Uracil/Tegafur Plus Cisplatin with Concurrent Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer: A Multi-institutional Phase II Trial

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ABSTRACT

Purpose: **To evaluate the efficacy and toxicity of a novel combination treatment using concurrent radiotherapy with cisplatin plus UFT, which is comprised of uracil and tegafur, in locally advanced non-small cell lung cancer (NSCLC) patients.**

Experimental Design: **In this Phase II trial, patients with unresectable stage III NSCLC were treated with the oral administration of UFT (400 mg/m^2/d tegafur) on days 1–14 and days 29–42 whereas 80 mg/m^2 cisplatin was administered i.v. on days 8 and 36. Radiotherapy, with a total dose of 60 Gy, was delivered in 30 fractions from day 1.**

Results: **Seventy patients were enrolled and eligible, as follows: 57 males/13 females; mean age 61 ranging from 36 to 74; performance status 0/1:45/25; stage IIIA/IIIB, 14/56. A complete response was observed in two patients and a partial response in 54 patients, and the overall response rate was 81% (95% confidence interval; 70–89%). The median survival, the 1- and 2-year survival rates were 16.5 months, 67% and 33%, respectively. Grade 3/4 leukopenia occurred in 14%/1% of the patients. Grades 3 non-hematological toxicities were only reported in three patients with nausea, two with esophagitis and one with pneumonitis whereas no grade 4 non-hematological toxicity was observed.**

Conclusions: **UFT plus cisplatin with concurrent radiotherapy is considered to be a feasible and effective treatment for locally advanced NSCLC patients. Additional study of this concurrent chemoradiotherapy is warranted.**

INTRODUCTION

For non-small cell lung cancer (NSCLC) patients with unresectable stage III disease and a good performance status, combined chemoradiotherapy is the standard treatment (1, 2). Recent randomized Phase III trials have shown that concurrent chemoradiotherapy is superior to chemotherapy followed by radiotherapy in terms of the response and survival in such patients (3, 4). However, concurrent chemoradiotherapy is also associated with an increased rate of bone marrow suppression and acute esophagitis compared with sequential chemoradiotherapy.

Combination chemotherapy comprising cisplatin and the protracted i.v. injection of 5-fluorouracil (5-FU) has been reported to be effective for NSCLC with possibly a lower hematological toxicity than with many other cisplatin-based regimens (5). In this combination chemotherapy, we replaced the protracted infusion of 5-FU that might hamper a quality of life of patients with a oral daily administration of UFT including tegafur (prodrug of 5-FU) and uracil in a 1:4 molar ratio concentration (6). The combination chemotherapy consisting of a daily administration of UFT for 2 or 3 weeks and a bolus injection of cisplatin in advanced NSCLC patients demonstrated a response rate of 29% to 38% and a median survival time of 10 to 13 months (6–8). In addition, the incidence of hematological adverse events is lower than that of those of a platinum-based two-drug combination chemotherapy currently used (9): the frequency of grade 3 or 4 neutropenia/leukopenia was reported to be 1–12% in the former and 63–75% in the latter.

Both cisplatin and 5-FU have been reported to have a radiosensitizing effect in preclinical and clinical studies including NSCLC (10–14). Although there is no information on the suitable combination modality of 5-FU and radiotherapy in NSCLC, continuous 5-FU infusion with concurrent radiotherapy has been reported to be superior to the use of bolus 5-FU schedules because of lower hematological toxicity and improved disease-free and overall survival rates in resected rectal cancer patients (15). Pharmacokinetic studies have shown that the 5-FU plasma levels in patients receiving protracted infusions of 5-FU are similar to those found in patients receiving oral UFT, although peak levels of 5-FU are higher with UFT (16).

On the basis of this background, we conducted a single institutional pilot trial in which the combination chemotherapy of UFT plus cisplatin was performed with concurrent radiother-

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apy for locally advanced NSCLC (17). Among the 23 enrolled patients, 21 (91%) demonstrated a partial response, and the median survival time was 16.6 months. Hematological toxicity was moderate whereas no severe non-hematological toxicities were observed. We thus conducted a multi-institutional Phase II trial to confirm the antitumor effect and toxicity of this concurrent chemoradiotherapy.

PATIENTS AND METHODS

Eligibility Criteria. The eligibility requirements were cytologically or histologically confirmed, unresectable stage III NSCLC for which radical dose radiotherapy could be prescribed. All patients were required to meet the following criteria: measurable disease; an Eastern Cooperative Oncology Group performance status of 0 or 1; a projected life expectancy of >3 months; a leukocyte count of ≥4,000/μl; a platelet count of ≥100,000/μl; a blood gas oxygen level of ≥70 Torr; a serum bilirubin level <1.5 mg/dl; serum glutamic oxaloacetic transaminase/glutamic pyruvic transaminase levels of no more than twice the upper limit of normal; a normal creatinine level; and a creatinine clearance level of ≥60 ml/min. Other eligibility criteria included no prior treatment and an age ≤75 years. All eligible patients underwent computed tomography scans of the thorax and upper abdomen and a radioisotope bone scan.

Any patients who had malignant pleural effusion, malignant pericardial effusion, a concomitant malignancy, or serious concomitant diseases were excluded from the study. Written informed consent was required from all patients, and the protocol was approved by the institutional ethics committee of each participating institute. On entrance to the study, the eligibility of patients was checked via facsimile by the central administration office of the Tokyo Cooperative Oncology Group (Tokyo).

Treatment Schedule. UFT (400 mg/m^2/d tegafur) in the form of a 100-mg capsule (100-mg tegafur and 224-mg uracil) was administered p.o. in two divided daily doses, before meals, from days 1 to 14 and from days 29 to 42. The dose was rounded up or down to the nearest 100 mg. If the number of capsules could not be equally divided, then the higher dose was administered in the morning and the lower dose administered in the evening. In practice, most patients received UFT 3 capsules (300 mg of tegafur and 672 mg of uracil) b.i.d. Cisplatin (80 mg/m^2) was administered by a 90-minuite infusion on days 8 and 36. The patients were also hydrated with ≥2500 ml of saline infusion on the day they received cisplatin. After undergoing concurrent chemoradiotherapy, administration of two further cycles of this chemotherapy regimen was recommended to all patients responding to the concurrent chemoradiotherapy. However, the part of this consolidation chemotherapy was not officially included in the present trial.

Radiotherapy was administered in five fractions per week from a megavolt linear accelerator or cobalt 60 at a daily dose of 2 Gy from day 1 up to a total of 60 Gy (30 fractions). One fraction had two beams. Among the 60 Gy, the first 40 Gy was delivered to the isocenter of anteroposterior/posteroanterior fields, which included the primary tumor, ipsilateral hilum, and mediastinum. When no tumor in the supraclavicular fossa was detected by a physical or on radiographic examinations, the area was not irradiated. Shaped custom blocks or multileaf collimator were used and included a margin of 2 cm between the target and block edge. Thereafter, the last 20 Gy was delivered using a pair of oblique fields that excluded the spinal cord. The oblique fields included gross tumor volume (primary tumor plus metastatic lymph nodes) with a 2-cm margin. Neither posterior spinal cord blocks nor lung inhomogeneity correction was used.

Complete blood cell counts and biochemistry were performed weekly. If the leukocytes decreased to <3000/μl, platelets decreased to <100,000/μl, or abnormal results of hepatic or renal function tests (level higher than eligibility criteria) were observed, then the administration of cisplatin was suspended. Whenever grade 2 diarrhea or stomatitis occurred, a 33% UFT dose reduction was required. When such adverse events were grade 3 or greater, the administration of UFT was suspended. Radiotherapy was suspended if either a grade 4 hematological toxicity or grade 3 or greater esophagitis occurred. When the hematological toxicity and esophagitis recovered to grade 2 and grade 1, respectively, radiotherapy was resumed.

Study Evaluation and Statistical Methods. Patients were evaluated for their response based on the standard WHO criteria (18). Toxicity was graded according to National Cancer Institute common toxicity criteria (version 2.0). The eligibility and response were assessed by extramural reviewers.

The primary end point of this study was to determine the tumor-response rate produced with this treatment protocol. On the basis of the assumption that a response rate of >75% would warrant a further investigation of this combined modality treatment and that a rate <60% would make such an investigation unnecessary, a sample size of 62 patients was required with a α error of 0.1 and a β error of 0.1. Therefore, the accrual of 70 patients was planned for a 2-year period because several ineligible patients might be identified in the course of the study.

For comparison of proportions for categorical variables, the χ^2 test was used. The overall survival was defined as the time from the initiation of treatment until death from any cause or last follow-up. Survival was estimated by the Kaplan-Meier method.

RESULTS

Characteristics of Patients. Between May 1999 and March 2001, a total of 70 patients were enrolled in this study, and the all patients were considered eligible. As shown in Table 1, 81% of patients were male with a mean age of 61 years (range, 36–74 years). Adenocarcinoma was the most common histology at 53%, and most patients had clinical stage IIIB disease (IIIA *versus* IIIB; 20% *versus* 80%). Frequently classified Tumor-Node-Metastasis category was $T_4N_2M_0$ (34%) and $T_{1-3}N_3$ (29%).

