical evaluation of a new anticancer agent alone for SCLC is usually carried out in previously treated patients. However, appropriate evaluation of efficacy is sometimes difficult when patients who are refractory to chemotherapy are included.[6] Recently, it has been proposed that the efficacy of a new anticancer agent should be evaluated in untreated patients (on the condition that the protocol specifies salvage therapy) or in previously treated patients who have responded to chemotherapy.[10,11] We conducted a phase II study of topotecan in the latter population. This study reports the efficacy and safety of topotecan in patients with advanced/relapsed SCLC.

Patients and Methods

Patients

A 5-day repeat dose study by intravenous infusion was conducted from January 1996 to January 1999 at 19 medical institutions. Patients with histologically or cytologically documented relapsed SCLC who met the following criteria were enrolled in this study: (1) The patient had been treated with one regimen of chemotherapy or radiotherapy and one regimen of chemotherapy; (2) the tumor responded to the first-line chemotherapy but recurred or progressed later; (3) the last chemotherapy was finished at least 8 weeks before commencing study treatment; and (4) the primary tumor was not surgically removed.
Complete histories and physical examinations were performed on all patients. The study was approved by each institutional review board and written informed consent was obtained from all patients.

To be eligible for inclusion in the study patients were required to be 15-75 years of age and have measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2, a life expectancy of ≥ 3 months, and no active concomitant malignancy. Measurable disease was defined as the tumor demonstrated by conventional chest roentgenography or computed tomography (CT) of the whole body. In addition, all patients underwent a routine staging evaluation that consisted of standard radiologic studies (including CT of the abdomen and brain) as well as bone scanning.

Eligibility requirements also included the following: white blood cell (WBC) count ≥ 4000/μL and ≤ 12,000/μL, platelet count ≥ 100,000/μL, hemoglobin ≥ 9.5 g/dL, serum bilirubin < 1.5 mg/dL, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ twice the upper limit of normal, and serum creatinine < the upper limit of normal. Patients with severe drug hypersensitivity, interstitial pneumonia, pulmonary fibrosis, symptomatic brain metastasis, massive pleural effusion, ascites, or other severe complications were excluded from the study. Patients who were pregnant, nursing, or expressed a desire to become pregnant were also ineligible.

In this study, patients were hospitalized during the first treatment course. In the second and subsequent courses patients whose clinical course could be evaluated on an outpatient basis could be discharged temporarily.

Dosage and Administration

One course of treatment consisted of a 5-day repeat dosing of topotecan 1.0 mg/m^2/day and a 16-day dose-free period. A sufficient amount of topotecan for 1 dose was dissolved in 100 mL of physiological saline and administered intravenously by drip infusion over a 30-minute period. No prophylactic antiemetics were used. Granulocyte colony-stimulating factor (G-CSF) was not administered routinely, but was used as needed according to the published guidelines.[12]

Subsequent courses were given after it was confirmed that the WBC count was ≥ 4000/μL and the platelet count was ≥ 100,000/μL. If G-CSF was given, it was confirmed that the WBC count was ≥ 4000/μL and the platelet count was ≥ 100,000/μL at least 48 hours after the end of administration of G-CSF. When WBC or platelet counts did not return to the above level, the treatment-free period could be extended up to 6 weeks.

Dose reductions/escalations were based on the lowest leukocyte count detected at weekly determinations. If leukopenia or thrombocytopenia was ≤ grade 2 (WBC count ≥ 2000/μL, platelet count ≥ 50,000/μL) at weekly determinations after the first course, the dose for the subsequent courses could be increased to 1.2 mg/m^2/day at the judgment of the investigator. If grade 4 leukopenia or thrombocytopenia (WBC count < 1000/μL, platelet count < 30,000/μL) occurred after study treatment, the dose was reduced to 0.8 mg/m^2/day in subsequent courses. More than 3 courses were given unless disease progression was observed.

Evaluation

In order to assess response and adverse effects, the following tests were done once a week during treatment: complete blood count, AST, ALT, alkaline phosphatase, lactate dehydrogenase, bilirubin, creatinine, blood urea nitrogen, serum electrolytes, urinalysis, and chest roentgenography.

Antitumor effects were evaluated according to the criteria established by the Japan Society for Cancer Therapy and the Japan Lung Cancer Society.[13] The investigator rated clinical symptoms at least once a week as grade 0-4 according to the grading scale established by the Japan Society for Cancer Therapy.[14] The severity of other symptoms was assessed on the 5-point scale: 0 = no symptom; 1 = mild; 2 = moderate; 3 = severe; and 4 = very severe.

Time to progression (TTP) was defined as the time from the commencement of study treatment to progressive disease (PD) or death. Patients who did not show progression were censored. Survival was defined as the time from the commencement of study treatment until death due to any cause. Patients lost to follow-up were censored on the date of last contact with the investigator.

