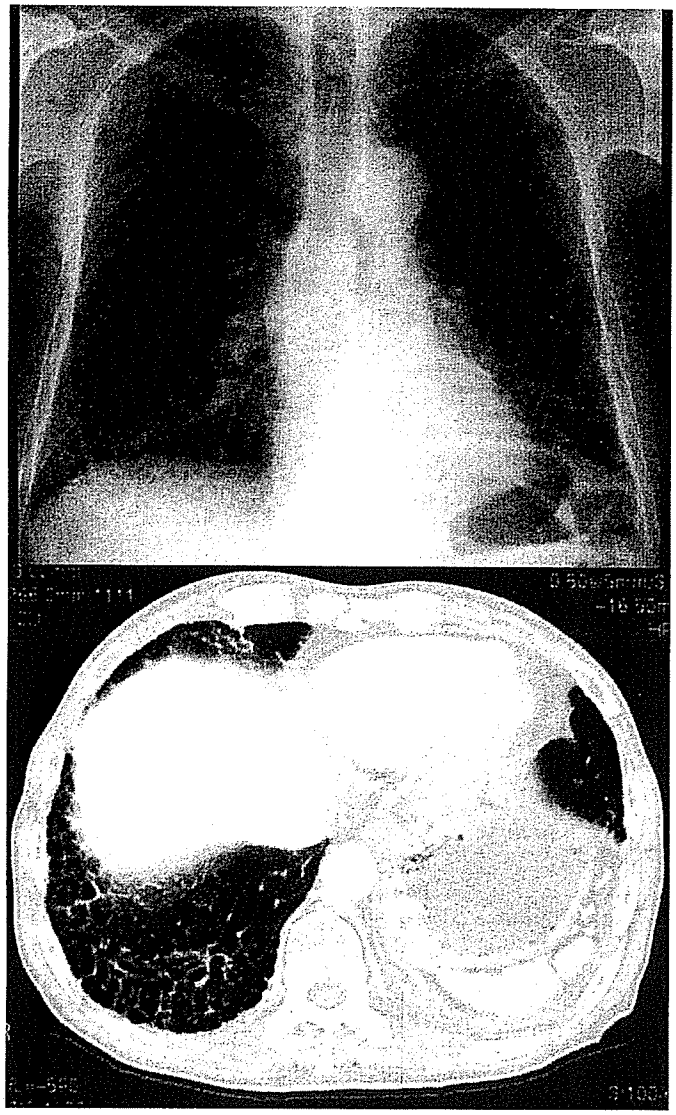

Figure 3. Severe interstitial shadow. An X-ray film of the chest shows bilateral reticular shadow. Reticular shadow is distributed in >30% of the bilateral lower lobes, with this being classified severe.

We identified patients developing ILD, utilizing medical records. ILD was diagnosed on the basis of standard or high-resolution CT findings of the chest (diffuse ground-glass opacity, reticular shadow or consolidation without segmental distribution), elevation of serum levels of lactate dehydrogenase (LDH) and/or KL-6, and lack of response to antibiotics. Bronchoalveolar lavage had not been performed to rule out infections. Most patients diagnosed as ILD were treated with corticosteroids. We compared patients who either had or had not developed ILD in terms of existence and severity of interstitial shadow, emphysema and/or pulmonary bullae on CT films of the chest, as well as patient characteristics including age, gender, smoking history and regimens of received chemotherapy. Comparisons between proportions were performed using a Fisher exact test or a Pearson chi-square test, as appropriate. Multivariate analyses were performed using the logistic regression procedure to determine the relationship between several factors and the onset of ILD.

RESULTS

A total of 502 patients were eligible, with the relevant patient characteristics shown in Table 1. A total of 74% of patients were male and 84% of patients had NSCLC, while the remaining 16% had small cell lung cancer; 79% of the patients were smokers, while 21% never smoked. Platinum-based chemotherapy was performed on 384 patients (76%). A total of 188 patients (37%) received tyrosine kinase inhibitor (TKI) treatment, namely gefitinib or erlotinib. TKI therapy was administered as a first-line (n = 48), second-line (n = 68), third-line (n = 62), fourth-line (n = 9) or fifth-line (n = 1) regimen. Out of 48 patients treated with TKI as a first-line treatment 41 had been entered into a phase II trial of single agent treatment with gefitinib (6).

Radiological findings on this patient cohort are listed in Table 2. Interstitial shadow was detected on chest X-ray and CT in 13 and 20% of patients, respectively. Mild, moderate or severe interstitial shadow was identified in 7, 8 or 5% of patients. Pulmonary emphysema was detected in 38% of patients. Mild, moderate or severe pulmonary emphysema was detected in 18, 10 or 10% of patients. Pulmonary bullae were detected in 20% of patients.

Twenty-six patients (5.2%) developed ILD either during or after chemotherapy. The last regimen of chemotherapy received prior to the onset of ILD included platinum plus vinorelbine or gemcitabine (n = 4), platinum plus taxane (n = 4), other platinum-based chemotherapy (n = 2), vinorelbine plus gemcitabine (n = 2), docetaxel plus gemcitabine (n = 2), single agent treatment with taxane (n = 2) and TKI treatment (n = 10). Out of 26 patients who developed ILD, 14 had a history of taking TKI. Four patients developed ILD after first- or second-line chemotherapy with TKI followed by combination chemotherapy of cisplatin plus vinorelbine (n = 2) or single agent treatment with docetaxel (n = 2).

Univariate analyses demonstrated that male gender (P = 0.0361) and interstitial shadow on CT films of the chest (P = 0.0096) were significantly associated with the onset of ILD (Tables 1 and 3). Multivariate analyses showed interstitial shadow on CT films of the chest [odds ratio (OR): 3.20, 95% confidence interval (CI): 1.34–7.59] and treatment history with gefitinib or erlotinib (OR: 3.17, 95% CI: 1.36–7.36) were associated with the onset of ILD. Male gender was not a significant risk factor for development of ILD in multivariate analysis (OR: 4.33, 95% CI: 0.97–19.38) (Table 4). Univariate and multivariate analyses demonstrated that neither interstitial shadow on X-ray films nor the number of chemotherapy regimens was associated with the onset of ILD.

DISCUSSION

Pulmonary fibrosis or interstitial pneumonia is considered to be a risk factor for ILD caused by drugs (5). In line with the

Table 1. Patient characteristics (n = 502)

	Total	Developed ILD	No ILD Development	P-value
Gender				
Male	371	24	347	0.0361
Female	131	2	129	
Age				
Median (range)	65 (33–83)	66 (53–77)	65 (33–83)	0.5253
ECOG PS				
0–1	443	26	417	0.0590
2–4	59	0	59	
Pathological type				
Adenocarcinoma	279	14	265	0.8775
Squamous cell carcinoma	84	6	78	
Poorly differentiated carcinoma	56	3	53	
Small cell carcinoma	79	3	76	
Others	4	0	4	
Smoking status				
Current smoker	272	14	258	0.1085
Former smoker	124	10	114	
Never smoked	106	2	104	
Clinical stage				
IB	10	0	10	0.6633
IIB	7	0	7	
IIIA	21	0	21	
IIIB	128	8	120	
IV or recurrence after operation	336	18	318	
Treatment history				
Platinum-based	384	18	366	0.3505
Vinorelbine-containing	295	13	282	0.4145
Gemcitabine-containing	110	7	103	0.4758
Taxane-containing	236	14	222	0.5470
Irinotecan-containing	72	2	70	0.5624
Etoposide-containing	67	2	65	0.5573
TKI	188	14	174	0.0954
Number of chemotherapy regimens				
1	212	9	203	0.7733
2	155	9	146	
3	106	7	99	
4 or 5	29	1	28	

ILD, interstitial lung disease; TKI, tyrosine kinase inhibitor.

Table 2. Radiological findings of plain X-ray and computerized tomography films of the chest

Interstitial shadow on plain X-ray films	65 (13%)
Interstitial shadow on CT films	102 (20%)
Mild	37 (7%)
Moderate	42 (8%)
Severe	23 (5%)
Pulmonary emphysema on CT films	189 (38%)
Mild	92 (18%)
Moderate	49 (10%)
Severe	48 (10%)
Pulmonary bullae	101 (20%)

Table 3. Radiological findings and interstitial lung disease

Radiological findings	Developed ILD	No ILD Development	P-value
Interstitial shadow on plain X-ray films of the chest			
No	23	414	1.000
Yes	3	62	
Interstitial shadow on CT film of the chest			
No	15	385	0.0096
Yes	11	91	
Severity of the interstitial shadow			
No	15	385	<0.0001
Mild	8	29	
Moderate	1	41	
Severe	2	21	
Pulmonary emphysema			
No	14	299	0.4075
Yes	12	177	
Severity of the emphysema			
No	14	299	0.6468
Mild	7	85	
Moderate	2	47	
Severe	3	45	
Pulmonary bullae			
No	18	383	0.2052
Yes	8	93	

ILD, interstitial lung disease.

information for prescription, patients with obvious interstitial shadow on chest X-ray should avoid gemcitabine or irinotecan. Although patients with interstitial shadow on chest X-ray were excluded in previous clinical trials in Japan, unexpectedly frequent ILD has been reported, as in the case of combination chemotherapy with docetaxel and gemcitabine (7). Is interstitial shadow on chest X-ray an appropriate criterion to detect interstitial pneumonia or pulmonary fibrosis and avoid ILD? Generally, chest CT can detect interstitial shadow more clearly than chest X-ray. Specifically, high-resolution CT of the chest is essential in diagnosing interstitial pneumonia. However, it has not been determined exactly how much more interstitial shadow detected by CT reveals the onset of ILD. We analyzed CT films of consecutive lung cancer patients who underwent

Table 4. Multivariate analysis of risk factors associated with the onset of interstitial lung disease

Variable	Odds ratio	95% CI	*P*-value
Interstitial shadow on CT films of the chest	3.20	1.34–7.59	0.0086
Treatment history with TKI	3.17	1.36–7.36	0.0073
Male gender	4.33	0.970–19.38	0.0551

CI, confidence interval; TKI, tyrosine kinase inhibitor.

chemotherapy without thoracic radiation therapy. Retrospective review of medical records identified that 26 out of 502 patients developed ILD. We found that interstitial shadow on CT films was associated with onset of ILD, but that interstitial shadow on X-ray was not. We divided interstitial shadow into three classes: mild, moderate and severe. Interstitial shadow on X-ray means moderate to severe interstitial pneumonia. Eight out of 37 patients (22%) with mild interstitial shadow not detected on chest X-ray developed ILD. The reason for the high rate of ILD in patients with mild interstitial shadow is unknown. The criteria of no interstitial shadow on chest X-ray did not sufficiently reduce the risk of ILD. Treatment history with TKI, either gefitinib or erlotinib, was also associated with onset of ILD in multivariate analysis. Conversely, treatment with gemcitabine or irinotecan was not associated with onset of ILD.

