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Received December 2, 2004
Accepted April 7, 2005

Advanced Age Is Not Correlated With Either Short-term or Long-term Postoperative Results in Lung Cancer Patients In Good Clinical Condition*

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Objectives: **Several investigators have reported that operative mortality in the elderly is acceptable. However, their patients are potentially biased with regard to some factors such as performance status (PS) and comorbidity. In this study, we discuss surgical indications for the elderly and effects on perioperative mortality and prognosis.**

Study design: **A retrospective study was carried out by reviewing the records of 1,114 patients who were referred for treatment of non-small cell lung cancer between January 1993 and December 2002. The patients were classified into younger (≤ 75 years of age) and elderly (≥ 76 years of age) groups. The histologic subtype, TNM stage, Eastern Cooperative Oncology Group PS, and treatment were reviewed for members of each group, and the proportion of patients who underwent surgery was compared between the two groups. The surgical procedures, perioperative mortality, and prognosis of the two groups were also compared.**

Results: **There was a significant difference in the histologic distribution with no difference in TNM staging between the two groups. Regarding treatment, 51.0% of those in the younger group and 36.1% of those in the elderly group underwent surgery. The proportion of elderly patients who underwent surgery was significantly lower than that of the younger patients, mainly due to worse PS and comorbidity in the elderly patients. The perioperative mortality rates for the younger and elderly groups were 0.9% and 4.1%, respectively, with no significant difference, and the overall survival was similar between the two groups.**

Conclusions: **When compared to younger patients, fewer elderly patients underwent surgery because of worse PS and comorbidity. However, in elderly patients with good PS and no comorbidity, the rate of perioperative mortality and the prognosis were similar to those in the younger patients. Therefore, advanced age only is not a negative factor for surgery in elderly patients.** ***(CHEST 2005; 128:1557–1563)***

Key words: elderly; limited resection; lobectomy; mortality; non-small cell lung cancer; performance status; prognosis

Abbreviations: ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; PS = performance status

Lung cancer is one of the most common forms of neoplasms and the leading cause of cancer-related death in Western countries as well as in Japan.[1] The peak incidence age was in the sixties in 1987 but shifted to the seventies in 2001 in Japan.[2] In addition, there is a general trend worldwide of an increasing incidence of lung cancer of the elderly.

The treatment of choice in patients with stages I, II, and some subsets of stage IIIA cancer is surgery, but this carries with it certain risks. Generally, the surgical risk becomes higher with age, since elderly patients usually have several types of comorbidities

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Manuscript received January 18, 2005; revision accepted March 23, 2005.

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and poor performance status (PS), although the perioperative mortality rate is similar between younger and elderly patients.[3–5] The patients reported in previous studies[6–7] were potentially selected in terms of PS and comorbidity, and surgery was performed only in those in good clinical condition.

Another issue to consider is the life span of the elderly, which is naturally shorter than that of younger patients. Lobectomy is now a standard surgical procedure for patients with lung cancer. However, the perioperative mortality rate associated with this procedure is approximately 1%. Lobectomy including bilobectomy is more invasive than limited resection such as segmentectomy and partial resection. When considering the perioperative risks and benefits of surgery, lobectomy might be less beneficial for the elderly compared to the young. To determine if this is true, we reviewed 1,114 non-small cell lung cancer (NSCLC) patients at a single institute and classified them into two groups by using the age of 75 years as an upper and lower cutoff. Differences were then examined for the selected surgical procedures between the young and elderly patients, with special interest paid to the conditions of the elderly patients when determining the surgical modality. We also evaluated the relationships between surgical procedures such as lobectomy or limited resection and the short-term and long-term results in the elderly group to discuss the optimal surgical procedure for these patients.