Adverse Events. Adverse events of concurrent chemoradiotherapy are listed in Table 2. Among the hematological toxicities, grade 4 leukopenia was observed only in one patient (1%) and 10 patients (14%) had grade 3 leukopenia. Grade 3 thrombocytopenia was observed only in one patient (1%), and no patient had grade 4 thrombocytopenia. Among the non-hematological toxicities, grade 3 esophagitis was observed in two patients (3%) whose radiotherapy was administered using cobalt-60. Dyspnea of grade 3 possibly attributable to radiation pneumonitis was observed in one patient (1%) who was treated successfully with the oral administration of prednisolone.

Table 1 Patient characteristics

No. of eligible patients			70	(100%)
Age, yrs.	Mean (range)		61	(36–74)
Gender	Male		57	(81%)
	Female		13	(19%)
ECOG PS[a]	0		45	(64%)
	1		25	(36%)
Histology	Adenocarcinoma		37	(53%)
	Squamous cell ca		30	(43%)
	Large cell ca		3	(4%)
TNM	Stage IIIA	$T_3N_1M_0$	1	(1%)
		$T_{1-3}N_2M_0$	13	(19%)
	Stage IIIB	$T_{1-3}N_3M_0$	20	(29%)
		$T_4N_{0-1}M_0$	6	(9%)
		$T_4N_2M_0$	24	(34%)
		$T_4N_3M_0$	6	(9%)
Radiation equipment used				
	Cobalt-60		8	(11%)
	Linear accelerator		62	(89%)

[a] ECOG, Eastern Cooperative Oncology Group; PS, performance status; ca, carcinoma; TNM, Tumor-Node-Metastasis.

Treatment Delivered. Sixty-one patients (87%) completed the concurrent treatment consisting of two cycles of chemotherapy and radiotherapy of 60 Gy according to the protocol. Five patients could not complete the scheduled concurrent chemoradiotherapy. Three and one patient could not complete the scheduled radiotherapy and chemotherapy, respectively. The reasons for the discontinuation of the treatment in these nine patients were attributable to adverse events in five patients (grade 3 esophagitis in two; grade 4 leukopenia, grade 2, or grade 3 nausea in one each), concomitant disease in two, withdrawal from the treatment protocol in one, and a poor general condition in one. The dose of cisplatin and UFT was reduced in one patient each attributable to either renal dysfunction or nausea. Among the 56 patients who experienced a response to the concurrent chemoradiotherapy, 17 and 12 patients received one cycle and two cycles of consolidation chemotherapy, respectively.

Response. Among all 70 patients including 4 patients whose response was not evaluable because of insufficient information, 56 patients had responses (80%; 95% confidence interval; 71% to 89%), including two patients (3%) with a complete response and 54 (77%) with a partial response. There were 10 patients (14%) with no change. There were no differences in the response rate by age (>65 *versus* <65, $P = 0.279$), gender (female *versus* male, $P = 0.759$), stage (IIIA *versus* IIIB, $P = 0.100$), performance status (0 *versus* 1, $P = 0.212$), and histology (adenocarcinoma *versus* others, $P = 0.402$).

Survival. The overall median follow-up time for all patients was 33 months (range, 18–45 months). As shown in Fig. 1, the median survival time of all 70 patients was 16.5 months, and the survival rates at 1 and 2 years were 67% (95% confidence interval; 56–78%) and 33% (95% confidence interval; 22–45%), respectively.

Sites of First Failures. With respect to the sites of first failure among 59 recurrent patients, 29 (49%) were distant, 25 (42%) were local (primary tumor site and/or regional lymph nodes including supraclavicular lymph nodes), and 3 (5%) were both local and distant (Table 3). Of a total of 28 patients with local recurrence, 18 patients had a recurrence within an irradiated field. In addition, isolated brain metastasis was reported in five patients.

DISCUSSION

The goals of chemoradiotherapy in NSCLC with stage III disease are to achieve local control, for which radiotherapy plays the main role, and eradicate occult distant metastases by chemotherapy. Therefore, the administration of the full doses of both chemotherapy and radiotherapy is ideal. Recent randomized trials comparing concurrent chemoradiotherapy with sequential chemoradiotherapy as a standard treatment have shown that the former is superior to the latter when chemotherapy and radiotherapy are given at full dose (19, 20). The chemotherapy regimen and total dose of radiotherapy was mitomycin, vindesine plus cisplatin, and 56 Gy (28 fractions of 2 Gy each for 6 weeks including a rest of 10 days at the first 28 Gy in the concurrent arm and 28 fractions of 2 Gy each for 5 weeks in the sequential arm) in the trial of the West Japan Lung Cancer Group (3) and vinblastine plus cisplatin and 60 Gy (30 fractions of 2 Gy each for 6 weeks in both arms) in the trial of the Radiation Therapy Oncology Group (4), respectively. The median survival time of the concurrent and sequential treatment groups was 16.5 *versus* 13.3 months in the Japanese trial and 17 *versus* 14.6 months in the Radiation Therapy Oncology Group trial. In the present study, the chemotherapy regimen using UFT plus cisplatin was demonstrated to be capable of being given at full dose with concurrent radiotherapy at full dose. As a result, this regimen achieved a survival comparable with the concurrent treatments reported previously.

The other well-known chemotherapy regimen that can be administered at full dose with concurrent radiotherapy is etoposide plus cisplatin. Because this regimen is considered to be a safe and active regimen, it is currently most often concurrently used with radiotherapy for both small and NSCLC with localized disease (19, 20). However, toxicity is well known to in-

Table 2 Hematologic and non-hematologic adverse events

	Grade[a]				Frequency of
Toxicity ($n = 70$)	1	2	3	4	3 or 4 (%)
Leukopenia	4	14	10	1	16
Neutropenia	4	7	4	1	7
Thrombocytopenia	9	4	1	0	1
Anemia	16	7	4	0	6
Bilirubin	2	1	0	0	0
Glutamic-oxaloacetic transaminase	8	0	0	0	0
Glutamic-pyruvic transaminase	7	1	0	0	0
Creatinine	5	0	0	0	0
Proteinuria	5	2	0	0	0
Hematuria	5	0	0	0	0
Nausea	16	11	3	0	4
Vomiting	11	8	0	0	0
Diarrhea	1	2	0	0	0
Stomatitis	3	0	0	0	0
Alopecia	5	0			0
Esophagitis	20	7	2	0	3
Pulmonary	24	8	1	0	1
Dermatitis	7	0	0	0	0

[a] National Cancer Institute common toxicity criteria.

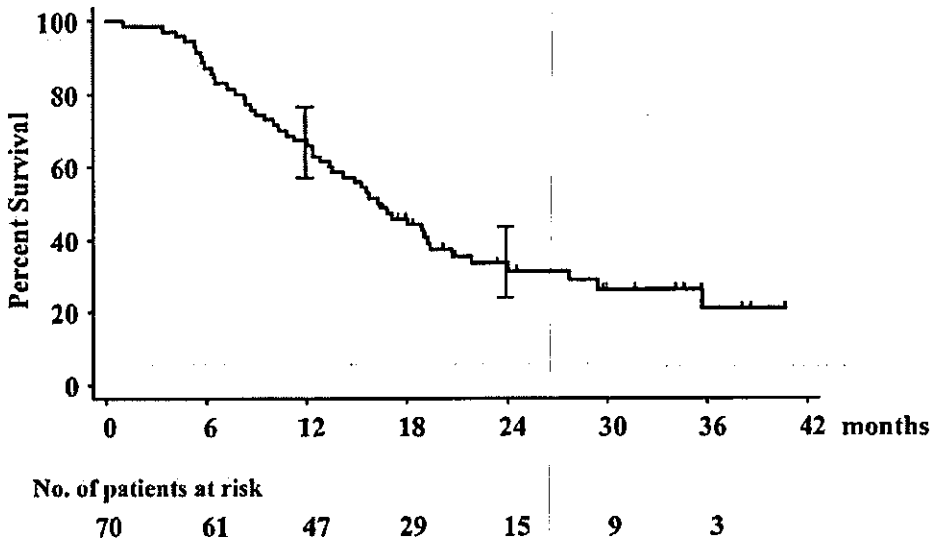

Fig. 1 Survival. Each tick mark represents a patient who is alive. The *bars* represent the 95% confidence interval of the survival rate at 1 and 2 years after treatment.

crease with greater myelotoxicity and esophagitis in such a concurrent treatment modality. Even in a safe regimen such as etoposide plus cisplatin, grade 3/4 esophagitis was observed in 20% of the patients, and grade 4 neutropenia occurred in 32%, when it was used with concurrent radiotherapy (20). In the present study, grade 4 neutropenia and grade 3 esophagitis were observed only in one (1%) and two patients (3%), respectively, whereas there was no grade 4 esophagitis. Although the difference in the frequency of those adverse events may be partly attributable to differences in the racial background of the patients, no severe hematological toxicity was observed in any trials including UFT with concurrent radiotherapy for rectal cancer, trials which were performed in the United States (21) and Europe (22).