Our retrospective analyses have several limitations. We avoided treatment with gemcitabine, irinotecan or TKI in the case of patients with moderate to severe interstitial shadow detectable on chest X-ray films. Some patients who were transferred to another hospital just after chemotherapy may have developed ILD, but detailed clinical courses after transfer were not available. Early death after chemotherapy due to disease progression might conceal the onset of ILD. Although these biases may exist, our analyses were made with an extensive cohort of patients, and therefore the results obtained are of significance.

The frequency of ILD in Japanese patients was reported to range between 3 and 15% in previous clinical trials (6–8). This rate appears to be higher than that observed in the rest of the world. Explanations include the possibility that ILD may be more prevalent among the Japanese or, alternatively, that a greater awareness of the disease could lead to more frequent diagnosis. Furthermore, there may be an increased genetic susceptibility to ILD specifically among the Japanese population (5).

Patients with interstitial shadow on chest X-ray have been excluded in previous clinical trials to avoid ILD caused by chemotherapeutic agents. However, this criterion alone is considered insufficient. It is recommended that patients with interstitial shadow on chest CT are excluded from future clinical trials until this issue is clarified, as it is anticipated that use of chemotherapeutic agents frequently mediate onset of ILD in this context. Therefore, physicians need to understand the associated risk of ILD in patients with interstitial shadow on chest CT and obtain informed consent from patients before administering chemotherapy in clinical practice.

Acknowledgments

This work was supported by the Public Trust Haraguchi Memorial Cancer Research Fund.

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Clinical Trials for Lung Cancer in Progress in Japan

Ikuo Sekine, Yuichiro Ohe, Nagahiro Saijo and Tomohide Tamura

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Contents

39.1 Introduction

Lung cancer has been the leading cause of death from cancer in many countries, despite extensive basic research and clinical trials. About 80% of patients with lung cancer have already developed distant metastases, either by the time of the initial diagnosis or by the time recurrence is detected after surgery for local disease. Systemic chemotherapy is the mainstay of lung cancer treatment, although its efficacy is still limited. Therefore, new chemotherapeutic agents continue to be developed against lung cancer [1].

39.2 Drug Approval System in Japan

Since 1955, 23 anticancer drugs have been approved for use against lung cancer in Japan. Of these, 9 were discovered and developed in Japan, including mitomycin, bleomycin, and the topoisomerase I inhibitor irinotecan, and are routinely used all over the world. The Japanese Pharmaceutical Affairs Law (PAL) was enacted in 1948, and was first amended in 1960 to provide for regulations to ensure the maintenance of the quality, efficacy, and safety of drugs and medical devices, and to promote research and development of these medical and pharmaceutical products. Good Clinical Practice was enforced by the Bureau Notification of the Ministry of Health and Welfare of Japan in 1989. In 1996, PAL and its related laws were amended to strengthen Good Clinical Practice, Good Laboratory Practice, Good Postmarketing Surveillance Practice, and standard compliance reviews, conforming to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [2]. In contrast to the laws prevailing in the US and EU, in Japan, marketing approval for anticancer agents can be granted based on reports of the antitumor effects of the new agents in phase II studies. Two independently conducted comparative phase III trials with survival as the endpoint are required after the approval, with at least one of these conducted as a post-marketing sponsored (PMS) trial in Japan [2].

39.3 Recent Clinical Trials for Non-Small-Cell Lung Cancer

Several randomized phase III trials for previously untreated advanced non-small cell lung cancer (NSCLC) have been conducted by Japanese pharmaceutical companies. A three-arm trial of cisplatin + vindesine versus cisplatin + irinotecan versus irinotecan alone conducted on 398 patients with stage IIIB or IV NSCLC between 1995 and 1998 showed that the overall response rate (31%, 43%, and 21%, respectively, $p < 0.001$), but not the overall survival rate (median survival time [MST], 47, 52, and 47 weeks, respectively, $p = 0.099$), was significantly better in the cisplatin + irinotecan arm than in the other two arms [3]. A second trial conducted on 210 patients with advanced NSCLC, comparing cisplatin + vindesine versus cisplatin + irinotecan, showed no statistically significant difference in the overall response rate (22% versus 29%) or survival rate (MST, 50 versus 45 weeks) between the two arms [4]. A randomized phase III trial of docetaxel + cisplatin versus vindesine + cisplatin was conducted between 1998 and 2000 on 305 patients with stage IV NSCLC. Both the overall response rate and the survival rate were significantly superior in the docetaxel + cisplatin arm as compared to the vindesine + cisplatin arm (response rate, 37% versus 21%, re-

spectively, $p<0.01$; MST, 11.3 versus 9.6 months, respectively, $p=0.014$) [5, 6]. After the commercial use of paclitaxel, gemcitabine, and vinorelbine was approved for NSCLC in 1999, a phase III study was conducted to confirm the efficacy and safety of these agents, to fulfill the requirements of PAL. A four-arm randomized phase III study of these agents for NSCLC was conducted in cooperation with three pharmaceutical companies. The four arms consisted of cisplatin (80 mg/m^2 on day 1) + irinotecan (60 mg/m^2 on days 1, 8, and 15) administered every 4 weeks as the reference arm; carboplatin (area under the curve [AUC] 6 on day 1) + paclitaxel (200 mg/m^2 on day 1) administered every 3 weeks; cisplatin (80 mg/m^2 on day 1) + gemcitabine (1,000 mg/m^2 on days 1 and 8) every 3 weeks; and cisplatin (80 mg/m^2 on day 1) + vinorelbine (25 mg/m^2 on days 1 and 8) administered every 3 weeks. Of a total of 602 patients registered from 44 institutes in Japan between 2000 and 2002, 581 were assessable for response, toxicity, and survival. The overall response rates in the four arms were 31%, 32%, 30%, and 33%, respectively, and the MST was 14.2, 12.3, 14.8, and 11.4 months, respectively. Non-inferiority of the three experimental arms as compared to the reference arm was not demonstrated in this study [5, 6].

Docetaxel monotherapy is the standard second-line treatment for NSCLC patients, based upon the demonstration of improved survival and quality of life in phase III studies [7, 8]. The Japan Clinical Oncology Group (JCOG) conducted a phase III trial (JCOG0104) to evaluate the efficacy and toxicity of gemcitabine combined with docetaxel in NSCLC patients with a history of prior platinum-based chemotherapy. The chemotherapeutic regimens compared in this study consisted of docetaxel alone (60 mg/m^2 on day 1) or docetaxel (60 mg/m^2 on day 8) + gemcitabine (800 mg/m^2 on days 1 and 8), repeated every 21 days until disease progression, with a planned sample size of 142 patients per arm. Between January 2002 and April 2003, 65 patients were accrued for each arm. However, this trial was terminated early because of the unexpectedly high incidence of interstitial lung disease (ILD) and three treatment-related (all due to ILD) deaths (5%) in the docetaxel + gemcitabine arm. While the incidence of grade 3–4 neutropenia and febrile neutropenia was similar in both the arms, the incidence of dyspnea (23% versus 14%) and ILD (21% versus 2%) was higher in the docetaxel + gemcitabine arm [9]. A randomized, double-blind, parallel-group, international, multicenter trial of gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, was conducted in patients with advanced NSCLC with recurrent or refractory disease following therapy with one or two chemotherapeutic regimens, at institutes in Europe, Australia, South Africa, and Japan. Patients were randomized to receive either 250 or 500 mg/day gefitinib using blinded tablets, until disease progression, intolerable toxicity, or withdrawal of consent. Between October 2000 and January 2001, 102 patients were enrolled from 19 institutes in Japan. The objective tumor response rate in the Japanese patients was 28% in both the 250- and the 500-mg/day arms. Thus, there was no difference in the objective response rate depending on the dose of gefitinib, although the incidence of toxicities, including rash, diarrhea, liver damage, and nausea, was relatively lower in the 250-mg/day arm [10]. A randomized, open-labeled phase III trial of second-line chemotherapy with docetaxel versus gefitinib in patients with advanced NSCLC previously treated with platinum-based chemotherapy is in progress in Japan as a PMS trial,

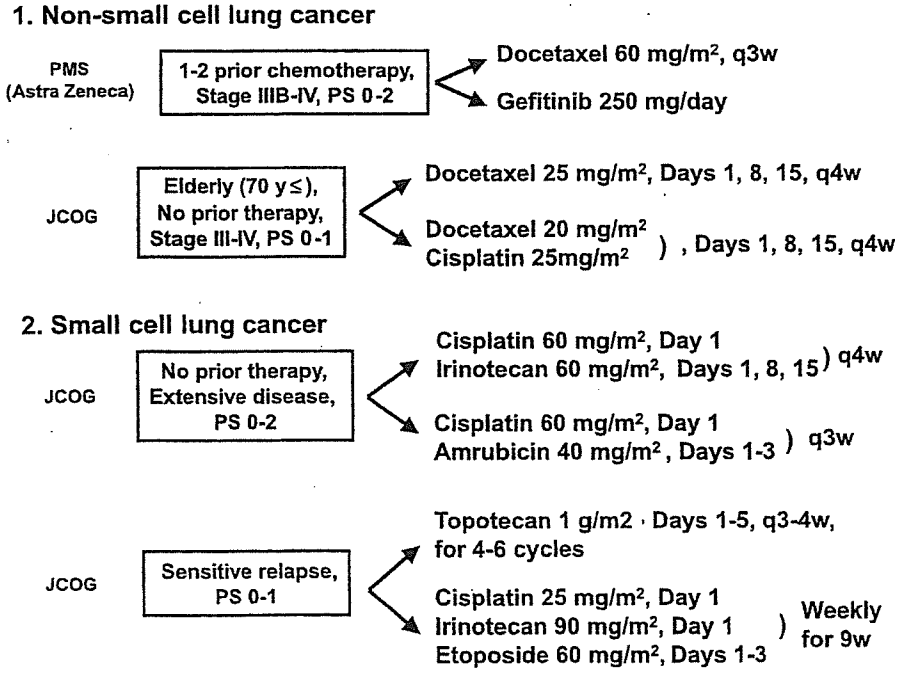


Fig. 39.1. Phase III trials in progress or being planned in Japan. *PMS* Post-marketing sponsored, *JCOG* Japan Clinical Oncology Group

since December 2003. The projected accrual for this study is a total of 484 patients (242 patients per treatment arm) (Fig. 39.1).

