TABLE 1. Characteristics of Gene Expression and Overall Survival*

			P Value	
		No. of Patients	Log-rank	Wilcoxon
Survivin	Negative	37	0.014	0.014
	Positive	35		
Cyclin D1	Negative	26	0.049	0.052
	Positive	46		
Integrin β1	Negative	66	0.021	0.01
	Positive	6		
VEGF	Negative	46	0.68	0.65
	Positive	26		
Combination	0–1	37	0.0011	0.0011
	2–4	35		

*Combination; survivin, cyclin D1, integrin β1, and VEGF were included.

Thirty-seven patients had tumor with positive expression of 0 or 1 gene and 35 patients had tumor with positive expression of 2 to 4 genes.

In an attempt to better understand tumor progression in NSCLC, expression of survivin, cyclin D1, integrin β1, and vascular endothelial growth factor (VEGF), which have different mechanisms in tumor progression, were investigated prognosis in adenocarcinoma <2 cm in diameter of stage I in the present study.

PATIENTS AND METHODS

Patients with lung adenocarcinoma <2 cm in diameter of pathologic stage I, resected between January 1992 and December 1999, were enrolled in the present study.

The tumor specimens obtained by resection were subjected to immunostaining for survivin, cyclin D1, integrin β1, and VEGF. Formalin-fixed, paraffin-embedded, 5-im-thick tumor sections were mounted on charged glass slides, deparaffinized and rehydrated in a graded alcohol series. Immunohistochemical staining was performed using an automated processor. Details of immunostaining were shown in previous reports.[8–11] Each factors immunostaining levels were classified as positive (>10% of cells stained for survivin, integrin β1, and VEGF, and >20% of cells stained for cyclin D1) or negative (≤10% of cells stained for survivin, integrin β1, and VEGF, and ≤20% of cells stained for cyclin D1).

Two pathologists examined the staining patterns of each factor independently, and recorded the percentage of positive cells in each specimen. At least 20 high-power fields were chosen randomly and 2000 cells were counted. The ratio of each gene-positive cell was calculated by dividing the number of positive cells by the total number of cells, and was expressed as a percentage.

Kaplan-Meier survival curves were constructed and analyzed for statistical significance by means of the log-rank and generalized Wilcoxon tests. The influence of each variable on survival was examined by the Cox proportional hazards model in multivariate regression analyses. Differences at $P < 0.05$ were considered to be statistically significant.

RESULTS

Seventy-two patients with resected tumors <2 cm in diameter of pathologic stage I were entered into the study. There were 29 males and 43 females, with a median age of 64 years (range 26–83 years). Each patient underwent curative surgical resection for lung cancer between July 1992 and November 1999. The resected tumors were subjected to immunostaining for each gene. Thirty-five, 26, 6, and 16 patients had tumors with >10% survivin-, >20% cyclin D1-, >10% integrin β1-, and >10% VEGF-positive cells, respectively.

When the survival of 72 patients was compared according to each gene expression, the overall survival of patients with positive expression of survivin, cyclin D1, and integrin β1 was significantly worse than that of individuals whose tumors had negative expression of each gene (Table 1). We analyzed how many of the 4 genes expressed positively in each resected tumor, 9, 28, 24, and 11 patients had tumors with positive expression of 0, 1, 2, and 3 genes, respectively. There were no patients with tumor expressed every 4 genes.

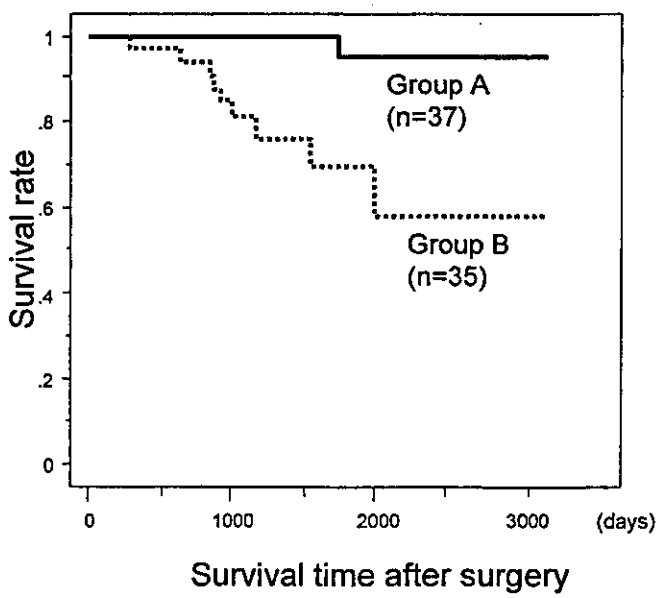

FIGURE 1. Survival curves according to gene immunostaining, constructed using the Kaplan-Meier method. Survival after surgery of patients with 2 or more positive expression of genes in tumor was worse than that of those with 0 or 1-positive expression of gene in tumor (log-rank $P = 0.0011$, Wilcoxon $P = 0.0011$).

TABLE 2. Multivariate Regression Analysis of Variables in Predicting Overall Survival

Variable	Assigned Score	Hazards Ratio	95% CI	*P* Value
Lymphatic invasion		0.488	0.094–2.549	0.400
Negative	0			
Positive	1			
Vessel invasion		0.493	0.098–2.473	0.390
Negative	0			
Positive	1			
Bronchioalveolar carcinoma		1.062	0.102–11.053	0.960
yes	0			
no	1			
Combination of gene expression		0.087	0.009–0.801	0.031
Positive 0–1	0			
Positive 2–4	1			

By multivariate analysis controlling for each gene expression, no gene expression was an independent marker of poor prognosis. When we examined whether the number of positive gene expression in the tumors influence the prognosis, the overall survival of complex gene expression (2 or more gene-positive) group (n = 35) was significantly worse than that of the 0 or 1 gene-positive group (n = 37; log-rank test, $P = 0.0011$; Wilcoxon test, $P = 0.0011$, Fig. 1 and Table 1). When the association between survival and pathologic factors, including lymphatic invasion, venous invasion, type of bronchioalveolar carcinoma, and complex gene expression was analyzed, only complex gene expression was found to be a significant independent factor (hazard ratio = 0.085, $P = 0.0299$, Table 2). It can be concluded that multiple but not single increased expression oncogene is a poor prognostic factor in patients with small adenocarcinoma of the lung.

DISCUSSION

Changes in gene expression are at the basis of many crucial physiological and pathologic processes. Tumorigenesis involves a loss of balance between regulators of cell proliferation and apoptosis. A previous study showed positive expression of survivin was a poor prognostic factor in small adenocarcinomas <2 cm in diameter.[11] However, the present study showed that not only survivin but also cyclin D1 and integrin β1 were poor prognostic factors. The present study demonstrated that 49%, 64%, 8%, and 22% of resected tumors <2 cm in diameter of pathologic stage I showed positive expression of survivin, cyclin D1, integrin β1, and VEGF, respectively. Only 9 patients (12.5%) had no expression of every 4 genes in resected small adenocarcinoma but many others had single or multiple gene expression in this study. This fact may explain that small adenocarcinoma <2 cm in diameter of pathologic stage I is in a transition from early to advanced stage. After all, multiple regression analysis demonstrated that no gene expression was an independent marker of poor prognosis, but complex gene expression show poor prognosis in small adenocarcinoma of the lung.

Lung cancer has a high potential of distant metastasis, and induction therapy followed by surgery and/or radiotherapy has become standard therapy for stage III disease.[12] Several gene expression analyzed in the present study is an important predictive factor for recurrence after curative resection in early stage lung cancer. The information obtained by this analysis is a powerful prognostic discriminator for patients with stage I disease and may be useful for decisions concerning which patients should and should not receive systemic treatment in addition to surgical resection. Furthermore, new strategies may be also considered with reference to multiple oncogene expression to improve treatment of locally advanced NSCLC. Targeted chemotherapy against positive expressed gene, such as using monoclonal antibodies, may be an ideal approach to treating multiple oncogene expressed tumors. When adjuvant chemotherapy after surgical resection is considered, not only single target therapy but also multitarget therapy such as combination of antiapoptotic, anticell cycle, antiadhesion and others, should be required, because multiple gene expressions in resected tumor is a poor prognostic factor presented in this study.