Whether there is any benefit to be obtained by administering induction or consolidation chemotherapy in addition to concurrent chemoradiotherapy remains to be determined. In the present study, two cycles of consolidation chemotherapy were recommended but not mandated in the patients who responded to concurrent chemoradiotherapy. Regardless of the rather low degree of toxicity observed with this concurrent regimen, only 29 patients (52%) received consolidation chemotherapy. This low figure may be partly attributable to the still unclear role of consolidation chemotherapy.

The Southwest Cooperative Oncology Group conducted a Phase II trial using cisplatin plus etoposide with concurrent radiotherapy followed by docetaxel, which is known to be the most active second-line agent in NSCLC (23). The median survival was 26 months, and the 3-year survival rate was 37%. Grade 4 neutropenia (57%) was the most common toxicity observed during consolidation, and it was manageable and expected based on the profile of adverse events related to docetaxel. We are now gathering unresectable stage III NSCLC patients to enter them into a randomized Phase III trial to compare UFT plus cisplatin with docetaxel as a consolidation chemotherapy after UFT plus cisplatin with concurrent radiotherapy.

Table 3 Sites of first failure (n = 59)

Site	Patients	
	No.	%
Local	25	42
Local + Distant	3	5
Distant	29	49
Lung	6	
Liver	6	
Bone	6	
Brain	5	
Others	6	
Unknown	2	3

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APPENDIX

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

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ABSTRACT

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

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

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

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

INTRODUCTION

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

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

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

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Note: additional participating institutions and principal investigators included National Shikoku Cancer Center Hospital (Yoshihiko Segawa), Jizankai Tsuboi Hospital (Koichi Hasegawa), Niigata Cancer Center Hospital (Akira Yokoyama), and Nippon Medical School (Akinobu Yoshimura).
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administration of UFT for 2 or 3 weeks and a bolus injection of cisplatin at mid-cycle of administration of UFT for advanced non–small-cell lung cancer yields a response rate of 29 to 38% and a median survival time of 10 to 13 months (9–11).

With these backgrounds, we conducted a phase II trial combining the oral administration of S-1 for 21 days and a bolus injection of cisplatin on day 8 in patients with advanced NSCLC.

PATIENTS AND METHODS

Patient Eligibility. The patients were eligible for this phase II trial if they had been either cytologically or histologically confirmed to have NSCLC; stage IIIB without any indications for radiotherapy or stage IV; measurable disease; no prior treatment; an age range from 20 to 74 years; an Eastern Cooperative Oncology Group performance status of 0, 1, or 2; and a projected life expectancy of at least 3 months. Other eligibility criteria for an organ function were as follows: a leukocyte count of 4,000 to 12,000/μL; platelet count ≥100,000/μL; hemoglobin level of ≥9 g/dl; a serum bilirubin level <1.5 mg/dl; serum aspartate aminotransferase and alanine aminotransferase levels <100 IU/L; alkaline phosphatase level of twice the upper limit or less; normal creatinine level; creatinine clearance rate of at least 60 mL/minute; partial pressure of arterial oxygen >70 Torr. For staging, all patients underwent a computed tomography scan of the thorax, including upper abdomen, and either a brain computed tomography scan or magnetic resonance images of brain, and a radioisotopic bone scan was also done in almost all patients.

Any patients who were pregnant or had concomitant serious diseases, a concomitant malignancy, pleural effusion necessitating treatment, or symptomatic cerebral involvement were excluded from the study. Written informed consent was required from all patients, and the protocol was approved by the institutional ethics committee of each of the participating institutions. On entrance to the study, the eligibility of patients was checked via facsimile by the central administration office of the Tokyo Cooperative Oncology Group (Tokyo).

Treatment Schedule. S-1 capsule in the form of a 20 and 25 mg capsule containing 20 and 25 mg tegafur, respectively, was provided by the Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan). S-1 was administered orally, 40 mg/m^2 twice a day, after meals between days 1 and 21. The actual dose of S-1 was selected as follows: in a patient with body surface area (BSA) < 1.25 m^2, 40 mg twice a day; BSA of 1.25 m^2 but <1.5 m^2, 50 mg twice a day; and BSA ≥ 1.5 m^2, 60 mg twice a day. Cisplatin (60 mg/m^2) was administered intravenously on day 8 when patients were hydrated with at least a 2,500 mL infusion. An antiemetic agent could be administered at the discretion of each patient's physician. The treatment regimen was repeated every 5 weeks at least two cycles unless disease progression or unacceptable toxicity occurred. A leukocyte count of ≥3,000/μL and the entry eligibility criteria regarding organ functions had to be satisfied to start the next cycle. If these criteria were satisfied 4 weeks after day 1 of each cycle of chemotherapy, the next cycle could be administered. The doses of S-1 were adjusted according to the degree of hematologic and nonhematologic toxicity. The dose was reduced by one level (20 mg per day) in patients whose BSA was ≥1.25 mg, with evidence of grade 4 hematologic toxicity or grade 3 or more nonhematologic toxicity during any cycle of administration. If recovery from such toxicities was confirmed at a reduced dose, administration at the reduced dose was continued. If a patient with BSA <1.25 m^2 experienced the above toxicities, then no further treatment with S-1 was done. If a rest period of >4 weeks was required, then the patient was withdrawn from the study.

Evaluation of Response and Toxicity. All eligible patients who received any part of the treatment were considered assessable for response and toxicity. Chest X-ray, complete blood count, and blood chemistry studies were repeated weekly. The response was assessed based on the chest X-ray or computed tomography scan findings that initially had been used to define the tumor extent. The response was evaluated in accordance with the criteria of the World Health Organization (12). A central radiological review was done to determine the eligibility of patients and the response of treatment. Adverse events were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0.

Statistical Analysis. The number of patients to be enrolled in this study was calculated to be 54, which was required to reject the null hypothesis that the lower bound of 95% CI of the expected response rate (50%) would be <30% under the conditions of α error of 0.025 (one side) and β error of 0.2. The overall survival of the eligible patients was defined as the time from the start of the treatment until death from any cause, and it was estimated by the Kaplan-Meier method. Differences between the proportions were evaluated by the χ^2 test. The data were considered to be significant when the P value was ≤0.05.

RESULTS

Patient Population. Between September 2000 and November 2001, 56 patients were enrolled in this study. One patient was considered to be ineligible because of prior treatment for pleurodesis in which OK432 was used for his malignant pleural effusion. The clinical characteristics of all eligible 55 patients are listed in Table 1. They included 41 men and 14 women, with a median age of 64 years. Thirty (55%) patients

Table 1 Patient characteristics

No. of patients	55
Age (years), median (range)	64 (46–74)
Gender	
Male	41 (75%)
Female	14 (26%)
Performance status (ECOG)	
0	30 (55%)
1	23 (42%)
2	2 (4%)
Stage	
IIIB	10 (18%)
IV	45 (82%)
Histology	
Adenocarcinoma	37 (67%)
Squamous cell carcinoma	14 (26%)
Others	4 (7%)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

had Eastern Cooperative Oncology Group performance status of 0 and 45 (82%) patients had stage IV disease. The predominant histology type was adenocarcinoma (67%).

Response and Survival. Among all 55 eligible patients, 1 had a complete response and 25 had a partial response. Thus, the overall response rate was 47% (95% CI, 34–61%). Because one ineligible patient had a partial response, the overall response of all registered 56 patients was 48% (95% CI, 35–62%). The responding patients were classified in terms of the items shown in Table 2. There was no statistically significant difference in the response rates between the items compared. The median response duration was 4.2 months.

The median follow-up period was 28 months (range, 20–33 months). As shown in Fig. 1, median survival time of the 55 eligible patients was 11 months and the 1-year and 2-year survival rates were 45% (95% CI, 32–59%) and 17% (95% CI, 6–27%), respectively.

Adverse Events. The adverse events observed throughout the treatment of the 55 eligible patients are shown in Table 3. Among the hematologic adverse event, grade 3/4 neutropenia and anemia was observed in 29 and 22% of the patients, respectively. However, grade 3 thrombocytopenia was observed in only one patient (2%), and no patient had grade 4 thrombocytopenia. Among the observed nonhematologic adverse events, no grade 4 level was observed. There were no unexpected toxicities.

Table 2 Patient characteristics in relation to the response

Characteristics	No. of patients	Response				Response rate (%)
		CR	PR	NC	PD	
All	55	1	25	23	6	47
Gender						
Male	41	1	20	15	5	51
Female	14	0	5	8	1	36
Stage						
IIIB	10	0	4	5	1	40
IV	45	1	21	18	5	49
Histology						
Adenocarcinoma	37	0	15	17	5	41
Squamous cell carcinoma	14	1	7	5	1	57
Others	4	0	3	1	0	75

Abbreviations: CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

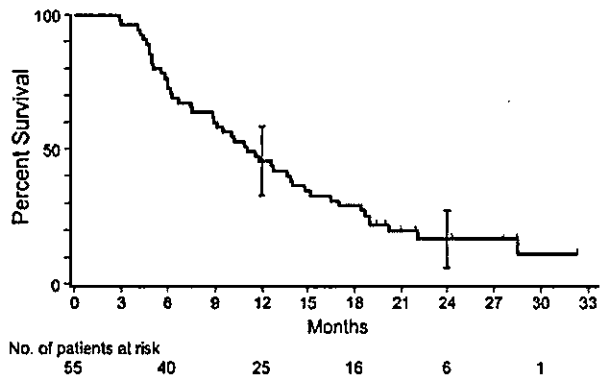

Fig. 1 Overall survival. Each *tick* represents a patient who is alive. The *bars* represent the 95% confidence interval of the survival rate at 1 year and 2 years after treatment.