The following parameters were examined in the study: tumor findings; laboratory tests (hematology, clinical chemistry, urinalysis, tumor markers); clinical findings (body temperature, body weight, PS, subjective symptoms/objective signs); and electrocardiography. Laboratory tests and other examinations were carried out just before the commencement of study treatment, at least

Table 1 Baseline Characteristics

Baseline Characteristics	Number of Patients (n = 50)
Sex	
Male	34
Female	16
Median Age, Years (Range)	63.5 (42–75)
ECOG Performance Status	
0	11
1	30
2	9
Previous Therapy	
Chemotherapy only	19
Chemotherapy + radiotherapy	29
Chemotherapy + radiotherapy + others	1
Chemotherapy + others	1
Previous Chemotherapy	
Platinum/Etoposide	30
Including irinotecan HCl	10
Others	10
Site of Lesion Evaluated	
Primary tumor	30
Metastatic tumor	
Lymph node	26
Brain	12
Liver	8
Lung	7
Adrenal	5
Hydrothorax	2
Kidney	2
Perivertebra	1

Abbreviation: ECOG = Eastern Cooperative Oncology Group

once a week, and whenever necessary after the commencement of study treatment. The measurable disease determined by the investigator was examined just before the commencement of study treatment and once a week, if possible, or at least every 4 weeks after the commencement of study treatment.

Results

Patient Disposition

Fifty of the 53 eligible patients completed protocol-specified treatment and procedures. One of the 3 patients who did not complete the study received no study treatment, and the 2 remaining patients were unable to continue study treatment due to an interruption in the supply of study medication.

Table 2 Results

	Number of Patients (n = 50)
Overall Response Rate	13 (26%)*
Complete response	0
Partial response	13 (26%)
Stable Disease	21 (42%)
Progressive Disease	11 (22%)
Unknown	5 (10%)

*90% CI, 16.1%-38.1%

Patient Characteristics

Table 1 shows the baseline characteristics of the 50 evaluable patients. Thirty-four patients were male, and approximately half of the patients (n = 24) were in their 60s. Eleven patients had an ECOG PS of 0, 30 had a PS of 1, and 9 had a PS of 2. As previous chemotherapy, combination therapy with a platinum preparation and etoposide was used in the majority of patients, and combination regimens including irinotecan were used in 10 patients. The majority of sites for evaluation were primary tumor, lymph nodes, and metastatic lesion in the brain.

The median number of courses was 2 (range, 1-7), and the mean and median total doses were 15.0 mg/m^2 ± 7.8 mg/m^2 and 13.38 mg/m^2 (range, 5.0-35.0 mg/m^2), respectively. The dose of topotecan was reduced in the second or subsequent courses in 5 patients.

Efficacy

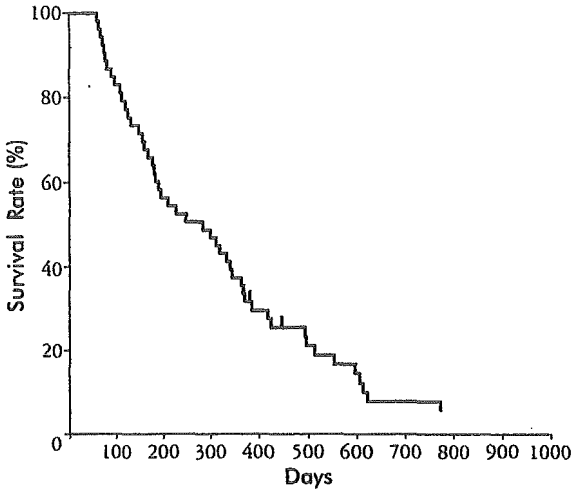
The antitumor effect of topotecan was evaluated by the investigator and confirmed by the extramural evaluation committee. The results are shown in Table 2. A PR was observed in 13 of 50 evaluable patients, stable disease in 21, and PD in 11. The response rate, percentage of CRs and PRs, was 26.0% with a 90% confidence interval (CI) of 16.1%-38.1%. The median number of courses given to the responders who achieved a PR was 4 (range, 3-6).

The median TTP was 133 days (95% CI, 70-178 days). Eleven patients were assessed as PD because of an increase in tumor size in the first course (n = 4) or second course (n = 7). The median survival time was 262 days (95% CI, 177-339 days). The survival curve is shown in Figure 1.

Safety

After excluding 1 eligible patient who did not receive any treatment with topotecan and 2 eligible patients who could not receive the prescribed number of courses because of the recall of the clinical supply, 50 patients were evaluable for safety. Table 3 shows the incidence of adverse drug reactions. The most frequently reported adverse drug reactions were anorexia (62%),

Figure 1 Survival Curve



nausea/vomiting (58%), fever (46%), fatigue (28%), and alopecia (34%). Grade 3 or 4 symptoms included anorexia (10%), nausea/vomiting (8%), and alopecia (6%). Two patients had a fever of ≥ 38°C and grade 3/4 neutropenia in 1 day, while 12 patients developed a fever of ≥ 38°C after the onset of grade 3/4 neutropenia in 1 course of treatment. Fifty-six percent of the patients evaluable for safety were treated with antibiotics. The incidence of diarrhea (1 of the DLTs of irinotecan, a drug in the same class as topotecan) was 20% and all events were grade 1/2.