Lung cancer appears as small nodules in the peripheral part of the lung, and pathologic or cytologic diagnosis is essential. Patients suspected of having lung cancer often undergo fiberscopic examination, with a tumor biopsy examination or a cytologic approach. When a lesion is inaccessible to bronchoscopic biopsy, or when the biopsy specimen is nondiagnostic, a diagnosis of cancer may be possible by cytologic examination of bronchoalveolar lavage fluid (BALF). In a previous report, we demonstrated that detection of the K-*ras* mutation in BALF cells, by PCR-PIREMA, aids the diagnosis of lung cancer in patients with small pulmonary lesions with negative cytologic findings.[13] BALF from patients with small adenocarcinoma may contain survivin, cyclinD1, integrin β1, and VEGF, and it is possible that the gene expressions can be detected as a diagnostic marker.

In conclusion, multiple but not single oncogene expressions in tumor cells is a poor prognostic factor in patients with small adenocarcinoma of the lung. Detection of the gene expressions appears to be not only a useful diagnostic marker but also a potential new target for anticancer therapy for early stage NSCLC.

ACKNOWLEDGMENTS

This work was supported in part by Grant for Scientific Research Expenses for Health Labor and Welfare Programs and

Foundation for the Promotion of Cancer Research and by 2nd Term Comprehensive 10-year Strategy for Cancer Control

REFERENCES

1. Martini N, Ginsberg R. Treatment of stage I and II disease, in Aisner J, Arriagada R, Green M, et al, eds. *Comprehensive Textbook of Thoracic Oncology*. Baltimore: Williams & Wilkins; 1996:339–350.
2. Tomizawa Y, Nakajima T, Kohno T, et al. Clinicopathological significance of Fhit protein expression in stage I non-small cell lung carcinoma. *Cancer Res.* 1998;58:5478–5483.
3. Ohta Y, Tomita Y, Oda M, et al. Tumor angiogenesis and recurrence in stage I non-small cell lung cancer. *Ann Thorac Surg.* 1999;68:1034–1038.
4. Herbst RS, Yano S, Kuniyasu H, et al. Differential expression of E-cadherin and type IV collagenase genes predicts outcome in patients with stage I non-small cell lung carcinoma. *Clin Cancer Res.* 2000;6: 790–797.
5. Khuri FR, Lotan R, Kemp BL, et al. Retinoic acid receptor-β as a prognostic indicator in stage I non-small-cell lung cancer. *J Clin Oncol.* 2000;18:2798–2804.
6. Hashimoto T, Tokuchi Y, Hayashi M, et al. p53 null mutations undetected by immunohistochemical staining predict a poor outcome with early-stage non-small cell lung carcinomas. *Cancer Res.* 1999;59:5572–5577.
7. Nelson HH, Christiani DC, Mark EJ, et al. Implications and prognostic value of K-ras mutation for early-stage lung cancer in women. *J Natl Cancer Inst.* 1999;91:2032–2038.
8. Betticher DC, Heighway J, Hasleton PS, et al. Prognostic significance of CCND (cyclin D1) overexpression in primary resected non-small-cell lung cancer. *Br J Cancer.* 1996;73:294–300.
9. Ito H, Oshita F, Kameda Y, et al. Expression of vascular endothelial growth factor and basic fibroblast growth factor in small adenocarcinoma. *Oncol Rep.* 2002;9:119–123.
10. Oshita F, Kameda Y, Ikehara M, et al. Increased expression of integrin β1 is a poor prognostic factor in small-cell lung cancer. *Anticancer Res.* 2002;22:1065–1070.
11. Ikehara M, Oshita F, Kameda Y, et al. Expression of survivin correlated with vessel invasion is a poor prognostic factor in small adenocarcinoma of the lung. *Oncol Rep.* 2002;9:835–838.
12. Van Zandwijk N, Smit EF, Krame GWP, et al. Gemcitabine and cisplatin as induction regimen for patients with biopsy-proven stage IIIA N2 non-small-cell lung cancer: A phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group (EORTC 08955). *J Clin Oncol.* 2000;18:2658–2664.
13. Oshita F, Nomura I, Yamada K, et al. Detection of K-ras mutation of bronchoalveolar lavage fluid cells aids the diagnosis of lung cancer in small pulmonary lesions. *Clin Cancer Res.* 1999;5:617–620.

Lung Cancer (2004) 43, 93–100

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Combination chemotherapy of gemcitabine and vinorelbine for patients in stage IIIB–IV non-small cell lung cancer: a phase II study of the West Japan Thoracic Oncology Group (WJTOG) 9908

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Received 12 November 2002; received in revised form 22 July 2003; accepted 22 August 2003

KEYWORDS
Gemcitabine;
Vinorelbine;
Combination chemotherapy;
Stage IIIB;
Stage IV;
Chemo-naïve;
Non-small cell lung cancer

Summary *Objectives:* Vinorelbine (V) and gemcitabine (G) are two active single agents used in the treatment of non-small cell lung cancer (NSCLC). A multicenter clinical trial (West Japan Thoracic Oncology Group (WJTOG) 9908) was conducted to evaluate the efficacy and toxicity of V and G in patients (pts) with advanced NSCLC. *Methods:* Eligibility criteria: no previous chemotherapy; performance status (PS) 0 or 1; age <75 years old. V, 25 mg/m^2, was given as a 2–3 min IV infusion, followed by a 30 min IV infusion of G, 1000 mg/m^2, on days 1 and 8 of each 21-day cycle. *Results:* From April 2000 to September 2000, 52 pts were enrolled in the study. Two pts were ineligible. Baseline characteristics: median age 60, males 30 (60%), Eastern Cooperative Oncology Group (ECOG) PS 0/1 = 21/29 (58%), stage IIIB/IV = 12/38 (76%), adenocarcinoma = 35 (70%). The median number of cycles administered was 2. Fifty pts were evaluable for response. The response rate was 18% by the Response Evaluation Criteria in Solid Tumors (RECIST) (no complete response (CR), 9 partial response (PR), 25 stable disease, 12 progressive disease, 4 not evaluable). Grade III/IV toxicities were as follows: neutropenia grade III/IV = 66%, anemia grade III/IV = 16%, thrombocytopenia grade III/IV = 2%, nausea grade III/IV = 10%, vomiting grade III/IV = 0%, documented infection grade III/IV = 10%, skin rash grade III/IV = 2%, and hepatic grade III/IV = 8%. There were no treatment-related deaths. The median time to progression was 4.1 months. The overall median survival time (MST) was 13.9 months (range, 2.4 to >16.2 months) with a median follow-up time of 13.9 months. The MST for stage IIIB and stage IV was >14.5 and 12.7 months, respectively. The overall estimated 1-year survival rate was 55.4%. *Conclusions:* This regimen has modest activity and is very well tolerated, with an encouraging 1-year survival rate.

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0169-5002/$ - see front matter © 2003 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2003.08.015

1. Introduction

Non-small cell lung cancer (NSCLC) represents about 80% of cases of lung cancer. The prognosis of patients (pts) with this cancer is poor, since less than a third of patients present with resectable disease at the time of diagnosis, and two-thirds of them are inoperable and are potential candidates for systemic chemotherapy. Four meta-analyses of trials comparing the use of chemotherapy with best supportive care concluded that chemotherapy could prolong survival time by a modest but statistically significant amount of time and should be offered to patients with good performance status (PS) [1–4]. Cisplatin-based combination therapy is currently considered to be the most active treatment for advanced NSCLC. However, cisplatin has a low therapeutic ratio, with significant toxicities including severe nausea and vomiting, general malaise, renal toxicity requiring adequate hydration, and ototoxicity.

Recently, several new drugs such as CPT-11, docetaxel, paclitaxel, gemcitabine (G), and vinorelbine (V) have also demonstrated a promising antitumor activity against NSCLC, with documented response ranging from 13 to 27% [5]. Among these agents, gemcitabine is a new nucleotide antimetabolite of deoxycytidine resembling cytarabine that has demonstrated activity both as a single agent and in combination with cisplatin [6–9]. The objective response rate obtained with combination chemotherapy ranges from 32 to 54% in chemotherapy-naïve patients with advanced NSCLC.