Materials and Methods

A retrospective study was carried out using the lung cancer database of the Shikoku Cancer Center on 1,114 patients with NSCLC who were treated between January 1993 and December 2002. Information regarding the Eastern Cooperative Oncology Group (ECOG) PS, histologic subtype, TNM stage, and treatment, including chemotherapy, radiotherapy, and surgical procedures, was carefully reviewed. The perioperative mortality rate and long-term results were also reviewed if surgery was carried out. TNM stage was determined according to the International Union Against Cancer classification.[8]

Our treatment diagram is shown in Figure 1. Chemotherapy and/or radiotherapy were performed in patients with nonresectable stage IIIA, IIIB, and IV cancer; patients with stage I, II, or resectable IIIA or IIIB were candidates for surgery. Preoperative examinations including spirometry, ECG, and arterial blood gas analysis were carried out, and more detail examinations including diffusion capacity of the lung for carbon monoxide, ultrasound cardiography, and a 6-min walking test were added if necessary. Lobectomy, bilobectomy, or pneumonectomy were indicated if a patient had a predicted FEV_1 of $\geq$ 0.8 L, a PS of 0 or 1, and no or slight comorbidity. For a predicted FEV_1 of $<$ 0.8 L and/or moderate comorbidity, limited resection was considered. Surgical resection was not indicated for patients with PS 3 or severe comorbidity. Hilar and mediastinal lymphoadenectomy were performed in case more than segmentectomy was required.

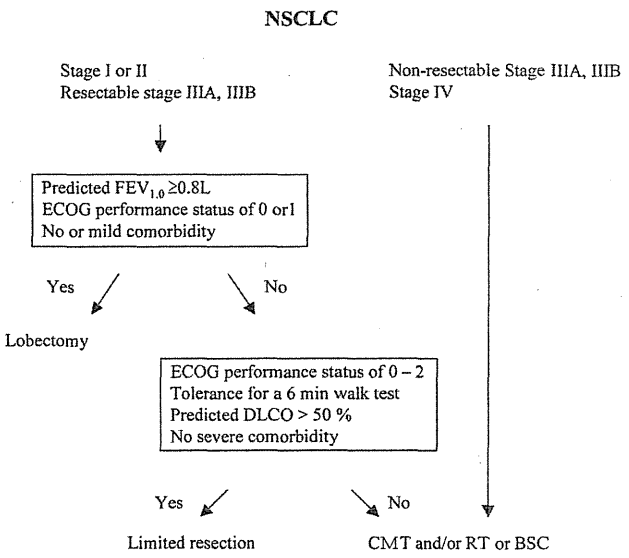

FIGURE 1. Flow chart of treatments. DLCO = diffusion capacity of the lung for carbon monoxide; CMT = chemotherapy; RT = radiotherapy; BSC = best supportive care.

Data Analysis

The differences in the proportions of histologic subtypes, TNM stage, PS, pulmonary function status, treatment, surgical procedure, and perioperative mortality rate were compared using the χ^2 method between the younger ($\leq$ 75 years of age) and elderly ($\geq$ 76 years of age) groups. The surgical procedures were classified into three groups: limited resection, lobectomy, and pneumonectomy. Segmentectomy and partial resection were classified as limited resection. Lobectomy and bilobectomy were classified as lobectomy. Death within 30 days postoperatively was considered to be perioperative death. In this study, prognostic data were analyzed only in patients who underwent limited resection and lobectomy, since the number of pneumonectomies was small. The overall survival and disease-specific survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. For disease-specific survival analysis, patients who died of any cause other than lung cancer were censored at the time of death. As subset analysis, in the elderly, the overall survival and disease-specific survival rates were compared in terms of the surgical procedures (lobectomy vs limited resection). In addition, the overall and disease-specific survival rates of the elderly treated by lobectomy were also compared to those of the younger patients treated in the same manner. A p value $<$ 0.05 was considered significant. Statistical analysis was performed using statistical software (Version 13; SPSS; Chicago, IL).

Results

Demographics and Clinical Presentation

Patient characteristics are shown in Table 1. The younger and elderly groups consisted of 917 patients (82.3%) and 197 patients (17.7%), respectively, and there was no difference in the male/female ratio between the two groups. Histologic examination revealed that adenocarcinoma was predominant in