Frequently observed hematological toxicities were anemia (92%), leukopenia (100%), neutropenia (100%), and thrombocytopenia (90%). Grade 3/4 abnormalities were decreased hemoglobin (46%), leukopenia (72%), neutropenia (92%), and thrombocytopenia (40%). All of these effects were reversible and resolved or showed a tendency toward resolution. Eight patients required a red blood cell transfusion, and 3 patients required a platelet transfusion. There were no deaths whose causality was attributed to study treatment.

Discussion

Topotecan is a semisynthetic camptothecin analogue. It is a topoisomerase I inhibitor with less toxicity than camptothecin. Irinotecan has a similar mechanism of action, and its efficacy against SCLC as monotherapy has been reported.[15] A randomized phase III trial in Japan suggested that the combination of irinotecan and cisplatin produced survival superior to the standard etoposide/cisplatin regimen in patients with extensive-stage SCLC.[16]

In this study of topotecan, the RR in previously treated patients with SCLC was 26.0%, which was similar to that reported for irinotecan alone (33.3%) in the same population.[15] In previous studies, the RR of topotecan alone for recurrent SCLC ranged from 19% to 33%.[6-8] In the present study, topotecan was shown to be effective at 1.0 mg/m^2/day, which is lower than the dose used in previously reported studies.[6-8] In this study, the median duration of response and the median time to response were 49 days and 28 days, respectively, which are similar to those reported for irinotecan (50 days and 28 days, respectively).[15] These findings suggest that the relatively low dose of topotecan has a promising efficacy against relapsed SCLC.

The DLT of topotecan was myelosuppression,[6-8] while myelosuppression and diarrhea were the DLTs of irinotecan.[17] In this phase II study, grade 3/4 neutropenia was reported in 92% of the patients, and neutropenic fever occurred in 24%. Neutropenia and fever were immediately alleviated by using G-

Table 3 Adverse Drug Reactions > 2% in 50 Safety Evaluable Patients

Adverse Drug Reaction	Number of Patients by Grade				
	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal System					
Anorexia	31 (62%)	11	15	5	–
Nausea/vomiting	29 (58%)	19	6	4	–
Diarrhea	10 (20%)	7	3	–	–
Abdominal pain	3 (6%)	2	1	–	–
Constipation	2 (4%)	1	1	–	–
Stomatitis	4 (8%)	4	–	–	–
Body as a Whole (General)					
Fever	23 (46%)	13	10	–	–
Fatigue	14 (28%)	7	7	–	–
Weight loss	7 (14%)	7	–	–	–
Skin and Appendages					
Alopecia	17 (34%)	13	1	3	–
Urinary System					
Hematuria	3 (6%)	3	–	–	–
Hematology					
Anemia	46 (92%)	10	13	20	3
Leukopenia	50 (100%)	3	11	34	2
Neutropenia	50 (100%)	1	3	22	24
Thrombocytopenia	45 (90%)	17	8	15	5
Clinical Chemistry					
AST	8 (16%)	7	1	–	–
ALT	10 (20%)	9	1	–	–
Total bilirubin	5 (10%)*	4	–	–	–
Urinalysis					
Urinary protein†	4 (8%)	4	–	–	–

Adverse drug reactions were graded according to criteria established by the Japan Society for Cancer Therapy.[14]
*1 patient < grade 1.
†The number of evaluable patients was 49 for urinary protein.
Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase

CSF and antibiotics. Grade 3/4 anemia and thrombocytopenia were reported in 46% and 40% of the patients, respectively. Myelosuppression was considered tolerable because most of the events resolved or showed a tendency toward resolution without treatment or after corrective therapy including G-CSF. Although the lower dose of topotecan is thought to be less toxic, the degree of myelosuppression reported in this study was similar to that reported in the previous studies of topotecan in relapsed SCLC.[6-8]

The incidence and severity of myelosuppression caused by topotecan were higher than those caused by irinotecan. Conversely, the incidence of diarrhea caused by irinotecan was 61.9% (in 700 of 1131 patients), and severe or life-threatening grade 3/4 diarrhea occurred in 20.4% (in 231 patients).[18] The total incidence of diarrhea (10.6% in 22 of 207 patients) and grade 3/4 diarrhea 1.0% (in 2 patients) were lower in the phase II clinical studies of topotecan.

Preclinical reports have suggested the usefulness of topotecan in combination with other anticancer agents.[19,20] Clinical data obtained from US and European studies have confirmed the tolerability and antitumor effect of topotecan in combination with etoposide or paclitaxel in patients with SCLC.[21-23] The efficacy of topotecan in combination with cisplatin or etoposide is currently being investigated in Japan. These results indicate that topotecan is effective against relapsed SCLC with good tolerability.