Vinorelbine, a semisynthetic vinca alkaloid, has also demonstrated activity for first-line treatment of patients with advanced NSCLC, with a response rate of between 20 and 25% and a median survival of 33 weeks [10]. A prospective randomized trial was also conducted to compare vinorelbine and cisplatin with vindesine and cisplatin, or vinorelbine alone to evaluate whether one of these regimens provided a survival advantage over the others [11]. Vinorelbine-cisplatin yielded a longer survival duration and a higher response rate than did vindesine-cisplatin or vinorelbine alone. Furthermore, vinorelbine was studied in a randomized Italian phase III trial in which vinorelbine, combined with best supportive care, was compared with best supportive therapy (BST) alone [12]. Vinorelbine was given 30 mg/m^2 on days 1 and 8 every 3 weeks for six cycles. A 20% response rate was seen in the vinorelbine arm, and a median survival difference of 27 weeks versus 21 weeks favored the vinorelbine arm.

A recent randomized Eastern Cooperative Oncology Group (ECOG) study that included four new popular platinum-based regimens did not show any survival differences among the more than 1000 patients, and it also documented a disappointingly low response rate with the range of 15.3–21.3% [13]. There is no one new chemotherapy combination that can be said to be clearly superior at the moment. In view of the single-agent activity in NSCLC and the lack of overlapping toxicity of gemcitabine and vinorelbine as well as their different mechanism of action, a multicenter phase II trial was conducted to evaluate the tolerance and efficacy of their combination.

2. Patients and methods

2.1. Eligibility criteria

Eligibility criteria for study entry included histologically or cytologically confirmed stage IIIB or IV NSCLC; no prior chemotherapy; the presence of at least one unidimensional measurable disease; age 20–74 years; an Eastern Cooperative Oncology Group performance status of 0–1; adequate baseline organ function, defined as 4000/μl ≤ WBC ≤ 12,000/μl, platelet ≥100,000/μl, hemoglobin ≥9.5 g/dl, serum transaminase levels ≤2.5× of the upper limit of normal, bilirubin ≤1.5× of the upper limit of normal, creatinine <1.5 mg/dl; PaO_2 ≥60 mmHg; a life expectancy of at least 3 months; and written informed consent. The study was conducted according to the Helsinki Declaration and was approved by the ethics committees of participating centers. Prior palliative radiotherapy to symptomatic metastases was allowed, provided that these lesions were not monitored for response. Patients with recurrence after operation were allowed. Patients with the following criteria were excluded from the study: signs and symptoms of brain metastases; pleural effusion requiring chest tube drainage; apparent pericardial effusion; uncontrollable angina pectoris, diabetes mellitus, hypertension, congestive heart failure and active infection; myocardial infarction <3 months before the date of diagnosis; interstitial pneumonitis diagnosed by plain chest X-ray; pregnant women. Patients in stage IIIB who were candidates for initial radiotherapy for a primary tumor were excluded from the study. Patients with other serious underlying medical conditions that would impair the ability of the patient to receive the protocol treatment were also ineligible for the study.

2.2. Treatment plan

The treatment consisted of vinorelbine, 25 mg/m^2 intravenous infusion in 20 ml of normal saline solution over 2–3 min, followed by gemcitabine 1000 mg/m^2 intravenous infusion in 100 ml of normal saline solution over 30 min on days 1 and 8 every 3 weeks. This dose schedule was taken according to the results from Gridelli et al. They reported the combination gemcitabine 1000 mg/m^2 plus vinorelbine 25 mg/m^2 had the less frequent and less severe toxicity with equal antitumor activity compared with other treatment schedules [14]. Dexamethasone and 5-hydroxytryptamine-3 receptor antagonists were given before chemotherapy as antiemetic prophylaxis. Treatment of day 8 was delayed until recovery (no longer than 1 week) if the WBC count fell <2000/μl and/or the platelet count was <70,000/μl and if nonhematologic toxicities were ≥grade 2 excluding those due to nausea/vomiting and alopecia. Otherwise, the patient was removed from the study.

The subsequent course of chemotherapy was begun on day 22 if the WBC count was >3000/μl, the platelet count was ≥100,000/μl, PS was 0–1, transaminases were ≤2.5× of the upper limit of normal, the serum bilirubin was ≤1.5× of the upper limit of normal, and the creatinine was <1.5 mg/dl. Two weeks delay of initiation of the subsequent course was allowed; otherwise, the patient was withdrawn from the study.

For dose adjustments in the subsequent cycle, vinorelbine and gemcitabine were reduced to 20 and 800 mg/m^2, respectively, when the patient suffered from grade 4 neutropenia lasting for more than 4 days, chemotherapy-induced neutropenic fever was higher than 38 °C, thrombocytopenia ≤20,000/μl, or nonhematologic toxicities ≥grade 3 excluding those due to nausea/vomiting and alopecia. Recombinant human granulocyte colony-stimulating factor was not used prophylactically. Patients with progressive disease at any time were withdrawn from the study; patients with stable disease received a minimum of two cycles, whereas patients with a complete response (CR) or partial response (PR) were treated until disease progression began. Radiation consolidation was planned for stage IIIB patients at the discretion of the treating physician.

2.3. Staging and follow-up procedures

Before entering the study, all patients underwent a physical examination, complete blood count, blood chemistry, urinalysis, chest X-ray, thoracic, abdominal, and brain CT scans, bone scan, ECG, pulmonary function tests, blood gas analysis, and other specific tests when indicated. Patients were monitored weekly throughout treatment by physical examination, recording of toxic effects, complete blood cell count with differential, and blood chemistry with repetition of all tests that were abnormal at baseline. Study drug-related toxicities were evaluated according to National Cancer Institute Common Toxicity Criteria (version 2).

2.4. Definition of response

Objective response of a tumor to an anticancer agent was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [15]. A CR of target lesions was defined as the disappearance of all target lesions for a minimum of 4 weeks, during which no new lesion could appear. A PR was defined as at least a 30% decrease in the sum of the longest diameter of target lesions for a minimum of 4 weeks, during which no new lesion could appear. PD was defined as at least a 20% increase in the sum of the longest diameter of the target lesion or the appearance of one or more new lesions. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

A CR of nontarget lesions was defined as the disappearance of all nontarget lesions and normalization of tumor marker level. An incomplete response/stable disease was defined as the persistence of one or more nontarget lesion(s) and/or the maintenance of tumor marker level above the normal limits. PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions. An extramural review was conducted to validate the eligibility of the patients, staging, responses, and toxicities during regular meetings of the WJTOG.

2.5. Statistical methods

A Simon two-stage minimax phase II design was used to estimate sample size. It was estimated that the power of this study to detect a true response rate of 40% was 0.8 at the 5% level, requiring the accrual of 45 patients. Fifty-two patients had been accrued at the end of the study. Overall survival and progression-free survival were analyzed using the method of Kaplan and Meier. Survival was measured from the date of initial treatment to the date of death or last follow-up examination. Progression-free survival was measured from the date of documentation of first response to the date of first evidence of progressive disease.

3. Results

From April 2000 until September 2000, 52 patients were recruited for the study from 19 centers of the West Japan Thoracic Oncology Group (WJTOG). Of these, two patients did not meet the eligibility criteria for efficacy analysis: one because of metastatic prostate cancer, and one who did not receive chemotherapy because of active pneumonia. Fifty patients fulfilling all eligibility criteria were treated on this study. Patient characteristics are listed in Table 1. There were 30 men and 20 women, with a median age of 60 years (range 28–74). Twenty-one patients had PS 0, and 29 had PS 1. Twelve patients had stage IIIB disease, and 38 patients had stage IV disease. Adenocarcinoma was the predominant histologic type. Two patients had previous therapy: one received gamma knife radiation for metastatic brain tumor, and the other received surgery for primary lung cancer. The median number of courses per patient was 2, with a range of 1–13 courses. Fifty patients were assessable for toxicity and fulfilled all criteria of assessment for response evaluation. Four patients received only one course of treatment. Of them, one patient developed a grade 3 allergic reaction after treatment on day 1. One patient withdrew his consent from the treatment because of grade 2 liver dysfunction. One patient had grade 3 skin eruption immediately after treatment of day 1, and the fourth patient had empyema on day 8. These four patients were not evaluable for response. Of the evaluable 46 patients, no patient achieved a CR, 9 achieved a PR, 25 had SD, and 12 had PD (Table 2). On an intent-to-treatment analysis, the objective response rate was 18% (9 of 50 patients; 95% CI = *8.6*–31.4%).