Table 3 Hematologic and nonhematologic toxicities

Toxicity	Grade				Frequency of 3 or 4 (%)
	1	2	3	4	
Leukopenia	8	18	2	1	6
Neutropenia	7	13	13	3	29
Anemia	14	24	10	2	22
Thrombocytopenia	28	4	1	0	2
Aspartate aminotransferase	7	0	1	0	2
Alanine aminotransferase	6	1	1	0	2
Creatinine	9	1	1	0	2
Anorexia	21	15	7	0	13
Vomiting	14	3	4	0	7
Diarrhea	12	3	4	0	7
Stomatitis	12	2	0	0	0
Dermatitis	13	0	0	0	0

Compliance. A range of 1 to 12 treatment cycles were administered (1 cycle, 6 patients; 2 cycles, 18 patients; 3 cycles, 5 patients; 4 cycles, 12 patients; >4 cycles, 14 patients). The reasons for only one cycle of treatment were progressive disease in 4 patients and adverse events in 2 patients. The dose of S-1 was reduced in 8 patients because of adverse events including myelosuppression in 4 patients, gastrointestinal toxicity in 2 patients, glycemia in 1 patient, and dermatitis in 1 patient. A total of 197 cycles were given to the 55 patients. Sixty-nine (49%) of 142 treatment cycles excluding the first cycle was given at 4-week interval, 58 (40%) were at a 5-week interval, and 15 (11%) were at a >5-week interval.

DISCUSSION

Because the half-life of 5-FU is as short as 5 to 20 minutes (13) and the antitumor activity of 5-FU is time dependent, the continuous intravenous administration of 5-FU is considered to be appropriate rather than a bolus intravenous injection of 5-FU. In fact, a meta-analysis of six randomized trials in patients with colorectal cancer showed that the response rate was clearly higher for continuous infusion of 5-FU over 5 consecutive days than for weekly bolus injection of 5-FU (14). Although NSCLC has also been reported not to respond to a bolus injection of 5-FU (15), whether or not continuous treatment with 5-FU is effective for NSCLC remains unclear. However, studies have shown that a combination of cisplatin and protracted intravenous injection of 5-FU is effective for NSCLC (16). In prior trials, we used this combination chemotherapy with daily oral administration of UFT in place of the protracted intravenous injection of 5-FU which negatively affects the quality of life of a patient for advanced NSCLC (9–11).

The combination chemotherapy of cisplatin and 5-FU has been proven to have synergic antitumor effect in many experimental and clinical studies (17, 18). However, the optimal sequence for the administration of these drugs has yet to be determined. The sequence of cisplatin followed by 5-FU has been shown to be more cytotoxic than the reverse succession in *in vitro* and *in vivo* studies (19, 20) whereas the sequence of 5-FU followed by cisplatin has been proven to have a greater

antitumor activity than the opposite order of administration in tumor-bearing animals (21). Therefore, in our prior trials using UFT, we designed a treatment regimen that is thought to be a compromise solution between the present conflicting experimental data; namely, a daily administration of UFT from day 1 to 14 or 21 and a bolus infusion of cisplatin on day 8 (9, 10).

In the present study with S-1, the treatment modality was determined based on the UFT trials (9, 10) and phase I/II trial of S-1 combined with cisplatin in patients with advanced gastric cancer (22). The dose of cisplatin was decreased from 80 mg/m^2 in prior UFT trial to 60 mg/m^2 in the present trial because phase I trial indicated that 60 mg/m^2 of cisplatin on day 8 was the recommended dose when it was combined with daily administration of S-1 from day 1 for 3 weeks (22). Concerning the dose of cisplatin in combination chemotherapy in NSCLC patients, the effect of the dosage on survival has not yet been clearly elucidated. Klastersky *et al.* (23) reported the median survival time of patients who received vindesine plus combination chemotherapy consisting of either 60 or 120 mg/m^2 of cisplatin to be 7.6 and 6.4 months, respectively, and no overall survival difference between the two groups was observed ($P = 0.138$). On the other hand, the incidence of adverse events was significantly higher in the 120-mg dose than that in 60-mg dose.

Although a comparison between the present S-1 trial and the prior UFT trial with 108 patients (10) has limitation because of different trials, the response rate and survival seems to be favorable in the present trial despite the fact that proportion of stage IV patients in the present trial was higher than that in the UFT trials (82% *versus* 68%). The response rate and median survival time was 47% and 11.2 months in the present study and 29% and 10 months in the UFT trial, respectively. The frequency of severe adverse events in the both trials was similarly low.

The standard chemotherapy regimen for NSCLC is considered to be a platinum-based two-drug combination chemotherapy that uses paclitaxel, docetaxel, gemcitabine, or vinorelbine. The response rate and median survival time in the recent phase III trials that use these combination chemotherapies have been reported to be 17 to 28% and 7 to 9 months, respectively. Grade 3 or 4 hematologic and nonhematologic adverse events were observed in 57 to 76% (neutropenia) and 4 to 35% (vomiting), respectively (24, 25). In the present study with S-1 and cisplatin, the incidence of those adverse events seems to be lower than the above mentioned data. In addition, the antitumor mechanism is different from those agents. On the basis of these observations, we plan to conduct a randomized trial comparing the present combination chemotherapy with standard platinum-based two-drug combination chemotherapy regarding survival and the quality of life.

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ORIGINAL REPORT

Phase III Randomized Trial of Docetaxel Plus Cisplatin Versus Vindesine Plus Cisplatin in Patients With Stage IV Non–Small-Cell Lung Cancer: The Japanese Taxotere Lung Cancer Study Group

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ABSTRACT

Purpose
Few randomized trials have demonstrated survival benefit of combination chemotherapy involving new agents plus cisplatin compared with classic combination chemotherapy in advanced non–small-cell lung cancer (NSCLC). The primary aim of this study was to test whether docetaxel plus cisplatin (DC) improves survival compared with vindesine plus cisplatin (VdsC) in patients with previously untreated stage IV NSCLC.

Patients and Methods
Eligible, stage IV, chemotherapy-naive patients (n = 311) were randomly assigned to receive docetaxel 60 mg/m^2 intravenously on day 1 plus cisplatin 80 mg/m^2 intravenously on day 1 of a 3- or 4-week cycle, or vindesine 3 mg/m^2 intravenously on days 1, 8, and 15 plus cisplatin 80 mg/m^2 intravenously on day 1 of a 4-week cycle. Cross-over administration of docetaxel and vindesine was prohibited for both treatment groups.

Results
Overall, 302 patients were eligible for evaluation. The DC arm demonstrated significant improvements compared with the VdsC arm in overall response rates (37% *v* 21%, respectively; $P < .01$) and median survival times (11.3 *v* 9.6 months, respectively; $P = .014$). Two-year survival rates were 24% for the DC arm compared with 12% for the VdsC arm. The physical domain of the Quality of Life for Cancer Patients Treated with Anticancer Drugs measure was significantly better in the DC arm than in the VdsC arm ($P = .020$). Toxicity was predominantly hematologic and was more severe in the VdsC arm.

Conclusion
As first-line treatment for stage IV NSCLC, DC resulted in greater clinical benefit in terms of response rate (with marked improvements in overall and 2-year survival rates) and quality of life than did treatment with VdsC.

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INTRODUCTION

Lung cancer has been a leading cause of cancer death in industrialized countries in the 20th century [1]. Non–small-cell lung cancer (NSCLC) accounts for 75% to 80% of all lung cancer histology. Meta-analyses of randomized trials comparing chemotherapy with supportive care in patients with advanced NSCLC have demonstrated that cisplatin-based combination chemotherapy prolongs survival, whereas some studies showed palliative effects of cancer-related symptoms with chemotherapy [2,3]. Although significant long-term survivors have been observed in the treatment of stage III NSCLC with chemoradiotherapy [4-6], improvements in stage IV disease have been dismal, with only 10% to 15% of stage IV patients surviving 1 year after diagnosis with best supportive care (BSC) alone and 20% to 25% of stage IV patients surviving 1 year

after diagnosis with cisplatin-based chemotherapy [7]. In the 1990s, randomized trials using platinum in combination with new agents (vinorelbine and gemcitabine) have shown 1-year survival rates ranging between 36% and 39% [8,9]. However, many trials have failed to show a significant survival advantage of new compared with older combinations [10-12].