Table 1—*Patient Demographics and Clinical Data

Variables	Younger Group (≤ 75 yr old)	Elderly Group (≥ 76 yr old)	p Value
Patients.	917 (82.3)	197 (17.7)	0.123
Gender			
Male	604 (65.9)	141 (71.6)	
Female	313 (34.1)	56 (28.4)	
Histology			< 0.001
Adenocarcinoma	620 (67.6)	94 (47.7)	
Squamous cell carcinoma	213 (23.2)	87 (44.2)	
Large cell carcinoma	37 (4.0)	3 (1.5)	
Others	47 (5.2)	13 (6.6)	
Final stage			0.225
I	358 (39.0)	62 (31.5)	
II	64 (7.0)	19 (9.6)	
IIIA	117 (12.8)	24 (12.2)	
IIIB	146 (15.9)	39 (19.8)	
IV	228 (24.9)	52 (26.4)	
Unknown	4 (0.4)	1 (0.5)	
ECOG performance status			< 0.001
0	485 (52.9)	73 (37.1)	
1	304 (33.1)	83 (42.1)	
2	50 (5.5)	17 (8.6)	
3	26 (2.8)	9 (4.6)	
4	17 (1.9)	9 (4.6)	
Unknown	35 (3.8)	6 (3.0)	
Smoking (Brinkman index)			0.007
None	231 (25.2)	30 (15.2)	
< 399	159 (17.3)	33 (16.8)	
> 400	522 (56.9)	133 (67.5)	
Unknown, No.	5	1	
Pulmonary function			
Vital capacity < 70%, % of patients	24.0	34.9	0.005
FEV_1 < 80 %, % of patients	18.1	37.5	0.225
Arterial blood gas, % of patients			
PaO_2 < 70 mm Hg	20.1	34.2	0.001
$PaCO_2$ > 50 mm Hg	2.2	3.9	0.227
Treatment			< 0.001
Surgery	468 (51.0)	66 (36.1)	
Nonsurgical	449 (49.0)	131 (63.9)	
Chemotherapy	197 (43.9)	26 (19.8)	
Radiotherapy	60 (13.4)	56 (42.7)	
Chemotherapy and radiotherapy	91 (20.3)	0 (0)	
Best supportive care	101 (22.4)	48 (37.5)	

*Data are presented as No. (%) unless otherwise indicated.

both groups. However, the incidence of adenocarcinoma in the younger patients (67.6%) was significantly higher than that in the elderly patients (47.7%). In contrast, the incidence of squamous cell carcinoma in the elderly patients (44.2%) was higher than that in the younger patients (23.2%). There was no difference in the distribution of the TNM stages between the two groups ($p = 0.225$), and the PS of the elderly patients was significantly worse than that of the younger patients ($p < 0.001$). In addition, the proportion of elderly smokers was significantly higher than that of younger smokers ($p = 0.007$). Concerning respiratory function, the percentages of patients with vital capacity < 70% and PaO_2 < 70 mm Hg in the elderly patients were significantly greater than those in the younger patients ($p = 0.005$ and $p = 0.001$, respectively).

Five hundred thirty-four of the 1,114 patients underwent surgery, and the percentage of younger patients who underwent surgery (51.0%) was significantly higher than the percentage of the elderly patients (36.1%) [$p < 0.001$]. Surgical procedures are shown in Table 2. Limited resection, including partial resection and segmentectomy, was performed in 86 younger patients (18.4%) and in 18 elderly patients (24.3%), while lobectomy was performed in 369 younger patients (78.8%) and in 55 elderly patients (74.3%). There was no significant difference in the selection of surgical procedures.

Table 2— *Surgical Procedures and Perioperative Mortality*

Variables	Younger Group (n = 468)	Elderly Group (n = 74)	p Value
Surgery (n = 534)			0.412
Limited resection	86 (18.4)	18 (24.3)	
Partial	66	12	
Segmental	20	6	
Lobectomy	369 (78.8)	55 (74.3)	
Lobectomy	357	52	
Bilobectomy	12	3	
Pneumonectomy	13 (2.8)	1 (1.4)	
Perioperative death (n = 7)	4 (0.9)	3 (4.1)	0.087
Limited resection	0	0	
Lobectomy	4	3	0.071
Pneumonectomy	0	0	

*Data are presented as No. (%) or No.

Four patients (0.9%) in the younger group and three patients (4.1%) in the elderly group died perioperatively, and there was a trend toward a higher perioperative mortality rate in the elderly group than in the younger group, although there was no significant difference (p = 0.087) [Table 2]. The background and cause of death of these seven patients are shown in Table 3. Causes of death were pulmonary embolism (n = 2), pneumonia (n = 1), and respiratory failure (n = 4), all associated with lobectomy.