Table 1 Patient characteristics

	Number of patients
Patients enrolled	50
Sex	
Male	30
Female	20
Age	
Median	60
Range	28–74
Performance status	
0	21
1	29
Stage	
IIIB	12
IV	38
Histology	
Adenocarcinoma	35
Squamous cell carcinoma	12
Large cell carcinoma	3
Prior treatment	
Surgery	1
X knife for brain metastasis	1
None	48

Table 2 Response rate

	Number of patients	Percentage
Complete response	0	0
Partial response	9	18
Stable disease	25	50
Progressive disease	12	24
Not evaluable	4	8
Response rate		18[a]
Total	50	100

[a] 95% confidence interval: 8.6–31.4%.

3.1. Toxicity

Toxicity was evaluated in all eligible patients and in all courses. Myelosuppression was the only toxicity that resulted in dose reduction (Table 3). Grade 3/4 adverse events were as follows: leukopenia in 22 patients (44%), neutropenia in 33 patients (66%), anemia in 8 patients (16%), and thrombocytopenia in 1 patient (4%). There were seven patients who suffered from neutropenic fever. All these patients were successfully treated with broad-spectrum antibiotics. No thrombocytopenic episode was complicated by hemorrhage, and no patient required platelet transfusion.

Nonhematologic adverse events were generally mild and well tolerated. Liver enzyme derangement was observed in 38 patients, grade 1 or 2 in 34 patients (68%) and grade 3 in 4 patients (8%). All these patients were treated successfully with supportive measures. Nephrotoxicity was not a problem. Grade 3 nausea/vomiting was observed in five patients (10%). Diarrhea and alopecia were mild. Grade 1 local vasculitis along side injected vein due to vinorelbine was observed in two patients (4%). Moderate deterioration in PS (grade 3) was observed in eight patients (16%). Details on adverse effects are listed in Table 3.

Four patients discontinued treatment because of adverse events. One patient developed a serious

Table 3 Hematologic and nonhemologic toxicity

Toxicity	National Cancer Institute Common Toxicity Criteria			
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
WBC	6 (12)	16 (32)	19 (38)	3 (6)
Neutrophil	8 (16)	4 (8)	13 (26)	20 (40)
Hemoglobin	30 (60)	11 (22)	7 (14)	1 (2)
Platelet	24 (48)	3 (6)	1 (2)	0
GOT/GPT	18 (36)	16 (32)	4 (8)	0
Creatinine	2 (4)	0	0	0
Nausea	8 (16)	7 (14)	5 (10)	0
Vomiting	5 (10)	5 (10)	0	0
Delayed vomiting	1 (2)	0	0	0
Diarrhea	4 (8)	3 (6)	0	0
Alopecia	18 (36)	1 (2)	0	0
Fever	17 (34)	2 (4)	0	0
Infection	6 (12)	4 (8)	5 (10)	
Dyspnea	5 (10)	6 (12)	0	0
Skin eruption	0	3 (6)	1 (2)	0
Neuropathy	2 (4)	0	0	0
Vasculitis	2 (4)	0	0	0
Performance status	21 (42)	4 (8)	8 (16)	0

allergic reaction that was treated with antihistamines and corticosteroids. One patient developed grade 3 skin eruption that was successfully treated. One patient developed grade 2 transaminase elevation that was reversible. The fourth patient developed empyema after the first course of treatment and was successfully treated with chest tube drainage and appropriate antibiotics. There were no treatment-related deaths.

3.2. Second-line therapy

Of 12 patients in stage IIIB, 5 were treated with platinum-based chemotherapy after the gemcitabine–vinorelbine regimen. Three patients were treated with thoracic radiotherapy for symptom palliation. Three patients received only best supportive therapy. One patient received surgery of the primary tumor. Of thirty-eight patients in stage IV, 28 were treated with systemic chemotherapy; 17 received platinum plus taxen; 3 received further courses of gemcitabine plus vinorelbine; 4 received taxen alone; and 4 received platinum-based combination regimen without taxen. Eight patients received only best supportive therapy. Two patients were treated with thoracic radiotherapy.

3.3. Survival

The median time to progression of 34 patients was 4.1 months (range, 0.1 to ≥13.7 months). The overall median survival time (MST) was 13.9 months (range, 2.4 to ≥16.2 months) with a median follow-up time of 13.9 months (Fig. 1a). The

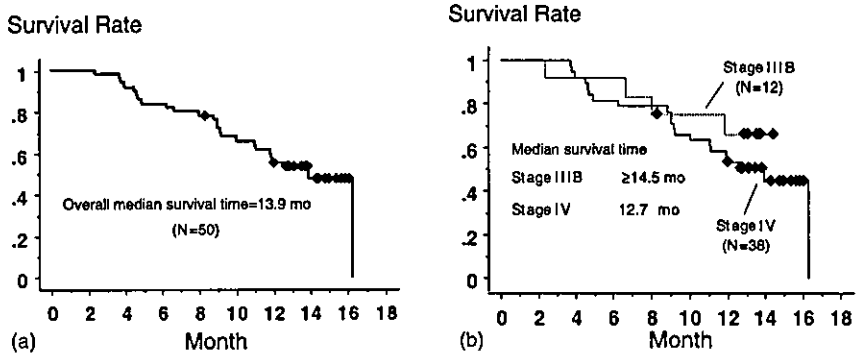

Fig. 1 (a) Overall survival time. (b) Survival time according to stage.

median survival time for stage IIIB was ≥14.5 months, and for stage IV, it was 12.7 months (Fig. 1b). The overall estimated 1-year survival rate was 55.4%. The estimated 1-year survival rate for stages IIIB and IV was 66 and 53%, respectively.

4. Discussion

The 1-year survival for patients with advanced NSCLC has increased from as low as 10–40% over the last two decades when patients are treated with cisplatin-based combination chemotherapy. Meta-analysis of multiple trials comparing chemotherapy to best supportive care proved that the cisplatin-based therapy improved the survival of these patients, although the benefits were modest [1–4]. On average, the median survival of the cisplatin-treated patients improved by 10 weeks, and the 1-year survival rate improved by 10%. Despite these data, some medical oncologists remain skeptical and do not routinely treat advanced NSCLC with cisplatin-based chemotherapy. This reluctance can be explained partly by the inherent toxicity of the chemotherapy regimens and perceived negative effect on quality of life. Recently it has been shown that new chemotherapeutic agents such as CTP-11, docetaxel, paclitaxel, gemcitabine, and vinorelbine result in improvement in response rates with an increase in 1- and 2-year survivors [5]. In addition to their antitumor activity, these agents are less toxic than cisplatin in terms of nausea, vomiting, ototoxity, and general malaise, and their use does not require a large amount of fluid to prevent renal impairment.

The present report describes the phase II trial combining gemcitabine and vinorelbine in the treatment of chemo-naïve patients with advanced NSCLC. There are at least five phase II trials (results in full paper) in which gemcitabine and vinorelbine treatment has been given to chemo-naïve patients with advanced NSCLC. The observed response rate of 18% in our study was not better than that reported in other gemcitabine–vinorelbine regimens for advanced NSCLC, which have shown responses ranging from 25 to 72.5% [16–20]. It should be noted, however, that not only the dosage of gemcitabine and vinorelbine but also the timing of the drug administration was variable from study to study. The gemcitabine and vinorelbine dose intensity attained in the present study was 667 and 16.7 mg/m^2 per week, respectively. The projected gemcitabine and vinorelbine dose intensity in other studies was 600–830 and 15–20 mg/m^2 per week, respectively. Chen et al reported the highest response rate of 72.5% and median survival time of 11 months [18]. The treatment in their study consisted of vinorelbine 20 mg/m^2 and gemcitabine 800 mg/m^2 on days 1, 8, and 15 every 4 weeks. The higher response may be partly attributed to the larger number of stage IIIB patients (45%) included in their study compared to ours (stage IIIB, 24%). The other reason may be due to the difference of median number of treatment courses (three–six courses in other studies versus two courses in ours), since some patients achieved PR only after three courses of chemotherapy.