Monotherapy with a third-generation cytotoxic agent is widely accepted for the treatment of advanced NSCLC in the elderly, after demonstration of the survival benefit of vinorelbine over standard supportive care alone, without deterioration of the quality of life, in a phase III trial [11]. The West Japan Thoracic Oncology Group (WJTOG) is conducting a phase III trial (WJTOG 9904) of docetaxel (60 mg/m^2 on day 1) versus vinorelbine (25 mg/m^2 on days 1 and 8) administered every 3 weeks for advanced NSCLC in patients aged 70 years or older with no prior history of chemotherapy, a performance status of 0–2, and adequate organ function, as indicated by routine blood counts and blood chemistry, and electrocardiography. The projected sample size for this trial is 90 patients for each arm, and patient accrual for this study has recently been completed.

There are limited data to support the use of platinum-based combination chemotherapeutic regimens in patients over 70 years of age, although platinum doublet is standard treatment for younger patients. A retrospective analysis of 401 patients 65 years of age or older in a large phase III trial of docetaxel + cisplatin versus docetaxel + carboplatin versus vinorelbine + cisplatin revealed no significant differences in the therapeutic outcomes based on the age, although a moderately higher incidence of grade 3–4 asthenia, infection, pulmonary toxicities, diarrhea, and sensory neurotoxicity was noted in the elderly patients [12]. A phase I and a phase II study showed that a combination of cisplatin and docetaxel administered as three consecutive weekly infusions was safe and effective in elderly patients with advanced NSCLC [13, 14]. Based on these data, a JCOG phase III trial of weekly docetaxel versus weekly docetaxel + cisplatin (JCOG0207) is under way (Fig. 39.1). The primary endpoint of this study is the overall survival of the patients treated with these regimens. The secondary endpoints are the response rate, progression-free survival, toxicity, and symptom score. Eligibility includes stage IV or IIIB disease, no history of previous chemotherapy, performance status of 0 or 1, age 70 years or older, and adequate organ functions. The chemotherapeutic regimens consisted of docetaxel (25 mg/m^2) administered on days 1, 8, and 15 every 4 weeks, or docetaxel (20 mg/m^2) + cisplatin (25 mg/m^2) administered on days 1, 8, and 15 every 4 weeks. The projected accrual for this study is a total of 230 patients (115 patients per treatment arm).

39.4 Recent Clinical Trials for Small-Cell Lung Cancer

The JCOG conducted a phase III study of cisplatin (60 mg/m^2 on day 1) + irinotecan (60 mg/m^2 on days 1, 8, and 15) administered every 4 weeks versus cisplatin (80 mg/m^2 on day 1) + etoposide (100 mg/m^2 on days 1, 2, and 3) administered every 3 weeks for untreated extensive small-cell lung cancer (E-SCLC) (JCOG9511). The projected sample size for this study was 230 patients (115 patients per treatment arm), however, enrollment was stopped early because of a statistically significant difference in the survival observed between the two treatment arms on interim analysis. In this interim analysis, 154 patients were randomized to the two treatments, 77 into each arm. The overall response rate and survival were significantly better in the cisplatin + irinotecan group (response rate, 84% versus 68%, respectively, $p = 0.02$; MST, 12.8 versus 9.4 months, respectively, $p = 0.002$) [15]. Based on these observations, the combination of cisplatin + irinotecan is used as the standard chemotherapeutic regimen for E-SCLC in Japan. A three-drug combination of cisplatin, irinotecan, and etoposide was investigated. The maximum tolerated dose of each of the three drugs was determined in phase I studies using two different schedules: a weekly (JCOG9507) and a 4-weekly (JCOG9512) schedule. The antitumor effects of these regimens were evaluated in a randomized phase II study (JCOG9902DI) [16]. The weekly arm consisted of cisplatin (25 mg/m^2 on day 1 at weeks 1–9), irinotecan (90 mg/m^2 on day 1 at weeks 1, 3, 5, 7, and 9), and etoposide (60 mg/m^2 on days 1–3 at weeks 2, 4, 6, and 8), administered with granulocyte colony-stimulating factor (G-CSF) support. The 4-weekly arm consisted of cisplatin (60 mg/m^2 on day 1), irinotecan (60 mg/m^2 on days 1, 8, and 15), and etoposide (50 mg/m^2 on days 1–3) administered with G-CSF support. From August 1999 to October 2000, 30 patients were entered in each of the two treatment arms of this study. Although 70% of all the patients received full cycles of chemotherapy in both arms, treatment delay in the weekly arm and skipping of irinotecan on day 15 in the 4-weekly arm were common because of toxicity. The complete and partial response rates and the MST were 7%, 77%, and 8.9 months, respectively, in the weekly arm, and 17%, 60%, and 12.9 months, respectively, in the 4-weekly arm. Since no overall survival benefit was obtained with the weekly schedule, and the dose of irinotecan on day 15 frequently needed to be skipped in the 4-weekly schedule, a 3-week schedule with irinotecan administered only on days 1 and 8 every 3 weeks might be appropriate for subsequent trials. A randomized phase II trial of cisplatin (60 mg/m^2 on day 1) + irinotecan (60 mg/m^2 on days 1 and 8) versus the same three-drug combination of cisplatin and irinotecan combined with etoposide (50 mg/m^2 on days 1–3) administered

every 3 weeks with G-CSF support in patients with previously untreated E-SCLC is in progress.

Amrubicin (SM-5887) is an entirely synthetic anthracycline that has been shown to possess topoisomerase II inhibitory activity. It has been shown to exert more potent antitumor activity than doxorubicin against various experimental tumors and human tumor xenografts in mice, without any cardiotoxicity. A phase II study of single-agent amrubicin using a schedule of 45 mg/m^2 administered on days 1–3 every 3 weeks yielded an overall response rate of 76%, a complete response rate of 9%, and an MST of 11.7 months in 33 previously untreated E-SCLC patients [17]. The recommended dose of amrubicin when combined with cisplatin was determined to be 40 mg/m^2 on days 1–3 every 3 weeks, and the response rate and MST for E-SCLC patients receiving this combination were 88% and 13.6 months, respectively [18]. The next JCOG phase III trial for this patient population should be of a combination of cisplatin + amrubicin versus cisplatin + irinotecan (Fig. 39.1).

Despite a high response rate to chemotherapy, the majority of SCLC patients eventually develop recurrent disease. At the time of recurrence, the tumor is broadly resistant to second-line chemotherapy and death occurs within a few to several months [19]. Thus, there is need for further development of effective salvage chemotherapy. We conducted a phase II study of cisplatin (25 mg/m^2) administered weekly for 9 weeks, etoposide (60 mg/m^2) administered for 3 days on weeks 1, 3, 5, 7, and 9, and irinotecan (90 mg/m^2) administered on weeks 2, 4, 6, and 8, with G-CSF support, in patients with sensitive relapsed SCLC [20]. Since the drug dose and treatment schedule can be easily modified according to the patient condition in the weekly regimen, it is considered that this regimen may be the most suitable for relapsed SCLC patients, who usually present with severe hematological toxicities during salvage chemotherapy because of poor bone marrow reserve. In a total of 40 patients registered, the overall response rate was 78% with 5 complete responses and 26 partial responses, and the MST was 11.8 months. Grade 3–4 neutropenia and thrombocytopenia were observed in 73% and 33% of the patients, respectively, and the non-hematological toxicities were mild and transient in all the patients. The JCOG is planning a phase III study to compare the efficacy of this regimen with that of topotecan monotherapy in sensitive relapsed SCLC patients (Fig. 39.1).

At diagnosis, 25–40% of patients with SCLC are 70 years old or older, and this percentage is expected to increase with the growing population of geriatric patients. Carboplatin is especially useful for the elderly because only minimum hydration of the patients is required, its non-hematological toxicity is mild, and the dose can be adjusted according to the patient's creatinine clearance [21]. The JCOG evaluated the toxicity and efficacy of this drug in a phase II study (JCOG9409), and observed grade 4 neutropenia and thrombocytopenia in 44% and 12% of the patients, respectively, and complete response and partial response in 6% and 69% of the patients, respectively [22]. We started a large phase III trial in 1998, to compare the clinical efficacy of etoposide (80 mg/m^2 on days 1–3) + carboplatin (AUC = 5) versus etoposide (same dose) + cisplatin (25 mg/m^2 on days 1–3) in elderly patients with SCLC (JCOG9702). The sample size was 220 patients (110 patients for each arm), and registration was completed in February 2004.

39.5 New Agents for the Treatment of Lung Cancer

The development of oral preparations of 5-fluorouracil (5-FU) began in Japan in 1971, based on the finding that 5-FU acts in a time-dependent manner and on the possibility of treating patients on an outpatient basis, without deterioration of the quality of life, when drugs can be administered orally. S-1 (Taiho Pharmaceutical) is a novel oral fluoropyrimidine derivative consisting of tegafur, a prodrug of 5-FU, and two modulators, 5-chloro-2, 4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo), in a molar ratio of 1:0.4:1 [23]. CDHP enhances the serum 5-FU concentrations by competitive inhibition of dihydropyrimidine dehydrogenase, an enzyme responsible for 5-FU catabolism. Oxo reduces 5-FU-induced diarrhea by inhibiting orotate phosphoribosyltransferase, a phosphoenzyme for 5-FU in gastrointestinal tissue. In a phase I trial, the maximum tolerated dose of S-1 was 75–100 mg/body, and the dose-limiting toxicity was myelosuppression. In a phase II trial of S-1 administered orally at approximately 40 mg/m^2 twice a day for 28 days followed by a 2-week rest period in 59 advanced NSCLC patients without prior history of chemotherapy, the response rate was 22% and the MST was 10.2 months, and the incidence of toxicity was relatively low, including grade 3–4 neutropenia in 7%, thrombocytopenia in 2%, diarrhea in 9%, and stomatitis in 2% of the patients [24]. A combination of S-1 and cisplatin was evaluated in a phase II trial for locally advanced and metastatic NSCLC, in which S-1 was administered orally (40 mg/m^2, twice daily) for 21 consecutive days and cisplatin was administered intravenously (60 mg/m^2 on day 8), and this schedule was repeated every 5 weeks. An overall response rate of 47% and MST of 11 months were obtained, with a mild toxicity profile, including grade 3–4 neutropenia in 29%, grade 3 anorexia in 13%, vomiting in 7%, and diarrhea in 7% of the patients [25]. This drug was approved for use in cases of advanced NSCLC by the Ministry of Health, Labor and Welfare of Japan in December 2004, on condition that a phase III trial of S-1 combined with platinum be conducted for advanced NSCLC patients with a reference arm of the standard regimen for this disease.

