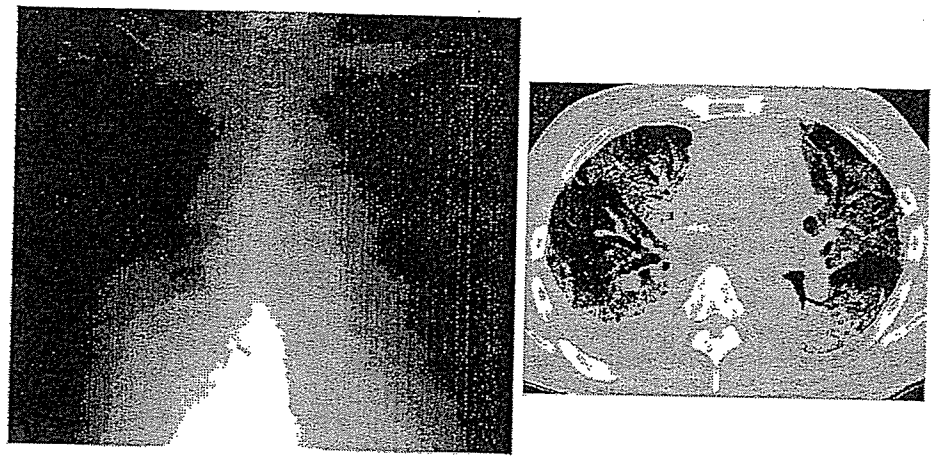

(a) (b)

Fig. 3 A 62-year-old male who had undergone right upper lobectomy complained of the acute onset of dyspnea on day 5 after the start of gefitinib therapy. The anterio-posterior chest radiography shows diffuse ground-glass densities in the lung parenchyma (a). The CT scan shows extensive bilateral ground-glass attenuation and airspace consolidations with traction bronchiectasis (b). The patient died 10 days after the onset of ILD despite treatment by steroid pulse therapy.

pulmonary edema, diffuse alveolar damage (DAD), eosinophilic pneumonia, BOOP, and chronic interstitial pneumonitis with fibrosis [9,10]. Since Akira et al. reported that the pulmonary damage by antineoplastic drugs was for the most part due to a direct cytotoxic effect and that a ground-glass attenuation was often seen on diagnostic images [10], it was assumed that the pulmonary damage caused by gefitinib was also attributable to a direct cytotoxic effect in the same way, but there is still no evidence that would make it possible to confirm that. There have been few studies on the relationship between the imaging findings and fatal cases in ILD caused by gefitinib [2,4]. In the present study the mortality rate was significantly higher in the patients with pattern D than in the patients with the other patterns. Pattern D was thought to represent the features of DAD, and this finding was consistent with the report by Ichikado et al. that traction bronchiectasis was an important prognostic CT finding in AIP [14]. On the other hand, some patients with pattern A died. However, they may have included patients whose findings should have been classified as pattern D, because the CT scanning conditions differed considerably from institution to institution and/or because breath-holding by some of the patients may have been insufficient. It is also a report claiming that ground-glass attenuation corresponds to DAD pathologically [12], and for that reason it appears that it should be borne in mind that the pattern A group may also have included cases with a poor prognosis. On the other hand, the mortality rate of pattern C was low, the same another report [12].

The AstraZeneca Expert Committee Meeting Report claims that the CT findings in ILD related by gefitinib mainly consist of patchy or diffuse ground-glass opacification and/or consolidation, and that there were no differences from the imaging findings in drug-related ILD that had been reported in the past [8]. It stated that pathological examination of the fatal cases showed that DAD was the main cause of death, and although no pathological assessment was conducted, the imaging findings in our own cases with a poor outcome suggested the same.

74.3% of the patients with gefitinib-related ILD had pre-existing pulmonary emphysema and 20% had IPF. Most of the patients had some pulmonary changes, including changes associated with surgery or radiotherapy, but the pre-existing changes were not statistically related to the imaging patterns of ILD or mortality due to ILD. Takano et al. reported that IPF was a significant risk factor for ILD according to the results of a multivariate analysis [15], but they said nothing in regard to associations with the outcome after the onset of

Table 3 Frequency of pulmonary comorbidities in surviving patients and fetal cases

Pulmonary comorbidities	Total (n = 70)	Surviving patients (n = 39)	Fetal cases (n = 31)	p
Emphysema	52 (74.3%)	29 (74.4%)	23 (74.2%)	0.987
Idiopathic pulmonary fibrosis	14 (20.0%)	8 (20.5%)	6 (19.4%)	0.904
Old inflammation	20 (28.6%)	8 (20.5%)	12 (38.7%)	0.094
Thoracic irradiation	16 (22.9%)	9 (23.1%)	7 (22.6%)	0.941
Post-resection	17 (24.3%)	12 (30.8%)	5 (16.1%)	0.156
None	6 (8.6%)	3 (7.7%)	3 (9.7%)	0.768

symptoms. The AstraZeneca Expert Meeting Report, on the other hand, states that IPF is a risk factor for ILD, and at the same time that it might be a negative-prognostic factor [8]. While there seems to be no doubt that IPF is a risk factor for ILD, we would like to await a future assessment of the association with the outcome.

This study is of great significance in terms of being the first to analyze the diagnostic images of a large number of patients for pulmonary toxicity caused by a single drug, because previous studies on drug-induced pulmonary toxicity have been limited to a single center, or are an accumulation of case report [9–12]. However, this study had several limitations: (1) the CT scanning and display conditions differed from center to center, (2) thin-section CT, which is most reliable method for the diagnosis of diffuse lung disease, was performed in a small number of patients, and (3) the diagnosis of pulmonary toxicity was based on the classification of images into known patterns in the absence of pathological evidence. However, depending on the condition of patients with ILD, the diagnosis of ILD must often be made on the basis of plain chest radiography alone. Ordinary CT may add diagnostically important information, even when breath-holding is poor, and be useful in indicating the extent of the damage or whether the image pattern predicts a high probability of death. Therefore, accurate diagnosis of ILD in the early stage based on the clinical course as well as the chest radiography and/or CT findings may be important for early treatment.

In conclusion, this is the first study to demonstrate that the molecular-targeting drug gefitinib induces pulmonary toxicity at a certain rate and that the imaging findings of ILD related by gefitinib are similar to those of pulmonary toxicity related by conventional antineoplastic agents. Physicians planning to use gefitinib in the future should be thoroughly familiar with these imaging findings.

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ORIGINAL REPORT

Predictive Factors for Interstitial Lung Disease, Antitumor Response, and Survival in Non–Small-Cell Lung Cancer Patients Treated With Gefitinib

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ABSTRACT

Purpose
Interstitial lung disease (ILD) is a serious adverse effect of gefitinib, but its prevalence and risk factors remain largely unknown. We examined the prevalence of and risk factors for gefitinib-induced ILD associated with practical use of the drug in Japanese with non–small-cell lung cancer (NSCLC).

Patients and Methods
Clinical information was retrospectively assembled for NSCLC patients who started gefitinib treatment at affiliated institutions of the West Japan Thoracic Oncology Group between August 31 and December 31, 2002. Medical records of patients who developed pulmonary infiltrates were reviewed by a central committee of extramural experts for identification of patients with gefitinib-induced ILD. Multivariate logistic or Cox regression analysis was performed to identify independent predictive factors for ILD, antitumor response, and survival.

Results
Seventy cases of and 31 deaths from gefitinib-induced ILD were identified among 1,976 consecutively treated patients at 84 institutions, corresponding to a prevalence of 3.5% and mortality of 1.6%. Gefitinib-induced ILD was significantly associated with male sex, a history of smoking, and coincidence of interstitial pneumonia (odds ratios = 3.10, 4.79, and 2.89, respectively). Predictive factors for response were female sex, no history of smoking, adenocarcinoma histology, metastatic disease, and good performance status (PS), whereas predictive factors for survival were female sex, no history of smoking, adenocarcinoma histology, nonmetastatic disease, good PS, and previous chest surgery.

Conclusion
ILD is a serious adverse effect of gefitinib in the clinical setting that cannot be ignored. However, patient selection based on sex and smoking history can minimize ILD risk and maximize the clinical benefit of gefitinib.

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INTRODUCTION

The discovery that signaling by the epidermal growth factor receptor (EGFR) plays an important role in tumorigenesis prompted efforts to target this receptor in anticancer therapy, leading to the development of inhibitors of its tyrosine kinase activity.[1-3] Gefitinib, an orally active inhibitor of the EGFR tyrosine kinase, is a leading agent in the field of EGFR-targeted therapy.[4,5] Two large phase II trials involving previously treated patients with advanced non–small-cell lung cancer (NSCLC) revealed that gefitinib monotherapy was well tolerated and manifested clinically meaningful antitumor activity.[6,7] Objective responses that were both rapid and persistent were apparent at a dose of 250 mg/d in 12% to 18% of patients; the median survival time was 7 to 8 months, with a 1-year survival rate of 27% to 35%, and the most common adverse effects were rash and diarrhea, which were generally mild. Similar response and survival rates were apparent at a dose of 500 mg/d but were accompanied by a higher frequency of adverse events. Higher response rates were apparent in women, Japanese patients, patients with no history of smoking, and patients with adenocarcinoma.[6-8]

Gefitinib was licensed in Japan for the treatment of inoperable or recurrent NSCLC in July 2002. Soon after its introduction, however, life-threatening interstitial lung disease (ILD) attributed to the drug became apparent, despite the absence of severe cases of ILD in the preceding phase I and II

trials, which included a total of 132 Japanese patients.[6,9-11] The publicity associated with this unexpected severe adverse event led to concern among patients and physicians about the risks of taking gefitinib. Although the prevalence of gefitinib-associated ILD in Japan was estimated at approximately 2%, this estimate was based only on case series studies, with no systematic survey allowing direct determination of the prevalence and identification of risk factors for gefitinib-induced ILD having been performed.[12]

In the present study, the West Japan Thoracic Oncology Group (WJTOG) conducted a retrospective survey of 1,976 individuals with NSCLC, representing all the patients who started gefitinib treatment at 84 WJTOG-affiliated institutions between August 31 and December 31, 2002. We examined the prevalence of and risk factors for gefitinib-induced ILD in this Japanese patient population. The therapeutic efficacy of gefitinib was also evaluated to assess risk and benefit in real-life use of gefitinib.