As far as MST is concerned, the MST of 13.9 months and the 1-year survival rate of 55.4% in our trial are superior to other established cisplatin-based regimens and are very encouraging in the context of advanced NSCLC [7–9,12,13]. This is particularly true for patients with stage IV, who had a MST of 12.7 months and a 1-year survival rate of 53%. The reported MST of other gemcitabine–vinorelbine regimens in phase II studies for advanced NSCLC ranged from 8 to 12.6 months and a 1-year survival rate of 30–48.1% [16,20]. There are at least three reasons why patients in our study had a good MST and a favorable 1-year survival rate. First of all, all our patients had an initial good PS, 0 or 1. The second reason is that only a limited number of patients (16%) deteriorated in their PS to grade 3 after chemotherapy, and most of the patients could receive platinum-based combination chemotherapy when they could not attain an objective response. Finally, 24% of patients received docetaxel as a second-line chemotherapy. Docetaxel has recently been demonstrated to be not only effective in first-line use but also to have considerable activity when used for second-line therapy [21,22].

Feliu et al. conducted a phase II study of a gemcitabine–vinorelbine regimen in NSCLC patients age 70 years or older or patients who cannot receive cisplatin [17]. Treatment comprised of vinorelbine, 25 mg/m^2 plus gemcitabine, 1000 mg/m^2, both on days 1, 8, and 15 every 28 days. Forty-nine patients were included, 38 of whom were age 70 years or older and 11 of whom were less than 70 years old but who had some contraindication to receiving cisplatin. The overall response rate was 26%, and the 1-year survival rate was 33%. They concluded that the gemcitabine–vinorelbine combination was moderately active and well tolerated except in patients age 75 years or older. Recently two randomized studies comparing a gemcitabine–vinorelbine combination to single-agent gemcitabine or vinorelbine has been reported in an elderly population with NSCLC. An improved survival with gemcitabine plus

vinorelbine regimen over vinorelbine alone and improvement in some tumor-related symptoms was reported in one study [23]. However this was not confirmed by the other larger randomized phase III study, which demonstrated that single-agent therapy is at least as good as combination therapy in terms of survival [24]. Therefore, additional comparative studies comparing nonplatinum-containing doublets chemotherapy to single-agent chemotherapy are needed to determine the most appropriate chemotherapy regimen in terms of tolerability, quality of life, and cost-effectiveness, especially for elderly patients. However, these data as a whole demonstrated that nonplatinum doublets combination chemotherapy with gemcitabine and vinorelbine is active and well tolerated in the elderly patients.

The toxicity of the current regimen was modest and easily managed. Myelosuppression was the main adverse effect, with grade 3 or 4 neutropenia of 66%. However, neither treatment-related deaths nor serious infection occurred, and patients recovered rapidly from neutropenia. Grade 2 or 3 elevation of serum transaminase was noted in 40% of patients, with no significant morbidity. The majority of our patients did not have any nausea or vomiting, and few patients suffered from alopecia. Only two patients (4%) suffered from grade 1 neuropathy, and very few patients developed vasculitis. In general, toxicity induced by this nonplatinum-containing doublets regimen was well tolerated and less toxic than cisplatin-containing regimens.

In conclusion, the combination of gemcitabine and vinorelbine is active and well tolerated in the treatment of advanced NSCLC. The randomized comparison with platinum-containing regimens is deserved, with particular interest not only in clinical response but also in quality of life and toxicity profile.

References

[1] Souquet PJ, Chauvin F, Boissel JP, et al. Polychemotherapy in advanced non-small cell lung cancer: a meta-analysis. Lancet 1993;343:19–21.

[2] Grilli R, Oxaman AD, Julian JM. Chemotherapy for advanced non-small cell lung cancer. How much benefit is enough? J Clin Oncol 1993;11:1866–72.

[3] Marino P, Pampallona S, Prestoni A, et al. Chemotherapy versus supportive care in advanced non-small cell lung cancer: results of a meta-analysis of the literature. Chest 1994;106:861–5.

[4] Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Br Med J 1995;311:899–909.

[5] Devita VT, Hellman S, Rosenberg SA. Cancer: principle & practice of oncology, 6th ed. Philadelphia, PA: Lippincott Williams & Wilins; 2001. p. 969.

[6] Abratt RP, Bezwoda WR, Falkson G, et al. Efficacy and safety profile of gemcitabine in non-small-cell lung cancer: a phase II study. J Clin Oncol 1994;12:1535–40.

[7] Sander AB, Nemunaitis J, Denham C, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small cell lung cancer. J Clin Oncol 2000;18:122–30.

[8] Crino L, Scagliotti G, Marangolo M, et al. Cisplatin-gemcitabine combination in advanced non-small-cell lung cancer: a phase II study. J Clin Oncol 1997;15:297–303.

[9] Crino L, Scagliotti GV, Ricci S, et al. Gemcitabine and cisplatin versus mitomycin non-small-cell lung cancer: a randomized phase III study of the Italian Lung Cancer Project. J Clin Oncol 1999;17:3522–30.

[10] Depierre A, Lemaria E, Dabouis G, et al. A phase II study of Navelbine (vinorelbine) in the treatment of non-small cell lung cancer. J Clin Oncol 1991;14:115–9.

[11] Le Chevalier T, Brisgand D, Doulillard JY, et al. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicentre trial including 612 patients. J Clin Oncol 1994;12:360–7.

[12] The Elderly Lung Cancer Vinorelbine Italian Study Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 1999;91:66–72.

[13] Shiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med 2002;346:92–8.

[14] Gridelli C, Frontini L, Perrone F, et al. Gemcitabine plus vinorelbine in advanced non-small cell lung cancer: a phase II trail of three different doses. Br J Cancer 2000;83:707–14.

[15] Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.

[16] Isokangas OP, Knuuttila A, Halme M, et al. Phase II study of vinorelbine and gemcitabine for inoperable stage IIIB–IV non-small-cell lung cancer. Ann Oncol 1999;10:1059–63.

[17] Feliu J, Lopez Gomez L, Madronal C, et al. Gemcitabine plus vinorelbine in nonsmall cell lung carcinoma patients age 70 year or older or patients who cannot receive cisplatin. Oncopaz Cooperative Group. Cancer 1999;86:1463–9.

[18] Chen YM, Perng RP, Yang KY, et al. A multicenter phase II trial of vinorelbine plus gemcitabine in previously untreated inoperable (stage IIIB/IV) non-small cell lung caner. Chest 2000;117:1583–9.

[19] Lilenbaum R, Cano R, Schwartz M, et al. Gemcitabine and vinorelbine in advanced nonsmall cell lung carcinoma: a phase II study. Cancer 2000;88:557–62.

[20] Lorusso V, Carpagnano F, Frasci G, et al. Phase I/II study of gemcitabine plus vinorelbine as first-line chemotherapy of non-small-cell lung cancer. J Clin Oncol 2000;18:405–11.

[21] Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small- cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095–103.

[22] Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously

treated with platinum containing chemotherapy regimens. J Clin Oncol 2000;18:2354–62.
[23] Frasci G, Lorusso V, Panza N, et al. Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol 2000;18:2529–36.
[24] Gridelli C, Perrone F, Cigolari S, et al. The MILES (multicenter Italian Lung Cancer in the Elderly Study) phase 3 trial: gemcitabine + vinorelbine vs. vinorelbine and vs. gemcitabine in elderly advanced NSCLC patients. Proc Am Clin Oncol 2001;20:308a.

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.