Several antifolates have been evaluated for the treatment of NSCLC, but none has as yet gained recognition as a useful drug in standard clinical practice. Pemetrexed (LY231514; Eli Lilly Japan) is a novel antifolate with multiple intracellular targets, including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase, all key folate enzymes involved in the de novo synthesis of purines and pyrimidines [26]. The recommended dose of pemetrexed from early phase I trials is 600 mg/m^2 administered every 3 weeks, and the dose-limiting toxicity was myelosuppression [27]. Phase II studies conducted with this drug at the dose of 500 mg/m^2 yielded response rates of 15–23% in untreated patients and 9% in previously treated patients with advanced NSCLC [28, 29]. A phase III trial of pemetrexed versus docetaxel as a second-line chemotherapy for NSCLC showed that this drug had the same antitumor activity as docetaxel, but with less toxicity [30]. Because folic acid and vitamin B_{12} supplementation was found to decrease the toxicity of this agent [31], a Japanese phase I trial of the drug was conducted with such vitamin supplementation [32]. In a total of 31 patients (19 with NSCLC, 7 with malignant pleural mesothelioma, 2 with thymoma, 1 with rectal cancer, and 2 others), grade 3 neutropenia was observed in 4 patients, elevated liver transaminase levels in 2 patients, and skin rash in 1 patient, and the recommended dose of pemetrexed was determined to be 1,000 mg/m^2 every 3 weeks. The pharmacokinetic profile of pemetrexed with vitamin supplementation in Japanese patients was essentially similar to that in western patients, with or without vitamin supplementation. In a total of 20 patients who were evaluable for antitumor activity, a partial response was observed in 4 of the 13 patients with NSCLC, and 1 of 2 patients with thymoma. A phase II trial of this drug in previously treated cases of NSCLC is under way in Japan.

Erlotinib (Chugai Pharmaceutical) is another selective inhibitor of EGFR tyrosine kinase sharing a common chemical backbone with gefitinib. Erlotinib was consistently twice as potent as gefitinib in preclinical studies, from cell-free systems to in vivo toxicity and efficacy studies [33]. At the dose of 150 mg, the recommended dose for phase II trials, the plasma AUC of erlotinib was higher by one order of magnitude than that of gefitinib administered at the dose of 250 mg/day [33]. The response rate of erlotinib in phase II trials in the USA was 12% in patients with NSCLC and 26% in patients with bronchoalveolar carcinoma. Phase III trials of standard platinum-based doublet with erlotinib versus placebo in patients with stage IIIB or IV NSCLC (TALENT and TRIBUTE) failed to show any survival benefit of erlotinib over placebo in a whole patient population [34]. A Japanese phase I trial of erlotinib was conducted in 11 patients with NSCLC, 3 patients with colon cancer, and 1 patient with head and neck cancer, using a dose in the range 50–150 mg/day [35]. The toxicity profile was mild, with grade 1–2 skin rash in 87%, grade 1 diarrhea in 53%, and grade 1–2 elevation of liver transaminases in 40% of patients, except for 1 patient who developed fatal ILD following treatment with 100 mg/day erlotinib. The C_{max} increased in a dose-related manner, but there was no clear trend in the AUC. A partial response was observed in 4 (36%) of the 11 NSCLC patients. A phase II trial in previously treated patients with NSCLC is in progress.

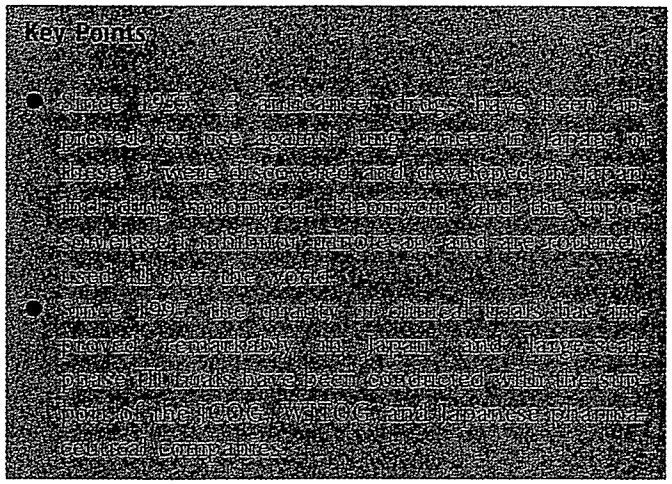
Vascular endothelial growth factor (VEGF) is a potent and specific mitogen for endothelial cells that activates the angiogenic switch in vivo through binding to two distinct receptors on endothelial cells: Flt-1 (VEGFR-1) and Flk-1/KDR receptor (VEGFR-2). Enhanced expression of VEGF is generally correlated with increased neovascularization within the tumor [36]. ZD6474 (AstraZeneca) is an orally bioavailable, small-molecule VEGFR-2 tyrosine kinase inhibitor that also possesses activity against the EGFR tyrosine kinase [37]. Oral administration of ZD6474 to athymic mice bearing various established human tumor xenografts produced a dose-dependent regression of the tumors in all the cases [37]. In addition, ZD6474 inhibited the growth of tumors resistant to EGFR inhibitors [38]. A phase I trial of ZD6474 in 18 Japanese patients with solid tumors refractory to standard therapy showed that ZD6474 was well tolerated when administered at the dose of 100–300 mg/day, with common toxicity, including skin rash in 14, asymptomatic QTc prolongation in 11, diarrhea in 10, and hypertension in 7 patients [39]. The C_{max} and AUC of ZD6474 increased linearly with the dose, and the terminal half-life was long, ranging from 72 to 167 h (median 96 h). The dose level of 100–300 mg/day yielded trough concentrations of the non-protein-bound drug of 0.08–0.31 μmol/l in 10 patients, which was over the IC_{50} (0.04 μmol/L) of ZD6474 for VEGFR-2. Preliminary suggestion of tumor regression was observed in 4 out of 9 patients with NSCLC. A phase II trial in advanced NSCLC patients with a history of prior chemotherapy is in progress in Japan.

Since 1995, the quality of clinical trials has improved remarkably in Japan, and large-scale phase III trials have been conducted with the support of the JCOG, WJTOG, and Japanese pharmaceutical companies:

1. Molecular-target drugs, including gefitinib, erlotinib, and ZD6474, have been evaluated in phase II–III trials of NSCLC in Japan.
2. Amrubicin, a new anthracycline, is promising for the treatment of SCLC, and phase III trials are being planned.

Acknowledgements

We thank Ms. Yuko Yabe for her assistance in the preparation of this manuscript.



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[総論]

小細胞肺がん

藤阪保仁（大阪医科大学附属病院呼吸器内科），西條長宏（国立がんセンター東病院副院長）

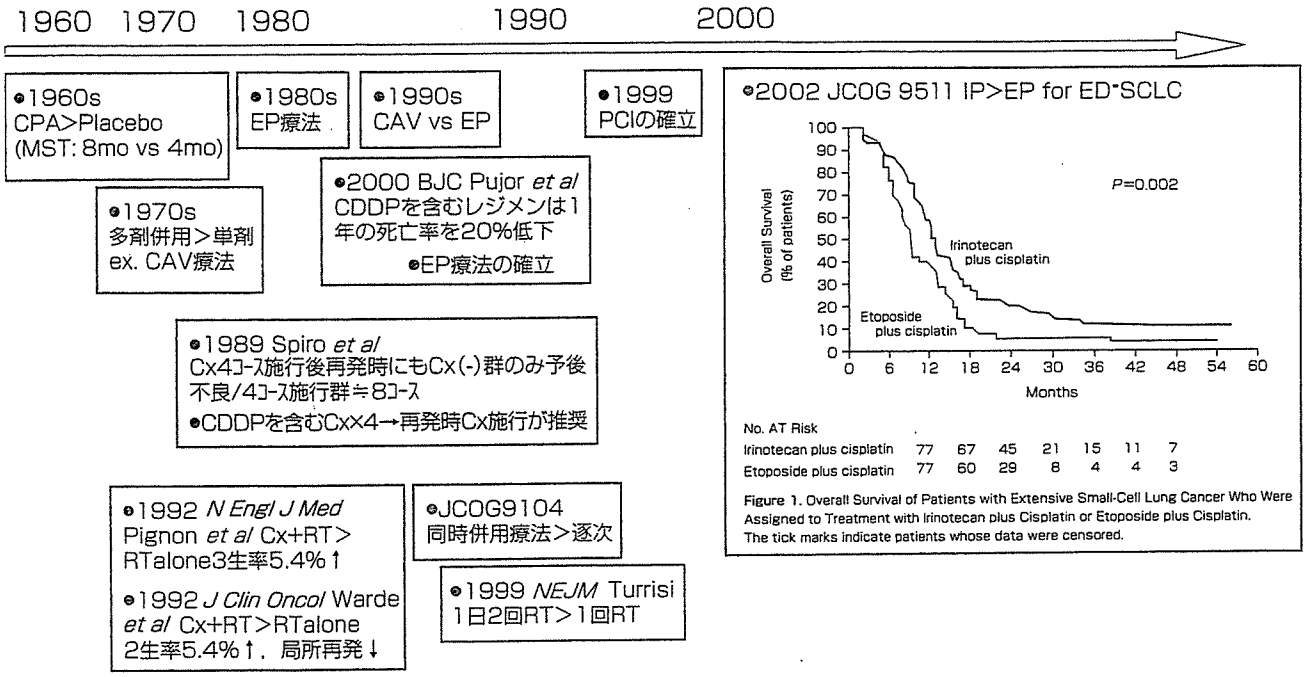
わが国における肺癌の死亡率は，1950年以降男女とも増加の一途にあり，2000年には肺癌死亡数が54,000人にのぼり，1993年以降は男性では胃癌を抜いて死亡数では悪性腫瘍中の第1位となっている．2010年には肺癌死亡数は10万人を超えると予想されている[1]．小細胞肺癌（SCLC）は，わが国では肺癌全体の約15%を占め喫煙との関連も高い腫瘍である[2]．SCLCは非小細胞肺癌（NSCLC）と比較して，広範かつ迅速に血行性，リンパ行性転移をきたし進行が早い反面，全身化学療法，放射線治療に対する感受性が高く，NSCLCとは著しく異なる臨床上の特徴を有している．切除不能SCLC患者を対象として1960年代に施行された臨床試験でのbest supportive care（BSC）群の生存期間中央値（MST）は限局型（LD）で12週，進展型（ED）で5週と報告[3]されていたが，近年，SCLCに対する治療法は数多くの臨床試験の結果により着実に進歩してきておりLD症例では，化学療法と同時に胸部放射線治療をおこなうことにより，MST約28ヵ月，ED症例では化学療法によりMST約13ヵ月の成績が報告されている[4]～[7]（表❶）．