PATIENTS AND METHODS

Study Patients

To collect all data of the potential patients with gefitinib-induced ILD, we initially asked 112 affiliated institutions of WJTOG to report the number of NSCLC patients who started gefitinib treatment between August 31 and December 31, 2002 and subsequently developed pulmonary infiltrates. We also asked them to report the total number of patients who started gefitinib treatment during the same period. After confirming the number of potential cases and total patients, we sent case report forms to the respective institutions and asked them to provide demographic and clinical data for the patients. We finally updated the information of all the patients concerning pulmonary infiltrates, antitumor response, and survival status on December 31, 2003, providing an observation period of at least 12 months. This study was approved by the Review Board of the WJTOG.

Confirmation of Gefitinib-Induced ILD

For patients who developed pulmonary infiltrates, in addition to the information collected on case report forms, we obtained detailed clinical data, including chest roentgenograms and computed tomograms taken before and after gefitinib administration; results of examination of bronchoalveolar lavage fluid or lung biopsies when performed at the onset of pulmonary infiltration; laboratory data obtained at the onset of pulmonary infiltration; gefitinib treatment duration before the development of pulmonary infiltrates; and details of treatment for the pulmonary injury. All this information was submitted to a central review committee of extramural experts, comprising at least three thoracic radiologists, one pulmonologist, and one oncologist, for determination of whether each patient indeed developed gefitinib-induced ILD. The committee reviewed all available information including findings of bronchoscopy, clinical course after development of pulmonary infiltrates, and radiologic findings. An infectious etiology was excluded on the basis of extensive microbiologic analysis of blood or other cultures, bronchoalveolar lavage examinations, and titers of antimicrobial antibodies. All experts evaluated the data together to reach unanimous final decisions.

Demographic and Clinical Variables

The following pretreatment demographic and clinical information was obtained from case report forms and evaluated for its relationship to gefitinib-induced ILD: age, sex, smoking status, Eastern Cooperative Oncology Group performance status (PS), coincidental complications, histology, disease stage, body-surface area (BSA), and previous anticancer treatments. Smoking status was classified as no history of smoking (smoking a total of < 100 cigarettes) or a positive history. With regard to coincidental complications, we assessed the presence of pulmonary diseases, diabetes mellitus, and sequelae of previous treatment such as radiation pneumonitis. Disease stage was determined according to the TNM system.[13] Previous anticancer treatment was classified as surgery, radiotherapy, or chemotherapy. We obtained additional information about the field, dose, and modality of radiotherapy and about the regimen, dose, and number of treatment cycles for chemotherapy. We also collected information about antitumor response and survival after the initiation of gefitinib treatment. We asked the participating institutions to report antitumor response according to the Response Evaluation Criteria in Solid Tumors Group criteria,[14] although it was not confirmed extramurally. Overall survival was calculated from the initiation of gefitinib treatment to the date of death. Patients still alive were censored as of the last known follow-up. Survival data were last updated on December 31, 2003.

Statistical Analysis

Variables were examined for association with ILD development or antitumor response by univariate analysis with the χ^2 test or Fisher's exact test. Multivariate logistic regression analysis was performed to identify predictors of ILD development or antitumor response.[15] Survival curves were calculated by the Kaplan-Meier method and compared with the log-rank test. Prognostic importance of factors was analyzed with the Cox regression model.[16] In multivariate analysis, a forward stepwise procedure was used to select factors for inclusion in the final model with a cutoff value of $P = .2$. For detection of possible synergistic effects of clinical factors, interaction terms of variables selected in the final model were sequentially included and evaluated by the likelihood ratio test. All significance levels were set at $P = .05$. Statistical analyses were performed with SAS version 9 software (SAS Institute, Cary, NC).

RESULTS

Prevalence and Mortality of Gefitinib-Induced ILD

A total of 1,976 patients with NSCLC from 84 (75%) of 112 institutions surveyed were reported as having started gefitinib treatment between August 31 and December 31, 2002 (Fig 1). Among these patients, 102 individuals developed pulmonary infiltrates after treatment initiation and were reported as potential cases of gefitinib-induced ILD. The central review committee evaluated the clinical data of these 102 patients and determined that 70 cases of ILD and 31 deaths were attributable to gefitinib, corresponding to a prevalence of 3.5% (95% CI, 2.8% to 4.5%) and a mortality of 1.6% (95% CI, 1.1% to 2.2%) for gefitinib-induced ILD. All ILD patients had been treated with gefitinib monotherapy, with the exception of one patient who received gefitinib concurrently with cisplatin. None of the ILD patients received radiotherapy simultaneously with gefitinib treatment. The median time from the start of gefitinib treatment to the development of ILD was 31 days (interquartile range, 18 to 50 days), and the median duration of gefitinib treatment before ILD development was 29 days (interquartile range, 18 to 49 days). Among the 70 patients with gefitinib-induced ILD, nine patients (13%) underwent bronchoscopic examination, including six lung biopsies and four bronchoalveolar lavages; all the lung biopsy specimens showed interstitial inflammation and fibrosis, and bronchoalveolar lavage revealed no signs (such as neutrophilia) of infection. Cultures of blood or other specimens were performed for 49 patients with ILD (70%), with no infection detected. After the development of gefitinib-induced ILD, 66 patients (94%) received corticosteroids, and additional antibiotic treatment in 17 of these patients did not increase the proportion of individuals whose ILD improved (18% and 61% with and without antibiotics, respectively).

Risk Factors for Gefitinib-Induced ILD

Of the 1,874 patients who did not develop pulmonary infiltrates, 245 individuals (13.1%) were excluded from further analysis because of insufficient clinical information (Fig 1). We also excluded the 11

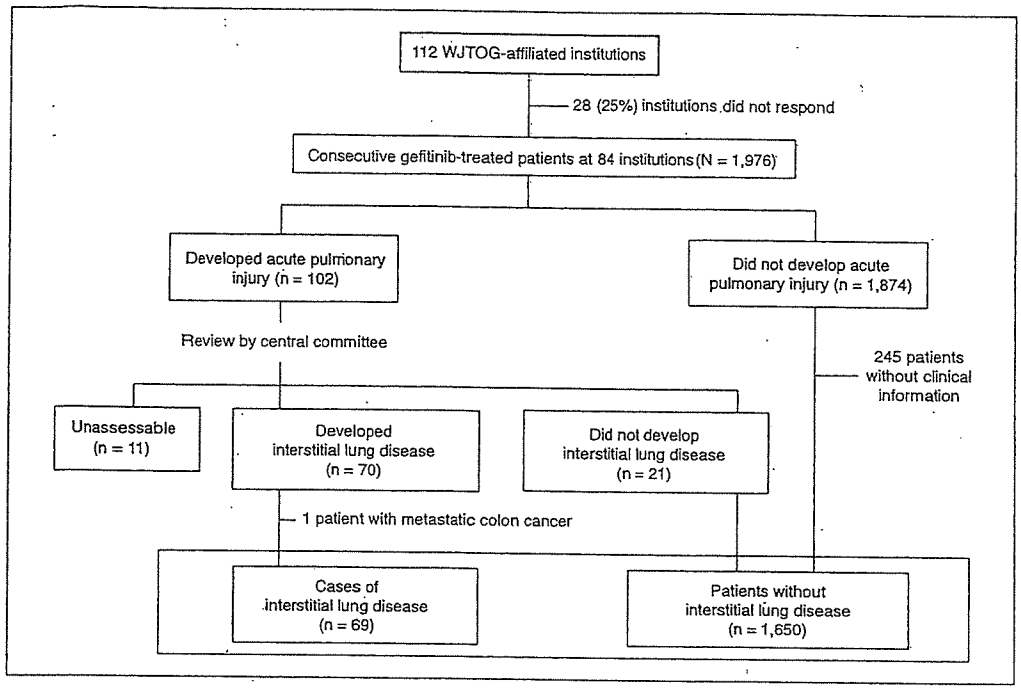

Fig 1. Outline of patient recruitment and classification. WJTOG, West Japan Thoracic Oncology Group.

unassessable patients with pulmonary infiltrates as well as one confirmed patient with gefitinib-induced ILD whose lung tumor proved to be metastatic colon cancer. Therefore, a total of 1,719 patients (69 patients with gefitinib-induced ILD and 1,650 patients without ILD) were subjected to subsequent analyses to identify predictive factors for the development of ILD, antitumor response, and survival. Among these 1,719 patients, 1,599 individuals (93%) received gefitinib as a monotherapy, whereas 71 and 49 individuals received gefitinib simultaneously with chemotherapy or palliative radiation, respectively. Univariate analysis identified male sex, a history of smoking, and the coincidence of interstitial pneumonia as being associated with the development of ILD (Table 1). Multivariate logistic regression analysis revealed sex, smoking status, and coincidence of interstitial pneumonia as independent risk factors for gefitinib-induced ILD; BSA was also selected in a forward stepwise procedure and included in the multivariate analysis to adjust for its potential confounding effect, although it was not significant in the final model (Table 2). A potential interaction between sex and smoking status was not significant ($P = .399$). The adjusted odds ratio for development of ILD was 20.5 (95% CI, 4.9 to 85.7) for males with a history of smoking compared with females with no history of smoking. Among 1,671 patients with known smoking status, the prevalence of ILD ranged from 0.4% in women with no history of smoking to 6.6% in men with a history of smoking (Table 3).