Docetaxel, a new agent, is a semisynthetic taxoid derived from the European yew *Taxus baccata* [13]. It is active against NSCLC and shows survival benefits not only in chemotherapy-naive patients, but also in those patients who have previously received platinum-based chemotherapy [14-21]. Phase II trials of docetaxel and platinum combinations have resulted in median survival rates ranging between 8.4 and 13.9 months, indicating that such combinations are active as first-line therapies [22-25]. Response rates of 30% to 67% for docetaxel with a platinum agent have also been demonstrated. Although docetaxel is usually administered as a 75 mg/m^2 dose, a phase II trial demonstrated that a response rate of 42% with an acceptable toxicity profile [26] could be achieved when 60 mg/m^2 of docetaxel and 80 mg/m^2 of cisplatin were administered to patients with stage IV NSCLC.

We conducted a randomized trial that compared docetaxel plus cisplatin (DC) with vindesine plus cisplatin (VdsC). The primary aim of this study was to compare the overall survival of stage IV NSCLC patients between the two regimens. Secondary end points included the response rate, duration of response, safety, and quality of life (QoL).

PATIENTS AND METHODS

Eligibility Criteria

This multicenter, randomized trial was conducted at 58 institutions in Japan between March 1998 and March 2000. Eligible patients were between the ages of 20 and 75 years, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; life expectancy ≥ 3 months; and previously untreated, stage IV, histologically or cytologically proven NSCLC with measurable lesions. Patients with PS of 3 because of pain from bone metastases were admitted to the study. Other eligibility criteria included leukocyte count ≥ 4,000/μL and ≤ 12,000/μL, neutrophil count ≥ 2,000/μL, platelet count ≥ 10^5/μL, hemoglobin ≥ 9.5 g/dL, blood urea nitrogen less than or equal to the upper limit of the institutional normal range (ULN), serum creatinine less than or equal to the ULN, creatinine clearance ≥ 60 mL/min, serum bilirubin less than or equal to the ULN, serum ALT and AST ≤ 2 × ULN, and Pao_2 ≥ 70 mm Hg. Women who were pregnant or lactating were excluded from the study. Other exclusion criteria included patients with active infection, uncontrolled heart disease, interstitial pneumonia or active lung fibrosis, peripheral neuropathy, pleural or pericardial effusion that required drainage, past history of drug hypersensitivity, symptomatic brain metastasis, or active concomitant malignancy.

Patient eligibility was determined by the Patient Registration Center at the Tokyo Cooperative Oncology Group before patient registration. This study was approved by the institutional review boards at each participating center and all patients provided written informed consent.

Treatment Plan

Patients were randomly assigned to one of two treatment arms (Fig 1). In the experimental arm (DC), patients received docetaxel 60 mg/m^2 as a 1-hour intravenous infusion followed by cisplatin 80 mg/m^2 as a 2-hour infusion on day 1. Patients in the control arm (VdsC) received a bolus infusion of vindesine 3 mg/m^2 on days 1, 8, and 15, and cisplatin 80 mg/m^2 as a 2-hour infusion on day 1. Courses of treatment were repeated every 3 to 4 weeks in the DC arm, and once every 4 weeks in the VdsC arm.

Patients received at least two cycles of treatment unless disease progression or unacceptable toxicity was documented. Thereafter, responders or patients without disease progression continued treatment until the appearance of progressive disease or

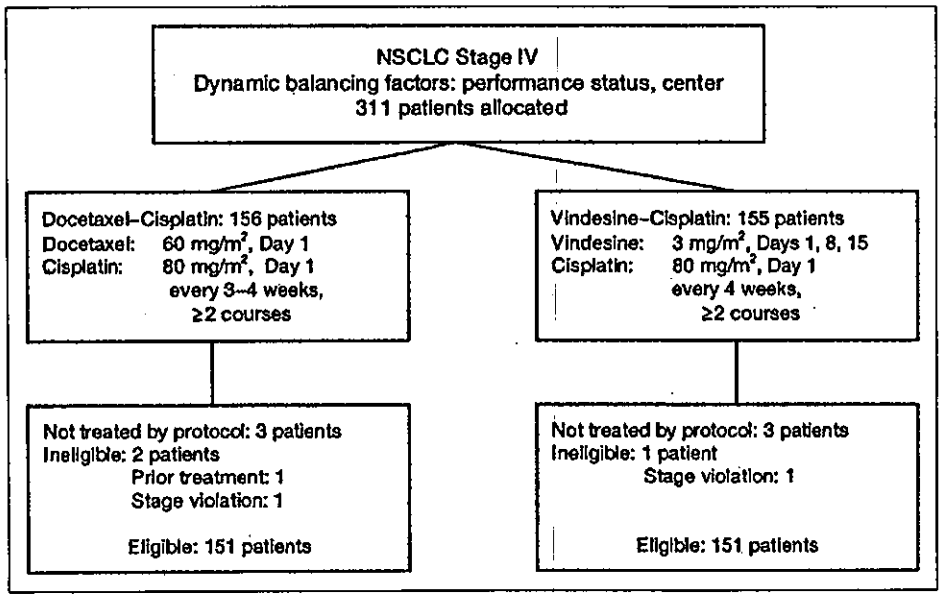

Fig 1. Study design and patient allocation. NSCLC, non-small-cell lung cancer.

a major toxicity. Because the efficacy of second-line docetaxel had not been established at the start of this study in 1998, cross-over administration of docetaxel and vindesine was prohibited in both treatment groups and the nature of second-line treatment was recorded.

No routine premedication was given for hypersensitivity reactions during the first cycle of treatment, although in subsequent cycles this was administered if a patient experienced a reaction. All hypersensitivity reactions were identified by the patient's physician and if deemed necessary, premedication drugs were administered by the investigator. However, recombinant human granulocyte colony-stimulating factor was administered when National Cancer Institute Common Toxicity Criteria grade 3 to 4 leukopenia or neutropenia occurred. If grade 4 neutropenia and/or leukopenia lasting for more than 3 days, grade 4 thrombocytopenia, grade 2 neuropathy, or grade 3 to 4 hepatotoxicity was observed, a 25% dose reduction of both drugs was implemented during the subsequent treatment cycle in both arms. If grade 3 stomatitis or renal toxicity occurred, the dose of cisplatin was reduced by 25%. Dose re-escalation was prohibited. Treatment was discontinued in the event of grade 3 neuropathy and again, dose re-escalation was prohibited. When leukocyte and platelet counts were less than 2,000/μL and 100,000/μL, respectively, or if infection developed at day 8 or 15, vindesine was withheld.

Patient Evaluation

Before chemotherapy, each patient underwent a complete medical history and physical examination, blood cell count determinations, biochemistry testing, chest x-ray, ECG, chest and whole-brain computed tomographic scan, abdominal ultrasound and/or computed tomographic scan, and isotope bone scan. Blood cell counts, differential WBC counts, and biochemistry testing were performed weekly during each course of chemotherapy.

Tumor responses were assessed radiographically and all responders were evaluated on extramural review. Treatment arms were blinded at the review. Standard WHO response criteria were used, and all responses were confirmed $\geq$ 28 days after initial documentation of the response.

QoL scores were measured using the validated instrument QoL Questionnaire for Cancer Patients Treated with Anticancer Drugs developed in Japan [27]. The instrument consists of five domains (functional, physical, mental, psychosocial, and global), and it was completed by the patient before treatment began, before the second and third therapy cycles, and 3 months after the last cycle of treatment. Evaluations were not only performed during the course of treatment but also 2 years after study treatment.

Statistical Considerations

Survival from the date of enrollment was the primary end point. The sample size was chosen on the basis of a log-rank test used to compare the two randomized groups. A sample size of 150 patients per group was estimated on the basis of a projected median survival of 42 weeks in the DC group and 30 weeks in the VdsC group, with an α level of 5% (two sided) and a power of 80% to compare both groups. Dynamic balancing factors (ie, prerandomization stratification factors) included ECOG PS and institutions, and these were used to minimize any imbalance in treatment assignment.

Secondary end points included objective tumor response, response duration, rate of adverse drug reactions, and changes in QoL. The survival time and response duration were estimated for each group using the Kaplan-Meier method [28]. Response duration was calculated from the first date of a 50% reduction in the tumor to the last date that tumor reduction was documented. The difference in response duration was evaluated using the generalized Wilcoxon test. Tumor responses in both groups were compared using Fisher's exact test. Other categoric data, such as treatment data and the incidence of adverse events, were compared between treatment groups using the χ^2 test. QoL analyses were performed using repeated-measures analysis of variance between treatment groups on data collected before the second and third treatment cycles, and 3 months after the last cycle of treatment, adjusting for baseline QoL values.

An interim analysis on the basis of overall survival was planned for 1 year after enrollment of the last patient. The predefined early-stopping rule was based on a two-sided significance level of 0.005. The DeMets and Lan method was applied for multiple comparisons [29]. The analysis was monitored by the Independent Data Monitoring Committee. The final analysis was conducted 2 years after enrollment of the last patient and the final significance level was maintained at 0.0491.