Acknowledgements

The following investigators have contributed to this study: Takahiko Sugiura, Toyoaki Hida, Aichi Prefectural Cancer Center; Yoshinori Hasegawa, Nagoya University; Atsushi Watanabe, Kosei Hospital, Aichi; Tsutomu Yoshida, Gifu Municipal Hospital; Takeshi Hourai, Shin-ichiro Nakamura, Center for Adult Diseases, Osaka; Kaoru Matsui, Osaka Prefectural Habikino Hospital; Nobuyuki Yamamoto, Kinki University; Minoru Takada, Shoji Hari, Izumisano Citizens' Hospital; Nobuyuki Katagami, Kobe City Hospital; Yoshiki Takada, Kayoko Obayashi, Hyogo Medical Center for Adults; Michio Yamakido, Hiroshima University; Hiroya Egawa, Hiroshima City Asa Hospital; Saburo Sone, Tokushima University; Nobuyuki Hara, Hirokazu Nakanishi, Kyushu University; Hidehiko Yamamoto, Aso Iizuka Hospital; Jun Araki, Sasebo City General Hospital.

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Int J Clin Oncol (2003) 8:207–211
DOI 10.1007/s10147-003-0320-1

REVIEW ARTICLE

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Molecular target-based cancer therapy: tyrosine kinase inhibitors

Received: March 25, 2003

Abstract Improved understanding of tumor biology has led to the identification of numerous growth factors that are involved in malignant transformation and tumor progression. Many of these factors induce cellular responses through receptors with intrinsic tyrosine kinase (TK) activity. Therefore, inhibiting the activity of TK receptors is one of the ways to effectively block the disordered proliferation of cancer that arises from these pathways. The human epidermal growth factor receptor (HER) family is overexpressed or dysfunctional in many human malignancies. Therefore, these receptors have been identified as targets for cancer therapy. Several agents have been developed that reversibly or irreversibly inhibit one, two, or all of the HER receptors. Iressa and Tarceva are HER1-specific TK inhibitors that are in advanced development. The large phase II study of Iressa (IDEAL1) in patients with non-small-cell lung cancer (NSCLC) in whom previous platinum-based therapy has failed, found that the median survival time (MST) was 7.6 months, which was no less than that with Docetaxel treatment. Other dual or pan-HER, reversible or irreversible, TK inhibitors are being investigated in phase I trials. Early data show that they are generally well tolerated and have provided evidence of against activity tumors. HER-TK inhibitors are likely to have a substantial impact on the treatment of cancer patients.

Key words Human epidermal growth factor receptor (HER) tyrosine kinase inhibitor · Iressa · Tarceva · Dual-HER inhibitor · Pan-HER inhibitor · Irreversible HER inhibitor

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Introduction

Most cellular protooncogenes encode proteins that participate in signaling pathways by which cells receive and execute instructions that lead to proliferation, differentiation, and programmed cell death. These protooncogenes include transmembrane receptor or intracellular molecules, which are overexpressed or mutationally activated in several cancers. Many members of the protein tyrosine kinase (TK) family have also been reported to be protooncogenes, and their tyrosine phosphorylation and activation produces critical events in growth control and transformation in malignancies. Therefore, they are theoretically targets for anticancer molecular therapies. Early developments of molecular targeted therapies include the anti-TK molecules, such as the BCR-ABL TK inhibitor Gleevec[1]; the vascular endothelial growth factor receptor (VEGFR)-TK inhibitors, SU5416, SU6668,[2] and ZD6474; and the human epidermal growth factor receptor (HER)-TK inhibitors. The most striking as tumor shrinkage has been produced by HER-TK inhibitors.

Blocking the HER family has two approaches, which are based on known structure and function. The first strategy is based on the development of monoclonal antibodies[3] against the receptor's nonconserved extracellular domain. These antibodies block ligand binding and can induce receptor down-regulation. The second approach is to generate small molecules that compete with adenosine triphosphate (ATP) for binding to the receptor's kinase pocket and inhibit the autophosphorylation of TK. This approach is based on the premise that EGFR with mutations in the ATP binding site lack tyrosine kinase function and do not display a full range of ligand-induced biochemical responses.[4] Table 1 shows a partial list of the HER-TK inhibitors currently in preclinical and clinical development. These inhibitors have been developed with different specificities for HER receptors. Some agents, such as Iressa and Tarceva, are specific for HER1 TK, whereas others inhibit HER1 and HER2 TKs (dual inhibitors) or all the members of the HER family (pan-HER inhibitors). In addition, TK

Table 1. Human epidermal growth factor receptor (HER)-targeted tyrosine kinase inhibitors