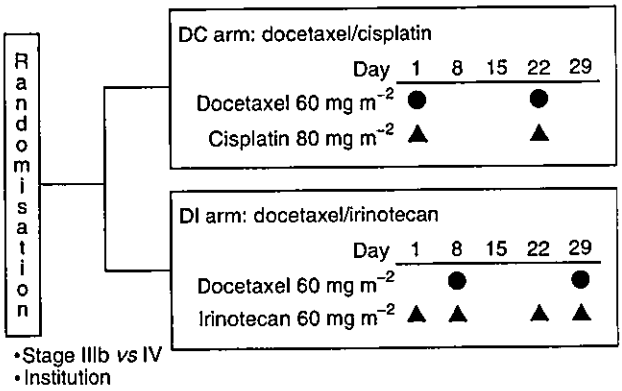

Figure 1 *Treatment schema*: after stratification by stage and institution, enrolled patients were randomly allocated to receive docetaxel plus cisplatin (DC) or docetaxel plus irinotecan (DI).

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. *$P=0.55$.

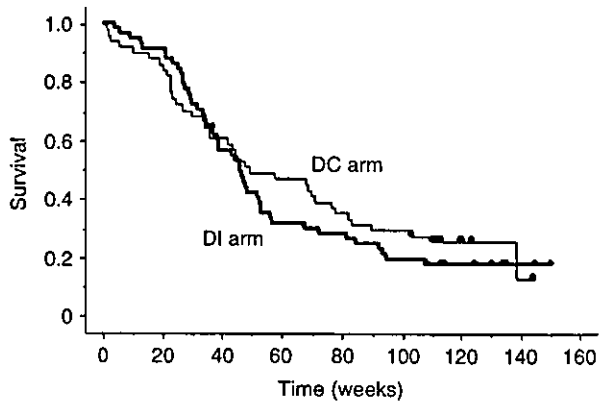

Figure 2 Overall survival according to treatment group, calculated by Kaplan–Meier method. Median survival times were 50 weeks for DC (docetaxel plus cisplatin) and 46 weeks for DI (docetaxel plus irinotecan). $P=0.50$ between treatment groups.

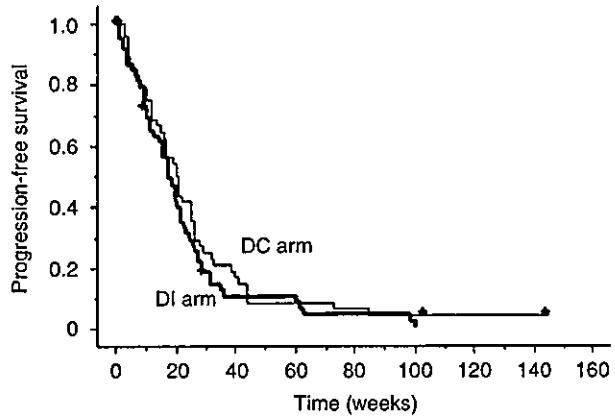

Figure 3 Progression-free survival according to treatment group, calculated by Kaplan–Meier method. Median progression-free survival times were 20 weeks for DC (docetaxel plus cisplatin) and 18 weeks for DI (docetaxel plus irinotecan). $P = 0.33$ between treatment groups.

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.

REFERENCES

Chen YM, Perng RP, Lee YC, Shih JF, Lee CS, Tsai CM, Whang-Peng J (2002) Paclitaxel plus carboplatin, compared with paclitaxel plus gemcitabine, shows similar efficacy while more cost-effective: a randomized phase II study of combination chemotherapy against inoperable non-small-cell lung cancer previously untreated. *Ann Oncol* 13: 108–115

Fleming (1982) One-sample multiple testing procedure for phase II clinical trials. *Biometrics* 38: 143–151

Fukuoka M, Nagao K, Ohashi Y, Niitani H (2000) Impact of irinotecan (CPT-11) and cisplatin (CDDP) on survival in previously untreated metastatic non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 19: 495a

Georgoulias V, Papadakis E, Alexopoulos A, Tsiafaki X, Rapti A, Veslemes M, Palamidas P, Vlachonikolis I (2001) Platinum-based and nonplatinum-based chemotherapy in advanced non-small-cell lung cancer: a randomized multicentre trial. *Lancet* 357: 1478–1484

Gridelli C, Shepherd F, Perrone F, Illiano A, Piantedosi FV, Robbiati SF, Manzione L, Barbera S, Frontini L, Veltri E, Cigolari S, Findlay BP, Hirsch V, Seymour L, Bezjak A, Gallo C (2002) Gemvin III: a phase III study of gemcitabine plus vinorelbine (GV) comparing to cisplatin plus vinorelbine or gemcitabine chemotherapy (PCT) for stage IIIb or IV non-small cell lung cancer (NSCLC): an Italo-Canadian study. *Proc Am Soc Clin Oncol* 21: 292a

Kosmidis P, Mylonakis N, Nicolaides C, Kalophonos C, Samantas E, Boukovinas J, Fountzilas G, Skarlos D, Economopoulos T, Tsavdaridis D, Papakostas P, Bacoyiannis C, Dimopoulos M (2002) Paclitaxel plus carboplatin versus gemcitabine plus paclitaxel in advanced non-small-cell lung cancer: a phase III randomized trial. *J Clin Oncol* 20: 3578–3585

Kubota K, Watanabe H, Kunitoh H, Noda K, Ichinose Y, Katakami N, Sugiura T, Kawahara M, Yokoyama A, Nishiwaki Y, Ohashi Y, Niitani H (2002) Final results of a randomized phase III trial of docetaxel and cisplatin versus vindesine and cisplatin in stage IV non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 21: 296a

Kunitoh H, Watanabe K, Onoshi T, Furuse K, Niitani H, Taguchi T (1996) Phase II trial of docetaxel in previously untreated advanced non-small-cell lung cancer: a Japanese Cooperative Study. *J Clin Oncol* 14: 1649–1655

Masuda N, Negoro S, Kudoh S, Sugiura T, Nakagawa K, Saka H, Takada M, Niitani H, Fukuoka M (2000) Phase I and pharmacologic study of docetaxel and irinotecan in advanced non-small cell lung cancer. *J Clin Oncol* 18: 2996–3003

Negoro S, Masuda N, Fukuoka M, Takada Y, Sugiura T, Kudoh S, Katakami N, Ariyoshi Y, Ohashi Y, Niitani H, Fukuoka M (2003) Randomized phase III trial of irinotecan combined with cisplatin for advanced non-small cell lung cancer. *Br J ancer* 88: 335–341

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

Okamoto H, Watanabe K, Segawa Y, Ichinose Y, Yokoyama A, Yoneda S, Niitani H (2002) Phase II study of docetaxel and cisplatin in patients with previously untreated metastatic non-small cell lung cancer. *Int J Clin Oncol* **5**: 316–322

Perng RP, Chen YM, Ming-Liu J, Tsai CM, Lin WC, Yang KY, Whang-Peng J (1997) Gemcitabine versus the combination of cisplatin and etoposide in patients with inoperable non-small-cell lung cancer in a phase II randomized study. *J Clin Oncol* **15**: 2097–2102

Ranson M, Davidson N, Nicolson M, Falk S, Carmichael J, Lopez P, Anderson H, Gustafson N, Jeynes A, Gallant G, Washington T, Thatcher N (2000) Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small-cell lung cancer. *J Natl Cancer Inst* **92**: 1074–1080

Rodriguez J, Pawel J, Pluzanska A, Gorbounova V, Fossella F, Kaukel E, Mattson K, Millward M, Kim YS, Gamza F, Berille J, Belani CP (2001) A multicenter, randomized phase III study of docetaxel+cisplatin (DC) and docetaxel+carboplatin (DCB) *vs* vinorelbine+cisplatin (VC) in chemotherapy-naïve patients with advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* **20**: 314a

Roszkowski K, Pluzanska A, Krzakowski M, Smith AP, Saigi E, Aasebo U, Parisi A, Pham Tran N, Olivares R, Berille J (2000) A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy-naive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). *Lung Cancer* **27**: 145–157

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

Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, Levitan N, Gressot L, Vincent M (2000) Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* **18**: 2095–2103

The Elderly Lung Cancer Vinorelbine Italian Study Group (1999) Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. *J Natl Cancer Inst* **91**: 66–72

Van Meerbeeck JP, Smit EF, Lianes P, Schramel F, Lenz MA, Debruyne C, Giaccone G (2001) A EORTC randomized phase III trial of three chemotherapy regimens in advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* **20**: 308a