Predictive Factors for Antitumor Response

An antitumor response was observed in 348 of the total of 1,976 patients (including 256 unassessable patients), corresponding to a response rate of 17.6% (95% CI, 16.0% to 19.4%). Univariate analysis revealed that an age of less than 70 years, female sex, no history of smoking, adenocarcinoma histology, metastatic disease, good PS, a history of chest surgery, no history of chest irradiation, the absence of interstitial pneumonia, and a BSA of less than 1.5 m^2 were associated with an antitumor response (Table 1). Multivariate logistic regression analysis revealed that sex, smoking status, histology, disease stage, and PS were independently associated with response rate (Table 4). No synergistic effect on antitumor response was apparent between sex and smoking status, sex and histology, or smoking status and histology ($P = .514$, .734, and .573, respectively). The adjusted odds ratio for an antitumor response was 9.2 (95% CI, 5.5 to 15.3) for women with adenocarcinoma and no history of smoking compared with male smokers with a nonadenocarcinoma histology.

Predictive Factors for Survival

We confirmed 1,076 deaths among the study population as of December 31, 2003. Overall, the median survival time and 1-year survival rate were 312 days (interquartile range, 114 to 579 days) and 44.8% (95% CI, 42.3% to 47.2%), respectively. Univariate analysis identified female sex, no history of smoking, adenocarcinoma histology, nonmetastatic disease, good PS, previous chest surgery, no history of chest irradiation, the absence of interstitial pneumonia or diabetes, and a BSA of less than 1.5 m^2 as being associated with longer survival (Table 1). Cox regression analysis showed that sex, smoking status, histology, disease stage, PS, and previous chest surgery were independent prognostic factors (Table 5). No synergistic effect on survival was observed between sex and smoking status, sex and histology, or smoking status and histology ($P = .490$, .785, and .531, respectively). Given that previous chemotherapy status is a clinically important factor, we re-examined the survival data separately according to chemotherapy history (Table 6). Survival curves for patients with metastatic disease and a history of chemotherapy (according to independent prognostic factors identified in the Cox regression model) are shown in Figure 2.

DISCUSSION

We have evaluated clinical data from 1,976 patients with advanced NSCLC who were treated with gefitinib since its licensure in Japan.

Table 1. Relationship Between Clinical Variables and ILD, Antitumor Response, and Survival in Non–Small-Cell Lung Cancer Patients Treated With Gefitinib

Variable	ILD				Antitumor Response				Survival		
	Total No. of Patients	Patients With ILD			Total No. of Patients	Responders			Total No. of Patients	Median Survival (days)	
		No.	%	*P*		No.	%	*P*			*P*
Age, years											
< 70	1,047	39	3.7	.446	1,042	230	22.1	.027	1,044	296	.418
≥ 70	672	30	4.5		670	118	17.6		669	339	
Sex											
Female	631	6	1.0	< .001	627	222	35.4	< .001	631	499	< .001
Male	1,088	63	5.8		1,086	126	11.6		1,082	230	
Smoking status											
No smoking history	659	5	0.8	.001	655	225	34.5	.001	656	467	< .001
Positive smoking history	1,015	63	6.2		1,012	116	11.5		1,008	227	
Histology											
Adenocarcinoma	1,294	47	3.6	.130	1,288	311	24.2	< .001	1,291	362	< .001
Others	414	22	5.3		414	34	8.2		411	190	
Disease stage											
Metastatic	1,416	59	4.5	.069	1,410	296	22.6	.001	1,409	280	.001
Nonmetastatic	296	10	2.5		293	52	12.9		404	435	
Performance status											
0-1	1,161	44	3.8	.664	1,157	274	23.7	< .001	1,157	441	< .001
2	336	14	4.2		336	47	14.0		335	147	
3-4	216	11	5.1		214	26	12.2		216	67	
Previous chest surgery											
Yes	528	15	2.8	.093	527	128	24.8	.008	527	466	.001
No	1,181	54	4.6		1,177	220	18.7		1,176	253	
Previous thoracic RT											
Yes	472	18	3.8	.767	471	73	15.5	.002	468	263	.005
No	1,235	51	4.1		1,230	273	22.2		1,233	335	
Previous chemotherapy											
Yes	1,356	57	4.2	.440	1,351	275	20.4	.937	1,353	301	.900
No	365	12	3.3		362	73	20.2		360	345	
Coincidence of IP											
Yes	36	5	13.9	.013*	36	1	2.8	.008	35	103	< .001
No	1,683	64	3.8		1,677	347	20.7		1,678	317	
Coincidence of diabetes											
Yes	285	17	5.9	.086	285	121	14.1	.45	285	190	.002
No	1,434	52	3.6		1,428	336	20.6		1,428	322	
Coincidence of renal failure											
Yes	10	1	10.0	.333*	10	2	20.0	.99*	10	353	.588
No	1,707	67	3.9		1,701	346	20.3		1,701	312	
Body surface area, m²											
< 1.5	755	30	4.0	.796	751	197	26.2	.001	755	355	.001
≥ 1.5	976	37	3.8		971	135	13.9		972	280	

Abbreviations: ILD, interstitial lung disease; RT, radiotherapy; IP, interstitial pneumonia.
*Calculated using Fisher's exact test.

The present study constitutes the first large-scale survey designed to assess the prevalence of and risk factors for gefitinib-induced ILD during practical use of this drug in the Japanese population. The development of ILD subsequent to treatment with conventional cytotoxic chemotherapeutic agents has been recognized for many years, with the use of standard drugs for treatment of NSCLC being associated with ILD at a prevalence of up to 5%.[17,18] Drug-induced ILD in lung cancer patients is difficult to diagnose because of the high prevalence of pre-existing lung disease and respiratory tract infections as well as the progressive malignancy in such individuals. Clinical symptoms of ILD, such as escalating dyspnea, cough, and fever, may be indistinguishable from the symptoms of progressive tumor growth or infection. Computed tomographic features of ILD include pulmonary reticular changes and ground-glass opacity, which are also nonspecific and may not readily indicate a precise etiology.[18] Diagnosis of drug-induced ILD thus relies on rigorous exclusion of all other differential diagnoses, especially those of infection and tumor progression.

In the present study, all suspected cases of ILD were meticulously reviewed at a single study site by extramural experts, including at least three thoracic radiologists, one pulmonologist, and one oncologist, taking into account clinical history, the results of clinical examination, and comparisons of current and previous radiologic findings. Seventy patients with gefitinib-related ILD were thereby confirmed, yielding an overall prevalence of 3.5% and mortality of 1.6%. The prevalence of

Table 2. Risk Factors for Interstitial Lung Disease Identified by Multivariate Logistic Regression Analysis (n = 1,586*)

Variable	Odds Ratio	95% CI	P
Male	3.10	1.15 to 8.36	.025
Positive smoking history	4.79	1.69 to 13.54	.003
Coincidence of IP	2.89	1.06 to 7.84	.038
BSA of < 1.5 m^2	1.67	0.98 to 2.83	.059

Abbreviations: IP, interstitial pneumonia; BSA, body-surface area.
*Including 66 patients with gefitinib-induced interstitial lung disease.

Table 4. Predictive Factors for Antitumor Response Identified by Multivariate Logistic Regression Analysis (n = 1,650*)

Variable	Odds Ratio	95% CI	P
Female	2.74	1.95 to 2.95	< .001
No smoking history	2.13	1.53 to 2.96	< .001
Adenocarcinoma	1.97	1.31 to 2.96	.001
Metastatic disease	1.88	1.32 to 2.67	< .001
Performance status†			
2	0.51	0.38 to 0.72	< .001
3-4	0.17	0.07 to 0.46	< .001

*Including 338 responders.
†Performance status of 0 to 1 set as reference category.

ILD in our study was slightly higher than the prevalence (1.1%) among gefitinib-treated patients in recent phase III trials of standard chemotherapy with or without gefitinib conducted in the United States and Europe.[19,20] In addition, the worldwide prevalence of ILD among 92,750 patients treated with gefitinib was approximately 1%, being approximately 0.3% in a US AstraZeneca Expanded Access Program.[21,22] The reason for the difference in the frequency of gefitinib-related ILD between Japan and Western countries remains unclear. It is possible that a greater awareness of the disease in Japan might lead to more careful and critical examination for ILD or that Japanese may have an increased genetic susceptibility to ILD.[22]

The mechanism of gefitinib-induced ILD has not been fully elucidated. EGFR and transforming growth factor alpha, a member of the EGF family of proteins that binds to and activates the EGFR, are both upregulated early in the response to acute lung injury,[23,24] and EGF family members are implicated in the repair of pulmonary damage.[25,26] In a rodent model of bleomycin-induced pulmonary fibrosis, treatment with gefitinib was shown to augment fibrosis.[27] These findings suggest that inhibition of EGFR signaling by gefitinib impairs the repair of and, thereby, exacerbates pulmonary injury, especially in patients with pulmonary comorbidities. In the present study, we have sought to identify clinical features of NSCLC patients that might increase the risk for development of ILD. Multivariate analysis identified male sex, a history of smoking, and coincidence of interstitial pneumonia as significant risk factors. Thus, the prevalence of gefitinib-induced ILD differed markedly according to sex and smoking status, ranging from 0.4% in females with no history of smoking to 6.6% in male smokers.