Compound	Chemical structure	Target	Reaction	IC_{50} (nM)		Company	Clinical trial
				HER1	HER2		
ZD1839 (Iressa)	Quinazoline	HER1	Competitive ATP inhibition	23	3700	AstraZeneca	III
OSI774 (Tarceva)	Quinazoline	HER1	Competitive ATP inhibition	20	350	OSI/Genentech	III
CI1033	Quinazoline	Pan-HER (HER1-4)	Irreversible (Cys773)	1.4	0.9	Pfizer	II
EKB569	Cyano-Quinazoline	HER1	Irreversible (Cys773)	39	1255	Wyeth-Ayerst	I
PKI166	Pyrollo-pyrimidine	HER1 HER2	Competitive ATP inhibition	25	10	Novartis	I
GW572016	Quinazoline	HER1 HER2	Competitive ATP inhibition	8	8	GlaxoSmith-Kline	I

ATP, adenosine triphosphate

chemical modification of some of these structures has led to the generation of irreversible inhibitors that bind covalently to specific Cys residues in the the EGFR ATP-binding pocket, such as CI1033 and EKB-569. Although theoretically the irreversible inhibitors should be able to achieve short plasma half-lives, low peak plasma concentrations, and prolonged target suppression, the clinical efficacy of this approach requires further investigation.

We review several HER-targeted TK inhibitors in advanced clinical and preclinical development, especially for patients with non-small-cell lung cancer (NSCLC).

The HER family and the chemical structure of HER1

The HER family consists of four structurally similar TK proteins: HER1 (EGFR, erbB1), HER2 (erbB2, Her2/neu), HER3 (erbB3), and HER4 (erbB4). The specific ligands for HER1 are EGF, TGFα, HB-EGF, and betacellulin. The ligand for HER2 has not been identified. Each HER exists as a monomer at the surface of the cellular membrane. Once a ligand binds to the extracellular domain, the HER proteins form homodimers or heterodimers with each other.[5] Ligand binding causes autophosphorylation of TK in the intracytoplasmic domain near the C-terminus of the receptors. Overexpression of HER1 or HER2 has been reported in many solid tumors[6] and is associated with a poor prognosis.[7]

The HER family are typical TK receptors, with an extracellular ligand-binding domain (transmembrane domain) and a cytoplasmic domain (Fig. 1). The amino-terminal extracellular domain of HER1 consists of 622 amino acids and two cysteine-rich regions that form the ligand-binding domain. The cysteine-rich domain 1 is deleted in EGFR vIII,[8] which is a variant receptor that is often detected in malignant tumors. The transmembrane region is a single alpha helix. The cytoplasmic domain contains a kinase region and a carboxy-terminal tail that contains several tyrosine phosphorylation sites (Fig. 1). It is unclear which tyrosine phosphorylation site is critical for the response to HER-TK inhibitors.

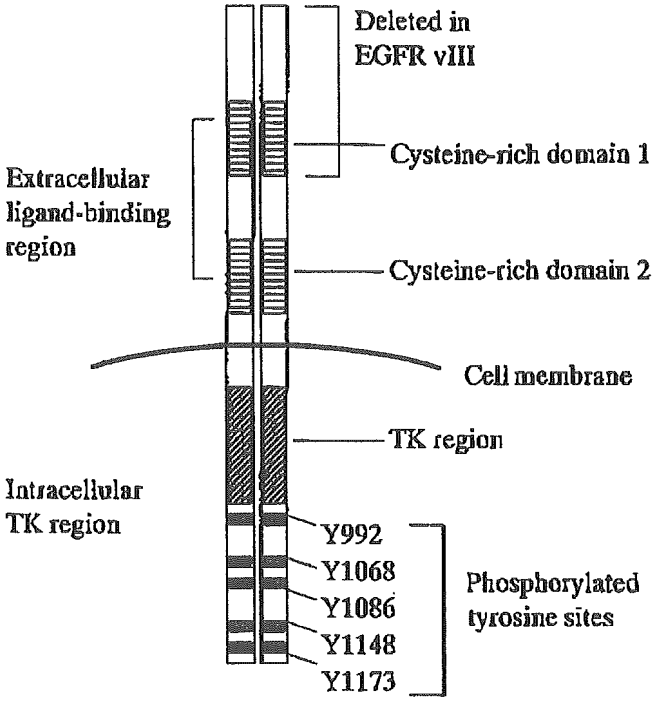

Fig. 1. Chemical structure of human epidermal growth factor receptor (HER)1. HER1 has an extracellular ligand-binding domain and a cytoplasmic domain. The extracellular domain consists of two cysteine-rich regions, although the amino-terminal domain of the two (domain 1) is deleted in epidermal growth factor receptor (EGFR) vIII. The transmembrane region is a single alpha helix. The cytoplasmic domain contains a kinase region and a carboxy-terminal tail that contains several tyrosine phosphorylation sites TK, tyrosine kinase

HER-targeted TK inhibitors in advanced clinical development

Iressa

Iressa (gefitinib) is a small molecule that selectively inhibits the intracellular TK domain of EGFR (HER1). It is orally active and is the first compound that was introduced in clinical studies as an HER-targeted TK inhibitor. This small

molecule is a synthetic anilinoquinazoline that inhibits isolated EGFR TK with a 50% inhibitory concentration (IC_{50}) of 23 nM (Table 1).