限局型小細胞肺癌（LD-SCLC）に対する標準的治療法はEP〔エトポシド（VP-16）＋シスプラチン（CDDP）〕療法＋胸部放射線加速多分割照射同時併用療法（accelerated hyperfractionated radiotherapy：AHF）であると考えられ，その3年生存率は約30％に達する[8]．進展型小細胞肺癌（ED-SCLC）の化学療法では，2002年の*N Engl J Med*誌に，IP〔イリノテカン（CPT-11)+シスプラチン（CDDP)〕療法がEP療法よりすぐれていたというJCOG9511の結果が発表された[9]．このレジメンをLD-SCLCに取り入れる試みがなされている．すなわち，full doseのIP療法と放射線療法を併用することは困難なことから，1コースのEP療法とAHFに引きつづく，標準的治療である3コースのEP療法（EP/TRT-EP）に対する3コースのイリノテカン＋CDDP療法（EP/TRT-IP）の優越性を検証する第Ⅲ相比較試験がJCOG0202にて実施されておりその結果が期待される．また，2005年のASCO総会では，CDDPを分割投与すると，IPの成績はEP療法と同程度まで低下すると報告されている[10]．さらにSWOGの第Ⅲ相試験はJCOG9511試験とまったく同スケジュールにてCPT-11を投与しておりその結果が期待される．

表❶ SCLCの治療成績

stage	year	CR(%)	RR(%)	MST(月)	3年生存率(%)
LD	1981	50	80	14	15～20
	2003	60	95	20～28	40
ED	1981	25	75	7	0
	2003	40	85	9～13	10

今回の小細胞肺がんでは，化学放射線併用療法，予防的全脳照射（PCI），多剤併用療法，Dose-intensive chemotherapy，高齢者およびPS不良例，New drugの各稿にそれぞれKey Trialとなる臨床試験数編を取り上げて解説を加えた．しかしながら，前号より約4年が経過しているにもかかわらず，教科書を書きかえるような新たな臨床試験の結果が得られていないのも現実である．事実，ASCOの年次総会においてもその演題数は少ない．現在までにわが国よりJCOG9104のLD-SCLCに対するconcurrent療法の有用性やJCOG9511のED-SCLCに対するIP療法の有用性を報告しておりSCLCの標準治療の確立に大きく貢献している．今後もSCLCもcurable malignancyとなることを目標としてクオリティーの高い臨床試験を計画実行されていくことを期待する



図❶小細胞肺癌の治療

(図❶).

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Docetaxel Consolidation Therapy Following Cisplatin, Vinorelbine, and Concurrent Thoracic Radiotherapy in Patients with Unresectable Stage III Non-small Cell Lung Cancer

Ikuo Sekine, Hiroshi Nokihara,* Minako Sumi,† Nagahiro Saijo,‡ Yutaka Nishiwaki,§ Satoshi Ishikura,|| Kiyoshi Mori,¶ Iwao Tsukiyama,# and Tomohide Tamura**

Background: To evaluate the feasibility and efficacy of docetaxel consolidation therapy after concurrent chemoradiotherapy for unresectable stage III non–small cell lung cancer (NSCLC).

Patients and Methods: The eligibility criteria included unresectable stage III NSCLC, no previous treatment, age between 20 and 74 years, and performance status 0 or 1. Treatment consisted of cisplatin (80 mg/m^2 on days 1, 29, and 57), vinorelbine (20 mg/m^2 on days 1, 8, 29, 36, 57, and 64), and thoracic radiotherapy (TRT) (60 Gy/30 fractions over 6 weeks starting on day 2), followed by consolidation docetaxel (60 mg/m^2 every 3 to 4 weeks for three cycles).

Results: Of 97 patients who were enrolled in this study between 2001 and 2003, 93 (76 males and 17 females with a median age of 60) could be evaluated. Chemoradiotherapy was well tolerated; three cycles of chemotherapy and 60 Gy of TRT were administered in 80 (86%) and 87 (94%) patients, respectively. Grade 3 or 4 neutropenia, esophagitis, and pneumonitis developed in 62, 11, and 3 patients, respectively. Docetaxel consolidation was administered in 59 (63%) patients, but three cycles were completed in only 34 (37%) patients. The most common reason for discontinuation was pneumonitis, which developed in 14 (24%) of the 59 patients. During consolidation therapy, grade 3 or 4 neutropenia, esophagitis, and pneumonitis developed in 51, 2, and 4 patients, respectively. A total of four patients died of pneumonitis. We calculated a V_{20} (the percent volume of the normal lung receiving 20 Gy or more) on a dose–volume histogram in 25 patients. Of these, five patients developed grade 3 or more severe radiation pneumonitis. A median V_{20} for these five patients was 35% (range, 26–40%), whereas the median V_{20} for the remaining 20 patients was 30% (range, 17–35%) (p = 0.035 by a Mann–Whitney test). The response rate was 81.7% (95% confidence interval [CI], 72.7–88.0%), with 5 complete and 71 partial responses. The median progression-free survival was 12.8 (CI, 10.2–15.4) months, and median survival was 30.4 (CI, 24.5–36.3) months. The 1-, 2-, and 3-year survival rates were 80.7, 60.2, and 42.6%, respectively.

Conclusion: This regimen produced promising overall survival in patients with stage III NSCLC, but the vast majority of patients could not continue with the docetaxel consolidation because of toxicity.

Key Words: Non-small cell lung cancer, Chemoradiotherapy, Consolidation, Docetaxel.

(*J Thorac Oncol.* 2006;1: 810–815)

Locally advanced unresectable non–small cell lung cancer (NSCLC), stage IIIA with bulky N2 and stage IIIB disease without pleural effusion, is characterized by large primary lesions and/or involvement of the mediastinal or supraclavicular lymph nodes and occult systemic micrometastases. A combination of thoracic radiotherapy and chemotherapy is the standard medical treatment for this disease, but the optimal combination has not been established.[1] Although the available data are insufficient to accurately define the size of a potential benefit,[2] concurrent chemoradiotherapy using a platinum doublet has been shown to be superior to the sequential approach in phase III trials of this disease.[3–5] However, third-generation cytotoxic agents, which have provided better patient survival with extrathoracic spread than the old-generation agents, must be reduced when administered concurrently with thoracic radiotherapy.[6] Thus, it has been hypothesized that the addition of systemic dose chemotherapy with a new cytotoxic agent to concurrent chemoradiotherapy, either as induction or as consolidation chemotherapy, might further improve patient survival.[1]

The consolidation chemotherapy with docetaxel was based on the observation that this drug was highly active in the primary treatment of metastatic NSCLC, producing a response rate (RR) as high as 20% after platinum-based chemotherapy failed.[7–9] Highly encouraging results of a me-

Divisions of *Internal Medicine and Thoracic Oncology, and †Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan; Divisions of ‡Internal Medicine, §Thoracic Oncology, and ||Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Japan; and Divisions of ¶Thoracic Oncology and #Radiotherapy, Tochigi Cancer Center, Utsunomiya, Japan.

Address for correspondence: Ikuo Sekine, Division of Thoracic Oncology and Internal Medicine, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. E-mail: isekine@ncc.go.jp

ISSN: 1556-0864/06/0108-0810

dian survival time (MST) of more than 2 years and a 3-year survival rate of nearly 40% were obtained in a phase II trial of docetaxel consolidation after chemoradiotherapy with cisplatin and etoposide in patients with stage IIIB NSCLC (SWOG study S9504).[10]

We have developed a combination chemotherapy schedule with cisplatin and vinorelbine concurrently administered with thoracic radiotherapy at a total dose of 60 Gy in 30 fractions in patients with unresectable stage III NSCLC. The results of a phase I study in 18 patients were very promising, with a RR of 83%, a MST of 30 months, and a 3-year survival rate of 50%.[6] Thus, addition of docetaxel consolidation to this regimen is a particularly interesting therapeutic strategy. The objectives of the current study were to evaluate the feasibility of docetaxel consolidation therapy after concurrent chemoradiotherapy with cisplatin and vinorelbine and to evaluate the efficacy and safety of the whole treatment regimen including both the chemoradiotherapy and consolidation therapy in patients with unresectable stage IIIA and IIIB NSCLC.

PATIENTS AND METHODS

Patient Selection

The eligibility criteria were histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease; no previous treatment; measurable disease; tumor within an estimated irradiation field no larger than half the hemithorax; age between 20 and 74 years; Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; adequate bone marrow function (12.0×10^9/liter ≥ white blood cell [WBC] count ≥4.0×10^9/liter, neutrophil count ≥2.0×10^9/liter, hemoglobin ≥10.0 g/dl, and platelet count ≥100×10^9/liter), liver function (total bilirubin ≤1.5 mg/dl and transaminase no more than twice the upper limit of the normal value), and renal function (serum creatinine ≤1.5 mg/dl and creatinine clearance ≥60 ml per minute); and a PaO_2 of 70 torr or more under room air conditions. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonia or lung fibrosis identified by a chest x-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or if they were breast feeding. All patients gave their written informed consent.