This is the first study in which predictive factors for ILD, antitumor response, and survival have been evaluated with the same data set. Multivariate analysis showed that sex, smoking status, tumor histology, disease stage, and PS were independently associated with both antitumor response and survival, mostly consistent with results of previous studies.[6-8] Although not confirmed by multivariate analysis, a smaller BSA might also confer greater efficacy on gefitinib, with further investigation of possible dose dependency being warranted. Female sex and the absence of a history of smoking were both associated with a lower risk for ILD, a higher response rate, and longer survival, suggesting that patient selection on the basis of this favorable profile will not only increase the clinical benefit of treatment with gefitinib but also reduce the risk for development of this life-threatening toxicity. Activating mutations of the EGFR have been identified in a subset of NSCLC patients, and tumors with EGFR mutations are highly sensitive to gefitinib.[28,29] However, these genetic factors have not been confirmed to be predictive of true clinical benefit because they have not yet been found to be associated with survival in NSCLC patients treated with gefitinib.[30] These previous studies showed that EGFR mutations were more frequent in females, individuals with no history of smoking, and patients with adenocarcinoma. We have no data on the frequency of EGFR mutations in the present patient cohort, and further studies to explore the relationship of genetic alterations with ILD risk and treatment efficacy are warranted.

The objective response rate in the present study was 17.6%, which is indicative of an acceptable single-agent activity of gefitinib outside clinical trial settings. Our data showed the median survival time and 1-year survival rate to be 10.0 months and 44%, respectively,

Table 3. Prevalence of ILD, Response Rate, and 1-Year Survival According to Sex and Smoking Status (n = 1,671)

	No Smoking History		Positive Smoking History	
Measure	Female	Male	Female	Male
Prevalence of ILD				
%	0.4	1.8	3.3	6.6
95% CI	0.0 to 1.5	0.4 to 5.3	0.9 to 8.2	2.1 to 14.1
Response rate				
%	38.2	22.1	23.1	9.9
95% CI	33.9 to 42.6	16.0 to 29.2	16.0 to 31.7	8.0 to 12.0
1-year survival				
%	64.6	54.7	50.7	32.4
95% CI	60.2 to 69.0	47.2 to 62.2	41.6 to 59.8	23.9 to 41.0

Abbreviation: ILD, interstitial lung disease.

Table 5. Survival Analysis by the Cox Regression Model (n = 1,643*)

Variable	Hazard Ratio	95% CI	P
Female	0.69	0.59 to 0.75	< .001
No smoking history	0.71	0.60 to 0.84	< .001
Adenocarcinoma	0.69	0.59 to 0.80	< .001
Metastatic disease	1.58	1.35 to 1.84	< .001
Performance status†			
2	2.58	2.29 to 2.90	< .001
3-4	4.71	3.71 to 5.98	< .001
Previous chest surgery	0.70	0.60 to 0.81	< .001

*Including 611 patients censored.
†Performance status of 0 to 1 set as reference category.

Table 6. Median Survival Time and 1-Year Survival According to Clinical Factors

Variable	Chemotherapy Naive			Previously Treated With Chemotherapy		
	No. of Patients	Median Survival Time (days)	1-Year Survival Rate (%)	No. of Patients	Median Survival Time (days)	1-Year Survival Rate (%)
Sex						
Female	131	401	64.0	500	502	61.9
Male	229	263	36.8	855	217	33.8
Smoking status						
No smoking history	137	433	60.7	521	482	60.1
Positive smoking history	208	263	36.8	800	217	33.8
Histology						
Adenocarcinoma	266	378	51.8	1,025	356	49.2
Other	89	216	29.7	327	199	29.2
Disease stage						
Metastatic	254	299	41.4	1,055	274	40.8
Nonmetastatic	106	433	58.5	298	435	57.0
Performance status						
0-1	225	433	56.6	932	413	57.2
2	65	204	31.2	270	141	18.7
3-4	70	91	26.7	145	69	10.1
Previous chest surgery						
Yes	131	481	63.6	396	462	57.5
No	224	247	36.7	952	262	39.0

in all patients who received gefitinib after the failure of prior chemotherapy. Given that the present study included many elderly and patients with a poor PS, these survival data do not differ substantially from those obtained with the Japanese cohort of a phase II study (11.8 months and 50%, respectively).[6] These findings suggest that gefitinib treatment in clinical practice may lead to clinical benefit as it did in the clinical trials. Furthermore, the survival data in the present study are similar to those obtained with previously treated patients with a PS of 0 to 2 in a phase III trial of docetaxel (7.5 months and 37%, respectively), which is a standard second-line treatment for NSCLC.[30] These observations emphasize the importance of further comparison of gefitinib with docetaxel as a second-line treatment for NSCLC in ongoing phase III studies. In previous phase III clinical trials, however, gefitinib failed to prolong survival in unselected patients, suggesting

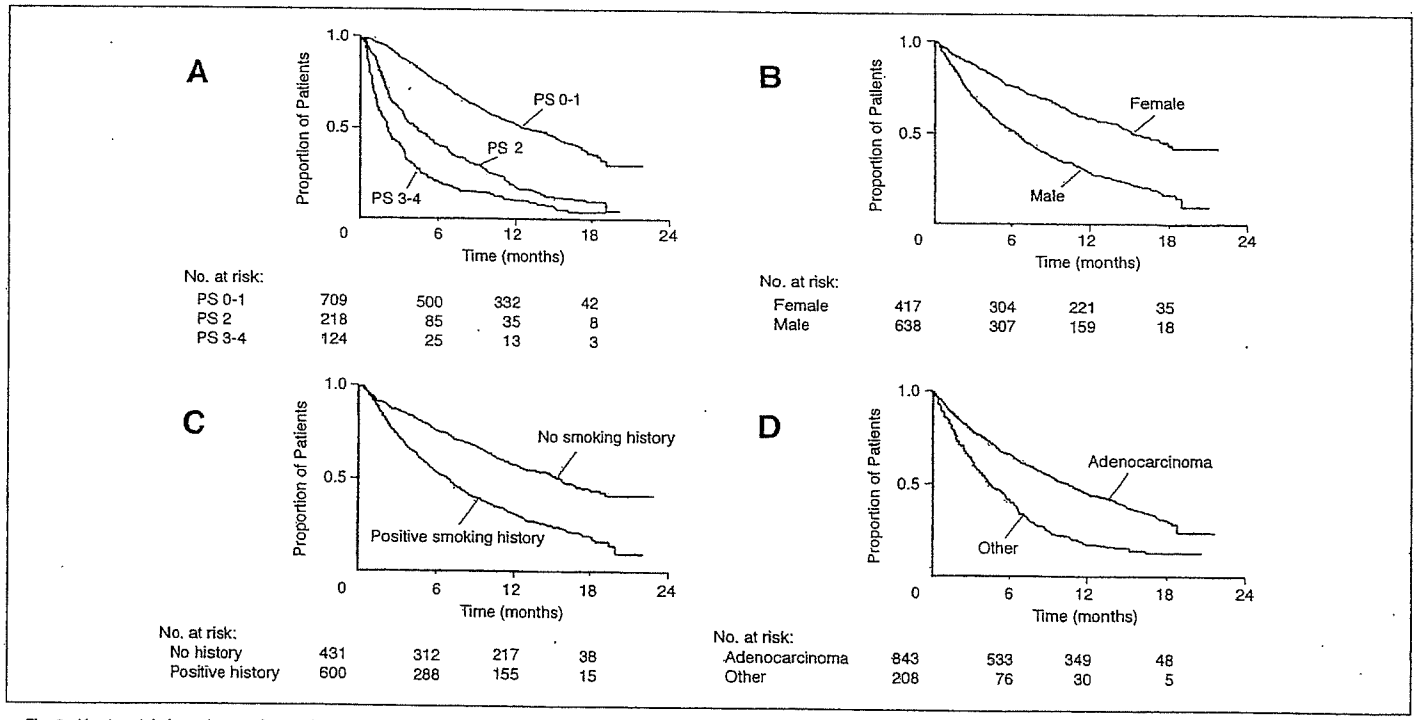

Fig 2. Kaplan-Meier plots of survival for patients with metastatic non–small-cell lung cancer previously treated with chemotherapy classified according to (A) performance status (PS), (B) sex, (C) smoking status, and (D) histology.

the necessity for patient selection on the basis of clinical or genetic factors if true clinical benefit is to be achieved from gefitinib treatment.[19,20,31] Indeed, a randomized phase III trial is now planned in Asian countries to assess the effect of gefitinib on survival in patients selected on the basis of clinical profile.

In conclusion, we have determined the prevalence of gefitinib-related ILD and identified risk factors for this life-threatening adverse event in a large population of Japanese patients with NSCLC treated with this drug. Our data confirmed an acceptable single-agent activity of gefitinib in routine clinical practice. We found that female sex and the absence of a history of smoking, which were known predictive factors for the efficacy of gefitinib, were also associated with a lower risk of gefitinib-induced ILD. Thus, our results indicate that patient selection on the basis of clinical factors can simultaneously minimize the risk of life-threatening ILD and maximize the clinical benefit of gefitinib treatment. They provide both important insight into individual risk-benefit assessment for gefitinib therapy in the practical setting as well as a basis for the planning of future clinical trials to accurately define the scope for gefitinib treatment in NSCLC patients.

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Appendix

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

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Randomized Phase II Study of Carboplatin/Gemcitabine versus Vinorelbine/Gemcitabine in Patients With Advanced Nonsmall Cell Lung Cancer

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BACKGROUND. Combined gemcitabine and carboplatin (GC) and combined gemcitabine and vinorelbine (GV) are active and well tolerated chemotherapeutic regimens for patients with advanced nonsmall cell lung cancer (NSCLC). The authors conducted a randomized Phase II study of GC versus GV to compare them in terms of efficacy and toxicity.