Phase I trials have evaluated both intermittent administration (14 days of treatment followed by 14 days of observation) and continuous delivery (once daily for 28 days) of Iressa.[9] Patients were eligible if they had tumors known to express EGFR, such as NSCLC, breast cancer, colon cancer, ovarian cancer, prostate cancer, and head and neck cancers, but were not prescreened for detectable EGFR in the tumor before study entry. Both schedules of administration were tolerated with minor toxicities, such as grade 1 or 2 skin rash, nausea, vomiting, and diarrhea. The most frequent toxicity was skin rash. The dose-limiting toxicity (DLT) was grade 3 diarrhea, which occurred at doses ≧700 mg/day. (In a Japanese trial, both diarrhea and liver dysfunction were DLTs.) Although not a primary end point for these studies, objective responses as well as disease stabilization, especially in patients with adenocarcinoma of NSCLC, were seen at several dose levels and were frequently associated with improvement of disease-related symptoms.

Two large phase II trials have examined Iressa (250 and 500 mg/day) monotherapy in patients in Europe, Japan, Australia, and New Zealand with NSCLC in whom previous platinum-based therapy has failed (IDEAL-1),[10] and patients in the United States in whom first-line platinum-based therapy and second-line docetaxel-based regimens have failed (IDEAL-2).[11] The overall response rates with Iressa at 250 and 500 mg/day were 18.4% and 19.0%, respectively, in IDEAL-1, and 11.8% and 8.8%, respectively, in IDEAL-2 (Table 2). At 250 mg/day, the median survival time (MST) was 7.6 months in IDEAL-1 and 6.1 months in IDEAL-2. The MST in IDEAL-1 was no less than that for docetaxel, which is a key drug in second-line chemotherapy for patients with NSCLC. In both trials there was evidence of rapid improvement of symptoms and benefit to quality of life with Iressa. The most frequently reported adverse events in both trials were skin rash, diarrhea, liver dysfunction, and nausea. Most of the toxicities were mild (grade 1 or 2). However, more grade 3 or 4 events occurred with 500 mg/day than with 250 mg/day of Iressa.

In preclinical studies, it was noted that Iressa enhanced the cytotoxic activity of different chemotherapeutic drugs, such as platinum compounds, gemcitabine, and taxanes. This synergy with chemotherapy was independent of the level of EGFR expression. These findings provided a strong rationale for combining Iressa with standard chemotherapy regimens in advanced NSCLC. The Iressa Non-small-cell lung cancer Trial Assessing Combination Treatment (INTACT) study investigated whether the addition of concurrent Iressa to standard chemotherapy in first-line chemotherapy would improve the outcome of patients with advanced NSCLC. The INTACT-1 randomized phase III study used cisplatin/gemcitabine plus Iressa,[12] and the INTACT-2 study used carboplatin/paclitaxel plus Iressa.[13] Recruitment to these trials has been completed, and the final results were reported in the European Society for Medical Oncology (ESMO) meeting in October 2002. In both the IDEAL-1 and the IDEAL-2 studies, Iressa concurrently used with platinum-based doublet chemotherapy in first-line chemotherapy failed to prolong survival time or decrease the time to progression of patients with advanced NSCLC (Table 3).

Tarceva

Like Iressa, Tarceva is an orally available and highly selective inhibitor of HER1. Two phase I studies of patients with treatment-refractory solid tumors have examined daily or weekly dosing regimens. In the daily-dosing study,[14] 40 patients received escalating doses of Tarceva (25–200 mg). The results showed that Tarceva has dose-independent pharmacokinetics, and daily dosing does not result in drug accumulation. Antitumor activity was observed in several patients: one patient with metastatic renal carcinoma remained tumor-free for more than 20 months, and one patient with colorectal carcinoma had a 30% reduction in liver metastases for 11 months. In the weekly-dosing study,[15] 27 patients received Tarceva (100–1000 mg). Four patients had stable disease for more than 6 months. Tarceva was well tolerated in both studies, and the most commonly reported adverse events were a dose-related acneiform rash, diar-

Table 2. Phase II study of Iressa (IDEAL1 and IDEAL2)

Treatment history	IDEAL1	IDEAL2
	1–2 regimens (+ platinum-based chemotherapy)	≧2 regimens (+ platinum-based chemotherapy, + docetaxel)
Countries	Japan/Europe (N = 210)	USA (N = 216)
Response rate (%)		
250 mg/day	18.4	11.8
500 mg/day	19.0	8.8
Median survival time (mo)		
250 mg/day	7.6	6.1
500 mg/day	7.9	5.9
Symptom improvement (%)		
250 mg/day	40	43
500 mg/day	37	35

Table 3. Phase III study of Iressa (in combination with standard chemotherapy)