The median follow-up interval was 30 months (range, 0 to 123 months). The overall and disease-specific survival curves are shown in Figure 2. There was a trend toward an inferior overall survival rate in the elderly group compared to the younger group, but this difference was not statistically significant (p = 0.193). In addition, there was no difference between the younger and elderly groups in disease-specific survival (p = 0.892). Lobectomy and limited resection in the elderly patients were compared with respect of the rates of overall survival and disease-specific death (Fig 3). In elderly patients, there were

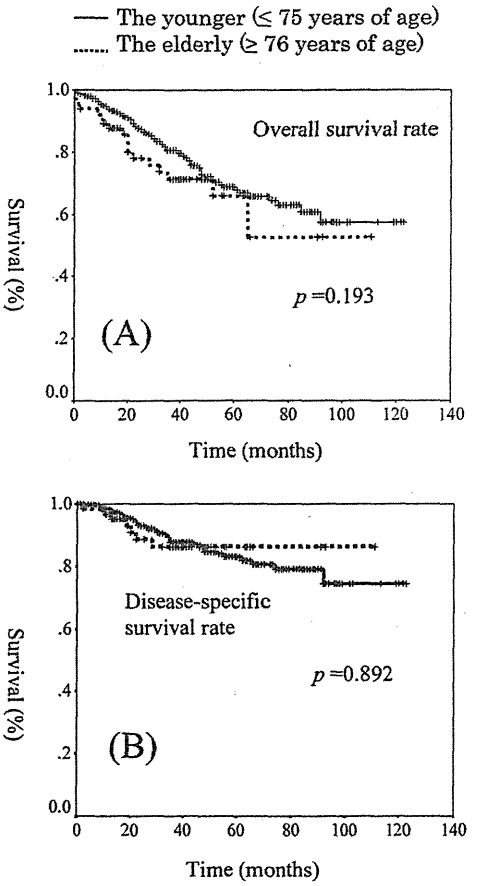

FIGURE 2. Overall survival (*top*, *A*) and disease-specific survival (*bottom*, *B*) for the younger and elderly groups.

no differences in both overall survival and disease-specific survival rates between the different surgical procedures. However, in the overall survival rate, during the early period after surgery, the elderly patients who underwent lobectomy had an associated inferior survival rate compared to those who underwent limited resection (Fig 3, *top*, *A*). Lobectomy between the younger and elderly groups was compared using the overall survival and disease-

Table 3—*Characteristics of the Seven Patients Who Died Perioperatively*

Age, yr	Gender	Comorbidity	Brickman Index	Surgical Procedure	Cause of Death
40	Female	None	None	Lobectomy	Pulmonary embolism
70	Female	Breast cancer	None	Lobectomy and partial lobectomy	Pulmonary embolism
72	Male	Hypertension, diabetes mellitus, tuberculosis, interstitial pneumonitis	1,000, active smoker	Lobectomy and partial lobectomy	ARDS
75	Male	Brain infarction, renal cell carcinoma	1,100, active smoker	Lobectomy	Interstitial pneumonitis
79	Male	Old myocardial infarction	1,060	Bilobectomy	Interstitial pneumonitis
79	Male	None	1,100	Lobectomy	Pneumonia
84	Male	Interstitial pneumonitis	800	Lobectomy	Interstitial pneumonitis