METHODS. One hundred twenty-eight patients with Stage IIIB or IV NSCLC were randomized to receive either carboplatin at an area under the curve of 5 on Day 1 combined with gemcitabine 1000 mg/m^2 on Days 1 and 8 ($n = 64$ patients) or vinorelbine 25 mg/m^2 combined with gemcitabine 1000 mg/m^2 on Days 1 and 8 ($n = 64$ patients) every 3 weeks.

RESULTS. Response rates were 20.3% for the GC patients and 21.0% for the GV patients. In the GC arm, the median survival was 432 days, and the a 1-year survival rate was 57.6%; in the GV arm, the median survival was 385 days, and the 1-year survival rate was 53.3% in the GV arm. The median progression-free survival was 165 days in the GC arm and 137 days in the GV arm. Severe hematologic toxicity (Grade 4) was significantly more frequent in the GC arm (45.3% vs. 25.8% in the GV arm; $P = .022$). Most notably, the incidence of Grade 3 or 4 thrombocytopenia was significantly higher in the GC arm (81.3% vs. 6.5% in the GV arm; $P < .001$). Conversely, severe nonhematologic toxicity (Grade 3 or 4) was more common in the GV arm (7.8% vs. 19.4% in the GC arm; $P = .057$).

CONCLUSIONS. Although the GV and GC regimens had different toxicity profiles, there was no significant difference in survival among patients with NSCLC in the current study. *Cancer* **2006;107:599–605.** © *2006 American Cancer Society.*

KEYWORDS: gemcitabine, carboplatin, vinorelbine, nonsmall cell lung cancer.

Unfortunately, nonsmall cell lung cancer (NSCLC) belongs to a group of relatively chemoresistant neoplastic diseases. Recent meta-analyses have shown that cisplatin-based chemotherapy regimens improve survival,[1] and they now are considered standard treatment for patients with NSCLC. Most cisplatin-based regimens have substantial toxicities that require close monitoring and supportive care. Thus, active and less toxic chemotherapeutic regimens that include new, active compounds with novel mechanisms of action need to be developed. The recommendations recently presented in the American Society Clinical Oncology guidelines for chemotherapy in patients with Stage IV NSCLC stated that nonplatinum-containing chemotherapeutic regimens may be used as alternatives to platinum-based regimens as first-line treatment.[2,3]

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Carboplatin, which is an analog of cisplatin, administered either alone or in combination therapy, is associated with less emesis, nephrotoxicity, and neurotoxicity than cisplatin and has been proven to be as effective as cisplatin in NSCLC.[4,5] Several novel chemotherapeutic agents currently are being evaluated for the treatment of patients with advanced NSCLC. The combination of gemcitabine and carboplatin (GC) is a promising carboplatin-containing regimen and has been evaluated in several randomized trials. Mazzanti et al. conducted a randomized Phase II study of GC versus gemcitabine and cisplatin (GP) and observed no differences in activity between the 2 regimens, although there was less emesis, neuropathy, and renal toxicity with GC.[6] The same results were confirmed in a Phase III study of GC versus GP that was conducted by Zatloukal et al.[7] Moreover, GC reportedly prolonged survival significantly compared with single-agent carboplatin in a randomized Phase III study.[8]

The combination of gemcitabine and vinorelbine (GV) is among the representative nonplatinum regimens. GV has demonstrated promising activity and mild toxicity in some Phase II studies. We also conducted a Phase II trial of GV in patients with Stage IIIB and IV NSCLC and observed that toxicity was modest and was managed easily, and overall survival was promising (median survival, 13.9 months).[9] Several randomized Phase III trials have shown that this regimen conferred a comparable survival advantage and was less toxic than standard cisplatin-based chemotherapy.[10,11]

Thus, we can state reasonably that both GC and GV are attractive alternatives to cisplatin-based chemotherapy. However, we have neither survival data nor toxicity data for GC in Japanese patients with NSCLC. Therefore, we conducted a randomized Phase II trial of GC versus GV in patients with advanced NSCLC to compare the efficacy, feasibility, and toxicity profiles of the 2 regimens. The primary endpoint was the 1-year survival rate, and secondary endpoints were overall survival, the time to progression, and the response rate.

MATERIALS AND METHODS

Patient Selection

The patients who were enrolled in this trial had histologically or cytologically confirmed Stage IIIB or IV NSCLC. Patients with Stage IIIB disease who were not candidates for thoracic radiation and patients with Stage IV disease were eligible if they had not received previous chemotherapy, had measurable disease, and had a life expectancy $\geq$3 months. Patients who had received previous radiotherapy were included if they had assessable disease outside of the radiation field. Patients with who had postoperative recurrences also were allowed. Additional entry criteria were age between 20 years and 74 years, a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale, and adequate bone marrow function (leukocyte count $\geq$3500/μL, neutrophil count $\geq$2000/μL, hemoglobin concentration $\geq$10.0 g/dL, platelet count $\geq$ 100,000/μL), kidney function (creatinine $\leq$1.2 mg/dL), liver function (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels $\leq$2.5 times the upper limit of normal; and total bilirubin $\leq$1.5 mg/dL), and pulmonary function (partial pressure of alveolar oxygen $\geq$60 torr). Patients were excluded if they had any active concomitant malignancies, symptomatic brain metastases, prior radiotherapy to the sole site of measurable disease, past history of severe allergic reactions to drugs, interstitial pneumonia identified by chest X-ray, cirrhosis, superior vena cava syndrome, or other serious complications, such as uncontrolled angina pectoris, myocardial infarction within 3 months, heart failure, uncontrolled diabetes mellitus or hypertension, and uncontrolled massive pleural effusion or ascites. All patients gave written informed consent, and the Institutional Review Board for Human Experimentation approved the protocol.

Randomization and Treatment Plan

Patients were assigned randomly to receive the GC regimen or the GV regimen and were stratified by disease stage (Stage IIIB vs. Stage IV), prior treatment (yes vs. no), and institution. On the GC regimen, gemcitabine was given at a dose of 1000 mg/m^2 in 100 mL of normal saline solution as a 30-minute intravenous infusion on Days 1 and 8. Carboplatin was administered at area under the curve (AUC) of 5 in 500 mL of normal saline solution as a 60-minute intravenous infusion on Day 1 only. We used the Calvert formula[12] to determine the dose of carboplatin as follows: dose in mg = target AUC $\times$ (creatinine clearance + 25). The glomerular filtration rate was estimated by using the formula described by Gault et al.[13]

The GV regimen consisted of gemcitabine 1000 mg/m^2 in 100 mL of normal saline solution as a 30-minute intravenous infusion and vinorelbine 25 mg/m^2 in 20 mL of normal saline solution as a 5-minute intravenous infusion on Days 1 and 8. The scheduled Day-8 treatment was delayed until recovery (no longer than 1 week) if patients had a leukocyte count <2000/μL, platelet count <75,000/μL, interstitial pneumonia Grade $\geq$1, constipation Grade $\geq$3, and/or other nonhematologic toxicities Grade $\geq$2. If these parameters did not improve sufficiently, then the Day-8 gemcitabine and vinorelbine doses were omitted.

Both regimens were repeated every 3 weeks. The subsequent course of chemotherapy was begun if patients had a leukocyte count $\geq$3000/μL, neutrophil count $\geq$1500/μL, platelet count $\geq$100,000/μL, creatinine $\leq$1.5 mg/dL, AST and ALT levels $\leq$2.5 times the upper limit of normal, and total bilirubin $\leq$1.5 times the upper limit of normal. A 2-week delay in initiating the subsequent course was allowed. Otherwise, the patient was withdrawn from the study. We planned for patients to receive at least 3 cycles, up to a maximum 6 cycles, of chemotherapy unless there was evidence of disease progression, intolerable toxicity, or patient refusal.

For dose modification in the subsequent cycle in both arms, if, during the previous course, Grade 4 leukopenia, chemotherapy-induced neutropenic fever >38°C, thrombocytopenia (< 20,000/μL), nonhemotologic toxicity Grade $\geq$3, or cancellation of Day-8 treatment had occurred, then the doses of gemcitabine, vinorelbine, and carboplatin were reduced by 200 mg/m^2, 5 mg/m^2, and AUC 1, respectively. Treatment was discontinued in patients who could not tolerate either gemcitabine 800 mg/m^2 and carboplatin AUC 4 or gemcitabine 800 mg/m^2 and vinorelbine 20 mg/m^2.

It was acceptable to administer a 5-hydroxytriptamine receptor antagonist and/or dexamethasone intravenously before the start of chemotherapy to prevent nausea and emesis. The use of granulocyte-colony stimulating factors was not allowed during treatment except in patients who had Grade 4 leukopenia, Grade 4 neutropenia, or febrile neutropenia, according to the investigator's decision. Transfusions of red blood cells and platelets were allowed in patients who had Grade $\geq$3 anemia and in patients who had platelet counts $\leq$20,000/μL and/or a tendency for bleeding.

Treatment Evaluation

Before enrollment in the study, all patients provided a complete medical history and underwent physical examination. We obtained a complete blood count, blood chemistry, blood gas analysis, chest X-ray, electrocardiography, computed tomographic (CT) scans of the brain and chest, a CT scan or ultrasound examination of the abdomen, and a bone scintigram. Patients were monitored weekly throughout treatment by physical examination, recording of toxic effects, complete blood cell counts, and blood chemistry. Studies of drug-related toxicities were evaluated according to National Cancer Institute Common Toxicity Criteria (version 2.0, revised 1994).