RESULTS

Patient Characteristics

From April 1998 to March 2000, 311 previously untreated patients from 58 institutions were randomly assigned to treatment in the trial (Fig 1). However, six patients did not receive any protocol treatment (three in the DC arm and three in the VdsC arm). In the DC arm, one patient withdrew informed consent, another experienced a rapid increase in serum bilirubin beyond levels acceptable for inclusion into the study, and the third patient had an accident causing a thoracic spine pressure fracture; all withdrawals occurred before the first cycle of treatment. Likewise, before the first cycle of treatment, one patient in the VdsC arm had superior vena cava syndrome, one patient contracted pneumonia and the investigator decided against this patient receiving protocol treatment, and one patient (who also had pneumonia) had brain metastases and was therefore excluded from the study. An additional three patients failed to fulfill the eligibility criteria for the following reasons: stage violations (two patients, one per treatment arm) and prior treatment (one patient, DC arm). Because nine patients were deemed ineligible, 302 patients were evaluated—151 in each arm. All 302 patients were evaluated for survival, response, and toxicity. The characteristics of eligible patients are listed in Table 1.

Treatment Delivery

The median number of cycles was three for the DC arm and two for the VdsC arm ($P < .01$; Table 2). One hundred thirty-two patients (87%) in the DC arm and 115 patients (76%) in the VdsC arm received at least two cycles of chemotherapy. The reasons for terminating chemotherapy before the second treatment cycle in the DC and VdsC arms, respectively, were disease progression (7% v 13%), adverse events (5% v 6%), patient refusal (0% v 2%), and adverse event with patient refusal (1% v 3%).

Table 1. Patient Characteristics

Characteristic	Treatment Group: DC (n = 151)	VdsC (n = 151)
Age, years		
Median	63	64
Range	30–74	39–74
Sex, No. of Patients		
Male	97	103
Female	54	48
Histology, No. of patients		
Adenocarcinoma	120	103
Squamous cell	17	33
Large cell	9	11
Adenosquamous	0	2
Other	5	2
ECOG performance status, No. of patients		
0	46	41
1	99	105
2	5	4
3	1	1

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin; ECOG, Eastern Cooperative Oncology Group.

Table 3. Treatment Outcomes

Outcome	Treatment Group: DC (n = 151)	VdsC (n = 151)	P
Tumor response, No. of patients			
Complete	3	0	
Partial	53	32	
No change	63	76	
Progressive disease	27	38	
Not assessable	5	5	
Overall response rate, %	37.1	21.2	< .01
95% CI	29.4 to 45.3	15.0 to 28.6	
Median duration of response, weeks	10.0	8.4	.02
Survival			
Median, months	11.3	9.6	.014
95% CI	10.2 to 13.1	8.4 to 11.4	
1 year, %	47.7	41.4	
95% CI	39.7 to 55.6	33.5 to 49.3	
2 year, %	24.4	12.3	
95% CI	17.5 to 31.2	7.0 to 17.6	

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.

Response

Patients receiving DC had a significantly higher overall response rate than those receiving VdsC ($P = .0035$; Table 3). There were three complete responses and 53 partial responses, with an overall response rate of 37.1% (95% CI, 29.4% to 45.3%) in the DC arm. The VdsC arm resulted in 32 partial responses, with an overall response rate of 21.2% (95% CI, 15.0% to 28.6%). The median duration of response was 10.0 weeks in the DC arm versus 8.4 weeks in the VdsC arm ($P = .20$).

Survival

The median survival time, 11.3 months (95% CI, 10.2 to 13.1 months) for the DC arm, was significantly greater than the 9.6-month (95% CI, 8.4 to 11.4 months) median survival of the VdsC arm (log-rank test, $P = .014$; Fig 2). The 1- and 2-year survival rates were 47.7% (95% CI, 39.7% to 55.6%) and 24.4% (95% CI, 17.5% to 31.2%) for the DC group, and 41.4% (95% CI, 33.5% to 49.3%) and 12.3% (95% CI, 7.0% to 17.6%) for the VdsC group, respectively (Fig 2).

Table 2. Treatment Delivery

Cycle of Treatment	Received Cycle of Treatment: DC (n = 151) No. of Patients	%	VdsC (n = 151) No. of Patients	%
1	151	100	151	100
2	132	87	115	76
3	84	56	53	35
4	41	27	17	11
5	6	4	1	1
6	2	1	0	0
No. of cycles*				
Median	3		2	
Range	1–9		1–5	

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.
*$P = .01$.

Toxicity

National Cancer Institute Common Toxicity Criteria grade 3 and 4 hematologic toxicities, anemia, and leukopenia were significantly more severe among patients receiving VdsC compared with those receiving DC ($P < .01$; Table 4). Grade 4 neutropenia also occurred more frequently in the VdsC regimen (50.3%) than in the DC regimen (35.1%), but grade 3 or 4 thrombocytopenia was rare in both arms.

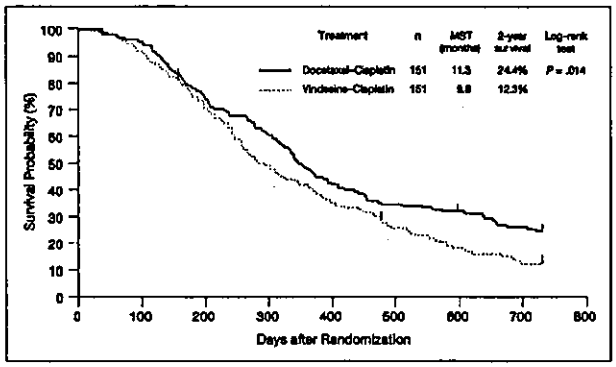

Fig 2. Kaplan-Meier survival estimates for patients treated with docetaxel plus cisplatin and patients treated with vindesine plus cisplatin. MST, median survival time.

Table 4. Grade 3 or 4 Hematologic Toxicities

Toxicity (grade)	Treatment Group: DC (n = 151) No. of Patients	%	VdsC (n = 151) No. of Patients	%	P
Anemia					< .01
3	15	10	34	23	
4	0		0		
Thrombocytopenia					
3	1	1	0	0	
4	0		0		
Leukopenia					< .01
3	66	46	92	68	
4	3		10		
Neutropenia					
3	59	74	41	77	
4	53		76		

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.

Table 6. Poststudy Treatment

Therapy	Treatment Group (% of patients): DC (n = 151)	VdsC (n = 151)
Chemotherapy	52	46
Platinum	29	23
Gemcitabine	26	19
Vinorelbine	15	15
Irinotecan	9	7
Paclitaxel	8	11
Gefitinib	3	1
Other	11	12
Docetaxel	23	5
Vindesine	0	7
Radiation	51	48
Surgery	2	2

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.

Grade 3 and 4 nonhematologic toxicities are listed in Table 5. The incidences of the majority of grade 3 or 4 nonhematologic toxicities were similar in both arms, with no significant differences between treatments. However, the incidences of grade 3 or 4 nausea and vomiting, anorexia, and diarrhea were significantly more frequent in the DC arm compared with the VdsC arm ($P < .05$, $P < .01$, and $P < .01$, respectively). There were two deaths in the DC arm that probably were related to treatment. One patient had acute myocardial infarction and died on day 2 of the first cycle of treatment; the second patient had obstructive pneumonia in the same lobe as the primary tumor and died on day 25 of the first course of therapy.

Table 5. Grade 3 or 4 Nonhematologic Toxicities*

Toxicity (grade)	Treatment Group: DC (n = 151) No. of Patients	%	VdsC (n = 151) No. of Patients	%	P
Nausea and vomiting					< .05
3	13	9	7	5	
4	0		0		
Anorexia					< .01
3	30	21	14	9	
4	1		0		
Diarrhea					< .01
3	6	9	2	1	
4	8		0		
Malaise					
3	6	4	3	3	
4	0		1		
Dysrhythmia					
3	3	2	2	1	
4	0		0		
AST elevation					
3	0		3	2	
4	0		0		
ALT elevation					
3	2	1	4	3	
4	0		0		
Bilirubin					
3	3	2	3	2	
4	0		0		

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.
*Occurring in ≥ 2% patients in at least one arm.

Poststudy Treatment

A total of 52% of patients receiving DC and 46% of patients receiving VdsC also received second-line chemotherapy. The agents used as second-line therapy in both arms were similar without usage of docetaxel and vindesine. Although cross-over treatments were considered to be protocol deviations, 5% of patients receiving first-line vindesine received second-line docetaxel, and these patients were included in survival analyses. Palliative radiotherapy was used in 51% of patients in the DC arm and 48% of patients in the VdsC arm (Table 6).

QoL

QoL questionnaires were completed at baseline, before the second and third treatment cycles, and 3 months after the last cycle of treatment by 82.1%, 83.1%, 76.6%, and 54.9% of patients in the DC arm (n = 151) and 82.8%, 89.6%, 61.6%, and 55.4% of patients in the VdsC arm (n = 151), respectively. Least squares mean scale values for the functional, physical, and mental domains tended to improve among patients receiving DC, but the difference only achieved statistical significance for the functional (nonphysical) domain ($P = .02$; Fig 3). A separate, more detailed analysis of QoL data currently is ongoing.