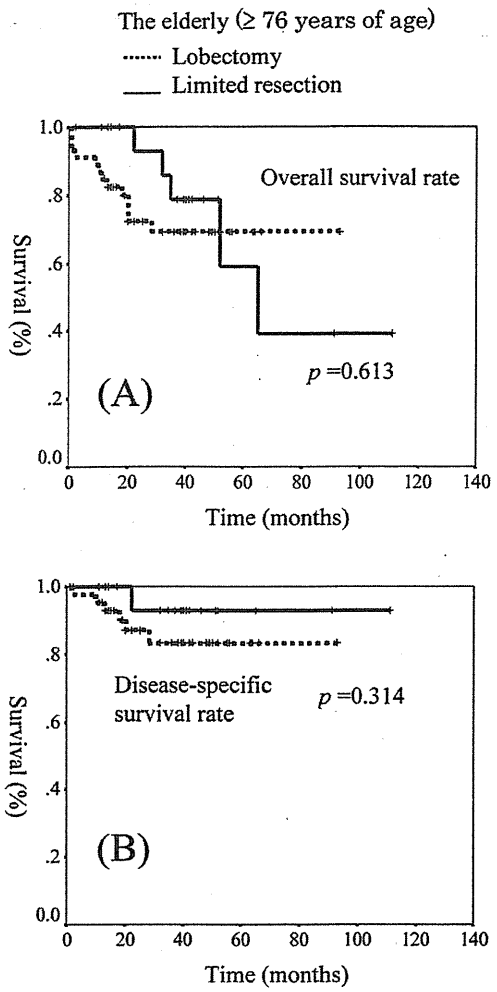

FIGURE 3. Overall survival (*top*, A) and disease-specific survival (*bottom*, *B*) for elderly patients according to the extent of surgery.

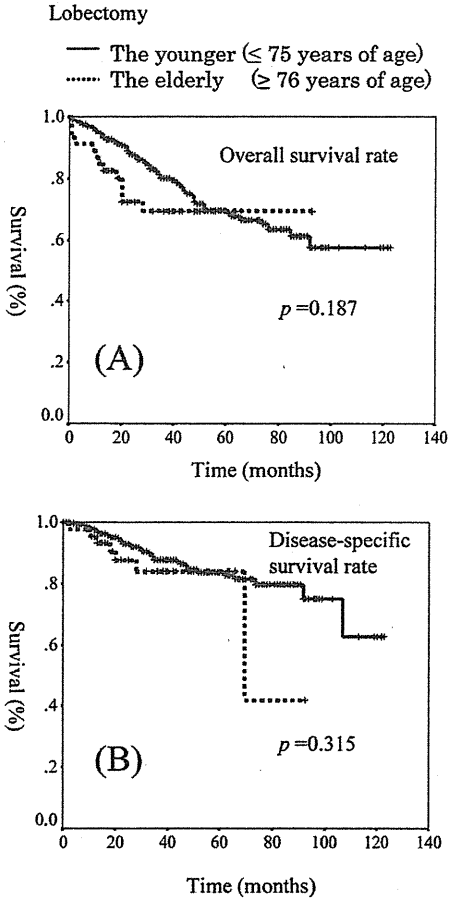

FIGURE 4. Overall survival (*top*, *A*) and disease-specific survival (*bottom*, *B*) after lobectomy for the younger and elderly groups.

specific survival rates (Fig 4), and there were no significant differences found. However, in the overall survival rate, during the early period after surgery, the elderly patients had an associated inferior survival rate compared to the younger patients.

DISCUSSION

The world population is aging, and the proportion of elderly patients with lung cancer is increasing. In this study, we found that elderly patients had worse PS and greater comorbidity than the younger patients, but the same surgical procedure can be performed and similar outcomes can be expected with respect to perioperative mortality and long-term results as long as patients who are > 75 years old have good PS and no or slight comorbidity.

In this study, we considered patients > 76 years old as elderly, but there is no clear definition for this distinction. In most of the literature, the age of 70 years is considered to be the cutoff.[9–12] In our data, 66% of patients would have been classified into the younger group and 34% would have been classified into the elderly group if the age of 70 years was used as the cutoff. We considered that it would have been difficult to clarify the differences between the younger and elderly groups with such a group balance. Therefore, in this study we classified the groups using the age of 75 years as the cutoff in order to emphasize the condition of highly aged patients.

Adenocarcinoma was the dominant histologic type of cancer found in both groups. The incidence of adenocarcinoma in the elderly patients was significantly lower than in the younger patients, but the incidence of squamous cell carcinoma was significantly higher, and this trend was also reported in other studies.[13–15] In our study, the percentage of smokers in the elderly group was significantly higher than in the younger group, and this might have had some influence on the higher percentage of cases of squamous cell carcinoma in the elderly group.

There was no difference in the TNM staging

between the groups, although several previous studies[16–21] showed that elderly patients more often have earlier stages, likely due to the slow progress of lung cancer in the elderly, and the tendency of younger patients to ignore or misinterpret nonspecific changes in their health. In contrast to these results, one study[11] conducted in Japan did not find a difference in the stage distribution, according to age. The method of lung cancer screening performed in Japan might affect the rate of early detection in the young and therefore led to no difference between the groups.