World Health Organization (1979) *WHO Handbook for Reporting Results of Cancer Treatment*. WHO Offset Publication No. 48. Geneva, Switzerland: World Health Organization

British Journal of Cancer (2004) 91, 1032–1037

www.bjcancer.com

Phase I–II study of irinotecan (CPT-11) plus nedaplatin (254-S) with recombinant human granulocyte colony-stimulating factor support in patients with advanced or recurrent cervical cancer

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Combination chemotherapy with irinotecan (CPT-11) and platinum compounds is effective for treating cervical cancer. Nedaplatin (254-S) is a new cisplatin analogue that achieves a high response rate (53%) in patients with primary cervical cancer. We performed a phase I–II study of combination chemotherapy with CPT-11 plus 254-S for advanced or recurrent cervical cancer. The inclusion criteria were stage IV disease or recurrence. CPT-11 and 254-S were administered intravenously on day 1, while rhG-CSF (50 μg) was given on days 3–12. This regimen was repeated after 4 weeks. Dose escalation was carried out in tandem (CPT-11/254-S: 50/70, 50/80, and 60/80 mg m^{-2}). A total of 27 patients (stage IV = seven, recurrence = 20) were enrolled. The phase I study enrolled eight patients. At dose levels 1 and 2, no dose-limiting toxicities were observed. At dose level 3, the first two patients developed DLTs. The maximum tolerated dose of CPT-11 and 254-S was 60 and 80 mg m^{-2}, respectively, and the recommended doses were 50 and 80 mg m^{-2}. Grade 3/4 haematologic toxicity occurred in 67% in phase II study, but there were no grade 3 nonhaematologic toxicities except fot nausea or lethargy. In all 27 patients, there were two complete responses (7%) and 14 Partial responses (52%), for an overall response rate of 59% (95% confidence interval: 39–78%). Among the 12 responders with recurrent disease, the median time to progression and median survival were 161 days (range: 61–711 days) and 415 days (range: 74–801 days). This new regimen is promising for cervical cancer.

British Journal of Cancer (2004) **91**, 1032–1037. doi:10.1038/sj.bjc.6602076 www.bjcancer.com
Published online 3 August 2004

Keywords: combination chemotherapy; adenocarcinoma of uterine cervix; cervical cancer; phase I study; phase II study

Cancer of the uterine cervix is one of the most common malignancies among women and remains the leading female malignancy in developing countries (Thigpen *et al*, 1994). In 1999, about 6500 patients developed cervical cancer in Japan (Sekiya, 2002). In the USA, approximately 13 000 patients developed cervical cancer in 2000 (Robert *et al*, 2001). This tumour is usually radiosensitive and highly curable at an early stage. For patients with stage IV disease or with recurrence after radiotherapy, however, the prognosis is still dismal (Thigpen *et al*, 1995). In such patients, most of the active chemotherapy agents achieve overall response rates of 20–35% when given as monotherapy, with a median response duration of 3–6 months and a survival time of 5–9 months (Thigpen *et al*, 1981; McGuire *et al*, 1996). Many combination chemotherapy regimens have also been explored during the last two decades. High response rates have been obtained in some studies, but it is difficult to assess the relative merits of the various regimens because of differences in patient selection (Buxton *et al*, 1989; Papadimitriou *et al*, 1999).

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Received 16 March 2004; revised 26 May 2004; accepted 21 June 2004; published online 3 August 2004

Nedaplatin (254-S) is a new cisplatin analogue with the same carrier ligands of ammine as cisplatin but has a different leaving group, a five-membered ring structure in which glycolate is bound to the platinum ion as a bidentate ligand (Figure 1). This product has an approximately 10 times higher water solubility than cisplatin and, unlike cisplatin, shows very limited binding to plasma protein (Sugeno *et al*, 1991). The plasma concentration profile of unbound platinum after 254-S infusion has been reported to be similar to that of total platinum, and the protein binding of 254-S to be lower than that of CDDP (Ota *et al*, 1994). Nedaplatin has a short elimination half-life and a phamacokinetic profile similar to that of CBDCA (Sasaki *et al*, 1989). Nephrotoxicity and gastrointestinal toxicity often limits the clinical use of antitumour agents such as CDDP, but 254-S causes less nephrotoxicity and gastrointestinal toxicity than CDDP, although its haematological toxicity can be a limiting factor at high dosage, as found with CBDCA (Kameyama *et al*, 1990; Ota *et al*, 1992; Suzumura *et al*, 1989). The dose-limiting toxicity (DLT) of 254-S is myelosuppression, especially thrombocytopenia. In the Phase II studies, 254-S monotherapy generated a 46.3% response rate against cervical cancer, especially 53.1% in patients with squamous cell carcinoma (Kato *et al*, 1992).

Irinotecan hydrochloride (CPT-11) is a semisynthetic derivative of camptothecin, an alkaloid contained in plants such as *Camptotheca acuminate* (Nitta *et al*, 1987). Irinotecan inhibits

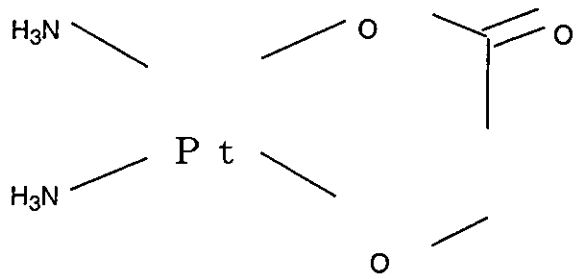

Figure 1 Structure of nedaplatin.

the activity of DNA topoisomerase I, which is necessary for replication of DNA. Several phase II studies have shown that CPT-11 is active against cervical cancer, and activity of CPT-11 monotherapy against recurrent or refractory cervical cancer was revealed in phase II studies performed by the Japan CPT-11 Study Group (24% response rate) and the MD Anderson Cancer Center (21% response rate) (Takeuchi *et al*, 1991; Verschraegen *et al*, 1997). However, a pilot study of CPT-11 in patients with platinum-resistant squamous cell carcinoma failed to show any tumour response (Ivrin *et al*, 1998).

Kanazawa *et al* (2001) reported that the combination of 254-S and CPT-11 showed marked synergistic activity against SBC-3 and PC-14 lung cancer cell lines. This synergistic effect was dependent on the treatment schedule and was produced by concurrent exposure to 254-S and CPT-11. They analysed the mechanism of synergy and demonstrated that the topoisomerase I inhibitory effect of CPT-11 was enhanced 10-fold in the presence of 254-S. Based on these findings, the combination of 254-S and CPT-11 may well be clinically useful. Machida *et al* (2003) performed a phase I study of chemotherapy using CPT-11 plus 254-S for advanced or recurrent cervical cancer. They concluded that the DLT was neutropenia, and their recommended doses of CPT-11 (days 1, 8, and 15) and 254-S (day 1) were 50 and 60 mg m^{-2}, respectively. Recombinant human granulocyte colony-stimulating factor (rhG-CSF) can activate haematopoiesis and thus prevent chemotherapy-induced neutropenia or accelerate recovery from this complication, allowing patients to receive full per protocol doses of anticancer drugs. The G-CSF was expected to increase the dose intensity of combination chemotherapy with 254-S plus CPT-11.

Accordingly, we performed a phase I–II study of CPT-11 plus 254-S with rhG-CSF support in patients with advanced or recurrent cervical cancer.

MATERIALS AND METHODS

Patient selection

The chief eligibility criteria were as follows: (1) histologically proven cervical cancer (stage IV or recurrent disease), (2) at least one measurable tumour lesion documented radiographically, and (3) an interval >4 weeks between the end of previous treatment (including radiotherapy) and this study. Other eligibility criteria were an age <75 years, performance status (WHO) ≤2 and life expectancy >3 months. Patients were also required to meet all of the following laboratory criteria: WBC count ≥3000 mm^{-3} or absolute neutrophil count ≥1500 mm^{-3}, platelet count ≥100 000 mm^{-3}, serum transaminases ≤60 IU ml^{-1}, total bilirubin ≤1.5 mg dl^{-1}, serum creatinine ≤1.5 mg dl^{-1}, and blood urea nitrogen ≤20 mg dl^{-1}. The nature and purpose of the study were fully explained to each patient and all patients gave written informed consent. The study was also approved by the institutional review board of Osaka City General Hospital. Patients were excluded for any of the following conditions: other cancer (metachronous or synchronous); concurrent infection; pre-existing diarrhoea; intestinal paralysis or obstruction; interstitial pneumonia or pulmonary fibrosis; massive ascites; pleural effusion; uncontrolled diabetes; or a history of severe drug hypersensitivity.