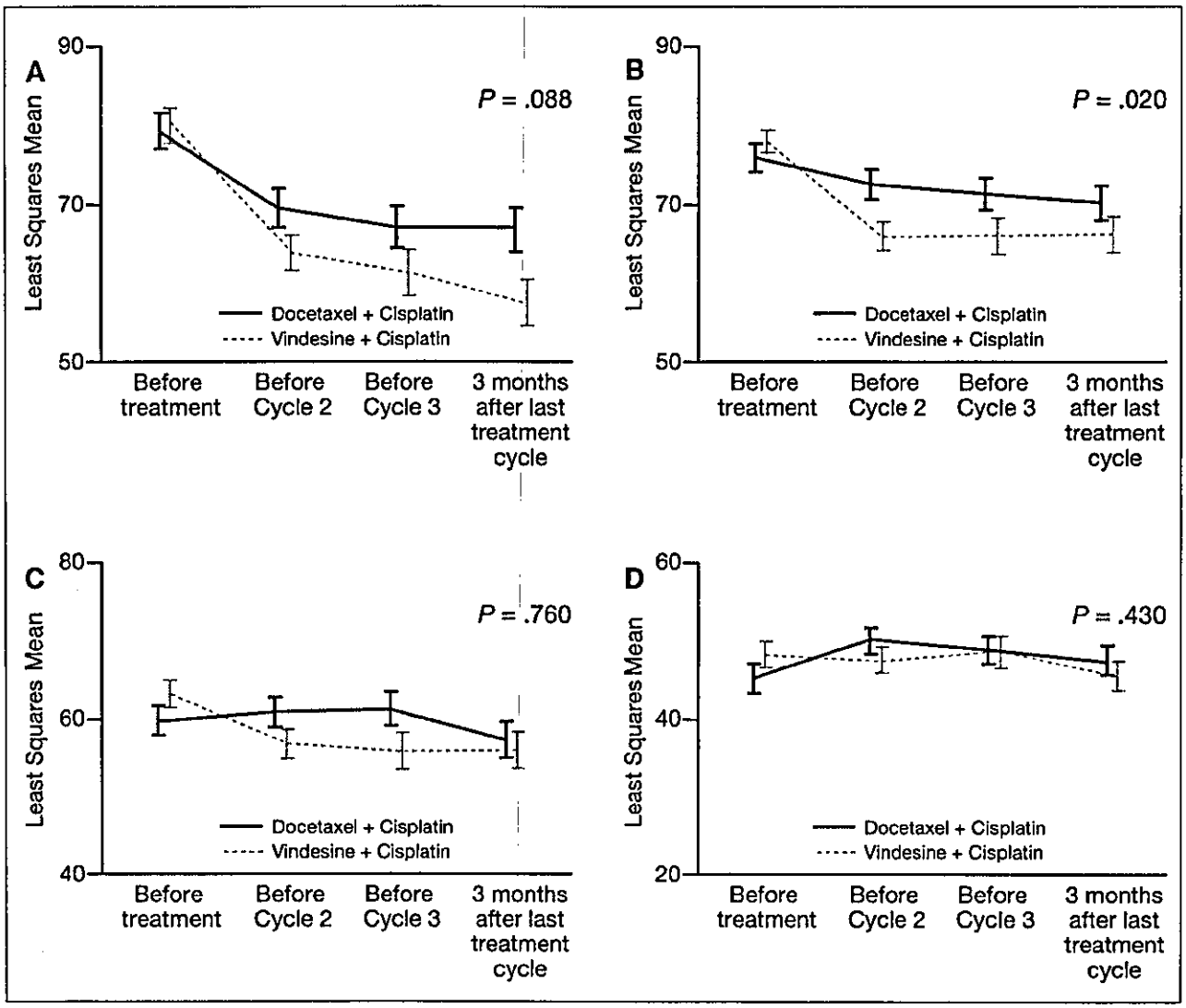

Fig 3. Quality-of-life assessments across four domains of the Quality of Life Questionnaire for Cancer Patients Treated with Anticancer Drugs instrument, among patients treated with docetaxel plus cisplatin and vindesine plus cisplatin. (A) Functional; (B) physical; (C) mental; and (D) psychosocial. Vertical bars represent least square means ± SE. Higher score indicates better quality of life.

DISCUSSION

Platinum-based combination chemotherapy is the treatment of choice for stage IV NSCLC patients with good performance status. The Big Lung Trial recently conducted in England confirmed the survival advantage of platinum-based combination chemotherapy in this setting [30]. The results of the present multicenter randomized trial reveal a significant survival advantage for DC when compared with VdsC in the treatment of patients with stage IV NSCLC. It is noteworthy that the 2-year survival rate in the DC arm was 24.3%—double that observed in the control arm. This is comparable to results for patients with stage III NSCLC who were treated with sequential chemoradiotherapy [4].

VdsC was chosen as the control arm because this regimen showed significant survival advantage over BSC in a Canadian trial [31]. In addition, this combination has long been the standard regimen for advanced NSCLC [22,31,32]. For instance, two randomized trials conducted in Japan, which compared the more recently developed agent irinotecan plus cisplatin with VdsC, failed to show an overall survival advantage for the irinotecan-containing regimen in advanced NSCLC [33,34]. In the European study, 612 patients were randomly assigned to receive vinorelbine plus cisplatin, vindesine plus cisplatin, or vinorelbine alone. In this study, the unadjusted log-rank test comparing the survival of patients who received vinorelbine plus cisplatin versus VdsC yielded a *P* value of .085 in favor of vinorelbine

plus cisplatin. Patients with both stage III and local recurrence (41%), or metastatic NSCLC (59%) were included, and nearly half of the patients received thoracic irradiation after chemotherapy [22]. The treatment strategy of locally advanced NSCLC is different from that of metastatic disease. Thus, the advantage of vinorelbine plus cisplatin over VdsC in patients with stage IV NSCLC has not been clearly defined.

Despite undergoing more treatment cycles, fewer patients on the DC arm experienced severe hematologic toxicities (including anemia and leukopenia) than patients treated with VdsC. Although diarrhea, nausea and vomiting, and anorexia were more frequently observed in the DC arm, such toxicities were easily managed with standard care.

DC has been evaluated in other phase III trials. In the ECOG trial, 1,207 patients were randomly assigned to paclitaxel plus cisplatin, gemcitabine plus cisplatin, docetaxel plus cisplatin, or paclitaxel plus carboplatin [35]. The response rate and median survival were similar among the four regimens for eligible patients at 19% and 7.9 months, respectively. In a large international trial (TAX-326), 1,218 chemotherapy-naive patients were randomly assigned to docetaxel plus cisplatin, docetaxel plus carboplatin, or vinorelbine plus cisplatin [36]. The DC arm favored a longer median survival time compared with the vinorelbine plus cisplatin arm (11.3 *v* 10.1 months) and response (31.6% *v* 24.5%). Although we must be careful when making retrospective comparisons, both survival figures and response data of the present study and TAX-326 were virtually identical and were better than those of the ECOG trial [35]. It is suggested that patients with more favorable prognostic factors entered in TAX-326 and the current study.

More recently, attention has focused on improving QoL as a goal of therapy for patients with advanced NSCLC [37]. One trial of docetaxel as second-line therapy versus BSC showed that chemotherapy resulted in significantly better control of pain and fatigue than did BSC [20]. In a similar comparative phase III trial, docetaxel, administered as first-line in chemotherapy-naive patients, was significantly better than BSC in controlling not only pain but also dyspnea and emotional functioning [19]. In the present study, QoL measures demonstrated that the physical domain was significantly better in the DC arm over the VdsC arm ($P = .020$). This finding of a QoL benefit with a docetaxel plus platinum combination is also supported by the results of TAX-326 [38]. This investigation indicated that patients in receipt of a docetaxel plus platinum combination reported greater global QoL benefit in terms of patient pain or less Karnofsky performance status deterioration than patients receiving vinorelbine plus cisplatin when the EuroQol and Lung Cancer Symptom Scale instruments were used [39,40].

In this study, we used 60 mg/m^2 of docetaxel on the basis of the phase II study conducted in Japan [26]. The dose of docetaxel is lower than the doses used in ECOG1594 and TAX-326 (docetaxel and cisplatin 75 mg/m^2) [35,36]. In a randomized trial comparing docetaxel alone with BSC in patients previously treated with platinum-based chemotherapy, docetaxel 100 mg/m^2 was not tolerated but docetaxel 75 mg/m^2 demonstrated significant survival benefit [20]. Therapeutic index was also better for the lower dose of docetaxel in another randomized trial of second-line chemotherapy, which compared 100 or 75 mg/m^2 of docetaxel against a control regimen of vinorelbine or ifosfamide [21]. The docetaxel dose of 60 mg/m^2 might be optimal when it is combined with a standard dose of cisplatin. Additional study is warranted regarding this dose issue.