Several studies[22–25] noted that surgical mortality, morbidity, and long-term results in the elderly are acceptable. However, these were not randomized with respect to the patients, and there might have been bias. It is, therefore, not advisable to make generalizations regarding elderly patients. In our study, 51.0% of the younger patients underwent surgery compared to 33.5% of the elderly patients, although the two groups had the same TNM staging distribution. In addition, when looking at the nonsurgical treatments, the number of patients treated with chemotherapy and/or radiotherapy in the elderly patients was less than in patients < 75 years of age, suggesting that the elderly patients had greater comorbidity and worse PS than the younger patients, and that not only surgery but chemotherapy and radiotherapy were not indicated.

Table 4 lists the patients who were > 76 years old and candidates for surgery indicated by their TNM stage but who eventually did not undergo surgery. Factors considered were a poor PS in 5 patients and poor pulmonary function in 13 patients. The remaining 11 patients had moderate comorbidity and a PS of approximately 1 to 2, and were > 81 years old. Surgery could have been safely performed, but when considering their age, PS, comorbidity, and disease status together, we decided to treat them with radiotherapy instead.

A potential criticism of this study is the histologic distribution that was observed: the incidence of adenocarcinoma in younger patients was greater than that in the elderly patients. This could have had an impact on survival that favored the elderly because adenocarcinoma generally has worse prognosis than squamous cell carcinoma. Survival rates by histologic subtype are shown in Figure 5. Adenocarcinoma showed a better prognosis than squamous cell carcinoma. Therefore, we considered histologic distribution did not impact survival in favor of the elderly in this study at least.

The Kaplan-Meier curve for the overall survival rate in the elderly was inferior to that in the younger group, although this was not significant (Fig 2, *top*, *A*); and it was expected that the overall survival of the elderly was inferior to that of the younger, because of their advanced age. However, the Kaplan-Meier curves for disease-specific death were almost identical (Fig 2, *bottom*, *B*), suggesting that more elderly patients died of causes other than lung cancer and that other forms of disease had more influence on their prognosis compared with the younger patients.

The Lung Cancer Study Group[26] reported in 1995 that limited pulmonary resection does not result in improved perioperative morbidity, mortality, or late postoperative pulmonary function compared with lobectomy. In our study, there was no significant difference, but the early overall survival rate for lobectomy in the elderly was inferior to that for limited resection (Fig 3, *top*, *A*). In addition, 3 of 55 elderly patients (5.5%) but only 4 of 369 younger patients (1.1%) died perioperatively after lobectomy. There was a tendency for perioperative mortality after lobectomy in the elderly patients to be higher than that in the younger patients (p = 0.071) [Table

Table 4—*Factors Not Indicated for Surgery Among the Elderly With Stage I or II Cancer*

Factors	Patients, No.
PS ≥ 2	5
Poor pulmonary function	13
Others	11
Total	23

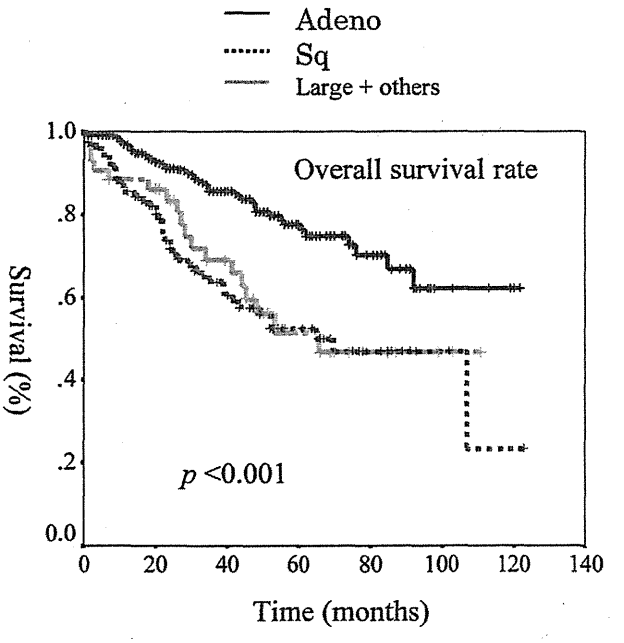

FIGURE 5. Overall survival according to histologic subtype. Adeno = adenocarcinoma; Sq = squamous cell carcinoma; Large = large cell carcinoma.