Measure	INTACT1			INTACT2		
	250 mg/day (N = 365)	500 mg/day (N = 365)	Placebo (N = 363)	250 mg/day (N = 345)	500 mg/day (N = 347)	Placebo (N = 345)
Median survival time (mo)	9.86	9.92	11.07	9.82	8.74	9.92
1-yr survival (%)	41	43	45	41	37	42
Time to progression (mo)	5.85	5.55	5.98	5.32	4.67	5.06
Response rate (%)	(N = 335)	(N = 332)	(N = 326)	(N = 306)	(N = 308)	(N = 289)
Complete response	3	2.1	0.9	2.3	0.6	1
Partial response	47.2	47.6	43.9	32.7	31.5	32.5

rhea, headache, and nausea and vomiting. Dose-limiting diarrhea was observed at 200 mg/day on the continuous regimen; at 150 mg/day the diarrhea was manageable with loperamide. Based on these data, progression to phase II and III studies was justified with a dose of 150 mg/day.

Three phase II trials of Tarceva for three different indications (ovarian cancer, head and neck cancer, and NSCLC) have been completed. All patients received Tarceva at 150 mg/day, although dose modifications were permitted based on predefined toxicity criteria. In the NSCLC study,[16] 57 patients with HER1-positive, stage IIIB or IV cancer, in whom prior chemotherapy, radiotherapy, or surgery had failed, received Tarceva for up to 52 weeks or until clinical deterioration or disease progression occurred. HER1 expression was confirmed by immunohistochemistry. One patient (2%) had a complete response that lasted for 23 weeks, and six patients (11%) had confirmed partial responses that lasted for 17 to 36 weeks. Thus, the overall response rate to Tarceva treatment in these patients was 12.3%. Twenty patients (35%) had prolonged stable disease. The overall survival was 8.4 months, and the one-year survival rate was 48%. In the three phase II studies, Tarceva was well tolerated, and the side effects were similar to those observed in phase I studies. An acneiform skin rash was the most common adverse event. This rarely exceeded grade 2 in severity, but it was reported by more than 70% of the patients in each of the three studies. The second most common side effect was diarrhea. In the ovarian cancer study, dose-limiting diarrhea was observed at 200 mg/day. The profile of toxicities was quite similar that of Iressa, suggesting that these events are related to the inhibition of HER1.

The monotherapy phase II data clearly indicate that Tarceva has the potential to benefit patients with various types of solid tumor, and studies are in progress to examine its efficacy in different clinical settings. Two large phase III studies have started that use Tarceva in combination with gemcitabine/cisplatin (TALENT) or carboplatin/paclitaxel (TRIBUTE) as first-line therapy for advanced NSCLC. Another phase III trial is examining Tarceva plus gemcitabine for advanced pancreatic cancer (IMPACT).

Other phase I or II trials are trying Tarceva in combination with various cytotoxic agents. Three reports of clinical studies using Tarceva in combination with docetaxel, gemcitabine/cisplatin, or paclitaxel/carboplatin in patients with advanced solid tumors were presented at the 2002 meeting of the American Society of Clinical Oncology. Preliminary findings show evidence of biological activity with all these combinations and no indication of pharmacokinetic interactions between the agents.

Novel HER-targeted TK inhibitors

CI-1033 is an irreversible, orally available pan-HER-TK inhibitor. In a phase I study, CI-1033 was given in doses of 100 to 1000 mg weekly.[17] The most common adverse effects were grade 1 and 2 diarrhea, emesis, and rash. Two patients receiving a dose of 560 mg developed dose-limiting hypersensitivity reactions. Six patients had stable disease that lasted for more than 3 months, including one patient with a chemotherapy-resistant osteosarcoma who had stable disease for 8 months. In another phase I study[18] in which therapy was given daily for 7 days every 3 weeks, diarrhea and skin rash were the most common adverse effects, three patients had reversible thrombocytopenia, and three had hypersensitivity reactions. The maximum tolerated dose (MTD) was 750 mg, and diarrhea and emesis were dose-limiting toxicities. One patient with squamous cell carcinoma of the skin had a partial response, and 13 patients (25%) had stable disease for more than 3 months.

EKB-569 is a 3-cyanoquinoline that irreversibly inhibits HER1-TK. EKB-569 is currently being evaluated in phase I trials, and recent data show it is generally well tolerated and has a maximum tolerated dose of 75 mg/day on both an intermittent and a continuous dosing schedule.

PKI-166 is a reversible, orally available pyrollo-pyrimidine that dually inhibits HER1 and HER2 TK. Two phase I trials have been initiated. Thirty-two patients with solid tumors known to overexpress HER1 have participated in an ongoing dose-escalation study of PKI-166 administrated continuously (50–600 mg). The results show that PKI-166 has linear pharmacokinetics. The most frequent adverse events were gastrointestinal reactions, skin rash, fatigue, and liver dysfunction. One patient with NSCLC had a partial response, and three patients had stable disease for more than 4 months.[19]

Like PKI-166, GW572016 is a selective reversible dual HER-TK inhibitor. Recent data from two phase I studies examining single and multiple dosing in healthy volunteers

show that GW572016 is well tolerated. The phase I study with solid tumors is continuing to recruit patients.