Pretreatment Evaluation

The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest x-rays, chest computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan or ultrasonography, and radionuclide bone scan.

Treatment Schedule

Treatment consisted of a chemoradiotherapy phase with three cycles of cisplatin and vinorelbine followed by a consolidation phase with three cycles of docetaxel (Figure 1). Cisplatin 80 mg/m^2 was administered on days 1, 29, and 57 by intravenous infusion for 60 minutes with 2500 to 3000 ml of fluid for hydration. Vinorelbine diluted in 50 ml of normal saline was administered intravenously on days 1, 8, 29, 36, 57, and 64. All patients received prophylactic antiemetic therapy consisting of a $5HT_3$-antagonist and a steroid.

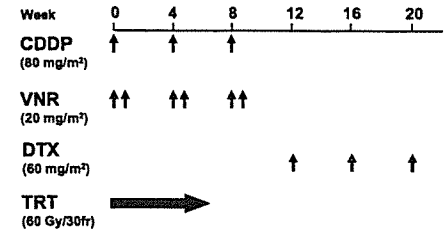

FIGURE 1. Treatment schema. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

Radiation therapy was delivered with megavoltage equipment (≥6 MV) using anterior/posterior opposed fields up to 40 Gy in 20 fractions including the primary tumor, the metastatic lymph nodes, and the regional nodes. A booster dose of 20 Gy in 10 fractions was given to the primary tumor and the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique fields. A CT scan–based treatment planning was used in all patients. The clinical target volume (CTV) for the primary tumor was defined as the gross tumor volume (GTV) plus 1 cm taking account of subclinical extension. CTV and GTV for the metastatic nodes (>1 cm in shortest dimension) were the same. Regional nodes, excluding the contralateral hilar and supraclavicular nodes, were included in the CTV, but the lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The planning target volumes for the primary tumor, the metastatic lymph nodes, and regional nodes were determined as CTVs plus 0.5- to 1.0-cm margins laterally and 1.0- to 2.0-cm margins craniocaudally, taking account of setup variations and internal organ motion. Lung heterogeneity corrections were not used.

The criteria for starting consolidation chemotherapy were completion of three cycles of cisplatin and vinorelbine and a full dose of thoracic radiotherapy, the absence of progressive disease, adequate general condition within 6 weeks of the start of the third cycle of cisplatin and vinorelbine (PS 0 or 1, WBC count ≥3.0×10^9/liter, neutrophil count ≥1.5×10^9/liter, hemoglobin ≥9.0 g/dl and platelet count ≥100×10^9/liter, total bilirubin ≤1.5 mg/dl and transaminase no more than twice the upper limit of the normal value, and a PaO_2 of 70 torr or more at room air). Docetaxel (60 mg/m^2) was administered intravenously for 1 hour every 3 to 4 weeks for three cycles.

Toxicity Assessment and Treatment Modification

Complete blood cell counts and differential counts, routine chemistry determinations, and a chest x-ray were performed once a week during the course of treatment. Acute toxicity was graded according to the NCI Common Toxicity Criteria, and late toxicity associated with thoracic radiother-

apy was graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. Vinorelbine administration on day 8 was omitted if any of the following were noted: WBC count $<3.0 \times 10^9$/liter, neutrophil count $<1.5 \times 10^9$/liter, platelet count $<100 \times 10^9$/liter, elevated hepatic transaminase level or total serum bilirubin of at least grade 2, fever ≥38°C, or PS ≥2. Subsequent cycles of cisplatin and vinorelbine chemotherapy were delayed if any of the following toxicities were noted on day 1: WBC count $<3.0 \times 10^9$/liter, neutrophil count $<1.5 \times 10^9$/liter, platelet count $<100 \times 10^9$/liter, serum creatinine level ≥1.6 mg/dl, elevated hepatic transaminase level or total serum bilirubin of at least grade 2, fever ≥38°C, or PS ≥2. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level rose to 2.0 mg/dl or higher. The dose of vinorelbine or docetaxel was reduced by 25% in all subsequent cycles if any of the following toxicities were noted: WBC count $<1.0 \times 10^9$/liter, platelet count $<10 \times 10^9$/liter, or grade 3 or 4 infection or liver dysfunction. Thoracic radiotherapy was suspended if any of the following were noted: fever ≥38°C, grade 3 esophagitis, PS of 3, or PaO_2 <70 torr. Thoracic radiotherapy was terminated if any of the following were noted: grade 4 esophagitis, grade 3 or 4 pneumonitis, PS of 4, or duration of radiotherapy of over 60 days. The use of granulocyte colony-stimulating factor during radiotherapy was not permitted unless radiotherapy was on hold. The criteria for termination of docetaxel consolidation were not defined in the protocol.

Response Evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumor.[11] Local recurrence was defined as tumor progression in the primary site and in the hilar, mediastinal, and supraclavicular lymph nodes after a partial or complete response; regional recurrence as the development of malignant pleural and pericardial effusions; and distant recurrence as the appearance of a distant metastasis.

Study Design, Data Management, and Statistical Considerations

This study was conducted at three institutions: the National Cancer Center Hospital, National Cancer Center Hospital East, and Tochigi Cancer Center. The protocol and consent form were approved by the institutional review board of each institution. Registration was conducted at the registration center. Data management, periodic monitoring, and the final analysis were performed by the study coordinator.

The primary objective of the current study was to evaluate the feasibility of docetaxel consolidation therapy. The secondary endpoints were toxicity observed during chemoradiotherapy and consolidation therapy, the best response, and overall survival in all patients eligible to participate in this study. Because no standard method to evaluate consolidation chemotherapy after chemoradiotherapy has been established, we arbitrarily defined the primary endpoint of this study as a ratio (R) of the number of patients receiving docetaxel without grade 4 nonhematological toxicity or treatment-related death to the total number of patients receiving docetaxel. The sample size was initially estimated to be 34 patients with a power of 0.80 at a significance level of 0.05, under the assumption that a R of 0.95 would indicate potential usefulness, whereas a R of 0.8 would be the lower limit of interest, and that 85% of patients would move into the consolidation phase. An analysis of the first 13 patients, however, showed that only 8 (61%) patients advanced into the consolidation phase. The reasons for not receiving docetaxel were disease progression in one, delay in completion of chemoradiotherapy in two, grade 3 esophagitis in one, and death due to hemoptysis in one patient. Considering that the SWOG trial S9504 included 83 patients, we decided to revise the number of patients in the current study. According to Simon's two-stage minimax design, the required number of patients was calculated to be 59 with a power of 0.80 at a significance level of 0.05, under the assumption that a R of 0.85 would indicate potential usefulness, whereas a R of 0.7 would be the lower limit of interest.[12] Assuming that 61% of registered patients would move into the consolidation phase, the sample size was determined to be 97 patients.

Overall survival time and progression-free survival time were estimated by the Kaplan–Meier method, and confidence intervals (CI) were based on Greenwood's formula.[13] Overall survival time was measured from the date of registration to the date of death (from any cause) or to the last follow-up. Progression-free survival time was measured from the date of registration to the date of disease progression, death (from any cause), or the last follow-up. Patients who were lost to follow-up without event were censored at the date of their last known follow-up. A CI for RR was calculated using methods for exact binomial CIs. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for statistical analyses.

RESULTS

Registration and Characteristics of the Patients

A total of 97 patients were enrolled in this study between April 2001 and June 2003. Four patients were excluded from this study before the treatment was started because the radiation treatment planning disclosed that their tumors were too advanced for curative thoracic radiotherapy. Thus, 93 patients who received the protocol-defined treatment were the subjects of this analysis (Figure 2). There were 76 males and 17 females, with a median age of 60 (range 31–74). Body weight loss was less than 5% in 77 patients; adenocarcinoma histology was noted in 57 patients, and stage IIIA disease was noted in 41 patients (Table 1).

Treatment Delivery

Treatment delivery was generally well maintained in the chemoradiotherapy phase (Table 2). Full cycles of cisplatin and vinorelbine and the full dose of thoracic radiotherapy were administered in 80 (86%) and 87 (94%) patients, respectively. Delay in radiotherapy was less than 5 days in 61 (66%) patients. In contrast, the delivery of docetaxel was poor (Table 2). A total of 59 (63%) patients could enter the consolidation phase, and only 34 (37%) patients completed three cycles of docetaxel chemotherapy. The reasons for not

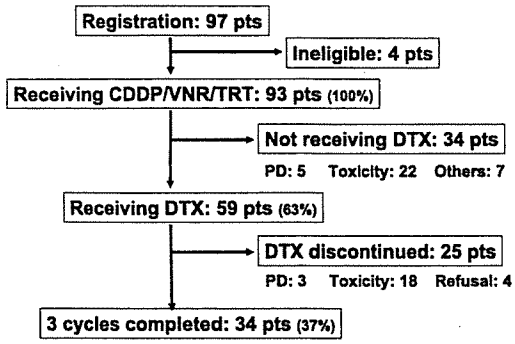

FIGURE 2. Patient registration. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

receiving consolidation were toxicity in 22 (65%) patients including pneumonitis in seven patients, myelosuppression in five patients, esophagitis in four patients, liver dysfunction in two patients, infection in two patients, other toxicity in two patients, progressive disease in five (15%) patients, patient refusal in three (9%) patients, early death due to hemoptysis in one (3%) patient, and other reasons in three (9%) patients. Of the 59 patients, 18 (31%) discontinued docetaxel consolidation because of toxicity, including pneumonitis (n = 14) and esophagitis, infection, gastric ulcer, and allergic reaction (n = 1 each), four (7%) because of patient refusal, and three (5%) because of progressive disease.