2]. Although the number of patients was not large and the study was not randomized, lobectomy including bilobectomy might have been too invasive; in some cases, limited resection may therefore have been preferable for those > 76 years old.

In our study, the elderly patients with a good PS and no or slight comorbidities could tolerate surgery and be expected to have a long-term survival rate similar to that of younger patients. However, when considering the drop in survival rate during the early survival period after lobectomy compared to limited resection, it is reasonable to consider limited resection as an alternative surgical management for the elderly.

Conclusions

There was a difference in the histologic distribution with regard to NSCLC between younger and elderly patients. The proportion of patients treated surgically was less than that in the younger patients due to severe comorbidity and poor PS, although the TNM staging distribution was similar between the groups. However, in elderly patients with a good PS and no or slight comorbidity, surgery was safely performed and long-term results were similar to those in the younger patients. Finally, we suggest that lobectomy including bilobectomy might be too invasive and that limited resection might be more beneficial for patients of advanced age.

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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-

Received 1/23/04; revised 3/7/04; accepted 3/24/04.
Grant support: Supported by Taiho Pharmaceutical Co., Ltd., Tokyo, Japan.
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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.

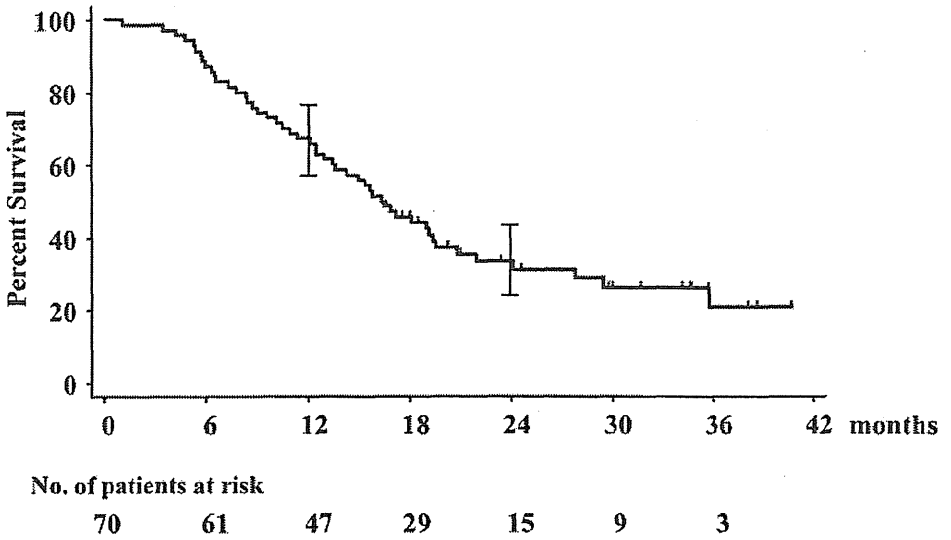

Fig. 1 Survival. Each tick mark represents a patient who is alive. The *bars* represent the 95% confidence interval of the survival rate at 1 and 2 years after treatment.

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

ACKNOWLEDGMENTS

We thank Brian Quinn and Dr. Hideki Hirata for critical review and Yumiko Oshima for help in preparing the manuscript.

APPENDIX

The following principal investigators and institutions also participated in this study: Yoshinobu Ohsaki, M.D., First Department of Internal Medicine, Asahikawa Medical College, Hokkaido; Saburo Sone, M.D., Ph.D., Third Department of Internal Medicine, The University of Tokushima School of Medicine, Tokushima; Ushijima Sunao, M.D., Department of Pulmonology, Kumamoto Chuou Hospital, Kumamoto; Hideki Yokoyama, M.D., Department of Chest Surgery, National Beppu Hospital, Oita; Tokujiro Yano, M.D., Department of Thoracic Surgery, Nakatsu Municipal Hospital, Oita; and Hiroo Nishijima, M.D., Department of Surgery, Kagoshima Kouseiren Hospital, Kagoshima.