Tumor responses were classified according to the Response Evaluation Criteria in Solid Tumors.[14] In target lesions, a complete response (CR) was defined as the complete disappearance of all target lesions for a minimum of 4 weeks, during which no new lesions appeared. A partial response (PR) was defined as a decrease $\geq$30% in the sum of the greatest dimensions of target lesions for a minimum of 4 weeks. Progressive disease (PD) was defined as an increase $\geq$20% in the sum of the greatest dimensions of target lesions or the appearance of $\geq$1 new lesion(s). Stable disease (SD) was defined as neither sufficient shrinkage to qualify for a PR nor a sufficient increase to qualify for PD for a minimum of 6 weeks. Response duration in patients who achieved a CR or PR was measured from the start of treatment to the date of disease progression.

In nontarget lesions, a CR was defined as the disappearance of all nontarget lesions. An incomplete response/SD was defined as the persistence of $\geq$1 nontarget lesion(s). PD was defined as the appearance of $\geq$1 new nontarget lesion(s) and/or unequivocal progression of existing nontarget lesions. An extramural review was conducted to validate staging and responses during a regular meeting of the West Japan Thoracic Oncology Group.

Statistical Methods

The main objective of this study was to test whether either of the 2 regimens had promise in terms of increasing survival. Each arm was to be analyzed separately. One or both of the regimens would be considered promising if the true 1-year survival rates were $\geq$55%, or the regimens would be of no additional interest if the true 1-year survival rates were $\leq$32%. The study was designed to accrue 57 patients to each arm over 12 months followed by 1 additional year of follow-up to confer a power of 0.80 for a 1-sided .05 level for a 1-year survival rate of 32% versus 55%.

We compared Kaplan–Meier curves for overall survival and progression-free survival by using the standard log-rank test. Overall survival was defined as the interval from the date of random treatment assignment to the date of death or last follow-up information for patients who remained alive. Progression-free survival was defined as the interval from the date of random treatment assignment to the date of progression or death, whichever occurred first, or last follow-up information for patients who remained alive and for patients whose disease did not progress.

Patient characteristics except for age, response rates, dose reduction rate in each cycle, and toxicity incidence, were compared by using Pearson chi-square contingency table analysis. Age and the number of treatment cycles were compared by using the Wilcoxon test.

TABLE 1
Baseline Patient Characteristics

Characteristic	No. of patients GC	GV	P
Total no. of patients	64	64	
Gender			.851
Male/female	43/21	42/22	
Age, y			
Median	60	62	.929
Range	30–74	36–74	
PS			
0/1	25/39	24/40	.855
Smoking history			
Yes/no	18/46	27/37	.095
Histology			
Adenocarcinoma	36	45	.128
Squamous cell carcinoma	21	16	
Others	7	3	
Disease stage			
Stage IIIB/IV	16/48	16/48	1.000
Prior treatment			
Yes/no	15/49	14/50	.832

GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine; PS, performance status.

RESULTS

Patient Characteristics

From June 2001 to October 2002, 128 patients were assigned to receive GC ($n = 64$ patients) or GV ($n = 64$ patients). All enrolled patients were eligible. Baseline patient characteristics according to treatment arm are shown in Table 1. Patients essentially were divided equally between the 2 treatment arms in terms of gender, age, performance status, disease stage, and histologic subtypes. Patients with Stage IIIB disease accounted for 27% of the study population, and patients with adenocarcinoma accounted for 63% of the study population. In the GV arm, 2 patients did not receive trial therapy because of deterioration in their condition. These 2 patients were excluded from the analysis of toxicity, response, and progression-free survival.

Treatment Delivery

Median numbers of 3 cycles and 4 cycles were administered in the GC and GV arms, respectively. Three or more cycles were delivered to 76.6% and 72.6% of patients, and 6 cycles were delivered to 7.8% and 32.3% of patients in the GC and GV arms, respectively. Differences between arms in the number of chemotherapy courses administered were not statistically significant ($P = .161$) (Table 2).

Chemotherapy was omitted on Day 8 for 6.4% of patients in the GC arm and for 3.8% of patients in the GV arm. Dose reductions in the second cycle were more frequent in the GC arm than in the GV arm (49.2% vs. 14.8%, respectively; $P < .001$). The dose reduction rates after the second cycle did not differ between the 2 arms (Table 2). Most dose reductions in the GC arm were because of hematologic toxicity, especially thrombocytopenia. Reasons for stopping treatment also differed between the 2 arms; Treatment was stopped before 3 cycles for disease-related causes (progression or death) in 46.7% and 58.8% of patients and because of toxicity or refusal in 40.0% and 29.4% of patients in the GC and GV arms, respectively.

TABLE 2
Treatment Delivery and Dose Reduction Rate

No. of cycles	Gemcitabine and carboplatin: No. of patients (%)	Gemcitabine and carboplatin: No. of patients who required dose reduction (%)	Gemcitabine and vinorelbine: No. of patients (%)	Gemcitabine and vinorelbine: No. of patients requiring dose reduction (%)
2	61 (95.3)	30 (49.2)	54 (87.1)	8 (14.8)
3	49 (76.6)	6 (12.2)	47 (75.8)	6 (13.3)
4	29 (45.3)	2 (6.7)	34 (54.8)	2 (5.9)
5	9 (14.1)	2 (22.2)	24 (38.7)	1 (4.2)
6	5 (7.8)	0	20 (32.2)	0

Treatment Response and Survival

In the GC arm, there was 1 CR and 12 PRs for an overall response rate of 20.3%. In addition, 34 patients (53.1%) had SD, and 17 patients (26.6%) had PD. In the GV arm, there were 2 CRs and 11 PRs for an overall response rate of 21.0%. There were 29 patients (46.8%) with SD and 17 patients (27.4%) with PD. The difference in the overall response rate between the 2 arms was not significant ($P = .60$).

Overall and progression-free survival curves for the 2 treatment arms are shown in Figures 1 and 2. The 1-year survival rate was 57.6% (95% confidence interval, 45.5–69.8%) in the GC arm versus 53.3% (95% confidence interval, 40.8–65.7%) in the GV arm. Respective median survival, 2-year survival rates, and median progression-free survival were 432 days, 38.3%, and 165 days in the GC arm and 385 days, 22.4%, and 137 days in the GV arm. No significant differences were noted between groups in progression-free survival ($P = .676$) or overall survival ($P = .298$), although there were trends toward higher 1-year and 2-year survival rates in the GC arm.

After primary chemotherapy, 94 patients (73.4%) received other chemotherapeutic agents with no difference between the 2 arms (47 patients in the GC arm and 47 patients in the GV arm received other chemotherapeutic agents). In the GC arm, 27 patients

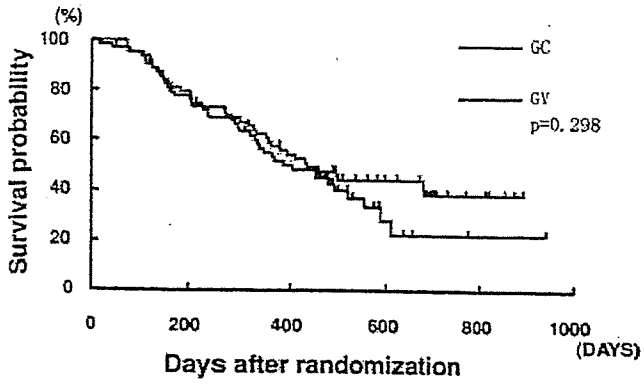

FIGURE 1. Overall survival is illustrated for the 2 treatment arms. GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine.

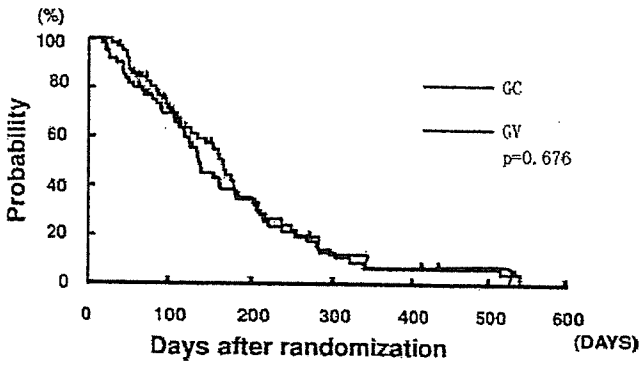

FIGURE 2. Progression-free survival is illustrated for the 2 treatment arms. GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine.

received a single anticancer agent (docetaxel, 17 patients; vinorelbine, 4 patients; gemcitabine, 3 patients; other agents, 3 patients). Platinum doublets were given to 12 patients (carboplatin and paclitaxel, 3 patients; cisplatin and docetaxel, 3 patients; carboplatin and docetaxel, 2 patients; other doublets, 4 patients). In the GV arm, 21 patients received platinum doublets (carboplatin and paclitaxel, 14 patients; carboplatin and docetaxel, 3 patients; other doublets, 4 patients). A single cytotoxic agent was given to 9 patients (docetaxel, 6 patients; vinorelbine, 1 patient; gemcitabine, 1 patient; other agents, 3 patients). There was a tendency for more patients to receive single-agent chemotherapy, whereas fewer patients received platinum doublets, in the GC arm. The number of patients who received gefitinib treatment apparently did not differ between the 2 arms (31 patients in the GC arm and 27 in the GV arm received gefitinib).

Toxicity

Severe hematologic toxicity (Grade 4) was significantly more frequent in the GC arm (45.3% vs. 25.8% in the GV arm; $P = .022$). Conversely, severe nonhematologic toxicity (Grade 3 or 4) occurred more often in the GV arm (7.8% vs. 19.4% in the GC arm; $P = .057$). There were no treatment-related deaths.