Toxicity

Acute severe toxicity in the chemoradiotherapy phase was mainly leukopenia and neutropenia, whereas grade 3 or 4 thrombocytopenia was not noted (Table 3). Severe nonhematological toxicity was sporadic, and grade 3 esophagitis and pneumonitis were observed in only 11 (12%) and 3 (3%) patients, respectively. Acute severe toxicity in the consolidation phase also consisted of neutropenia and associated infection (Table 4). In addition, grade 3 or 4 pneumonitis developed in 4 (7%) patients. The R observed in this study was 0.05 (3 out of 57 patients), which was much lower than the hypothetical value. Grade 3 or 4 late toxicities were included lung toxicity in four patients, esophageal toxicity in two patients, renal toxicity in one patient, and a second esophageal cancer that developed 35.4 months after the start of the chemoradiotherapy in one patient. Treatment-related

TABLE 1. Patient Characteristics

Characteristics	n	%
Gender		
Male	76	82
Female	17	18
Age median (range)	60	31–74
Weight loss		
<5%	76	81
5–9%	12	13
≥10%	3	3
Unknown	2	2
Histology		
Adenocarcinoma	57	61
Squamous cell carcinoma	23	25
Large cell carcinoma	12	13
Others	1	1
Stage		
IIIA	41	44
IIIB	52	56

TABLE 2. Treatment Delivery

Variables	n	%
Cisplatin and vinorelbine chemotherapy		
Total number of cycles		
3	80	86
2	10	11
1	3	3
Number of vinorelbine skips		
0	63	68
1	25	27
2–3	5	5
Thoracic radiotherapy		
Total dose (Gy)		
60	87	94
50–59	4	4
<50	2	2
Delay (days)		
<5	61	66
5–9	20	22
10–16	6	6
Not evaluable (<60 Gy)	6	6
Docetaxel consolidation		
Number of cycles		
3	34	37
2	12	13
1	13	14
0	34	34

TABLE 3. Acute Toxicity in Chemoradiotherapy (n = 93)

	Grade			
Toxicity	3	4	3 + 4	%
Leukopenia	54	18	72	77
Neutropenia	33	29	62	67
Anemia	21	0	21	23
Infection	15	1	16	17
Esophagitis	11	0	11	12
Hyponatremia	11	0	11	12
Anorexia	9	1	10	11
Nausea	5	—	5	5
Pneumonitis	3	0	3	3
Syncope	2	0	2	2
Hyperkalemia	2	0	2	2
Ileus	0	1	1	1
Cardiac ischemia	1	0	1	1

TABLE 4. Acute Toxicity in Consolidation Therapy (n = 57)

Toxicity	Grade 3	Grade 4	Grade 3 + 4	%
Leukopenia	33	11	44	77
Neutropenia	24	26	50	88
Anemia	5	0	5	9
Infection	5	1	6	11
Esophagitis	2	0	2	3
Anorexia	1	0	1	2
Pneumonitis	2	2	4	7

death was observed in four (4%) patients. Of these, three received docetaxel, and one did not. The reason for death was pneumonitis in all patients. We calculated a V_{20} (the percent volume of the normal lung receiving 20 Gy or more) on a dose–volume histogram in 25 patients. Of these, five patients developed grade 3 or severer radiation pneumonitis. A median V_{20} for these five patients was 35% (range, 26–40%), whereas that for the remaining 20 patients was 30% (range, 17–35%) (p = 0.035 by a Mann–Whitney test).

Objective Responses, Relapse Pattern, and Survival

All 93 patients were included in the analyses of tumor response and survival. Complete and partial responses were obtained in 5 (5%) and 71 patients (76%), respectively, for an overall RR of 81.7% (95% CI, 72.7–88.0%). Stable and progressive diseases occurred in 12 (13%) and 5 (5%) patients, respectively. With a median follow-up period of 29.7 months, 38 patients developed locoregional recurrence, 32 developed distant recurrence, 4 developed both locoregional and distant recurrences, and 19 did not. The median progression-free survival time was 12.8 (95% CI, 10.2–15.4) months (Figure 3). Two patients underwent salvage surgery for a recurrent primary tumors. Conventional chemotherapy and gefitinib monotherapy were administered after recurrence in 20 and 25 patients, respectively. The median overall survival time was 30.4 (95% CI, 24.5–36.3) months. The 1-, 2-, and 3-year survival rates were 80.7, 60.2, and 42.6%, respectively. (Figure 4).

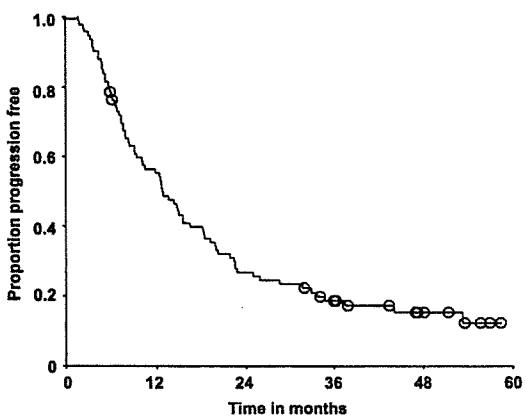

FIGURE 3. Progression-free survival (n = 93). The median progression-free survival time was 12.8 (95% CI, 10.2–15.4) months.

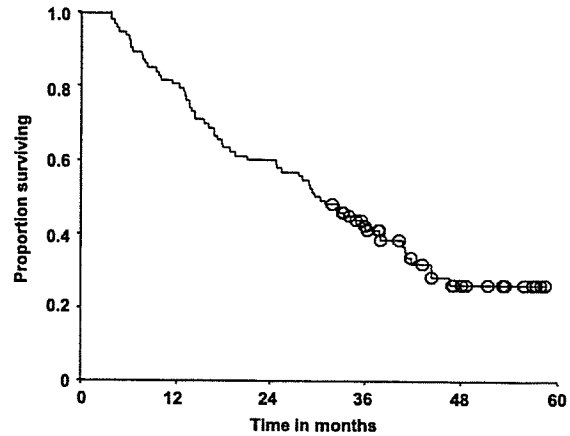

FIGURE 4. Overall survival (n = 93). The median overall survival time was 30.4 (95% CI, 25.4–35.4) months. The 1-, 2-, and 3-year survival rates were 80, 60, and 40%, respectively.

DISCUSSION

This study showed that concurrent chemoradiotherapy with cisplatin, vinorelbine, and standard thoracic radiotherapy was well tolerated, with a high completion rate exceeding 80%. The incidence of acute toxicity, including 67% (62/93) of grade 3 or 4 neutropenia, 12% (11/93) of grade 3 esophagitis, and 3% (3/93) of grade 3 pneumonitis, were comparable with other reports of concurrent chemoradiotherapy.[3,4,10] In contrast, consolidation docetaxel could be administered in only 59 of 93 (63%) patients eligible to participate in this study. Of the remaining 34 patients, 22 (65%) patients did not receive consolidation chemotherapy because of toxicities affecting various organs. Other studies also showed that not all patients proceeded to the consolidation phase after completion of concurrent chemoradiotherapy: 61 to 78% of patients after two cycles of cisplatin and etoposide with radiotherapy,[3,10] and 54 to 75% of patients after weekly carboplatin and paclitaxel with radiotherapy.[14,15] Thus, for 20 to 40% of the patients, concurrent chemoradiotherapy was as much as they could undergo, and the additional chemotherapy was not practical.

Furthermore, the number of patients who fulfilled the three cycles of consolidation docetaxel was only 34 (58%) of the 59 patients, which corresponded to only 37% of those eligible in this study. The reason for the termination of docetaxel in the 25 patients was toxicity in 18 (72%) patients, especially pneumonitis in 14 (56%) patients. The grade of pneumonitis during the consolidation phase was within grade 2 in most cases, and this was probably because docetaxel was discontinued early. Considering that pneumonitis associated with cancer treatment is more common in Japan, docetaxel consolidation is not thought to be feasible in the Japanese population. The MST and the 3-year survival rate in all eligible patients were 33 months and 44% in this study, but docetaxel consolidation was unlikely to contribute to these promising results because only 37% of patients received full cycles of docetaxel. This contrasts clearly with the result of

the SWOG study S9504, a phase II trial of two cycles of cisplatin and etoposide with thoracic radiation followed by three cycles of docetaxel. In this trial, 75% of patients starting consolidation and 59% of those entering the trial received full cycles. In addition, docetaxel consolidation seemed to prolong survival, although this was drawn from a retrospective comparison of the results between the two SWOG studies S9504 and S9019.[10]

There is no widely used definition of consolidation therapy following chemoradiotherapy. Given that consolidation therapy is arbitrarily defined as chemotherapy with three cycles or more after the completion of concurrent chemoradiotherapy, only one randomized trial is available in the literature. The randomized phase III trial of standard chemoradiotherapy with carboplatin and paclitaxel followed by either weekly paclitaxel or observation in patients with stage III NSCLC showed that only 54% of patients proceeded to randomization, and overall survival was worse in the consolidation arm (MST, 16 versus 27 months).[15] Thus, there have been no data supporting the use of consolidation therapy, especially when a third-generation cytotoxic agent such as paclitaxel and vinorelbine is incorporated into concurrent chemoradiation therapy.

The low complete-response rate of 5% in this study may be explained partly by an inability to distinguish between inactive scarring or necrotic tumor and active tumor after radiotherapy. Positron emission tomography (PET) using 18F-fluorodeoxyglucose showed a much higher rate of complete response than conventional CT scanning and provided a better correlation of the response assessment using PET with patterns of failure and patient survival.[16] In addition, the high locoregional relapse rate in this study clearly showed that the conventional total dose of 60 Gy was insufficient. Three-dimensional treatment planning, omission of elective nodal irradiation, and precise evaluation of the gross tumor volume by PET may facilitate the escalation of the total radiation dose without enhanced toxicity.

In conclusion, cisplatin and vinorelbine chemotherapy concurrently combined with standard thoracic radiotherapy and followed by docetaxel consolidation produced promising overall survival in patients with stage III NSCLC, but the vast majority of patients could not continue with the docetaxel consolidation because of toxicity.

ACKNOWLEDGMENTS

We thank residents and staff doctors in the National Cancer Center Hospital, National Cancer Center Hospital East, and Tochigi Cancer Center for their care of patients and valuable suggestions and comments on this study. We would also like to thank Fumiko Koh, Yuko Yabe, and Mika Nagai for preparation of the manuscript.

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

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VOLUME 24 · NUMBER 1 · JANUARY 1 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

First-Line Single Agent Treatment With Gefitinib in Patients With Advanced Non–Small-Cell Lung Cancer: A Phase II Study

Seiji Niho, Kaoru Kubota, Koichi Goto, Kiyotaka Yoh, Hironobu Ohmatsu, Ryutaro Kakinuma, Nagahiro Saijo, and Yutaka Nishiwaki

From the Division of Thoracic Oncology, National Cancer Center Hospital East, Chiba, Japan.