Table 1 Dose escalation schedule

Dose level	Irinotecan (mg m^{-2})	Nedaplatin (mg m^{-2})
1	50	70
2	50	80
3	60	80

Treatment schedule

A 90-min intravenous infusion of CPT-11 (in 500 ml of 0.9% normal saline) was given on day 1, after which 254-S (in 500 ml of 0.9% normal saline) was also administered intravenously over 90 min. Then, patients received intravenous hydration with 1000 ml of 0.9% saline or 5% dextrose. All patients were treated with a 5-HT3 receptor antagonist before administration of the anticancer drugs. Recombinant human granulocyte colony-stimulating factor (50 μg) was given on days 3–12. Before starting the next cycle, it was confirmed that the leukocyte was ≥3000 μl^{-1}, the neutrophil count was ≥1500 μl^{-1}, and the platelet count was ≥100 000 μl^{-1}, with no diarrhoea, and hepatorenal function meeting the eligibility criteria. Treatment was repeated every 4 weeks for at least two cycles, unless the disease progressed. Treatment was, generally, also stopped if the response was defined as no change (NC) after two cycles. The doses of the two anticancer agents were escalated in tandem, as shown in Table 1. Recombinant human granulocyte colony-stimulating factor was also administered when grade 4 neutropenia or grade 3 neutropenia associated with infection occurred. Additionally, if the leukocyte count was <1000 μl^{-1}, neutrophil count was <500 μl^{-1}, or platelet count was <25 000 μl^{-1} during any cycle, the doses of CPT-11 and 254-S were reduced by one level for the next cycle. Physical examination, complete blood count, and biochemistry tests were carried out weekly.

Evaluation of response and toxicity

Tumour response was evaluated according to World Health Organization (WHO) criteria (WHO, 1979). Tumours were measured using contrast-enhanced computed tomography (CT) after two cycles of chemotherapy and also 1 month after the end of the treatment. Computed tomography scans were subsequently performed every 3 months for 2 years. The response was assessed from the product of the two largest perpendicular diameters using the following criteria: complete response (CR) was defined as the disappearance of all detectable lesions with no new lesions for at least 4 weeks; partial response (PR) was defined as ≥50% reduction of the sum of the products of measurable lesions for at least 4 weeks. Progressive disease (PD) was defined as a ≥25% increase in the sum of the products of all measurable lesions, reappearance of any lesion that had disappeared, or appearance of a new lesion. No change was defined as any outcome that did not qualify as response or progression. Measurements were performed by an experienced radiologist who was blinded to patient information. Patients were considered evaluable for response if they received at least one full cycle of per protocol therapy.

Toxicity was evaluated by the Japan Clinical Oncology Group (JCOG) criteria (Tobina *et al*, 1993). Complete blood counts, biochemistry tests, and liver function tests were performed weekly.

Patients were considered evaluable for toxicity if they received at least one full cycle according to the protocol. Dose-limiting toxicity was defined as grade 4 haematologic toxicity (a leukocyte count $<1000\,\mu l^{-1}$, neutrophil count $<500\,\mu l^{-1}$, or platelet count $<25\,000\,\mu l^{-1}$), or grades 3–4 nonhaematologic toxicity (except for alopecia, nausea, and vomiting) or failure to recover sufficiently to start the second cycle within 6 weeks. At least three assessable patients were treated at each dose level. If none of these three patients experienced DLT, then the next dose level was started. If one patient developed DLT, the cohort was expanded to six patients. The maximum tolerated dose (MTD) was defined as the dose level at which at least two out of three patients or three out of six patients experienced DLT. The recommended dose (RD) of 254-S and CPT-11 for the subsequent phase II study was set at one level below the MTD.

Statistical analysis

When the number of subjects required for a 95% confidence interval (95% CI) of ±20% was calculated by setting the expected response rate as 35%, it was 22 subjects. Therefore, the target number of subjects for this study was set as 22. Primary statistical analysis consisted of estimation of the complete and partial response rates. The response rate was calculated as the percentage of complete plus partial responders relative to the total number of assessable patients and 95% CIs for the response were computed using the binomial distribution function.

RESULTS

Patient characteristics

A total of 27 patients were enrolled in this study between 10 January 1998 and 1 March 2003. Four patients were in stage IVA, three patients were in stage IVB, and 20 patients had recurrent cancer. Among those recurrent 20 patients, the duration from primary therapy to recurrence was <1 year for 10 patients, from ⩾1 to <2 years for seven patients, and >2 years for three patients. Their median age was 54 years (range: 32–67 years). In all, 22 patients had a PS of 0, four had a PS of 1, and one had a PS of 2. A total of 20 patients had squamous cell carcinoma, four had adenosquamous cell carcinoma, and three had adenocarcinoma. Seven patients had no prior therapy, two had received chemoradiotherapy, five had undergone surgery, and 13 had received both surgery and chemoradiation. The chemoradiotherapy consisted of radiotherapy for whole pelivis and intravenous weekly CDDP treatment ($30\,mg\,m^{-2}\,week^{-1}$) with or without brachytherapy. The tumour was located in the pelvic cavity in 11 cases, lung in nine cases, liver in five cases, paraaortic lymph nodes in four cases, and Virchow's node in one case. All patients were assessable for toxicity and response. A total of 71 cycles of therapy were administered. The clinical features of the patients are summarised in Table 2.

Toxicity

Phase I study The phase I study enrolled eight patients. At dose levels 1 and 2, no DLTs were observed. At dose level 1, three patients developed grade 3 neutropenia, while one out of three patients had grade 3 neutropenia at dose level 2. At dose level 2, one out of three patients only received one course because of PD. At dose level three, the first two patients developed grade 4 neutropenia and one of them had febrile neutropenia for 4 days. Both received rhG-CSF and one of them also received intravenous antibiotics. None of the patients experienced nonhaematologic DLTs. In five cases, treatment could be performed every 4 weeks, but treatment delay occurred in two cases (3 days and 7 days). Therefore, the MTD was set as 60 and $80\,mg\,m^{-2}$ for CPT-11 and 254-S, respectively, and the doses for the phase II study were set at 50 and $80\,mg\,m^{-2}$. Toxicities are summarised in Tables 3 and 4.

Phase II study A total of 22 patients, including three patients from the phase I study, were registered for the phase II study. In 7

Table 2 Characteristics of the eligible patients ($n=27$)

Characteristic	n
Age (years)	
Median	54
Range	32–67
WHO PS	
0	22
1	4
2	1
FIGO stage	
IVA	4
IVB	3
Recurrent	20
Site of recurrent	
Inside radiation field	5
Outside radiation field	22
Histology	
Squamous cell carcinoma	20
Adenosquamous cell carcinoma	4
Adenocarcinoma	3
Prior therapy	
None	7
Chemoradiation	2
Surgery	5
Surgery plus chemoradiation	13

Table 3 Haematologic toxicity

	Leukopenia				Neutropenia				Anemia			Thrombocytopenia				
Dose level	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**	**G4**	**Grade 3/4 toxicity (%)**
Phase I																
1 ($n=3$)	0	0	3	0	0	1	2	0	0	1	1	1	0	0	0	100
2 ($n=3$)	0	2	1	0	0	2	1	0	1	1	0	0	0	0	0	33
3 ($n=2$)	0	0	1	1	0	0	0	2	0	0	2	0	0	1	1	100
Phase II																
2 (cycles = 50)[a]	6	19	18	1	9	9	22	6	17	17	10	4	8	4	1	62[a]
1 (cycles = 8)	0	2	5	1	0	1	3	4	1	2	5	1	2	2	1	100
Total (cycles = 58)	6	21	23	2	9	10	25	10	18	19	15	5	10	6	2	67

[a]Three patients were from the phase I study.