TABLE 3
Hematologic Toxicity: Maximum Toxicity Grade in Any Course*

Toxicity	No. of patients (%) GC	GV	P
Leukopenia			
Grade ≥3	34 (53.1)	26 (41.9)	.208
Grade 4	1 (1.6)	1 (1.6)	.981
Neutropenia			
Grade ≥3	51 (79.7)	40 (64.5)	.057
Grade 4	22 (34.4)	16 (25.8)	.294
Anemia			
Grade ≥3	32 (50.0)	3 (4.8)	<.001
Grade 4	9 (14.1)	0	.002
Thrombocytopenia			
Grade ≥3	52 (81.3)	4 (6.5)	<.001
Grade 4	6 (9.4)	0	.013
Platelet transfusion			
Yes	29 (45.3)	0	<.001
Febrile neutropenia	20		
Yes	5 (7.8)	7 (11.3)	.506

GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine.
* Studies of drug-related toxicities were evaluated according to National Cancer Institute Common Toxicity Criteria (version 2.0, revised 1994).

Hematologic and nonhematologic toxicities are listed in Tables 3 and 4. Hematologic toxicity was prominent. In particular, the incidence of Grade 3 or 4 thrombocytopenia was significantly higher in the GC arm (81.3% vs. 6.5% in the GV arm; $P < .001$). However, most patients who had thrombocytopenia in the GC arm did not experience bleeding. Two patients had Grade 3 bleeding in the GC arm. Patients in the GC arm required more platelet transfusions (45.3% vs. 0.0% in the GV arm; $P < .001$). Grade 3 or 4 neutropenia and anemia also occurred in a significantly higher percentage of patients in the GC arm (neutropenia, 79.7% vs. 62.5% in the GV arm; $P < .031$; anemia, 50.0% vs. 4.7% in the GV arm; $P < .001$). The difference in febrile neutropenia incidence was not significant. ($P = .264$).

Nonhematologic toxicity was mild. Grade ≥2 nausea occurred significantly more often in the GC arm than in the GV arm (21.0% vs. 42.2%; $P = .010$). Conversely, Grade ≥2 phlebitis (29.0% vs. 0%; $P < .001$) and hepatic toxicity (elevation of AST or ALT, 43.5% vs. 25.0%; $P = .028$) were significantly more common in the GV arm than in the GC arm. Other nonhematologic toxicities occurred with similar frequency in the 2 treatment arms.

There was 1 treatment-related death in the GV arm, which was caused by pneumonitis. No treatment-related deaths occurred in the GC arm.

TABLE 4
Nonhematologic Toxicity: Maximum Toxicity Grade in Any Course*

Toxicity	No. of patients (%) GC	GV	P
Nausea			
Grade ≥2	27 (42.2)	13 (21.0)	.010
Grade 3	5 (7.8)	0	-
Emesis			
Grade ≥2	8 (12.5)	5 (8.1)	.413
Grade 3	0	0	-
Fatigue			
Grade ≥2	9 (14.1)	15 (24.2)	.147
Grade 3	2 (3.1)	2 (3.2)†	-
Diarrhea			
Grade ≥2	0	2 (3.2)	.147
Grade 3	0	1 (1.6)	-
Constipation			
Grade ≥2	28 (43.8)	19 (30.6)	.128
Grade 3	3 (4.7)	1 (1.6)	-
Rash			
Grade ≥2	11 (17.2)	11 (17.7)	.934
Grade 3	2 (3.1)	1 (1.6)	-
Phlebitis			
Grade ≥2	0	18 (29.0)	<.001
Grade 3	0	0	-
Pneumonitis			
Grade ≥2	0	3 (4.8)	.074
Grade 3	0	2 (3.2)‡	-
ALT/AST			
Grade ≥2	16 (25.0)	27 (43.5)	.028
Grade 3	5 (7.8)	12 (19.4)	.057
Creatinine			
Grade ≥2	0	1 (1.6)	.307
Grade 3	0	1 (1.6)	-

GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

* Studies of drug-related toxicities were evaluated according to National Cancer Institute Common Toxicity Criteria (version 2.0, revised 1994).

† One patient had Grade 3 fatigue, and 1 patient had Grade 4 fatigue.

‡ One patient had Grade 3 pneumonitis, and 1 patient had Grade 5 pneumonitis.

DISCUSSION

This study, the first cooperative group trial to our knowledge of the GC regimen, demonstrated the feasibility of the GC regimen compared with the GV regimen. The GC regimen was identified as a promising regimen for patients with advanced NSCLC. Sederholm et al. of the Swedish Lung Cancer Group demonstrated that GC conferred a significant survival advantage compared with gemcitabine alone.[8] Other Phase III trials demonstrated that the GC regimen was tolerated better; conferred a survival advantage over the combination of mitomycin, ifosfamide, and cisplatin;[15] and resulted in a comparable survival advantage and less nausea and emesis compared with GC.[7]

Based on a large body of Phase II data, including those from our study,[9] and Phase III data, the GV regimen apparently produces less hematologic and nonhematologic toxicity, when it is compared indirectly with more standard combinations. In recent Phase III studies, GV was compared with cisplatin-based regimens. Overall, there was no significant difference in survival, but toxicity was less pronounced.[10,11,16]

GC and GV have comparable efficacy and less toxicity than platinum doublets, as discussed above. However, we do not know which regimen, GC or GV, is more feasible or more effective. Thus, we conducted a randomized study to compare the 2 regimens.

This randomized Phase II study showed that GC and GV are tolerated well and have comparable activity in patients with advanced NSCLC. However, there were marked differences in hematologic toxicity and moderate differences in nonhematologic toxicity. GC resulted in higher incidences of Grade 3 or 4 neutropenia, anemia, and thrombocytopenia. Conversely, hepatic toxicity and phlebitis were increased in patients who received GV.

GC was associated with more thrombocytopenia. The difference in the incidence of severe thrombocytopenia between our study and European or American studies may be attributable to blood counts that were obtained more often in Japan (more than once or twice per week) or to ethnic differences. It is unknown whether there are any the ethnic differences between Japanese and European or American patients concerning thrombocytopenia on the GC regimen. However, a report described severe hematologic toxicity with the combination of paclitaxel and carboplatin that may have been caused by an ethnic difference. Gandara et al. performed a comparative analysis of paclitaxel and carboplatin from cooperative group studies in Japan and the United States. Their analysis showed that the incidence of Grade 4 neutropenia (69% vs. 26%) and Grade 3 or 4 febrile neutropenia (16% vs. 3%) was significantly higher in Japanese patients despite the lower paclitaxel dose.[17]

Overall efficacy was comparable between the GC and GV arms in the current study. There was a trend toward inferior overall survival in the GV arm, but the differences were small numerically, and the study did not have adequate power to detect survival differences. Survival in the current study was better than that reported in other studies of patients with advanced NSCLC. The median progression-free survival in the GC arm in our study was 165 days and was almost equal to that of GC reported by Rudd et al. (5.3 months)[15]; however, overall survival in our study was much longer (432 days vs. 10 months, respectively). Moreover, the proportion of patients who received second-line therapies

in our study was higher (73% vs. 8%).[15] Thus, we believe that better survival in the current study was because a higher proportion of our patients received second-line therapies.

In conclusion, the current results demonstrated that the GC and GV regimens both were active and well tolerated. Although Grade 3 and 4 thrombocytopenia was more frequent in the GC arm, the low incidence of bleeding indicated that thrombocytopenia was not major clinical problem. Thus, we believe that both the GC regimen and the GV regimen are reasonable treatment options for patients with advanced NSCLC.

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A phase I study of pemetrexed (LY231514) supplemented with folate and vitamin B_{12} in Japanese patients with solid tumours

K Nakagawa, S Kudoh, K Matsui, S Negoro, N Yamamoto, JE Latz, S Adachi and M Fukuoka

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Full Paper

A phase I study of pemetrexed (LY231514) supplemented with folate and vitamin B_{12} in Japanese patients with solid tumours

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The purpose of this study was to determine the maximum tolerated dose (MTD) and recommended dose (RD) of pemetrexed with folate and vitamin B12 supplementation (FA/VB_{12}) in Japanese patients with solid tumours and to investigate the safety, efficacy, and pharmacokinetics of pemetrexed. Eligible patients had incurable solid tumours by standard treatments, a performance status 0–2, and adequate organ function. Pemetrexed from 300 to 1200 mg m^{-2} was administered as a 10-min infusion on day 1 of a 21-day cycle with FA/VB_{12}. Totally, 31 patients were treated. Dose-limiting toxicities were alanine aminotransferase (ALT) elevation at 700 mg m^{-2}, and infection and skin rash at 1200 mg m^{-2}. The MTD/RD were determined to be 1200/1000 mg m^{-2}, respectively. The most common grade 3/4 toxicities were neutropenia (grade (G) 3:29, G4:3%), leucopenia (G3:13, G4:3%), lympopenia (G3:13%) and ALT elevation (G3:13%). Pemetrexed pharmacokinetics in Japanese were not overtly different from those in western patients. Partial response was achieved for 5/23 evaluable patients (four with non-small cell lung cancer (NSCLC) and one with thymoma). The MTD/RD of pemetrexed were determined to be 1200/1000 mg m^{-2}, respectively, that is, a higher RD than without FA/VB_{12} (500 mg m^{-2}). Pemetrexed with FA/VB_{12} showed a tolerable toxicity profile and potent antitumour activity against NSCLC in this study.