In summary, this randomized phase III trial demonstrates that DC is superior, in terms of response rate and survival, to VdsC in the treatment of previously untreated patients with stage IV NSCLC. A doubling in the 2-year survival rate is reported for DC compared with the classic standard regimen. Given the results of this trial, DC should be considered as a standard regimen for the first-line treatment of stage IV NSCLC, and it is suggested that the classic combination regimen should no longer be regarded as a suitable control arm in future randomized studies of patients with stage IV NSCLC.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Performed contract work within the last 2 years: Kaoru Kubota, Aventis Pharma Ltd; Koshiro Watanabe, Aventis Pharma Ltd; Hideo Kunitoh, Aventis Pharma Ltd; Kazumasa Noda, Aventis Pharma Ltd; Yukito Ichinose, Aventis Pharma Ltd; Nobuyuki Katakami, Aventis Pharma Ltd; Takahiko Sugiura, Aventis Pharma Ltd; Masaaki Kawahara, Aventis Pharma Ltd; Akira Yokoyama, Aventis Pharma Ltd; Soichiro Yokota, Aventis Pharma Ltd; Shuichi Yoneda, Aventis Pharma Ltd; Kaoru Matsui, Aventis Pharma Ltd; Shinzo Kudo, Aventis Pharma Ltd; Masahiko Shibuya, Aventis Pharma Ltd; Takeshi Isobe, Aventis Pharma Ltd; Yoshihiko Segawa, Aventis Pharma Ltd; Yutaka Nishiwaki, Aventis Pharma Ltd; Yasuo Ohashi, Aventis Pharma Ltd; Hisanobu Niitani, Aventis Pharma Ltd.

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Prognostic value of visceral pleural invasion in resected non–small cell lung cancer diagnosed by using a jet stream of saline solution

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Front row, left to right: Asoh, Nakamura, Ichinose, Ikeda, Inoue, Oshima, Nishida; *back row, left to right:* Watanabe, Maruyama, Miyamoto, Shoji, Okamoto

Objective: Visceral pleural invasion caused by non–small cell lung cancer is a factor in the poor prognosis of patients with that disease. We investigated the relationship between the diagnosis of visceral pleural invasion by using a jet stream of saline solution, which was previously reported as a new cytologic method to more accurately detect the presence of visceral pleural invasion, and prognosis.

Methods: From January 1992 through December 1998, 143 consecutive patients with peripheral non–small cell lung cancer that appeared to reach the visceral pleura underwent a surgical resection at the Department of Thoracic Oncology, National Kyushu Cancer Center. The surface of the visceral pleura in patients undergoing lung cancer resection was irrigated with a jet stream of saline solution. The diagnosis of visceral pleural invasion was determined by means of either a pathologic examination or by means of a jet stream of saline solution. In addition, a cytologic examination of the pleural lavage fluid obtained immediately after a thoracotomy was evaluated.

Results: Forty-nine (34%) resected tumors were identified as having visceral pleural invasion. The diagnosis of visceral pleural invasion in 31, 6, and 12 patients was determined by using a jet stream of saline solution alone, pathologic examination alone, or both, respectively. The visceral pleural invasion and positive findings of intrapleural lavage cytology were linked. Although there was no significant difference between the incidence of distant metastases in the patients with visceral pleural invasion and those without visceral pleural invasion, the incidence of local recurrence, especially regarding carcinomatous pleuritis (malignant pleural effusion, pleural dissemination, or both), in the patients with visceral pleural invasion was significantly higher than in those without visceral pleural invasion. The recurrence-free survival of patients with visceral pleural invasion was significantly shorter than that of patients without visceral pleural invasion ($P = .004$), even patients with stage I disease ($P = .02$). There was also a significant difference between the patients with or without visceral pleural invasion in the overall survival ($P = .02$). Visceral pleural invasion was independently associated with a poor recurrence-free survival on the basis of multivariate analyses ($P = .03$), as were sex ($P = .03$), age ($P = 002$), and the stage of the disease ($P < .0001$).

Conclusions: This study confirmed that the jet stream of saline solution method in addition to ordinary pathologic examination was useful for detecting visceral pleural invasion, which is considered to be one of the causes of local recurrence, especially in carcinomatous pleuritis.

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GTS

Visceral pleural invasion (VPI) is a factor in the poor prognosis of patients with non-small cell lung cancer (NSCLC).[1,2] The diagnosis of VPI is usually confirmed by means of a pathologic examination (PE) alone. PE is based on 1 or 2 cut slices of the resected tumor. Although PE can easily confirm VPI when the tumor is clearly visible on the visceral pleura, such cases are relatively rare. Therefore it remains unclear as to whether a tumor can be reliably considered to have no VPI on the basis of PE alone. To resolve this problem, we previously reported a simple method involving a cytologic examination of cells desquamated from the visceral pleura by using a jet stream of saline solution (JSS). This method is considered to be significantly more sensitive and accurate than ordinary PE in detecting VPI by lung cancer.[3]

We retrospectively investigated the relationship between a diagnosis of VPI in patients with resected NSCLC by using the JSS method and recurrent site and the prognosis.

Methods

Patients and Methods

From January 1992 through December 1998, 143 consecutive patients with peripheral NSCLC that appeared to reach the visceral pleura and that either did not adhere to or did not invade the surrounding tissue underwent a surgical resection at the Department of Thoracic Oncology, National Kyushu Cancer Center. This study included the 90 cases of a former report about JSS.[3] Any patients with diffuse pleural adhesions, distant metastases, and T4 disease were excluded. The patients consisted of 81 men and 62 women. The median age of the patients was 64 years, with a range of 24 to 90 years. A complete surgical resection consisted of a lobectomy (n = 132), bilobectomy (n = 5), pneumonectomy (n = 3), or segmentectomy (n = 3). The JSS method was performed as previously described.[3] Briefly, the surface of the visceral pleura in patients with resected lung cancer was irrigated twice with a jet stream of heparinized saline solution by using a 20-mL syringe with a 21-gauge needle immediately after performing a surgical resection. The distance between the tip of the needle and the pleural surface was kept at approximately 2 cm, and a total of 40 mL of saline solution containing cells desquamated from the visceral pleural surface was collected and then centrifuged at 1000 rpm for 10 minutes. Thereafter, the obtained sediment was stained by using the Giemsa and Papanicolaou method for cytologic examination. When it was necessary to distinguish cancer cells from reactive mesothelial cells, anticarcinoembryonic antigen staining, alcian blue staining, and periodic acid–Schiff reactions were performed. In addition, a cytologic examination of pleural lavage fluid obtained immediately after a thoracotomy was evaluated in all but 5 patients. The pathologic stage of the disease was based on the TNM classification of the Union Internationale Contre Cancer.[4] The pathologic stage of the tumors in this series was IA in 49 patients, IB in 46 patients, IIA in 3 patients, IIB in 14 patients, IIIA in 28 patients, and IIIB in 3 patients. The histologic analysis of the tumor was based on the World Health Organization classification for cell types.[5] One hundred sixteen patients had adenocarcinoma, 19 had squamous cell carcinoma, 6 had adenosquamous cell carcinoma, and 2 had large cell carcinoma. After the operation, the patients were re-examined once every 3 months for 5 years and thereafter at 6-month intervals. The evaluations included a physical examination and chest roentgenography at each visit and computed tomography of the chest, magnetic resonance imaging of the brain, and a bone scan every year.

TABLE 1. Rate of positive findings of VPI classified by means of JSS, PE, or either method according to the tumor stage

Pathologic stage	No. of positive findings: JSS	No. of positive findings: PE	Total no. of positive findings
IA (n = 49)	11 (22%)	—	11 (22%)
IB (n = 46)	17 (37%)	9 (20%)	21 (46%)
II (n = 17)	3 (18%)	3 (18%)	4 (24%)
III (n = 31)	12 (39%)	6 (19%)	13 (42%)
Total (n = 143)	43 (30%)	18 (13%)	49 (34%)

VPI, Visceral pleural invasion; *JSS,* jet stream of saline solution; *PE,* pathologic examination.

TABLE 2. Rate of positive findings of VPI classified by means of JSS, PE, or either method according to N status

N status	No. of positive findings: JSS	No. of positive findings: PE	Total no. of positive findings
n0 (n = 95)	28 (29%)	9 (9%)	32 (34%)
n1 (n = 17)	3 (18%)	3 (18%)	4 (24%)
n2 or more (n = 31)	12 (39%)	6 (19%)	13 (42%)

VPI, Visceral pleural invasion; *JSS,* jet stream of saline solution; *PE,* pathologic examination.

TABLE 3. Relationship between pleural lavage cytologic findings and VPI as diagnosed with either diagnostic method

Cytologic findings on intrapleural lavage	VPI: Present	VPI: Absent
Positive (n = 13)	13	0
Negative (n = 125)	33	92

VPI, Visceral pleural invasion.

Statistical Analysis

Statistical analyses were performed by using either χ^2 analysis or the Fisher exact test for various clinicopathologic factors. The duration of the recurrence-free survival was calculated from the date of operation until either the first evidence of recurrence or death of any cause. Survival was calculated from the date of operation until death of any cause or the date of the last follow-up (censored). The recurrence-free interval and survival curves were determined by using the Kaplan-Meier method, and differences in