Conclusion

Advances in molecular biology have led to novel anticancer drugs that target the specific abnormalities responsible for tumor progression. HER-TK inhibitors are in the forefront of molecular targeted drugs. In clinical trials, Iressa and Tarceva showed objective responses in the refractory setting in a higher proportion of patients (from 10% to 20%) than that reported with standard cytotoxic drugs. However, the proportion of responders seemed to be quite restricted. Although multivariate proportional-hazards model analysis in IDEAL suggested that female sex and adenocarcinoma are associated with a response to Iressa in NSCLC, the biological mechanism has not been explained. No study has yet determined whether there is a relationship between response and receptor expression or phosphorylation of the patient's tumor. Translational studies are needed to clarify the population of patients who should respond to HER-TK inhibitors, and these data will give great hope for this new class of cancer therapy in the next generation.

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British Journal of Cancer (2004) 90, 87–92

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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)

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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.
British Journal of Cancer (2004) **90,** 87–92. doi:10.1038/sj.bjc.6601462 www.bjcancer.com

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

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Received 2 May 2003; revised 9 September 2003; accepted 6 October 2003

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.

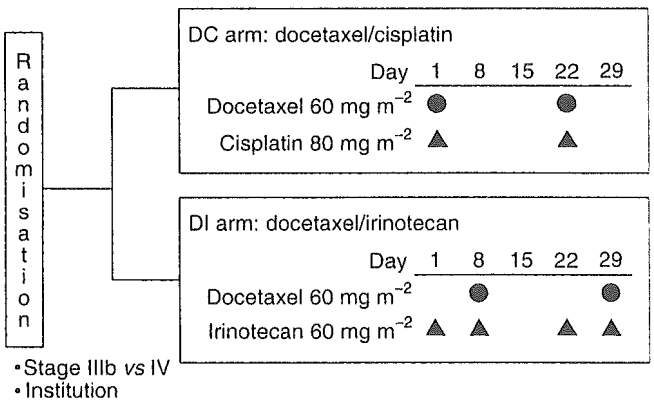

Figure 1 *Treatment schema*: after stratification by stage and institution, enrolled patients were randomly allocated to receive docetaxel plus cisplatin (DC) or docetaxel plus irinotecan (DI).

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. *$P=0.55$.

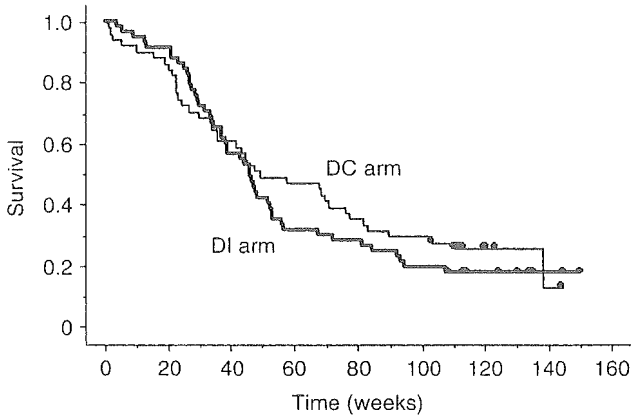

Figure 2 Overall survival according to treatment group, calculated by Kaplan–Meier method. Median survival times were 50 weeks for DC (docetaxel plus cisplatin) and 46 weeks for DI (docetaxel plus irinotecan). $P=0.50$ between treatment groups.

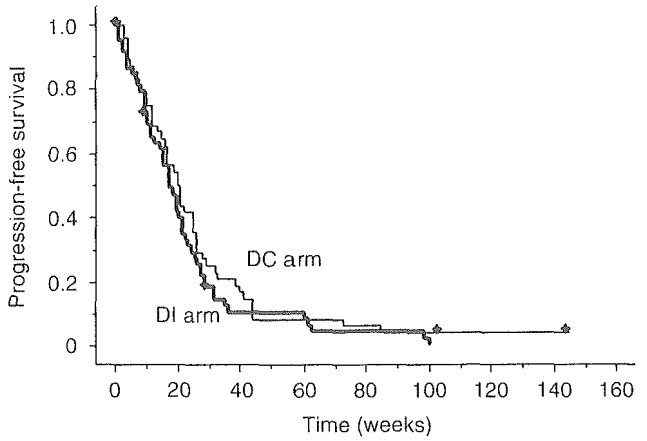

Figure 3 Progression-free survival according to treatment group, calculated by Kaplan–Meier method. Median progression-free survival times were 20 weeks for DC (docetaxel plus cisplatin) and 18 weeks for DI (docetaxel plus irinotecan). $P = 0.33$ between treatment groups.

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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