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Keywords: antifolate; lung cancer; pemetrexed; pharmacokinetics; vitamin supplementation

Pemetrexed (LY231514, Alimta®, Eli Lilly and Company, IN, USA) is a novel antifolate (Taylor and Patel, 1992) that is approved in the United States and a number of European Union countries , for treatment of patients with malignant pleural mesothelioma (MPM) in combination with cisplatin, and non-small cell lung cancer (NSCLC) after prior chemotherapy as a single agent. *In vitro* experiments show that pemetrexed inhibits three enzymes in folate metabolism: thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT) (Shih *et al*, 1998). Given the schedule dependency observed preclinically, three regimens were explored in phase I studies: (1) 0.2–5.2 mg m^{-2} daily for 5 days every 3 weeks (McDonald *et al*, 1998); (2) 10–40 mg m^{-2} weekly for 4 weeks repeated every 6 weeks (Rinaldi *et al*, 1995); and (3) 50–700 mg m^{-2} every 3 weeks (Rinaldi *et al*, 1999).

The third regimen (one dose every 3 weeks) was chosen for subsequent phase II studies because of its convenient administration, ability to give repeated doses, and occurrence of objective responses. The original maximum tolerated dose (MTD) and the recommended dose (RD) was 600 mg m^{-2}, but was decreased to 500 mg m^{-2} owing to toxicities experienced early in phase II studies. The initial phase I and II studies showed that myelosuppression was the principle drug-related toxicity, with a frequency of grade 3/4 neutropenia of 50% and grade 3/4 thrombocytopenia of 15% (Hanauske *et al*, 2001). Less than 10% of patients experienced gastrointestinal toxicities such as diarrhoea or mucositis. Although the prevalence of gastrointestinal toxicities and severe hematologic toxicities was low, these toxicities were associated with a high risk of mortality.

Infrequent severe myelosuppression with gastrointestinal toxicity has been observed not only for pemetrexed, but for the class of antifolates, including the DHFR inhibitor methotrexate (Morgan *et al*, 1990), the TS inhibitor raltitrexed (Maughan *et al*, 1999), and the GARFT inhibitor lometrexol (Alati *et al*, 1996; Mendelsohn *et al*, 1996). Clinical experience and nonclinical studies with methotrexate and lometrexol indicated that severe toxicity may be associated with nutritional folate status (Morgan *et al*, 1990; Alati *et al*, 1996; Mendelsohn *et al*, 1996). In fact, in the study of lometrexol, a significant effect of folate supplementation on toxicity was observed (Laohavinij *et al*, 1996). Based on these experiences, Niyikiza *et al* (2002a) investigated relationships between toxicity and baseline patient characteristics for early pemetrexed studies. They found total plasma homocysteine and methylmalonic acid levels to predict severe neutropenia and

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thrombocytopenia, with or without grade 3/4 diarrhoea, mucositis, or infection. Homocysteine and methylmalonic acid are known as indicators of folate and vitamin B_{12} deficiencies (Rosenberg and Fenton, 1989; Savage *et al*, 1994). Thus, it was hypothesized that a patient's risk for severe toxicity could be reduced by decreasing the levels of homocysteine and methylmalonic acid with folate and vitamin B_{12} supplementation (FA/VB_{12}) (Niyikiza *et al*, 2002a).

FA/VB_{12} is now required for all patients participating in pemetrexed studies. Using this strategy, the pivotal phase III studies for MPM and NSCLC were successfully conducted with amelioration of severe drug-related toxicity (Niyikiza *et al*, 2002b; Vogelzang *et al*, 2003; Hanna *et al*, 2004).

One may expect that pemetrexed administration with supplementation would be more tolerable for patients and permit significant dose escalation above the current RD of 500 mg m^{-2}. Therefore, we conducted a phase I study to determine the MTD of pemetrexed with FA/VB_{12} for Japanese patients with solid tumours and to identify the RD for subsequent Japanese phase II studies. Our secondary objectives were to investigate the safety, antitumour effect, and pharmacokinetics of pemetrexed with supplementation in Japanese patients. A similar phase I study has been conducted outside Japan, but only preliminary data are available at this time (Hammond *et al*, 2003).

PATIENTS AND METHODS

Patient selection

Eligible patients had histologic or cytologic diagnosis of solid cancer that was incurable by standard treatments. Patients also must have been between 20 and 75 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and have an estimated life expectancy of at least 3 months. Adequate organ function was required, which included bone marrow reserve (white blood cell count $4.0-12.0\times10^3$ mm^{-3}, platelets $\geqslant100\times10^3$ mm^{-3}, haemoglobin $\geqslant9.0$ g dl^{-1}, and absolute granulocyte count $\geqslant2.0\times10^3$ mm^{-3}), hepatic function (bilirubin $\leqslant1.5\times$ upper limit of normal, aspartate/alanine transaminase (AST/ALT) $\leqslant2.5\times$ upper limit of normal, and serum albumin $\geqslant2.5$ g dl^{-1}), renal function (serum creatinine $\leqslant$ upper limit of normal and Cockcroft and Gault creatinine clearance $\geqslant60$ ml min^{-1}), and lung function (PaO2 $\geqslant60$ torr).

Prior chemotherapy or hormone therapy was allowed if it was carried out $\geqslant14$ days before study entry ($\geqslant35$ days for nitrosourea or mitomycin-C). Previous radiotherapy was also allowed, but only if $\leqslant25\%$ of marrow was irradiated and if it was completed $\geqslant21$ days before study entry. Pretreated patients must have recovered from all toxicities before study entry. Prior surgery was allowed if patients recovered from the effect of the operation. Patients were excluded from this study for active infection, symptomatic brain metastasis, interstitial pneumonitis, or pulmonary fibrosis diagnosed by chest X-ray, serious concomitant systemic disorders incompatible with the study, clinically significant effusions, or the inability to discontinue aspirin and other nonsteroidal anti-inflammatory agents during the study.

This study was conducted in compliance with the guidelines of good clinical practice and the Declaration of Helsinki Principles, and it was approved by the local institutional review boards. All patients gave written informed consent before study entry.

Treatment

Pemetrexed was administered as a 10-min infusion on day 1 of a 21-day cycle. Patients remained on study unless they were discontinued because of disease progression, unacceptable adverse events, inadvertent enrollment, use of excluded concomitant therapy, cycle delay >42 days, or patient refusal.

Patients were instructed to take a daily 1 g multivitamin with 500 μg of folate beginning 1 week before day 1 of cycle 1 until study discontinuation. Vitamin B_{12} (1000 μg) was intramuscularly injected, starting 1 week before day 1 of cycle 1 and repeated every 9 weeks until study discontinuation.

Patients enrolled in pemetrexed clinical studies have received dexamethasone prophylactically to avoid pemetrexed-induced rash. As this was the first study of pemetrexed in Japanese patients and the incidence of the drug-induced rash in Japanese patients was unknown, the steroid was not to be administered prophylactically.

Dose escalation

In this study, 10 dose levels of pemetrexed, 300, 500, 600, 700, 800, 900, 1000, 1200, 1450, and 1750 mg m^{-2}, were to be examined with a starting dose of 300 mg m^{-2}. At dose levels from 300 to 1000 mg m^{-2}, three patients were to be treated initially. If no dose-limiting toxicities (DLTs) occurred during cycle 1, escalation proceeded to the next dose level. If 1 DLT occurred, three patients were added. If no additional DLTs were observed, escalation proceeded to the next dose level. At dose levels from 1200 to 1750 mg m^{-2}, six patients were to be treated at once. If two or more patients had DLTs at any dose level, dose escalation stopped, and this dose level was considered the MTD. The RD was then established by discussion with principal investigators, and the Efficacy and Safety Evaluation Committee.

A DLT was defined as the occurrence of one of the following toxicities during cycle 1: any grade 3/4 nonhematologic toxicity (except grade 3 nausea/vomiting and AST, ALT, or alkaline phosphatase elevation $<10\times$ upper limit of normal that returns to grade 0–1 by the beginning of cycle 2), grade 3/4 febrile neutropenia (<1000 mm^{-3} with $\geqslant38.0$°C), grade 4 leucopenia (<1000 mm^{-3}) or neutropenia (<500 mm^{-3}) lasting $\geqslant4$ days, thrombocytopenia ($<20\,000$ mm^{-3}), or thrombocytopenia ($\geqslant20\,000$ mm^{-3}) requiring platelet transfusion. A failure to start the second cycle by day 42 owing to toxicity was also considered a DLT. All toxicities were assessed according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.

Treatment assessments

Tumour response was assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Evaluable patients were subjected to CT or MRI measurement to determine the size of tumours at anytime at the discretion of investigators.

Pharmacokinetic analysis

Blood and urine were collected from each patient over a period of 72 h following administration in cycle 1. Blood samples were taken just before administration, at the end of infusion, and approximately 5, 15, 30 min and 1, 2, 4, 6, 8, 24, 48 and 72 h after the start of infusion. Urine was collected over the following time intervals: 0–4, 4–8, 8–12, 12–24, 24–36, 36–48, 48–60, and 60–72 h. Plasma and urine samples were analysed for pemetrexed at Taylor Technology Inc., Princeton, NJ, USA. Plasma samples were analysed using a validated liquid chromatography/electrospray ionisation-tandem mass spectrometry method that generated a linear response over the concentration ranges of 10–2000 ng/ml and 1000–200 000 ng/ml (Latz *et al*, 2006). Urine samples were analysed using a similar analytical technique (Chaudhary *et al*, 1999).

Pharmacokinetics were evaluated using noncompartmental methods (WinNonlin Professional Version 3.1; Pharsight Corporation, Cary NC, USA). Pharmacokinetic parameters determined