Submitted May 2, 2005; accepted October 5, 2005.

Presented in part at the 40th Annual Meeting of the American Society of Clinical Oncology, New Orleans, LA, June 5-8, 2004.

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

Address reprint requests to Seiji Niho, MD, Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwanoha 6-5-1, Kashiwa, Chiba 277-8577, Japan; e-mail: siniho@east.ncc.go.jp.

0732-183X/06/2401-64/$20.00

DOI: 10 1200/JCO.2005.02.5825

ABSTRACT

Purpose
We conducted a phase II study of single agent treatment with gefitinib in chemotherapy-naïve patients with advanced non–small-cell lung cancer (NSCLC) to assess its efficacy and toxicity.

Patients and Methods
Patients received 250 mg doses of gefitinib daily. Administration of gefitinib was terminated if partial response (PR) was not achieved within 8 weeks or if tumor reduction was not observed within 4 weeks. In these cases, platinum-based doublet chemotherapy was given as a salvage treatment. We evaluated mutation status of the epidermal growth factor receptor (EGFR) gene in cases with available tumor samples.

Results
Forty-two patients were enrolled between March and November 2003, with 40 of these patients being eligible. The response rate was 30% (95% CI, 17% to 47%). The most common toxicity included grade 1 or 2 acne-like rash (50%) and grade 1 diarrhea (18%). Grade 2 or 3 hepatic toxicity was observed in 8% of patients. Four patients developed grade 5 interstitial lung disease (ILD). Thirty patients received second-line chemotherapy. Median survival time was 13.9 months (95% CI, 9.1 to 18.7 months), and the 1-year survival rate was 55%. Tumor samples were available in 13 patients, including four cases of PR, six cases of stable disease, and three cases of progressive disease. *EGFR* mutations (deletions in exon 19 or point mutations [L858R or E746V]) were detected in four tumor tissues. All four patients with *EGFR* mutation achieved PR with gefitinib treatment.

Conclusion
Single agent treatment with gefitinib is active in chemotherapy-naïve patients with advanced NSCLC, but produces unacceptably frequent ILD in the Japanese population.

J Clin Oncol 24:64-69. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Previous meta-analysis demonstrated that cisplatin-based chemotherapy yielded a modest but significant survival benefit over best supportive care in advanced non–small-cell lung cancer (NSCLC).[1-4] In the 1990s, new agents, including vinorelbine, gemcitabine, paclitaxel, docetaxel, and irinotecan became available for the treatment of NSCLC. Several phase III trials comparing doublet platinum-based chemotherapies demonstrated no significant difference with respect to response rate, survival, or quality of life.[5,6] Nonplatinum or triplet platinum-based combination chemotherapies have been investigated, but none of these produced longer survival than standard doublet platinum-based chemotherapy.[7-9]

Recently, molecular-targeted agents have been introduced for the treatment of NSCLC. Gefitinib is an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, which displays activity against recurrent NSCLC after platinum-based chemotherapy. Two international, randomized phase II trials in patients with advanced or metastatic NSCLC after platinum-based chemotherapy demonstrated response rates of 12% to 18% (28% in the Japanese population).[10,11] Two international, randomized, double-blinded, placebo-controlled phase III trials investigated the role of gefitinib combined with platinum-based chemotherapy regimens, including carboplatin and paclitaxel, or cisplatin and gemcitabine in chemotherapy-naïve patients with advanced NSCLC.[12,13] Surprisingly, there were no improvements in overall survival,

time to progression, or response rate. There are no data available regarding first-line treatment with single agent gefitinib against NSCLC in the Japanese population. Here, we conducted a phase II study of single agent treatment with gefitinib in chemotherapy-naïve patients with advanced NSCLC. If a failure with gefitinib treatment was perceived, standard platinum-based doublet chemotherapy was performed as salvage. The primary end point of this phase II trial was response rate, and the secondary end points were toxicity, survival, and response rate of salvage chemotherapy.

PATIENTS AND METHODS

Patient Population

Patients were required to have histologically or cytologically confirmed stage IIIB (malignant pleural or pericardial effusion and/or metastasis in the same lobe) or stage IV NSCLC. Recurrences after surgical resection were permitted. Other criteria included: (1) age 20 years or older, but younger than 75 years; (2) Eastern Cooperative Oncology Group performance status (PS) 0 or 1; (3) measurable disease; (4) PaO2 $\geq$ 60 mmHg; (5) adequate organ function (ie, total bilirubin $\leq$ 2.0, AST and ALT $\leq$ 100 U/L, serum creatinine $\leq$ 1.5 mg/dL, leukocyte count 4,000 to 12,000/mm^3, neutrophil count $\geq$ 2,000/mm^3, hemoglobin $\geq$ 9.5 g/dL, and platelets $\geq$ 100,000/mm^3); (6) no prior chemotherapy or thoracic radiotherapy; (7) no interstitial pneumonia or pulmonary fibrosis, as determined by chest x-ray; (8) no paralytic ileus or vomiting, (9) no symptomatic brain metastases, (10) no active infection; (11) no active concomitant malignancy; (12) no pregnancy or breast-feeding; (13) no severe allergy to drugs. Patients with PaO2 less than 60 mmHg were excluded, because those patients might have pulmonary fibrosis, which is a risk factor of interstitial lung disease (ILD).[14] All patients were required to provide written informed consent and the institutional review board at the National Cancer Center approved the protocol.

Treatment Plan

Treatment was started within a week after enrollment in the study. Patients received 250 mg of gefitinib orally daily. In the event of grade 3 or more and/or unacceptable toxicities, gefitinib was postponed until these toxicities were improved to grade 2 or less. Dose reduction was not performed. If treatment was postponed four times or more, the treatment was terminated. Therapy was continued unless the patient experienced unacceptable toxicity or progressive disease, partial response (PR) was not achieved within 8 weeks, or the sum of the longest diameters of the target lesions decreased less than 10% within 4 weeks. If the gefitinib treatment failed according to these criteria, platinum-based doublet chemotherapy was performed as a salvage regimen.

Previous trials of gefitinib for pretreated patients with NSCLC reported that most responding patients showed rapid tumor regression within 4 or 8 weeks.[11] Furthermore, most responses by gefitinib were extreme shrinkage of the tumor. Minor response, as frequently seen by the treatment with cytotoxic agents, was seldom experienced. Stable disease with gefitinib corresponded to no tumor reduction or slight progression. If patients with stable disease continued the treatment with gefitinib until progressive disease became obvious, those patients might not be able to receive platinum-based salvage chemotherapy because of poor PS due to progressive disease. Platinum-based combination chemotherapy is the standard care for patients with advanced NSCLC and good PS. Platinum-based chemotherapy was thought to be essential for patients with no response from the first-line single agent treatment with gefitinib. Therefore, we implemented these early stopping criteria for treatment with gefitinib.

Study Evaluations

Pretreatment evaluations consisted of a complete medical history, determination of performance status, physical examination, hematologic and biochemical profiles, arterial blood gas examination, ECG, chest x-ray, bone scan, and computed tomography (CT) scan of the chest, ultrasound or CT scan of the abdomen, and magnetic resonance imaging or CT scan of the whole brain. Evaluations performed included a weekly chest x-ray for 4 weeks, and once every 2 weeks for biochemistry, complete blood cell, platelet, leukocyte differential counts, physical examination, determination of performance status, and toxicity assessment. Imaging studies were scheduled to assess objective response every month.

Response and Toxicity Criteria

Response evaluation criteria in solid tumors (RECIST) guidelines were used for evaluation of antitumor activity.[15] The target lesions were defined as $\geq$ 2 cm in the longest diameter on CT scans. A complete response (CR) was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks. A PR was defined as an at least 30% decrease in the sum of the longest diameters of the target lesions for more than 4 weeks with no new area of malignant disease. Progressive disease (PD) indicated at least a 20% increase in the sum of the longest diameter of the target lesions or a new malignant lesion. Stable disease was defined as insufficient shrinkage to qualify for PR and insufficient increase to qualify for PD. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.

Mutation Analysis of the EGFR Gene

Tumor specimens were obtained during diagnostic or surgical procedures. Biopsied or surgically resected specimens were fixed with formalin or 100% methanol, respectively. Tumor genomic DNA was prepared from paraffin-embedded sections using laser capture microdissection in biopsied specimens or macrodissection in surgically resected specimens at Mitsubishi Chemical Safety Institute LTD. Exons 18, 19, and 21 of the *EGFR* gene were amplified and sequenced as previously described.[16]

Statistical Analysis

In accordance with the minimax two-stage phase II study design by Simon,[17] the treatment program was designed to refuse response rates of 10% (P_0) and to provide a significance level of .05 with a statistical power of 80% in assessing the activity of the regimen as a 25% response rate (P_1). The upper limit for first-stage drug rejection was two responses in the 22 assessable patients; the upper limit of second-stage rejection was seven responses within the cohort of 40 assessable patients. Overall survival was defined as the interval between enrollment in this study and death or the final follow-up visit. Median overall survival was estimated by the Kaplan-Meier analysis method.[18] Fisher's exact test was used in a contingency table.

RESULTS

Patient Population

A total of 42 patients were enrolled in this study between March and November, 2003, with 40 of these patients being eligible. One patient was found ineligible due to anemia, the other because spinal magnetic resonance imaging could not confirm a positive bone scan. Patient characteristics are listed in Table 1. Sixty percent of patients were male; median age was 61 years. The most common histologic subtype was adenocarcinoma (75%). Most patients (93%) had stage IV disease or recurrence after surgical resection. Eighty percent of patients were current or former smokers.

Efficacy

One patient (3%) has been receiving gefitinib after 22 months. Four patients suspended gefitinib for 11, 14, 27, or 29 days, because of liver dysfunction (n = 3) and fever due to urinary tract infection (n = 1). Thirty-nine patients terminated gefitinib because of progressive disease (n = 20), no tumor reduction within 4 weeks (n = 12), not achieving PR within 8 weeks (n = 1), toxicities including pulmonary (n = 3), nausea and vomiting (n = 1), rash (n = 1), or hepatic dysfunction (n = 1).

There were 12 PRs in 40 eligible patients, and the objective response rate was 30% (95% CI, 17% to 47%; Table 2). All but one