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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

Received 6/21/04; revised 8/5/04; accepted 8/18/04.
Grant support: Taiho Pharmaceutical Co., Ltd., Tokyo, Japan.
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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.

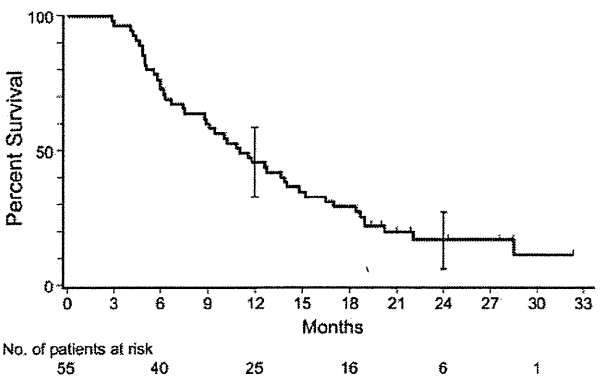

Fig. 1 Overall survival. Each *tick* represents a patient who is alive. The *bars* represent the 95% confidence interval of the survival rate at 1 year and 2 years after treatment.

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.

ACKNOWLEDGMENTS

We thank Brian Quinn for critical review and Yumiko Oshima for help in preparing the report.

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VOLUME 22 · NUMBER 2 · JANUARY 15 2004

JOURNAL OF CLINICAL ONCOLOGY 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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Submitted June 24, 2003; accepted November 7, 2003.

Supported by a grant from Aventis Pharma Ltd, Tokyo, Japan.

Previously presented in part at the Annual Meetings of the American Society of Clinical Oncology, San Francisco, CA, May 12-15, 2001, and Orlando, FL, May 18-21, 2002.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/04/2202-254/$20.00

DOI: 10.1200/JCO.2004.06.114

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.

J Clin Oncol 22:254-261. © 2004 by American Society of Clinical Oncology

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 $\geq$ 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 $\geq$ 4,000/μL and $\leq$ 12,000/μL, neutrophil count $\geq$ 2,000/μL, platelet count $\geq$ 10^5/μL, hemoglobin $\geq$ 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 $\geq$ 60 mL/min, serum bilirubin less than or equal to the ULN, serum ALT and AST $\leq 2 \times$ ULN, and $Pao_2 \geq 70$ 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

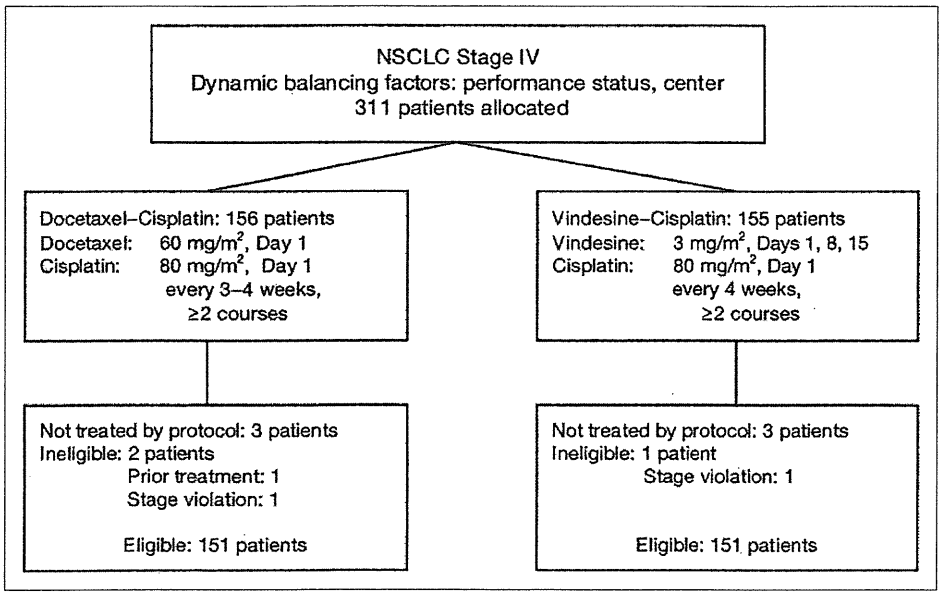

Fig 1. Study design and patient allocation. NSCLC, non–small-cell lung cancer.